frontiers | Research Topics

Integration of HIV prevention with sexual and reproductive health services

Edited by
Renee Heffron and Thesla Palanee-Phillips

Published in
Frontiers in Reproductive Health

ISSN 1664-8714
ISBN 978-2-83251-610-2
DOI 10.3389/978-2-83251-610-2

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Integration of HIV prevention with sexual and reproductive health services

Topic editors

Renee Heffron — University of Washington, United States

Thesla Palanee-Phillips — Wits Reproductive Health and HIV Institute, South Africa

Citation

Heffron, R., Palanee-Phillips, T., eds. (2023). *Integration of HIV prevention with sexual and reproductive health services*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-83251-610-2

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frontiers | Frontiers in Reproductive Health

TYPE Editorial
PUBLISHED 23 January 2023
DOI 10.3389/frph.2023.1129881

OPEN ACCESS

EDITED AND REVIEWED BY
Elizabeth Bukusi,
Kenya Medical Research Institute (KEMRI), Kenya

*CORRESPONDENCE
Thesla Palanee-Phillips
✉ tpalanee@wrhi.ac.za

SPECIALTY SECTION
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

RECEIVED 22 December 2022
ACCEPTED 04 January 2023
PUBLISHED 23 January 2023

CITATION
Palanee-Phillips T (2023) Editorial: Integration of HIV prevention with sexual and reproductive health services.
Front. Reprod. Health 5:1129881.
doi: 10.3389/frph.2023.1129881

Editorial: Integration of HIV prevention with sexual and reproductive health services

Thesla Palanee-Phillips[1,2]*

[1]School of Public Health, University of the Witwatersrand, Wits Reproductive Health and HIV Institute, Johannesburg, South Africa, [2]Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, United States

KEYWORDS

HIV prevention, sexual and reproductive health services, integrated healthcare, PrEP, STIs

Editorial on the Research Topic
Integration of HIV prevention with sexual and reproductive health services

Sub-Saharan Africa (SSA) has the highest burden HIV infection globally, and over 57% of those infected are adolescent girls and young women (AGYW). AGYW of reproductive age in this region are at heightened risk of HIV infection, unplanned pregnancy and sexually transmitted infections (STI) due to a host of socio-behavioural, contextual, gender and relationship dynamics compounded by challenges related to access to sexual reproductive health (SRH) services. Annually, more than 200 million women globally experience unplanned pregnancies due to lack of access, uptake or awareness of availability to reliable contraceptive methods. The vast majority, 70%–80% of these women, reside in SSA. Consequently, almost 50% of pregnancies are unintended and 35 million unsafe abortions occur annually in this region.

Despite efforts to scale up SRH initiatives for the general population, progress made to reduce rates of HIV amongst the most marginalised groups are sub-optimal and high infection rates persist. As highly effective HIV prevention methods including treatment as prevention, HIV pre-exposure prophylaxis (PrEP), condoms and male circumcision have been available for more than a decade now, there are increasing challenges related to measuring impact of a single HIV prevention effort as combination prevention is usually recommended. Furthermore, evidence of pockets of HIV micro-epidemics (1) exist, reflecting hotspots of increased infection rates. AGYW exist in a socioecological matrix where multiple levels of influence exist leading to complex interplay between an individual, their relationships, community, and environment (2) when it comes to health seeking ability. Low perceived risk of HIV acquisition, side effects of PrEP/STI management, disapproval sexual partners, intermittent sexual acts, stigma, intimate partner violence, and perceived limited access to services reflect critical barriers to uptake of SRH care. While some programs have focused on oral PrEP uptake and refills, others adopt a more holistic approach, including counselling on risk reduction, contraceptives and condom use. While PrEP initiation among AGYW is high in some settings, known barriers of intermittent and poor adherence paired with high discontinuation rates reflect lack of sustained efforts to reduce HIV risk.

Aside from HIV, STIs are underdiagnosed in public healthcare facilities due to clinical management being driven by a syndromic symptom-based approach in SSA. Often asymptomatic or having non-specific symptoms, STIs are often unmanaged, increasing HIV transmissibility. Data from ECHO conducted among women seeking family planning (FP) services in HIV burdened settings in Africa demonstrated high HIV incidence of 3.8 per 100 woman-years with higher incidence in some community settings (1, 3). In addition, genitourinary STI rates among

the same cohort from baseline through to trial completion remained high with baseline chlamydia and gonorrhoea prevalence rates at 18% and 5%, respectively (4) and final visit rates at 15% and 5% - a reflection of reinfection and persistence of infection despite initial lab diagnosed management and treatment on entry to the trial.

The World Health Organization (WHO) recommends that SRH services, including contraceptive method delivery, be integrated within HIV prevention and care services. Integration is associated with increased offers and uptake of SRH services, including contraceptive uptake, and STI services and reducing unwanted pregnancies, perinatal HIV transmission and maternal and infant mortality among people living with or without HIV. It is envisaged an integrated SRH model would improve equitable access, yield holistic and comprehensive care, raise the quality of maternal and antenatal care, be cost-effective to the client and the health system, increase financial sustainability with co-location of services and diversify healthcare provider capacity. Most critically, it would reduce stigma being a barrier to access due to shifts away from siloed care. With scale-up of oral PrEP and multiple novel HIV/STI prevention products on the horizon, it would offer a unique opportunity to expand innovative approaches to deliver comprehensive, integrated HIV prevention/SRH services.

However, despite the WHO call and theoretical support for integration, SRH services continue to remain predominantly distinct in most African countries. This may be attributed to the impact of legacy siloed structures that are challenging to modify due to lack of widespread funding or national ministries of health support, need for investment in provider training to support shifts to integration and concerns related to sustainability in this new model. Despite these limitations, research efforts continue to be encouraged to identify approaches for streamlined integration of SRH services. In an ideal world, provision of a comprehensive SRH programme should incorporate five major components: maternal and newborn health; family planning; prevention of unsafe abortion; management of reproductive tract infections and STIs, including HIV/AIDS; and promotion of sexual health all integrated within one discrete cohesive health care facility.

Researchers continue to launch and refine programs to provide evidence of best practices to inform wider scale-up and implementation. These programs span the breadth of HIV care – from testing to prevention to treatment and ongoing management – and leverage the breadth of SRH services – for pregnancy, family planning, and STI prevention and management – to offer myriad opportunities for client-centred, efficient, and comprehensive care. HIV/SRH service integration must be built on evidence of best practice implementation by those who have made efforts for better efficiency in processes. In order to showcase such evidence, a special Research Topic focussing on "Integration of HIV Prevention with SRH Services" was opened and invited submissions for consideration. Two guest editors facilitated the solicitation, peer-review and publication of manuscripts from multiple studies. A total of 14 manuscripts were received; one was rejected and 13 accepted for publication post peer review informed updates were made. By January 2022, the series achieved over 14, 000 views. The breadth of coverage within the series showcased evidence from across Africa and the United States and assesses ongoing integration efforts from different perspectives.

Publications include desktop scoping and landscape analyses across a number of African countries offering HIV testing services and PrEP delivery with family planning (FP) and SRH services to AGYW within the public healthcare space, in programmes and research studies (Drake et al., Mugwanya et al., Pleaner et al., Kasaro et al.) to a focus on the structural and motivational challenges faced by healthcare providers delivering PrEP alongside SRH services (O' Malley et al.). There was also focus on design of PrEP-FP integration matrices and assessing country-specific progress to identify common enablers of and barriers to PrEP-FP integration but also propose the matrix use as a potential roadmap to guide work towards more efficient achievement of integration (Bhavaraju et al.). Utilizing access to AGYW FP services attendees, Nyaboe et al. sought to better understand young women's risk profiling using contraceptive option selection as a proxy to determine risk categorisation when assessed alongside behavioural risk factors and how they may infer potential preferences for a range of short and long term PrEP delivery modalities. There was also evidence of a step further in integration beyond services to a focus in on products with dual or multiple indications within one modality offering both HIV/STI and pregnancy prevention (Friedland et al. and Young Holt et al.). These were recognised conceptually as options that are appealing with potential to revolutionise women's health – all with balance to also recognising opportunities and challenges that would accompany multi-indication product delivery and roll-out. The potential impact and appetite for discrete products with multiple indications would offer an alternate but very appealing integration of SRH services for AGYW who may face challenges disclosing use of methods for indications often stigmatised (e.g., HIV/STI prevention).

Overall, the evidence suggests more is needed to support SRH integration. Despite integration being theoretically and conceptually sound, there is insufficient evidence from the real world to demonstrate long term impact and benefit due to low uptake. Purely offering services in a facility does not speak to actual process integration and natural seamlessness of routine care. A standardised offering with opt-out options vs. opt-in may be useful to inform better SRH care. Evidence indicates that a one-stop women centred care approach would provide holistic care and reduce burden on the service dispersed models. One caveat remains; lack of adequate self-assessed risk awareness. AGYW generally have inaccurate and often low perceptions of their own risk. Design of age appropriate risk assessment tools with repeated opportunities for use will ultimately impact individual uptake of SRH services decreasing incidence of unplanned pregnancies, HIV and STIs.

Author contributions

I would like to acknowledge all authors who contributed to the series and are helping advance work in this crucial area of integration of SRH services. The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers in Reproductive Health

POLICY AND PRACTICE REVIEWS
published: 26 May 2021
doi: 10.3389/frph.2021.657728

A Landscape Analysis of Offering HIV Testing Services Within Family Planning Service Delivery

Alison L. Drake[1], Caitlin Quinn[2], Nancy Kidula[3], Euphemia Sibanda[4], Petrus Steyn[5], Magdalena Barr-DiChiara[2], Muhammad S. Jamil[2], Michelle Rodolph[2], Mary E. Gaffield[5], James Kiarie[5], Rachel Baggaley[2] and Cheryl Johnson[2]*

[1] Department of Global Health, University of Washington, Seattle, WA, United States, [2] Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, World Health Organization, Geneva, Switzerland, [3] WHO Regional Office for Africa, Intercounty Support Team for Eastern and Southern Africa, Harare, Zimbabwe, [4] Centre for Sexual Health and HIV/AIDS Research, Harare, Zimbabwe, [5] The United Nations Development Programme/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP Research), Geneva, Switzerland

OPEN ACCESS

Edited by:
Thesla Palanee-Phillips, Wits Reproductive Health and HIV Institute, South Africa

Reviewed by:
Mike Pickles, Imperial College London, United Kingdom
Lisa Lazarus, University of Manitoba, Canada
Peter Gichangi, Technical University of Mombasa, Kenya
Lisa Haddad, Population Council, United States

***Correspondence:**
Alison L. Drake
adrake2@uw.edu

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *23 January 2021*
Accepted: *01 April 2021*
Published: *26 May 2021*

Citation:
Drake AL, Quinn C, Kidula N, Sibanda E, Steyn P, Barr-DiChiara M, Jamil MS, Rodolph M, Gaffield ME, Kiarie J, Baggaley R and Johnson C (2021) A Landscape Analysis of Offering HIV Testing Services Within Family Planning Service Delivery. Front. Reprod. Health 3:657728. doi: 10.3389/frph.2021.657728

Introduction: Offering HIV testing services (HTS) within sexual and reproductive health (SRH) services is a priority, especially for women who have a substantial risk. To reach women with HIV who do not know their status and prevent mother-to-child HIV transmission, the World Health Organization (WHO) recommends routinely offering HTS as part of family planning (FP) service delivery in high HIV burden settings. We conducted a landscape analysis to assess HTS uptake and HIV positivity in the context of FP/SRH services.

Assessment of Research and Programs: We searched records from PubMed, four gray literature databases, and 13 organization websites, and emailed 24 organizations for data on HTS in FP/SRH services. We also obtained data from International Planned Parenthood Federation (IPPF) affiliates in Eswatini, Kenya, Lesotho, Malawi, Namibia, Uganda, Zambia, and Zimbabwe. Unique programs/studies from records were included if they provided data on, or barriers/facilitators to, offering HTS in FP/SRH. Overall, 2,197 records were screened and 12 unique programs/studies were eligible, including 10 from sub-Saharan Africa. Four reported on co-delivery of SRH services (including FP), with reported HTS uptake between 17 and 94%. Six reported data on HTS in FP services: four among general FP clients; one among couples; and one among female sex workers, adolescent girls, and young women. Two of the six reported HTS uptake >50% (51%, 419/814 Kenya; 63%, 5,930/9,439 Uganda), with positivity rates of 2% and 4.1%, respectively. Uptake was low (8%, 74/969 Kenya) in the one FP program offering pre-exposure prophylaxis. In the IPPF program, seven countries reported HTS uptake in FP services and ranged from 4% in Eswatini to 90% in Lesotho; between 0.6% (Uganda) and 8% (Eswatini) of those tested were HIV positive.

Implications: Data on providing HTS in FP/SRH service delivery were sparse and HTS uptake varied widely across programs.

Actionable Recommendations: As countries expand HTS in FP/SRH appropriate to epidemiology, they should ensure data are reported and monitored for progress and impact.

Keywords: HIV testing services, family planning, sexual and reproctive health, service delivery, service integration

INTRODUCTION

Women of reproductive age have disproportionately high risks of HIV in sub-Saharan Africa (1, 2). Increased efforts to identify women with HIV and link them to care and treatment are imperative to reach the UN 95-95-95 fast track targets (3). Recent data from the ECHO trial conducted among women seeking family planning (FP) services in high HIV burden settings in Africa demonstrated high HIV incidence of 3.8 per 100 woman-years (4). These results highlight the need for integrated HIV service delivery among women who seek FP for pregnancy prevention. Integrating HIV and sexual reproductive health (SRH) has long been considered a priority and routinely offering testing in antenatal care clinics has been widely accepted with high uptake (5). To reach the women with unknown HIV status and prevent mother-to-child HIV transmission, routine offer of HIV testing services (HTS) for women seeking FP services in high HIV burden countries is also recommended by the World Health Organization (WHO) (6, 7). However, there has been much less global commitment and focus on HIV testing within the context of FP and SRH services. Failure to test women seeking FP services represents a missed opportunity to identify women with undiagnosed HIV who can be linked to antiretroviral treatment (ART), re-engage women who have been previously diagnosed with HIV and are not on ART, identify HIV-negative women who could benefit from a range of HIV prevention choices [including pre-exposure prophylaxis (PrEP)], and provide the opportunity to deliver partner services for those with HIV.

Despite the recognition of benefits of improving HIV-SRH linkages for many years (8, 9) and development of resources to support integrated services, little real-world progress has been made beyond some efforts to integrate FP into postnatal care in prevention of mother-to-child transmission (PMTCT) programs and offering FP for women receiving HIV care and treatment (10–13). Providing HTS in FP settings as a specific approach to integrated service delivery has received considerably less attention.

A recent systematic review suggested that integration of HTS in FP settings was feasible and showed potential to improve client satisfaction with services (14). However, evidence was limited to data from six comparative studies conducted in four countries (Kenya, Eswatini, Uganda, and USA) (14). In order to examine country implementation of HTS in routine FP service delivery, we conducted a landscape analysis to assess HTS uptake and HIV positivity in the context of FP service delivery using reports from research and programs, as well as programmatic experiences. We highlight approaches to provide HTS within FP/SRH service delivery to inform implementation.

ASSESSMENT OF RESEARCH AND PROGRAMS

Overview and Inclusion Criteria

A review of comparative studies on integrating HTS into FP was previously conducted (14); we sought to analyze data from non-comparative studies excluded from this review and data published after the review was conducted. Comparative studies from the prior review were excluded from this analysis in order to focus on real-world program implementation that differs from controlled environments. We obtained and reviewed a list of references identified as relevant but excluded in the prior review due to lack of a comparison (i.e., intervention) group, by contacting authors (14). We searched PubMed to capture articles published after the prior review as well as gray literature databases. No geographical restrictions were applied to the references from the prior review or database searches. We also reviewed organizational websites [including government and non-government organizations (NGOs)] known to implement or research HIV and FP/SRH in sub-Saharan Africa and emailed contacts at these organizations to request study or program data on HTS in FP/SRH services. In addition, we conducted semi-structured phone interviews with program managers from International Planned Parenthood Federation (IPPF) member associations in eight countries: Eswatini, Kenya, Lesotho, Malawi, Namibia, Uganda, Zambia, and Zimbabwe. These countries were selected for specific inquiry as they have been identified as priority countries based on their prevalence of HIV in women of reproductive age and contraceptive prevalence rate $< 67\%$ (15).

We assessed the proportion of women of reproductive age (age 15–49) who were offered HTS, HTS uptake (defined as providing tests after they are offered), and HIV test positivity as primary outcomes in FP programs. Programs, reports, and other data were included in the review if they (1) described offering HTS into FP services, including offering HTS to women of reproductive age (age 15–49) seeking FP or SRH through clinic- or community-based service delivery, and (2) measured one or more of the primary outcomes or included qualitative perspectives on offering HTS with FP alone or FP in conjunction with other SRH services. Records were excluded if data represented household or community surveys among a general population rather than individuals offered HTS in FP/SRH program service delivery. There were no language restrictions; however, only English terms were used in the search.

Search Strategy

We used a keyword search in PubMed and four gray literature electronic databases, including Think Tank Search, Gray Literature Report, Open Gray, and Union of International Associations IGO. Key words were "HIV" AND "contraception," "HIV" AND "family planning," "HIV" AND "birth control," and "HIV" AND "integration." For databases that accept MeSH terms, we used the following MeSH terms: (("HIV Infections/diagnosis"[Mesh] OR "AIDS Serodiagnosis"[Mesh]) OR ("Diagnostic Tests, Routine"[Mesh] OR "Mass Screening"[Mesh] OR "testing"[tiab]) AND ("Contraception"[Mesh] OR "FP" OR "birth control"[tiab])). PubMed databases were searched through from June 21, 2017 to March 20, 2020. Gray literature searches were performed between May 15 and 24, 2019. A snowball approach was used to search websites, in which new organizations identified from searching the initial list were added to the search. The websites included in the search included Center for Strategic and International Studies (CSIS), Family Planning 2020,

FHI 360, Frontline AIDS, Integra Initiative, International Planned Parenthood Federation (IPPF), JHPIEGO, MEASURE Evaluation, PATH, Population Council/The Evidence Project, Sexual and Reproductive Health & HIV Linkages (SRH & HIV Linkages), and United Nations Population Fund (UNFPA). We searched websites using "HIV" and each of the following other terms, individually: "contraception," "family planning," "birth control," and "integration."

We directly contacted individuals representing government and non-government organizations (NGOs) though email and requested any relevant documents or reports on service delivery of integrating HTS into FP, with a maximum of three reminders to prompt a reply. Individuals could also refer the research team to other contacts. IPPF program managers were invited to participate in a semi-structured phone interview with the research team to discuss data and experiences of implementing integrated programs. Documents and reports from websites and contacts were collected through December 16, 2019.

Titles, abstracts, data summaries, and reports were evaluated for inclusion in the full-text review by a single reviewer. Relevant records were selected for full-text review, and data were extracted independently by one reviewer using a standardized extraction form. We used the following definitions in our analysis to guide decisions on eligibility for inclusion and abstraction of outcomes:

- **FP services:** Health care programs or services designed to assist individuals in preventing or delaying pregnancy, including counseling, referral, dispensing, providing, or removing FP/contraceptive methods.
- **HIV testing services (HTS), including HIV self-testing:** Execution of HIV test procedures, including pre-test information and post-test counseling. We also aimed to abstract data from programs on linkage to HIV prevention, treatment and care services and other clinical and support services.
- **Sexual and reproductive health (SRH) services:** SRH care includes providing antenatal, perinatal, postpartum, and newborn care; FP, fertility, and abortion services; sexually transmitted infections (STIs) screening and treatment, including HIV, reproductive tract infections, cervical cancer, and other gynecological morbidities; and counseling on sexuality (16).
- **Integration:** Integration was defined as the provision of HTS alongside or within FP programs or services (i.e., co-located and/or sharing services and resources) but excludes the provision of FP services within HIV prevention, treatment, and care programs.
- **Social Harms:** Any intended or unintended cause of physical, economic, emotional, or psychosocial injury or hurt from one person to another, a person to themselves, or an institution to a person, occurring before, during, or after testing for HIV (17).

Analysis

We refer to all data, reported from studies and programs, as program data for simplicity and analyzed the program as the unit of analysis. We classified HTS uptake, among those offered as high (>85%), moderate (50–85%), and low (<50%). HIV positivity was reported if available and was calculated among those who were tested for HIV, excluding those offered and not tested. We used data from UNAIDS from the study period for HIV prevalence and calculated treatment-adjusted prevalence by combining HIV prevalence with population data from World Bank (18, 19). To estimate the expected HTS positivity, we also calculated the treatment-adjusted prevalence (20), which removes the number of PLHIV who are on ART from HIV prevalence and population estimates to determine the expected HTS positivity among those receiving HTS. Due to the heterogeneity in approaches to integrate HTS within FP/SRH service delivery, we did not pool results.

The semi-structured phone interviews with IPPF member association managers were conducted by one interviewer and transcribed during the call. The interviewer contacted respondents by email after the interview for any required clarifications and further collection of programmatic data. We analyzed the qualitative data by organizing responses into conceptual categories and tracking emerging themes from the data. Representative quotes were extracted from the interview notes and organized by themes and sub-themes. Summary text from other included studies that address perspectives on successes and challenges of HIV/FP integration was also extracted and incorporated into the thematic table to further draw out salient themes and experiences related to integration.

Results

We identified 2,197 records in the search, of which 1,453 were from organizational websites, 626 from online gray literature databases, 58 from the prior review, 40 from direct email contacts, 18 from PubMed, and 2 others that the team was aware of (**Figure 1**). After screening titles and abstracts, 320 full-text records were assessed for eligibility and 29 records met eligibility criteria for inclusion. Included records spanned between 2010 and 2019. The 29 eligible records represented 12 unique programs included in the analysis (21–57) (**Figure 1**). All data were reported or extracted from programs, with the exception of one pilot study of a couples intervention (40). Two-thirds of programs (8/12) reported cross-sectional program data, two programs reported data at different time points (multiple records from the same program) using cross-sectional and pre–post-program reports, one reported pre- and post-program data only, and one was longitudinal. In addition, three programs included qualitative data on program implementation. The majority (10/12) of programs were conducted in sub-Saharan Africa, eight in one or more of the priority countries (**Table 1**). One SRH program was conducted in multiple locations (four countries in sub-Saharan Africa, India, and Tunisia) (44–46) and two programs were delivered in the United States ($n = 2$) (22, 39). Due to the small number of records outside of sub-Saharan Africa, we summarized results within and outside sub-Saharan Africa separately. Among 10 programs from sub-Saharan Africa, we identified six that were focused on offering HTS within the context of FP service delivery and four within broader SRH programs that included FP.

HTS Uptake and HIV Positivity in Sub-Saharan Africa

Six programs in sub-Saharan Africa offered HTS within the context of FP service delivery; four providing HTS to women

seeking FP services (two in Kenya, one in Uganda, and one in Tanzania) (23–25, 35, 56), one providing HIV counseling in FP clinics and referring women elsewhere for testing in Nigeria (34, 37), and one co-delivering FP and HTS to couples in households in Malawi (40). No programs reported data on linkage to HIV prevention, treatment and care services and other clinical and support services. The Tanzania program targeted female sex workers (FSW), adolescent girls and young women (AGYW), and other "hotspot" populations specifically ("hotspot" was not further defined) (23). Descriptions of programs, including details on the approach to offering HTS in FP/SRH service delivery, are in **Table 1** with article extraction sheets in the **Supplementary Table**.

Only two programs reported data on the proportion offered HTS (**Figure 2**); all others only provided HTS uptake and/or positivity among those offered HTS. An observational study of FP clinics in Mombasa, Kenya found 59% (23/58) of clinics offered HIV testing to new FP clients, uptake of HTS was 51% (419/814), and 2% were HIV-positive (35). In Malawi, couples received HIV pre-test information together, were individually tested, and then received FP services and condoms in the 20–40 min while awaiting their HIV test results. Couples could also opt to receive only HTS, or only FP services. In this study, 93% of couples (167/180) were offered testing, 87% of couples were tested, and 16% of women were HIV-positive. Over one-quarter (26%, 94/360) of all individuals tested were first-time testers. Prevalence of first-time testing among those tested was 48% among men ($n = 69$) and 17% among women ($n = 25$). Overall, 22.1% (32/145) of couples had at least one positive partner, 12.4% were serodiscordant and 9.7% were concordant positive (40). HTS uptake was also high in the Tanzania study (93–97%), with 11% of FSW, 4% of AGYW, and 8% of "hotspot" populations testing positive (23). Low to moderate HTS uptake was reported in Nigeria (7–14%), Uganda (63%), and in a PrEP implementation program in Kenya (8%) (34, 35, 37, 56). In a larger ($n = 39$ facilities) evaluation conducted over 2 years (2007–2009) in one of the Nigeria programs, uptake of HTS was 7% (2,372 of 32,237 referred received tested). In a separate evaluation of HTS referral models in 40 FP clinics in Nigeria, receipt of an HIV test was 46% higher among women who accepted HTS through

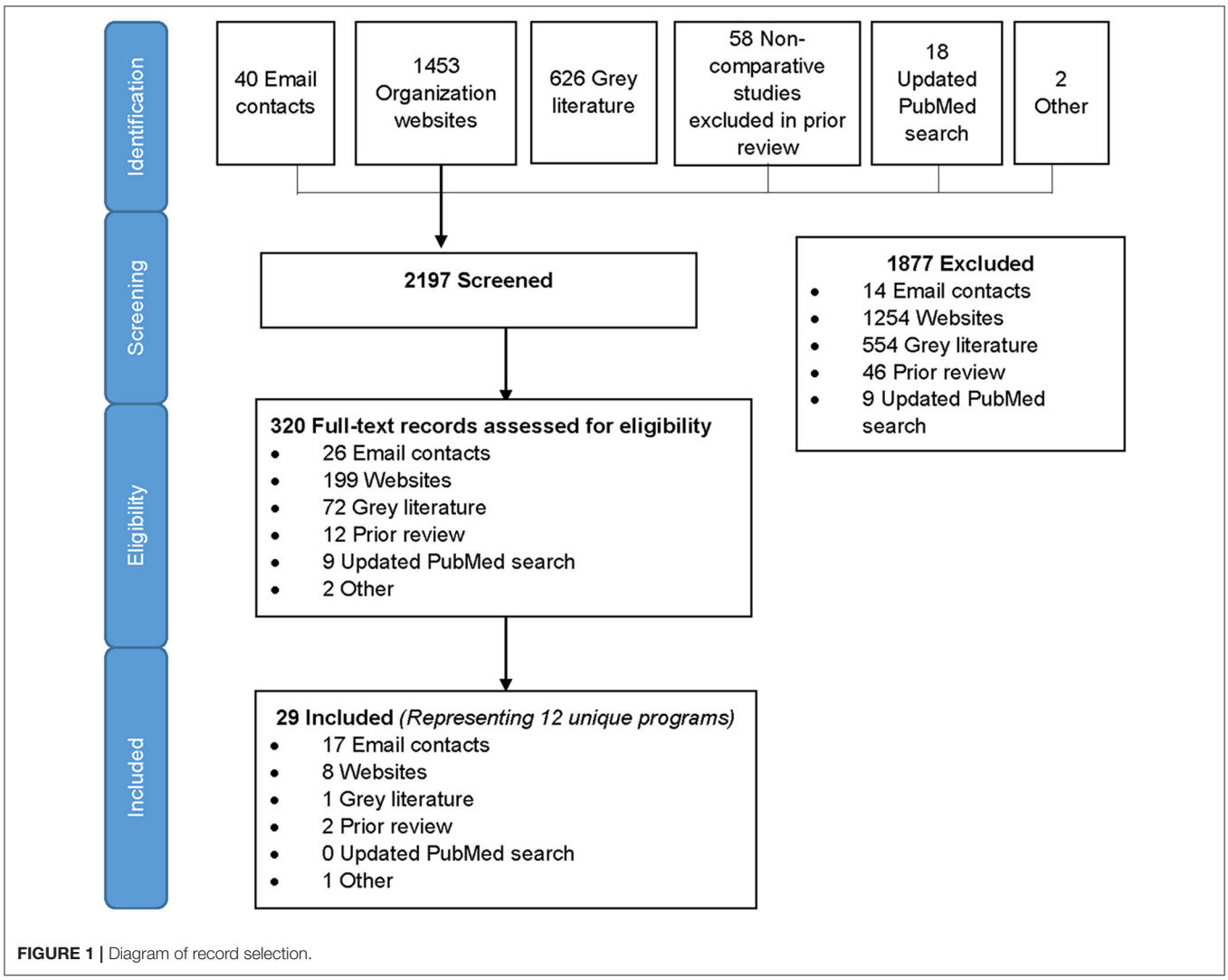

FIGURE 1 | Diagram of record selection.

TABLE 1 | Characteristics of included programs/studies from sub-Saharan African countries, by population.

References	Location	Target population	Time period	Adult HIV prevalence (95% CI)**	Treatment-adjusted prevalence*	Study design	Description of approach to offering HTS
Becker et al. (40)	Malawi (home-based)	Male–female married/unioned couples	2009	10.1 (8.9–11.1)	7.8%	Pre–post	**HTS + FP:** Co-delivery of couples HTS and couples FP on-site in households. Men only offered services if women received services independently (HTS, FP or both) ($N = 180$ couples)
Eastment et al. (35)	Mombasa, Kenya (facility)	New FP clients (female implied)	2016	5.1 (4.4–5.9)	1.4%	Cross-sectional (Review of service delivery statistics)	**HTS + FP:** Measured on-site HTS in a random sample ($n = 58$) FP clinics over 3 months
Mugwanya et al. N.D. and Personal communication (Pintye, Jillian) (24, 25)[a]	Western Kenya (facility)	Female FP clients, including AGYW	2017–2018	5.0 (4.4–5.8)	1.3%	Longitudinal	**HTS + FP:** HTS offered on-site in 8 high-volume FP clinics via a PrEP implementation program
Tassi (56)	Uganda	FP clients (sex not specified)	July–Sept 2018	6.2 (5.8–6.9) 22.9 (21.6–24.8) 26.6 (25.1–28.2)	1.8% 15.1% 18.3%	Cross-sectional (Review of service delivery statistics)	**HTS + FP:** Co-delivery of HTS and FP (on-site and referral) in majority of government facilities in Uganda. Data of HTS among FP clients were provided from 49 selected facilities
SRH & HIV Linkages (21, 42, 44, 58, 59)[b]	All			22.7 (20.8–24.0)	11.9%		**HTS + SRH: Comprehensive on-site co-delivery of SRH/HIV** **"**Linkages Project" HTS, ART, VMMC scaled-up through partnerships with civil service organizations.
	Lesotho (facility)	Male and female SRH clients; also adolescents, survivors of gender-based violence, FSW, and people with HIV	2012–2013	22.6 (20.9–24.0)	10.2%	Pre–post	HTS, ART, VMMC scaled-up through partnerships with civil service organizations.
	Eswatini (facility)	Female SRH clients	2011–2013	2.3 (1.9–2.8)	0.8%	Cross-sectional (Review of service delivery statistics; patient and provider satisfaction surveys)	5 centers; one-stop shop delivery enhanced by peer mentorship for HCW
	Botswana (facility)	Female SRH clients	2012–2014	5.2 (4.6–5.6)	2.7%	Pre–post	ART, FP, STIs, CaCx screening in 9 pilot sites; one-stop shop delivery enhanced by training and technical support on integration, task-shifting and task-sharing, NGO partnerships.

(Continued)

TABLE 1 | Continued

References	Location	Target population	Time period	Adult HIV prevalence (95% CI)**	Treatment-adjusted prevalence*	Study design	Description of approach to offering HTS
		Male and female SRH clients	2015	1.2 (0.9–1.7)	1.0%	Cross-sectional (interviews with patients, providers and policymakers)	9 sites using "kiosk" (services by single HCW in same room), "supermarket" (services in multiple rooms by different HCW at large clinics), or "mall" (referral to different rooms within same facility for different services by different HCW in hospitals) models. FP registers updated with HTS and youth-friendly campaign launched.
	Togo (facility)	Male and female SRH clients	Not reported	1.2 (0.9–1.7)	1.1%	Cross-sectional (Service delivery statistics; interviews with patients, providers and policymakers)	Enhanced training providers on SRH and HIV integration
Personal communication (JHPIEGO) (41, 43)[c]	Tanzania (community)	Female SRH clients who were FSW, out of school AGYW, or other hotspot female populations	2014–2017	10.8 (8.6–13.4)	10.4%	Cross-sectional (Review of service delivery statistics)	**HTS + FP:** Co-delivery of HTS and FP with HIV prevention and linkage to ART on-site for key and vulnerable populations. "Sauti Project"
Chukwujekwu et al. and GHAIN report, N.D. (34, 37)[d]	Nigeria (facility)	FP clients (sex not specified)	All	27.1 (25.4–28.8)	1.9%	–	**HTS + FP:** HTS and FP delivered through one-stop shop (FP providers provide both FP and HTS during same visit) and referral-based models (FP providers offer FP and HIV counseling only and refer clients to co-located HTS). Included tools for HIV-FP integration, provider training and supportive supervision. "Global HIV/AIDS Initiative Nigeria (GHAIN)"
			2007–2009	4.8 (4.2–5.6)	1.2%	Pre–post	71 public health facilities.
			2007–2011	23.1 (21.5–25.0)	10.3%	Review of service delivery statistics	141 public health facilities.
Lafort et al. International Centre for Reproductive Health (ICRH) (33)[e]	Tete, Mozambique (community)	FSW	2004–2009	12.7 (11.7–13.8)	2.4%	Cross-sectional (Service delivery statistics; key informant interviews; FGDs)	**HTS + SRH:** Co-delivery of FP, STI, and HTS on-site at a night clinic (4–10 PM) for FSW with free services and expanded peer outreach activities. "Diagonal Interventions to Fast-Forward Reproductive Health (DIFFER)"
International Planned Parenthood Federation (IPPF) (49–55, 57)[f]	All (facility and community)	Male and female SRH clients	2019	9.5 (8.8–10.1)	2.3%	Cross-sectional (Program data & interview with program managers)	**HTS + SRH:** Comprehensive co-delivery of SRH and HIV services in static and mobile clinics (on-site and referral).

(Continued)

TABLE 1 | Continued

References	Location	Target population	Time period	Adult HIV prevalence (95% CI)**	Treatment-adjusted prevalence*	Study design	Description of approach to offering HTS
	Eswatini (FLAS)		–	12.1 (11.3–13.1)	2.0%	–	HIV services include HTS, ART, VMMC, and PEP
	Kenya (FHOK)	–	–	6.1 (5.7–6.8)	1.0%	(Interview only)	HTS for HIV services and referral for ART
	Lesotho (LPPA)		–	13.4 (11.8–15.3)	2.6%	–	HIV services include HTS, ART, and VMMC; clinics include men's and youth clinics.
	Namibia (NAPPA)	Focus on youth (10–24 years)	–	5.1 (4.5–5.5)	3.7%	–	HIV services include HTS, ART, and VMMC; all clinics youth friendly.
	Malawi (FPAM)	Focus on youth (10–24 years)	–	10.1 (8.9–11.1)	7.8%	–	HIV services include HTS, ART, and VMMC; all clinics youth friendly.
	Zambia (PPAZ)	–	–	5.1 (4.4–5.9)	1.4%	–	Co-delivery of FP (and related SRH) with HTS in 3 static clinics, 11 mobile units, and 10 community-based services (on-site and referral). Referral for ART and PMTCT.
	Uganda (RHU)	–	–	5.0 (4.4–5.8)	1.3%	–	Mainly focused on reaching key populations. Offer of HTS is routine in every interface with client.
	Zimbabwe (ZNFPC)	–	–	6.2 (5.8–6.9)	1.8%	–	Co-delivery of FP (and related SRH) with HTS in 10 static and mobile clinics (plus a few youth-focused centers) (on-site and referral).
Plotkin et al. (23)[g]	Tanzania (facility)	Female SRH clients	2010–2013	22.9 (21.6–24.8)	15.1%	Cross-sectional (Review of service delivery statistics)	**HTS + SRH:** Co-delivery of HTS and cervical cancer screening on-site in SRH/MCH department (where FP also co-located) at 21 government health facilities. Services provided at the same visit and location; enhanced by provider training. "Cervical Cancer Prevention (CECAP) program"

AGYW, Adolescent girls and young women; ART, antiretroviral therapy; CaCx, cervical cancer; FHOK, Family Health Options Kenya; FLAS, Family Life Association of Eswatini; FP, family planning; FPAM, Family Planning Association of Malawi; FGD, focus group discussion; FSW, female sex worker; HCW, healthcare worker; HTS, HIV testing services; IPPF, International Planned Parenthood Federation; LPPA, Lesotho Planned Parenthood Association; MCH, Mother and Child Health; NAPPA, Namibia Planned Parenthood Association; PMTCT, prevention of mother-to-child HIV transmission; PPAZ, Planned Parenthood Association of Zambia; PrEP, pre-exposure prophylaxis; RHU, Reproductive Health Uganda; SRH, sexual and reproductive health; STI, sexually transmitted infection; VMMC, voluntary male medical circumcision; ZNFPC, Zimbabwe National Family Planning Council.

**HIV Prevalence, Total # PLHIV, and % ART coverage among PLHIV (age ≥ 15) (18); **Treatment-adjusted HIV prevalence = (Total PLHIV age ≥15 – PLHIV on ART age ≥ 15)/Total Population 15≥ – PLHIV on ART age ≥ 15. Data source for total population data (19). Data sources for treatment-adjusted prevalence: [a]2017 data from UNAIDS and UN POP, [b]Lesotho (2012 data); Eswatini (2012 data); Botswana (2013 and 2015 data, PLHIV ART coverage for ≥15 not available—thus overall ART coverage was used); Togo (2019 data), [c]2017 data from UNAIDS and UN POP, [d]2008 and 2009 data from UNAIDS and UN POP, [e]Mozambique, 2009 data, [f]2019 data, [g]Tanzania, 2012 data.*

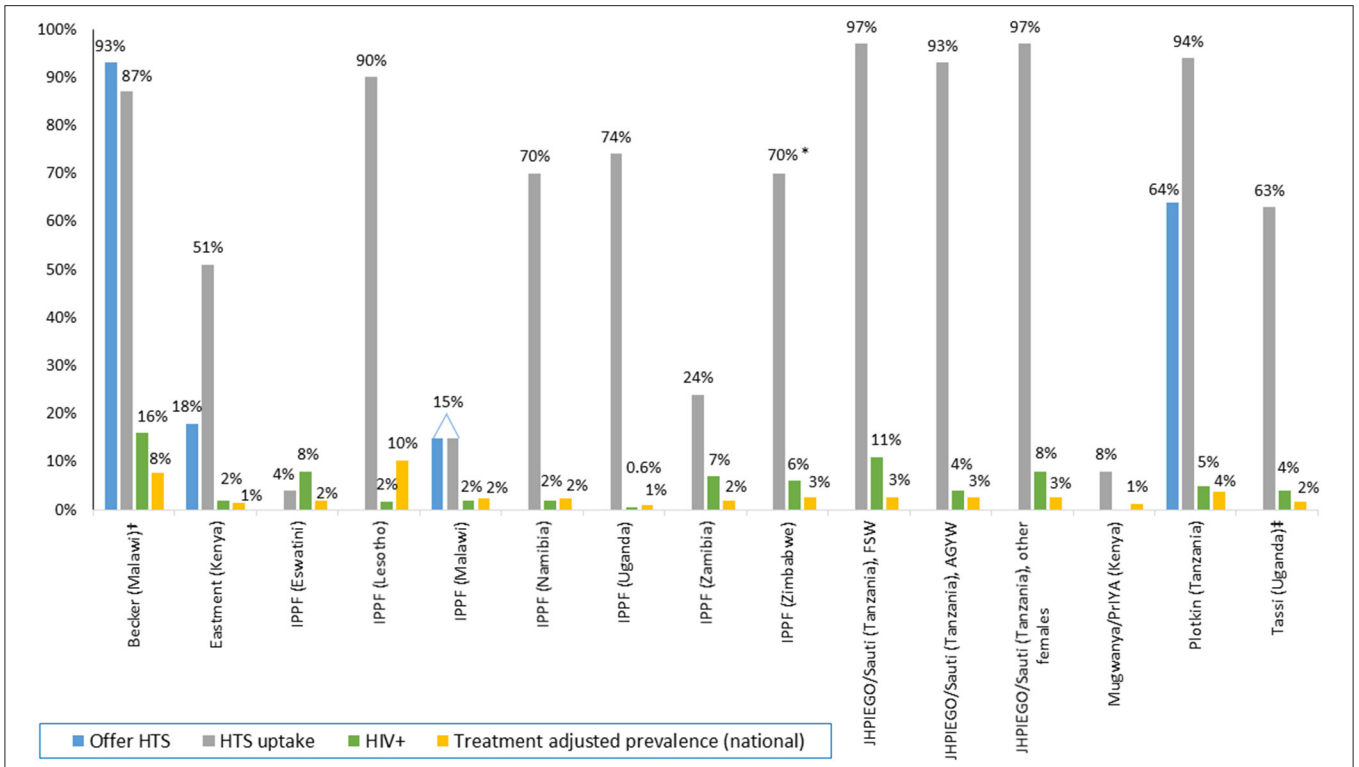

FIGURE 2 | HTS offered, uptake, and positivity among integrated FP programs, by program. Data presented in the figure are rounded to the nearest whole number if it is >1%. Adolescent girls and young women (AGYW); female sex worker (FSW); HIV testing services (HTS); International Planned Parenthood Federation (IPPF). *Range 70–95%. †HTS offer and uptake among male–female couples, HIV positivity among women only. ‡Sex not specified.

the one-stop-shop ("kiosk") delivery model (100% tested) vs. the referral ("supermarket") model (77% tested) (34, 37).

Four programs included HTS as part of a package of SRH services; services included varied by program. IPPF member associations offered comprehensive co-delivery of SRH and HIV (HTS, ART, and PrEP) by the same provider in youth-friendly static and mobile clinics (49–55, 57). Some IPPF member associations (Namibia, Zambia) also incorporated the option of referring women to stand-alone HTS services. Seven of eight IPPF countries provided data on HTS; only Malawi reported the frequency of offering HTS (15%). Among individuals offered HTS, uptake was highest in Lesotho (90%), followed by Zimbabwe (80%), Uganda (74%), and Namibia (70%). IPPF member associations in Zambia, Malawi, and Eswatini had low uptake (24, 15, and 4%, respectively). Program managers in Eswatini attributed low HTS uptake to widespread access to HTS elsewhere and large number of clients who were recently tested or women living with HIV already in care, limiting eligibility for HIV testing while seeking FP/SRH services. Despite low HTS uptake, HIV positivity was highest in IPPF programs in Eswatini (8%) and Zambia (7%). HIV positivity was lower in Lesotho, Namibia, and Malawi (all 3%) and Uganda (0.6%).

Another large program delivering bi-directional HIV and SRH services was the SRH & HIV Linkages Project, an interagency collaboration with IPPF, UNAIDS, UNFPA, and WHO; records from this project included in the analysis were from four countries in sub-Saharan Africa (as well as Tunisia and India) (21, 44, 58, 59). The program included different HIV and SRH services and approaches to integration across countries. In Eswatini, enhanced peer mentorship for health care workers was used to provide one-stop-shop co-delivery of services, and data on patient and provider satisfaction were obtained through surveys. Between 2011 and 2013, HTS uptake increased from 0 to 20% (58). Botswana also initially used a one-stop-shop model, offering ART, FP, STI, and cervical cancer screening services in nine sites, incorporating task-shifting and enhanced training though partnerships with NGOs. The proportion of women accessing both HIV and FP services increased from 0% in 2012 to 89% in 2013. In 2015, the Botswana sites offered several approaches to service delivery to both men and women through one-stop-shop models ("kiosk"), delivering services in multiple rooms by different HCW at large clinics ("supermarket"), or referring to different rooms in the same facility with different HCW within a hospital ("mall"). In this integrated program, 63% of male and female clients received both HIV and FP services; 89% of female clients received dual services (21). In Lesotho, an integrated, comprehensive SRH package was offered to a broad range of populations, including men, FSW, adolescents, and gender-based violence survivors. HTS uptake nearly tripled when the program was introduced in 2012 from 3,170 to 8,114 in 2013 based on service delivery statistics (59). In contrast to uptake in Lesotho, provision of integrated services with enhanced training

on SRH and HIV within the Togo program led to only 17% HTS uptake among male and female SRH clients (44).

In Nigeria, both one-stop-shop and referral-based approaches to HTS in FP clinics were implemented (34, 37). One year following implementation, 14% (n = 32,337) of FP clients received HTS. HTS uptake was higher with the one-stop-shop model than the on-site referral model (100% of individuals accepting HTS at the one-stop-shop completed testing vs. 77% who were referred). Two programs in Tanzania offered HTS in other SRH programs (23, 35). A cervical cancer screening program co-located with FP services offered HTS to 64% (11,819/18,539) of women screened for cervical cancer, of which 94% (11,072/11,819) were tested and 5% were positive (582/11,072) (23). A community-based program (Sauti Project) that targeted FSW, out-of-school adolescent girls and young women (AGYW, ages 15–24), and other female populations in HIV hotspots found high HTS uptake across all populations: 96–97% among FSW, 93–99% among AGYW, and 97–99% among other populations (38). HIV positivity was 5–11% among FSW, 2–4% among AGYW, and 3–8% among other populations (38). International Centre for Reproductive Health (ICRH) also targeted FSW using a night clinic in Mozambique, which included integrated services (30–33). Program evaluations of this model found high client satisfaction (33) and substantial increases on HTS uptake among FSW (30, 32).

HTS for Male Partners

Overall, only three programs identified in our review included male partners in their HTS strategies and one reported partner HTS outcomes. The couple study in Malawi found that 45% of male partners were first-time testers (69/145), and HTS uptake was 91% among men who had never tested before (69/76) (40). Male partner HIV status in the PrEP program was also reported; 31% of women did not know their partner's HIV status and 5% of women had an HIV-positive partner (25).

Social Harms

The couple study in Malawi was also the only study reporting on social harm resulting from testing, and no social harms were reported (40).

Perspectives on Successes and Challenges in Sub-Saharan Africa

Experiences and perceptions of delivering HTS in FP or SRH services were reported by providers and male and female clients from the SRH & HIV Linkages Project in three countries (21, 44, 58), by FSW clients from ICRH in Mozambique (33), and during phone interviews with IPPF program managers from eight countries (49–55, 57) (**Table 2**). Program managers believed that HTS delivery in an FP/SRH setting was "*easy to do*" [IPPF, Eswatini] at FP initiation and noted many benefits to service integration for clients, including reduced number of trips to health facilities and consultations (42, 44, 58). They also believed that clients were appreciative of delivering integrated service delivery, stating "*People seem to really like when you bring services together*" (IPPF, Malawi). However, they also expressed several concerns about this delivery model. Some program managers acknowledged they had initial fears that adding HTS would overwhelm providers, but IPPF Kenya said concerns were alleviated after the program was implemented. Overall, structural barriers commonly cited by providers and clients include lack of adequate clinic space (54), concerns about longer queues and wait time (42, 44, 58), lack of trained providers (54, 57), and shortage of trained staff (58) and test kits (49, 57).

One site reported no current challenges to providing integrated FP and HTS, but stated, "*Maybe clients are waiting a little longer [for HTS] because counseling gets extended by 15 minutes or so with the provider*" [IPPF, Kenya]. Program managers from other countries believed that a challenge for integration was that, "*when [clients] come for FP, they usually aren't interested in other services*" (IPPF, Eswatini). Some countries said integration can be duplicative because HTS is "*readily available, and in most cases, people already have test kits*" (IPPF, Eswatini) with wider availability of HTS generally, and HIV self-test kits for direct consumer purchase in pharmacies, specifically.

Overwhelmingly, women who received integrated services were very supportive of offering HTS in FP/SRH services whether in the same site or by the same provider. Women appreciated the efficient approach to delivering co-located services, citing fewer trips to the facilities and lower travel and health care costs (33, 42, 44, 58). Women did have varied perceptions about waiting times, with some saying their wait time to receive HTS within FP/SRH was shorter (33), while others said waiting times were longer (42, 44). Some women from a few of the HIV & SRH Linkages Project sites did report that providers seemed overwhelmed or too busy, and the provision of integrated services was perceived by some to be lower quality with less confidentiality (42, 44).

Additional Integrated HTS and FP/SRH Programs From Other Regions

Beyond sub-Saharan Africa, the SRH & HIV Linkages Project also integrated SRH and HTS in India, in which 36% of FP clients received HIV counseling and were referred for testing in 2012 (45). From a rapid assessment of the program in India, 48% (9/27) of clients interviewed reported receiving at least one HIV service at the integrated site (45). Additionally, two programs from the USA were included in the analysis (22, 39). An assessment of publicly funded US FP clinics offering HTS and STI services found that 19% of FP clients were tested for HIV (22). HIV testing data from 10 FP clinics serving adolescents and young adults were also collected over a 4-year period in a US study; 86% (34,299/39,698) of clinic patients were tested for HIV. Nearly a quarter (22%, n = 7,820) of testers were men and half (51%, 17,585/34,299) were young people (20–24 years). The average number of HIV tests administered at the clinics doubled after implementing routine, opt-out HTS. Overall HIV positivity was 0.3% (88/34,299), 0.8% among men and 0.1% among women.

IMPLICATIONS

We observed a wide range of studies and programs with variable HTS positivity in this review, reflecting inherent differences in testing uptake, as well as differences in contexts and populations

TABLE 2 | Perspectives of clients, providers, and program managers on successes and challenges of integrating HTS in FP programs.

Theme	Sub-theme	Representative quotes
Successes of integrating HTS and FP	*Integration is easy to do*	• "HTS is very easy to do at initiation of FP services." *Program manager, IPPF Eswatini* (50) • "At first, it was thought [providing HTS] would be a big increase in workload for providers, but that is not an issue anymore [after implementation]." *Program manager, IPPF Kenya* (53)
	Integration is beneficial	• Providers believed integration was beneficial for the client. *Providers, SRH & HIV Linkages Project, Eswatini* (58)
	Clients prefer co-located services	• "People really like it when you bring services together." *Program manager, IPPF Malawi* (54) • FGD participants were highly satisfied with integrated services. They experienced positive reception by providers, short waiting times, close proximity, and free services. *FSW, ICRH Mozambique* (33) • Clients preferred to receive SRH and HIV services at the same facility because of reduced travel costs, reduced number of visits, and receipt of complementary and efficient services. Thirty-five percent of SRH clients and 41% of HIV clients preferred to receive both services from the same provider. *Male and female clients, SRH & HIV Linkages Project, Togo* (44) • Eighty-three percent of clients said they were satisfied with service quality. Many (73.6%) preferred SRH and HIV services to be provided at same facility because it reduced travel (57.1%). *Male and female clients, SRH & HIV Linkages Project, Botswana* (21) • Clients reported SRH and HIV integration yielded several benefits, including reduced trips to health facilities, increased service efficiency, and reduced overall health expenditures. *Female clients, SRH & HIV Linkages Project, Eswatini* (58)
	Integration reduces strain on health providers	• Providers reported that integrated services preserved nurses' energy with less time moving from one room to another and reduced number of client visits and general consultations. *Providers, SRH & HIV Linkages Project, Botswana* (21)
Challenges of integrating HTS and FP	*Clients do not prefer to test in FP program*	• "When [clients] come for FP, they usually aren't interested in other services. The main thing is that people don't want to test [here]. [Testing] Services are generally readily available and in most cases people have HIV test kits [HIVST]." *Program manager, IPPF Eswatini* (50) • "There is low acceptance [of HTS] because clients say they have already tested or are already HIV+ or on treatment. Sometimes they have other reasons they are not ready to be tested." *Program manager, IPPF Eswatini* (50)
	Resources are limited for providing testing in FP settings	• "Since the shift to new guidelines of providing HTS to high risk populations, the number of HIV test kits has also been reduced in the country [and to the FP facility], but we feel it is an important service to provide in the FP setting." *Program manager, IPPF Uganda* (57) • "Due to social stigma and criminalization, we need closed, confidential spaces [to provide HTS] for key populations." *Program manager, IPPF Uganda* (57)
	Integration strains capacity of health providers	• "Maybe clients are waiting a little longer [for HTS] because counseling gets extended by 15 minutes or so with the provider." *Program manager, IPPF Kenya* (53) • "It is overwhelming to provide all integrated services to all clients because it takes time to get all the services and we have limited providers. The best way to address this would be to have a robust outreach team so tasks can be shared." *Program manager, IPPF Uganda* (57) • Most providers (94.4%) experienced challenges due to increased time spent with clients and many (83.3%) felt an increased workload. *Providers, SRH & HIV Linkages Project, Botswana* (21) • Disadvantages of integration were that service providers would be overwhelmed (35.2%), there would be increased wait times (26.9%), and decreased service quality (10.4%). *Male and female clients, SRH & HIV Linkages Project, Botswana* (21) • Challenges of integration included longer queues, staff shortages, and an increased workload. *Providers, SRH & HIV Linkages Project, Eswatini* (58)

Direct quotes are only available from IPPF phone interviews conducted for this review. Qualitative reporting from remaining programs was extracted from summary text.

served. These findings also illustrate global shifts in the HIV epidemic due to the scale-up of HIV testing and treatment. In 2019, 87% of people with HIV knew their status and 72% of those who knew their status were on treatment in east and southern Africa (60). As a result of this scale-up and fewer people with HIV who are unaware of their status, despite many countries having high HIV prevalence (>20% in some settings), the national HTS positivity and HIV prevalence among those not on treatment is <5% (61). When we compare HTS positivity from FP clinics within sub-Saharan Africa to other approaches, results are comparable to many facility and community settings (62). Nevertheless, as with all HTS, it is essential to find ways to efficiently target HTS within FP clinics. Strategies are urgently needed to support effective and efficient integration of HTS in FP services so that women with undiagnosed HIV infection or at high ongoing risk can learn their status and benefit from HIV prevention and treatment services.

ACTIONABLE RECOMMENDATIONS

Based on our review, integrating HTS within FP/SRH services was highly variable with limited information about how integration was implemented. We found some examples that suggest that task-shifting and on-site service provision (as

opposed to referrals) may be effective approaches to improve co-delivery of services and warrant further exploration. Qualitative data from programs implementing HTS in FP/SRH also highlight structural barriers to consider. Based on these findings, and gaps in the literature that have not previously been reported on, we identify several possible actionable recommendations for consideration.

1. In high HIV burden settings, routine offer of HTS for women seeking FP services may be appropriate, while in medium burden settings, offering HTS may be based on risk or if requested by women. In low burden settings, HTS should not be prioritized in FP clinics unless women are at high risk for HIV, including women who are in serodiscordant couples or are from key populations (people who inject drugs or FSW).
2. Incorporate task-shifting, provision of specific training or supervision for integrating HTS in FP service delivery, peer mentorship for health care workers, or campaigns to support integrated service delivery.
3. Invest in demand creation efforts to reach AGYW and provide a package of SRH services including HTS, FP, and PrEP.
4. Offer HIV self-tests as an alternative approach to overcoming provider concerns and logistical barriers to HTS in FP settings.
5. Develop robust monitoring and evaluation plans to document approaches used to offer HTS within FP services, including the number and type of services offered. Programs should consider monitoring and evaluating a HIV care cascade (offering testing, diagnosis, treatment, and prevention) for women seeking FP/SRH services, similar to the one used in prevention of mother-to-child HIV prevention programs. In addition to measuring the proportion of women who are offered HTS, HTS uptake, and HIV positivity—programs may find it useful to also track linkage to care, treatment, and prevention.
6. Document resources, trainings, and changes in HTS outcomes following program implementation to measure the impact of providing HTS in programs, including details of the service delivery model.
7. Document fidelity of interventions or new programmatic elements introduced to increase HTS to assess validity of these approaches.
8. Apply implementation science frameworks, such as the Consolidated Framework for Implementation Research, to guide efforts to evaluate and optimize design of integrated service delivery models (63).

DISCUSSION

In our review, few programs (12 overall, 10 in sub-Saharan Africa) had data available on providing HTS in the context of FP and contraception, SRH, or service delivery. HTS uptake was moderate in programs that only reported observational data on efforts to provide HTS with FP/SRH. HTS uptake was higher in some programs where programs included activities such as task-sharing, providing specific training or supervision, peer mentorship for health care workers, or campaigns to support integrated service delivery. In addition, only two programs documented the frequency of offering HTS. Overall HTS uptake in clinics offering FP services in sub-Saharan African to women with considerable HIV risk will likely remain low if HTS is not routinely offered.

Programs used a variety of approaches to offer HTS in FP/SRH services, including co-delivery of services to couples at home, targeting key populations such as FSW, or AGYW, and combining HTS with cervical cancer screening and other SRH programs. While most programs offered one-stop-shop models to deliver services, a few explored models where clients are referred to different providers and rooms within the health care facility. Only one program in Nigeria that offered both one-stop-shop and referral models directly compared HTS outcomes by delivery model, and found HTS uptake was universal (100%) in the one-stop-shop compared to 75% in the referral model.

Our findings concur with those from a prior review on studies with integrated vs. non-integrated approaches to HTS in FP service delivery, which also concluded providing HTS within FP was feasible based on limited evidence (14). In high burden settings, routinely offering HTS within FP service delivery could be a successful strategy to detect HIV among women seeking SRH services (64, 65) and accelerate progress toward 95% of people with HIV knowing their status in the UNAIDS 95-95-95 targets (3). However, the lack of robust, comparative evaluations makes it challenging to determine specific attributes of programs that contribute to success or hinder service delivery. Variability in HTS outcomes across findings may be due to specific approaches used to provide HTS in programs, type and number of SRH services included in the delivery approach, or inconsistencies in program implementation. These inconsistencies could be due to lack of prioritization in providing HTS by health care providers or programs, lack of monitoring and evaluation efforts to measure impact, or perceptions of poor yield/utility. In some programs with low HTS uptake but high HIV positivity, such as Eswatini and Zambia, programs may be differentially offering HTS to high-risk clients, or filling gaps in HTS in settings where HTS is widely available elsewhere. Benefits of integrating HTS into FP service delivery may be attenuated in real-world settings with limited time and training to co-deliver high-quality, rights-based HTS in addition to FP services. Integrated service delivery models may overstretch providers and facilities and increase client waiting time (21, 53, 57, 58). These concerns were articulated in programs that have not yet implemented HTS in FP/SRH or are not consistently implementing HTS, as well as some programs where integration of HTS was underway. However, some providers and program leaders voiced these concerns before the program launched, but later felt that it was feasible to conduct HTS in FP/SRH settings (53). In addition, HIV self-tests may help overcome some barriers to integrating HTS in FP. HIV self-tests have been shown to increase uptake of HIV testing, offer a convenient and confidential testing option, and are recommended by the WHO (66, 67).

A few programs also mentioned that siloed program delivery was another barrier to offering services, with services offered in multiple settings and clients receiving testing in these other settings. Some programs with sub-optimal testing uptake may need to be educated on testing coverage, highlighting gaps in

testing, to overcome misconceptions that women do not have a need for testing. In contrast, in highly developed HIV testing programs, testing in FP may not be necessary if test coverage for individuals seeking these services is high through other avenues. If it is desirable to offer integrated HTS and FP service delivery, we will need to invest in coordination between programs to maximize resources.

While many countries have some guidance on offering integrated HTS within SRH, integration of HTS within FP service delivery specifically is only stated in 50% of guidelines of the eight priority country policies we included in this analysis, and lack of clarity on specific services to integrate within guidelines was common (**Supplementary Figure**) (68–77). The majority of country policies recognize the importance of providing integrated HIV and FP services, but typically related to "reverse" integration, offering FP and contraception in the context of HIV care delivery rather than HTS in FP and contraception services or within the context of MCH (ANC/FP) services. Bi-directional integration of services into both programs is important to improve reproductive health and HIV outcomes.

Programs may consider measuring the effectiveness of a HIV care cascade (offering testing, diagnosis, treatment, and prevention) for women seeking FP/SRH services, similar to the one used in prevention of mother-to-child HIV prevention programs. In addition to measuring the proportion of women who are offered HTS, HTS uptake, and HIV positivity, programs may find it useful to also measure linkage to care, treatment, and prevention. While there is potential that providing HTS alongside FP services has potential to improve both HIV and reproductive health outcomes, none of the studies or programs in our review, or the prior review, reported on these outcomes (14). Furthermore, there is an opportunity to measure benefits of HTS programs by also measuring outcomes for women who test negative, including linkage to HIV prevention services such as PrEP and partner services. In the Kenya PrEP implementation program, offering PrEP in FP clinics led to modest (22%) uptake of PrEP (25).

High HIV incidence was recently reported among women seeking contraception in the ECHO trial in sites in South Africa and Eswatini, but significantly lower in Kenya and Zambia sites, which has led to WHO emphasizing a differentiated approach (78). A different approach, and urgency, to offering HTS within FP/SRH services will be needed depending on local epidemiology and demographic characteristics of women attending services (79).

Strengths and Limitations

This landscape review had several strengths. We included a diverse range of sources on implementation of HTS in both FP and SRH service delivery, including published articles, gray literature, program reports, and data from qualitative interviews. We included data from high-income settings, low and middle income settings, and focused some aspects of the review on areas of sub-Saharan Africa where HIV prevalence is high. This approach allows us to not only collate lessons learned across settings but also focus in areas with the highest need for integrated HTS and FP/SRH services. Our review is also subject to some limitations. Many details were not provided on program implementation, including training and fidelity of integration approaches. Only one reviewer conducted the primary abstraction, which may have biased inclusion of specific programs included in the review; however, a secondary reviewer did confirm the selection of the programs that were included and contributed to data abstraction. Our search terms were restricted to limit the volume of articles that are on "reverse" integration, which has many more citations but would use a similar search strategy; therefore, we may have missed some articles with this restricted search. We selectively reached out to programs to inquire about availability of data on this topic, but some programs do not have available data while others were excluded from the catchment, which limits the generalizability of our findings.

Conclusion

Overall, there is limited evidence available to fully evaluate feasibility and efficiency of providing HTS in FP services or SRH settings. Though infrequently reported, we know that these data exist in some countries based on instruction in national policies (76). Future efforts should focus on better outcome ascertainment and characterization of the context surrounding provision of HTS within FP/SRH service delivery. Investments to support integration efforts, including time and training to deliver high-quality services, are needed to ensure high HTS coverage and prevent MTCT.

AUTHOR CONTRIBUTIONS

AD and CJ developed and designed this landscape analysis, with engagement from MG, JK, and RB. AD and CQ collected, analyzed, and interpreted the evidence for the review. AD drafted the manuscript. All authors provided critical revision and final approval of the article.

FUNDING

This study was funded by the World Health Organization (WHO) #2018/865307-0, the United States Agency for International Development (USAID) GHA-G-00-09-00003, and the Bill and Melinda Gates Foundation (BMGF) OPP1177903, and supported by NIH/NIAID P30-AI027757 and NIH/NIAID K01 AI116298 (AD).

ACKNOWLEDGMENTS

We are appreciative of all the partners who provided information for this analysis, including International Planned Parenthood Federation, IntraHealth, JHPIEGO, PATH, Uganda Ministry of Health, University of Washington, USAID, WHO, and WHO Regional Office for Africa. In particular, we would like to thank the International Planned Parenthood Federation member associations who provided insight into their programs for our qualitative data collection: Family Health Options Kenya (FHOK), Family Life Association of Eswatini (FLAS), Family Planning Association of Malawi (FPAM), Lesotho Planned Parenthood Association (LPPA), Namibia Planned Parenthood Association (NAPPA), Planned Parenthood Association of

Zambia (PPAZ), Reproductive Health Uganda (RHU), and Zimbabwe National Family Planning Council (ZNFPC). Also, we are grateful to Caitlin Kennedy (Johns Hopkins Bloomberg School of Public Health) for giving us access to literature collected in the prior review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2021.657728/full#supplementary-material

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

ORIGINAL RESEARCH
published: 28 May 2021
doi: 10.3389/frph.2021.668672

Health Care Providers as Agents of Change: Integrating PrEP With Other Sexual and Reproductive Health Services for Adolescent Girls and Young Women

Gabrielle O'Malley[1], Kristin M. Beima-Sofie[1], Stephanie D. Roche[1], Elzette Rousseau[2], Danielle Travill[3], Victor Omollo[4], Sinead Delany-Moretlwe[3], Linda-Gail Bekker[2], Elizabeth A. Bukusi[1,4,5], John Kinuthia[1,6], Gena Barnabee[1], Julie C. Dettinger[1], Anjuli D. Wagner[1], Jillian Pintye[1], Jennifer F. Morton[1], Rachel E. Johnson[1], Jared M. Baeten[1,7,8‡], Grace John-Stewart[1,7,9†] and Connie L. Celum[1,7,8†] on behalf of the Prevention Options for the Women Evaluation Research (POWER) and the PrEP Implementation for Young Women and Adolescents (PrIYA) Program study teams*

[1] Department of Global Health, University of Washington, Seattle, WA, United States, [2] The Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa, [3] Wits Reproductive Health and HIV Institute (Wits RHI), Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa, [4] Centre for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya, [5] Departments of Obstetrics and Gynecology, University of Washington, Seattle, WA, United States, [6] Department of Research & Programs, Kenyatta National Hospital, Nairobi, Kenya, [7] Department of Medicine, University of Washington, Seattle, WA, United States, [8] Department of Epidemiology, University of Washington, Seattle, WA, United States, [9] Department of Pediatrics, University of Washington, Seattle, WA, United States

Background: Successful integration of pre-exposure prophylaxis (PrEP) with existing reproductive health services will require iterative learning and adaptation. The interaction between the problem-solving required to implement new interventions and health worker motivation has been well-described in the public health literature. This study describes structural and motivational challenges faced by health care providers delivering PrEP to adolescent girls and young women (AGYW) alongside other SRH services, and the strategies used to overcome them.

Methods: We conducted in-depth interviews (IDIs) and focus group discussions (FGDs) with HCWs from two demonstration projects delivering PrEP to AGYW alongside other SRH services. The Prevention Options for the Women Evaluation Research (POWER) is an open label PrEP study with a focus on learning about PrEP delivery in Kenyan and South African family planning, youth mobile services, and public clinics at six facilities. PrIYA focused on PrEP delivery to AGYW via maternal and child health (MCH) and family planning (FP) clinics in Kenya across 37 facilities. IDIs and FGDs were transcribed *verbatim* and analyzed using a combination of inductive and deductive methods.

Results: We conducted IDIs with 36 participants and 8 FGDs with 50 participants. HCW described a dynamic process of operationalizing PrEP delivery to better respond to patient needs, including modifying patient flow, pill packaging, and counseling. HCWs believed the biggest challenge to sustained integration and scaling of PrEP for AGYW would be lack of health care worker motivation, primarily due to a misalignment

OPEN ACCESS

Edited by:
Agnes N. Kiragga, Makerere University, Uganda

Reviewed by:
Maria Pyra, Howard Brown Health Center, United States
David Meya, Makerere University, Uganda
Sylivia Nalubega, Soroti University, Uganda

****Correspondence:***
Gabrielle O'Malley
gomalley@uw.edu

† These authors have contributed equally to this work and share senior authorship

‡Present address:
Jared M. Baeten, Gilead Sciences, Foster City, CA, United States

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *16 February 2021*
Accepted: *22 April 2021*
Published: *28 May 2021*

Citation:
O'Malley G, Beima-Sofie KM, Roche SD, Rousseau E, Travill D, Omollo V, Delany-Moretlwe S, Bekker L-G, Bukusi EA, Kinuthia J, Barnabee G, Dettinger JC, Wagner AD, Pintye J, Morton JF, Johnson RE, Baeten JM, John-Stewart G and Celum CL (2021) Health Care Providers as Agents of Change: Integrating PrEP With Other Sexual and Reproductive Health Services for Adolescent Girls and Young Women. Front. Reprod. Health 3:668672. doi: 10.3389/frph.2021.668672

of personal and professional values and expectations. HCWs frequently described concerns of PrEP provision being seen as condoning or promoting unprotected sex among young unmarried, sexually active women. Persuasive techniques used to overcome these reservations included emphasizing the social realities of HIV risk, health care worker professional identities, and vocational commitments to keeping young women healthy.

Conclusion: Sustained scale-up of PrEP will require HCWs to value and prioritize its incorporation into daily practice. As with the provision of other SRH services, HCWs may have moral reservations about providing PrEP to AGYW. Strategies that strengthen alignment of HCW personal values with professional goals will be important for strengthening motivation to overcome delivery challenges.

Keywords: PrEP, AGYW HIV prevention, sexual and reproductive health services, service integration, health care worker motivation

INTRODUCTION

Adolescent girls and young women (AGYW) in sub-Saharan Africa have among the highest HIV incidence rates globally. In southern and eastern Africa, HIV prevalence among young women aged 15–24 is approximately three times as high as males in the same age group (1, 2). Although voluntary medical male circumcision, community-wide HIV testing, and increased antiretroviral therapy (ART) coverage for people living with HIV have all contributed to reductions in global HIV incidence, young African women have not significantly benefited from these prevention strategies (3, 4). HIV incidence in African AGYW has remained ∼4% in recent HIV vaccine and prevention trials (5, 6). Oral tenofovir-based pre-exposure prophylaxis (PrEP) has been proven safe and effective in preventing HIV (7), and has tremendous potential to empower young women to protect themselves (8, 9). Longer-acting PrEP formulations with the dapivirine vaginal ring (10, 11) and injectable cabotegravir (12) have also been shown to be safe and efficacious and will provide a choice of PrEP options once they have received regulatory approval. Although oral tenofovir-based PrEP has been included in national guidelines in most sub-Saharan African countries, identifying and refining pathways for its delivery to AGYW is a work in progress.

Integrating PrEP with other sexual and reproductive health (SRH) services has significant potential for reaching young women (13). Over the past 20 years, advocates have argued that integrating HIV testing, care, and treatment into SRH services produces benefits and efficiencies for both facilities and clients (14–17). Some evidence has shown that such integration at antenatal care clinics (ANC), maternal and child health (MCH) clinics, and family planning (FP) clinics results in increased provision, uptake, and efficiency of services while improving client satisfaction and service outcomes (14, 16, 18, 19). However, process evaluations have shown a high degree of heterogeneity in both implementation and results (20–22).

Recently, African countries with high HIV prevalence have begun promoting the integration of PrEP into routinely delivered SRH services. Theoretically, health care workers (HCWs) in FP clinics may be especially well-positioned to counsel on PrEP as they already counsel women on SRH and routinely screen for sexual behavior and HIV risk factors (23, 24). Although there are some early indications that integrated delivery in these clinics is feasible and acceptable to clients, and reach significant numbers of women (23, 25), there is little in the peer-reviewed literature describing potential challenges to sustained, scaled implementation in routine practice settings. This study describes experiences of HCWs delivering PrEP to adolescent girls and young women (AGYW) alongside other SRH services in Kenya and South Africa, the challenges they foresee in scaling integrated PrEP and SRH services, and the strategies they suggest to overcome them.

MATERIALS AND METHODS

Study Settings

Qualitative data were drawn from two different studies exploring PrEP delivery to AGYW aged 15–25 as an integrated component of SRH services. The Prevention Options for Women Evaluation Research (POWER) study was a prospective cohort implementation science study to evaluate PrEP delivery in six facilities across three locations: two family planning clinics in Kisumu, Kenya; a mobile clinic serving youth in disadvantaged communities and a primary care facility in Cape Town, South Africa; and an adolescent friendly clinic and a primary health care facility in Johannesburg, South Africa. The PrEP Implementation in Young Women and Adolescents (PrIYA) study evaluated the integration of PrEP delivery into existing SRH healthcare services provided in FP and MCH clinics at 37 facilities in Kisumu, Kenya (26). POWER hired study staff to integrate PrEP into other SRH services at four primary study facilities and these staff then provided technical assistance to provide PrEP at two additional facilities. PrIYA hired study nurses to integrate PrEP into existing SRH services at 16 facilities and then provided technical assistance to 21 additional facilities.

The POWER study was reviewed and approved by ethics committees at the University of Cape Town, the University of the Witwatersrand in Johannesburg, the Kenya Medical Research

TABLE 1 | POWER key informant characteristics.

	Cape town	Johannesburg	Kisumu	All sites
N participants interviewed	11	10	15	36
Age	32 (27–43)	40 (36–43)	30 (29–42)	33 (29–42)
Female	7 (64%)	8 (80%)	9 (60%)	24 (67%)
POWER-affiliated[a]	10 (91%)	6 (60%)	10 (67%)	26 (72%)
Primary occupational role[b]				
Healthcare provider	8 (73%)	6 (60%)	10 (67%)	24 (67%)
HCT counselor	3 (37.5%)	2 (33%)	3 (30%)	8 (33%)
Clinician[c]	3 (37.5%)	2 (33%)	6 (60%)	11 (46%)
Other	2 (25%)	2 (33%)	1 (10%)	5 (21%)
Other key informant	3 (27%)	4 (40%)	5 (33%)	12 (33%)
Years working as healthcare provider[d]	8 (5–10)	10 (6–10)	6 (3–8)	6 (4–10)
Years working in PrEP delivery	2 (1–2)	3 (2–3)	2 (1–2)	2 (1–2)

[a] *Participant was considered POWER-affiliated if s/he currently or formerly worked for the POWER study.*

[b] *Based on participants primary role vis-à-vis PrEP and POWER. For example, a participant who is a doctor by profession but whose primary role in POWER is as a study coordinator, is counted as "other key informant."*

[c] *Clinicians include nurses and doctors/medical officers.*

[d] *Excludes interviewees from the category "other key informant."*

Institute (KEMRI), and the University of Washington. The PrIYA study was reviewed and approved by the Kenyatta National Hospital Ethics and Research Committee and the University of Washington Institutional Review Board.

Data Collection

As part of the POWER study, we conducted in-depth interviews (IDIs) from October 2019 through January 2020 using a semi-structured interview guide. We used purposive sampling to recruit HCWs with different roles and responsibilities in PrEP delivery. Sample size was based on estimates of informational saturation and through extensive conversations with study team members who have extensive experience working with the study facilities. Interviews were conducted in English by two highly experienced, formally trained American qualitative researchers. Interviews lasted between 60 and 90 min and were audio recorded. Interviewers debriefed impressions and experiences of the interview process on telephone calls and via emails throughout the process. POWER staff in Kenya and South Africa hired individuals to transcribed the audio recordings of the interviews *verbatim* and audio recordings were reviewed and quality checked by the primary interviewers. As part of the PrIYA study, we conducted focus group discussions (FGDs) between October and December 2018. The sample size for FGDs was based on estimates of information saturation and arrived at through extensive discussions with study team members with extensive experience working with Kenyan facilities. FGDs were led by formally trained and highly experienced Kenyan facilitators who had worked with study researchers in other projects. FGDs were conducted in a mix of English, Kiswahili, and/or Dholuo, lasted between 65 and 140 min, and were audio-recorded. FGD facilitators wrote debriefing reports after each interview, highlighting main observations and their own reflections on the group dynamics, including their interactions with the group. Interviewers transcribed audio recordings of the FGD they facilitated verbatim, and then translated them where necessary. Transcripts were quality checked by senior study team members. Both IDIs and FGDs explored perspectives and experiences of delivering PrEP as an integrated component of SRH services provided to AGYW. Participants in both IDIs and FGDs provided written informed consent.

Data Analysis

Interview transcripts were uploaded to Atlas.ti version 8 (Scientific Software Development GmbH, Berlin, Germany). FGD transcripts were uploaded into Dedoose version 6.1.18 (SocioCultural Research Consultants, LLC, Los Angeles, California, USA). Codebooks for each project were developed through a combination of deductive and inductive methods. Deductive codes were generated from several implementation science frameworks (27–29). Inductive codes were then added through multiple reviews of the transcripts by qualitative analysts. Using a final codebook, interview transcripts were coded by one researcher (SR) while a second researcher (GO) reviewed coded transcripts and noted areas of disagreement. For FGD transcripts, three qualitative researchers (KB-S, AW, and GO'M) divided and independently coded transcripts which were then exchanged and reviewed by a secondary coder who noted areas of disagreement. Disagreements in coding for both IDIs and FGDs were resolved through discussion and consensus. Thematic content analysis (30) was conducted first for each data set (PrIYA FGDs and POWER IDIs) separately, and then common themes across both projects were compiled for this analysis.

RESULTS

We conducted 36 IDIs with HCWs engaged with the POWER study in six facilities in Kisumu, Cape Town and Johannesburg. We conducted eight FGDs with a total of 50 HCWs affiliated with the PrIYA study across 37 facilities in Kisumu. Most, though not all, of our participants were recruited and trained by the

TABLE 2 | PrIYA focus group characteristics.

	Value
Number of Focus Groups	8
Number of Focus Group Participants	50
Age in years: median (IQR)	28.0 (26.0, 32.0)
Cadre	
Peer counselor	3 (6%)
Clinical officer	8 (16%)
Nurse counselor	6 (12%)
Doctor	2 (4%)
Nurse	31 (62%)
Counselor	4 (8%)
Other	2 (4%)
Number of years at current clinic, median (IQR)	1.5 (1.0, 2.7)
Number of years delivering PrEP, median (IQR)	1.1 (0.8, 1.5)
PrIYA staff	27 (54%)

POWER and PrIYA studies. Demographic information about study participants is described in **Tables 1**, **2**. FGD and IDI participants described an active 'learning by doing' approach as needed to successfully integrate delivery of PrEP into existing SRH services at their facilities. Participants anticipated HCW motivation as being the biggest challenge to sustained and scaled service integration. Common thematic challenges and strategies related to service integration and PrEP delivery to AGYW are described below. Additional illustrative quotations are included in **Table A1**.

Learning by Doing: Problem-Solving by Front-Line HCWs Aimed to Strengthen Provision of Patient Centered PrEP Services

HCWs described an ongoing process of active learning and modification of practices to integrate PrEP into existing reproductive health services within the context specific to each clinic.

> *… [W]e, from different facilities, had to find something that would work in wherever we were working, because at the end of the day what will work for this facility might not work for the other, and we had to come up with ways to make PrEP delivery better for the future generation* (PrIYA, FGD 2, Participant 1).

HCWs noted that AGYW were extremely sensitive to perceived judgmental attitudes and stigma associated with sexual activity and PrEP, and hence were very concerned with their privacy. Once initial plans were made and PrEP delivery begun, HCWs reworked delivery processes aimed at improving patient centered care for their AGYW population.

For example, HCWs identified several approaches to minimize the time their young PrEP clients spent in public queues at the clinic, thus lessening their exposure to other clients at the facility whom AGYW feared might judge them. In many clinics HCWs implemented a practice of "fast tracking" PrEP clients by either moving PrEP clients to the head of the queue or by having a single clinician provide multiple aspects of PrEP services in the same consulting room, e.g., HIV testing, counseling, and prescribing.

> *...[O]nce they come for their clinic day, they need to be fast tracked. … She just goes straight to the clinician, she is given a prescription, then straight to pharmacy. [She] doesn't want to be in the line. When you do like that, you will find them coming back* (PrIYA FGD 5, Participant 4).

In many facilities in Kenya, PrEP is dispensed from "ART pharmacies," that is, pharmacies known to be dedicated to provision of antiretroviral therapy for individuals living with HIV. HCWs reported AGYW did not want to be seen queuing outside these pharmacies due to the stigma associated with being thought to be HIV-infected. In response, some nurses volunteered to pick up PrEP themselves from the ART pharmacy and then dispensed it from their clinic rooms.

HCWs also learned that AGYW often wanted to keep their PrEP use private and were concerned their family members or friends might see the PrEP bottle or hear the tablets rattling. To respond to this concern, some HCWs reported transferring the medication to small plastic bags for distribution so storage of a month's supply of tablets would be more discrete.

> *Okay, we always repackage the PrEP into a zip lock bag, yeah, that one after we had a meeting of all the employees of the program and we agreed that even if you repackage it, it will not affect the efficacy. So, we always repackage it to a zip lock bag, and they like it that way* (PrIYA FGD 1, Participant 1).

Finally, although both South Africa and Kenya have formal PrEP risk assessment tools, HCWs explained that these formal risk assessments could make clients feel judged. In response, many HCW described fine-tuning their risk assessment and counseling techniques to support AGYW in making their decisions about whether they needed/wanted PrEP.

> *You tell them, "Hey, I'm here for you. So, tell me about your partner." So, once they start telling you about their life and their partner, you—both of you together—you can start to do assessments like, "So you said he comes late and he's drinking. It's okay. That is his life, and you are used to it. But, you see, there are certain risks." So, you explore [PrEP] with them and ask, "Is it viable for you or not?"* (POWER, Kisumu IDI 3).

HCWs also reported adjusting their counseling advice to acknowledge the fluidity of AGYW sexual relationships, the multiple demands on their time and attention, and affirming their clients' autonomy in deciding whether or how long to use PrEP. Several health care providers used analogies between PrEP and family planning methods to convey key messages about duration of use.

> *I found that comparing it [PrEP] to contraceptives, it works a lot, like, "You are doing contraceptives, and you can stop anytime*

you want when you feel that you no longer want to use them.… [Similarly, PrEP] will help you for as long as you need it…" It [the analogy] works well, and you realize that they understand it quickly when you go that route (POWER, Johannesburg IDI 11).

Motivational Challenges Due to PrEP Delivery Being Seen as Extra Work and Potential Solutions

Although HCWs in POWER and PrIYA experienced a learning curve in terms of incorporating PrEP into existing SRH services, they all described such service integration as feasible, as long as there was health care worker motivation. Lack of front-line staff motivation was highlighted by participants as the biggest anticipated challenge to scaling up PrEP. They predicted that since HCWs in public SRH clinics typically experience challengingly high patient volumes, they would consider PrEP provision as "added work."

If you want to add a service to an existing service, the first words you will hear are, "We're already working so hard. You want to add extra now for the same pay?" It's not going to happen. So that in itself is a barrier (POWER, Cape Town IDI 10).

Despite the inclusion of oral PrEP in national HIV prevention strategic frameworks, many HCWs reported having had minimal training or exposure to PrEP, little awareness of why they were being asked to engage in PrEP service delivery, and uncertainty about PrEP's safety and efficacy.

At first … I was like, "Why do you want to give people ARVs and they are not HIV-positive? …. It is going to lead to maybe drug resistance?…" At that point, I was not that enlightened about PrEP because I had known about HIV and ARVs and stuff, but very little about PrEP (POWER, Kisumu IDI 17).

Study participants emphasized that in order for scaled delivery of PrEP as an integrated component of SRH to succeed, HCWs need to understand not only *what* PrEP is but *why* it is being brought in. Our study participants emphasized the important role of sensitization and training of those who are responsible for direct service provision.

It's good to prepare staff. That is the first point for me, because when we arrived at [site name], people were raw in terms of "What are we doing? What is PrEP all about? Why is it necessary?" … If they understand how PrEP works, and you try to troubleshoot whatever fears or concerns they may have, it'll be easy [to scale PrEP up] if these other sites are convinced from the word 'go' of why PrEP has to be rolled out (POWER, Johannesburg IDI 04).

Study participants reported that many of the HCWs they encountered were generally unaware that PrEP was part of national healthcare policy. Participants believed that if PrEP policies were disseminated more purposively to HCWs, they would be less inclined to view PrEP provision as extra work.

[One potential challenge to scale-up] is if it's seen as extra work rather than standard of care. …. [P]eople see all the new programs—HIV and AIDS [services], PrEP, even AYFS [adolescent and youth-friendly services]—they see it as extra work. And [they think] that's not their work because they were employed to do this [other thing] … But if you have a memo from the National [Department of] Health, people will do whatever the memo says (POWER, Johannesburg IDI 1).

They also emphasized the importance of the in-charge nurse or lead clinical officer being able to refer to national guidelines to normalize PrEP provision as an integrated component of SRH services.

"[T]he nurse in-charge and the clinical officer, they made us realize that PrEP is in the guidelines. So, it's not that we're doing something new. It is something that's supposed to be in existence already running.… So that made us not feel like, "This is out of place" … (POWER, Kisumu IDI 3).

Finally, several of our participants advised addressing short-term workload concerns by emphasizing the longer-term benefits of reducing HIV incidence in the population, and thus stemming increases in HIV client volume at their health facility.

I think often the problem with something like PrEP … is that the benefits of them are long-term. And it's hard as someone in the thick of it who sees 60 patients a day to see that, by doing this now, you're … reducing your patient load [in the] long term (POWER, IDI Johannesburg 10).

Motivational Challenges Due to Social Stigma and Concerns Around Promiscuity

The most frequently referenced barrier to HCW motivation to deliver PrEP was their uneasiness with adolescent sexuality and their moral concerns regarding sexual activity among unmarried young women. Participants were often told by their colleagues that suggesting a young woman begin PrEP would be the same as encouraging her to have unprotected sex.

I think most people, including some of the health workers, still think that when we talk about PrEP we are encouraging promiscuity or early sex (PrIYA FGD, participant 1).

[Initially,] there was a belief [among some health care workers] that this [PrEP] will cause young women to be more promiscuous … [and HCW were] not wanting to have those conversations with young women … (POWER, Cape Town IDI 2).

IDI and FGD participants frequently described working in locations with "conservative" community and religious norms. Participants emphasized that HCWs are also part of these communities, and frequently share community moral concerns about young women's sexual relationships. These moral reservations in turn negatively impacted motivation and willingness to provide PrEP services.

Actually, when it started, it was a slow move because people would argue, "Why give the medication? That one is promotion for promiscuity" (POWER, Kisumu IDI 9).

They [HCW] are still reluctant about it [providing PrEP]…[T]hey are thinking if you are making this PrEP available and so effective in preventing HIV, you are saying to these kids, to these women, to be promiscuous, that's some of their thinking (POWER, Johannesburg IDI 11).

Overcoming Moral Concerns and Reluctance to Provide PrEP

Study participants reported a variety of strategies to overcome HCW moral reservations about providing PrEP. One approach was to link HIV prevention to a woman's valued role in society, e.g., that of mother.

[I told colleagues] "This PrEP is not for people to be promiscuous. It's for helping people. And even if someone is a kind of sex worker and she's using PrEP, it's still better for her because you know at least she'll stay HIV negative for her children" (POWER, Kisumu IDI 3).

HCWs in our study also tried to overcome colleagues' moral reservations by prioritizing HCWs' professional obligation to keep clients healthy, regardless of their personal opinions about sexually active AGYW.

What I would advise them [colleagues] is when trying to talk to the adolescent, "Try and push that client first. Irrespective of your opinion or the feelings you have, put the interests of the client first … so that you may be able to ... help as a healthcare worker" (PrIYA FGD 2, Participant 1).

Study participants also reported trying to persuade their colleagues of the value of providing PrEP through a pragmatic emphasis on the empirical realities of AGYW being sexually active, and their professional responsibility to keep them HIV-free.

Now, you need to realize why did this adolescent come to the clinic for family planning, meaning this girl is going to have unprotected sex, meaning HIV here is not catered for. So, they [HCWs] need to understand that these people are having sex, and they need to take action, yes, despite their values, because at the end of the day they need to protect them. Yes, you will continue shouting, "Abstain! Abstain!" They are not abstaining (PrIYA FGD 4, Participant 5).

In addition, our study participants tried to motivate colleagues to offer PrEP by highlighting the social reality of power differentials between young women and their male partners. In terms of HIV protection, this meant emphasizing PrEP as an empowerment option for women.

PrEP is better when compared with other methods of HIV prevention because, you see, for PrEP, the woman or the lady herself controls it. You see, for a man, he might decide whether to wear condom or not, or when you tell a lady to abstain, the guy might decide whether to abstain or not. But you see, for PrEP, it is within her own control… (PrIYA FGD 2, Participant 5).

[PrEP] gave people more options and more room to make more informed decision and to really feel empowered… [you] don't depend on [your] partners' 'go-ahead'.…So I thought it was a really great option" (POWER, Johannesburg IDI 06).

Some of the health providers interviewed in this study reported urging colleagues to empathize with their young clients' vulnerability. One participant described how encouraging co-workers to imagine members of their own family needing PrEP convinced them that delivering PrEP to AGYW was the right thing to do.

Initially, there was the issue of staff attitude in [facility name], but you know, the good thing is that we got to explain to them that "It can also be your daughter [who needs PrEP] or it can also be you. Maybe today you are here, you know your partner's status, [but] next time, he may be HIV-positive, and you need PrEP." … So, I think that is what made them feel like, "I am also a human being" (POWER, Kisumu IDI 3).

Several of our participants described how their own initial moral reservations to providing PrEP to AGYW dissipated over time as they gained a greater appreciation of AGYW's HIV risk and began viewing PrEP as an opportunity to intervene.

[Sometimes I'm] like, "Oh my goodness" … But now you think [to yourself], "This is a girl who is at risk. Okay, I have my own values. I have my own beliefs, you know, but now I have to help these young girls, because if I don't, maybe no one will" (POWER, Kisumu IDI 8).

DISCUSSION

HCWs in Kenya and South Africa engaged in delivering PrEP in two studies across 43 facilities described iterative learning to integrate PrEP into SRH services for AGYW. Examples of 'learning by doing' included repackaging PrEP pills from bottles to plastic bags, modifying their counseling messages, and streamlining client flow in an effort to make integrated PrEP delivery with SRH services friendlier to adolescents. HCWs believed the biggest challenge to sustained integration and scaling of PrEP for AGYW would be health care worker motivation, primarily due to a tension between personal and professional values and expectations.

The need for iterative learning and practice modifications in order to integrate and scale new health services has been extensively described in the implementation science literature (31–39). Given significant variability in capacity and infrastructure across facilities where SRH services are delivered as well as in the communities they serve, there will not be a single "blue print" for integration of PrEP (40). Successfully integrating new services has been described as mirroring other complex adaptive systems, wherein actors (HCWs and other stakeholders) must continually reinvest energy over time to mobilize resources and engage in an ongoing process of adaptation to refine and realign clinical practices to make them workable, and to meet evolving stakeholder choices, concerns, and expectations (35, 39, 39, 41, 42). This ongoing investment of time and effort relies on frontline health workers being motivated to exercise agency in the adaption and implementation process.

Within the context of these two implementation studies, IDI and FGD participants described their on-going efforts to make PrEP service integration workable and to meet client needs.

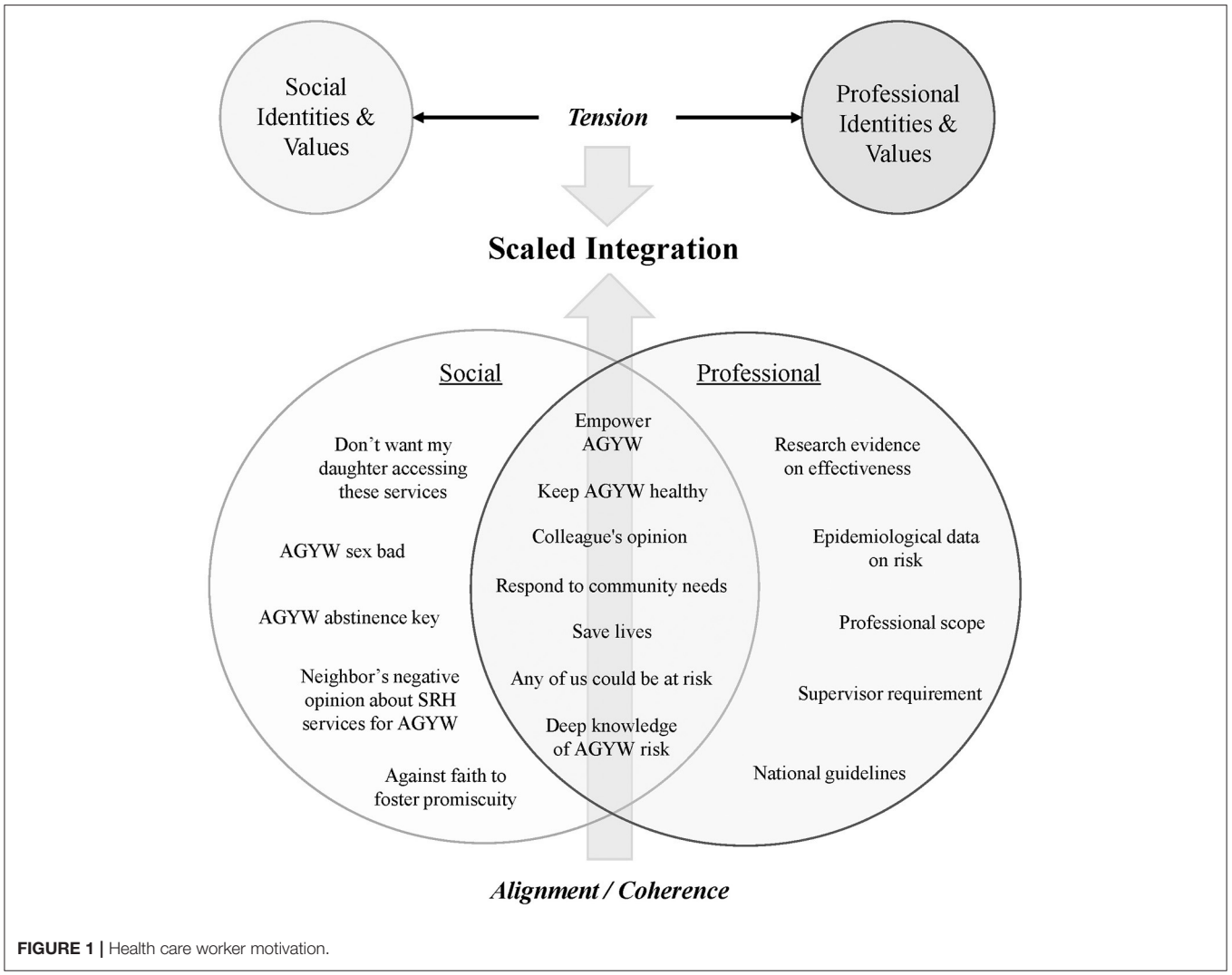

FIGURE 1 | Health care worker motivation.

However, they also predicted health worker motivation would be one of the most likely barriers to delivering PrEP at scale as an integrated component of SRH outside of study contexts. Process evaluations of the interaction of HIV testing, care, and treatment services have similarly identified motivation as a key factor influencing service integration (14, 20, 42). More broadly, health worker motivation has been identified as a prime factor influencing performance of an expected task (39, 41, 43–46). Capacity to provide a new service consists of both "*can do*" and "*will do*" components. Skills-based training, national guidelines, and basic materials (e.g., PrEP medication) facilitate the *can do* of service integration. However, intrinsic motivation is essential to whether providers *will* do so [(36, 47, 48); **Figure 1**].

Participants in our study highlighted moral reservations about providing PrEP to AGYW which negatively impacted HCW motivation to invest in the work necessary for service integration. The primary moral concern expressed was not wanting to foster sexual promiscuity. Other studies have similarly described HCW concerns with PrEP provision as condoning or encouraging sexual promiscuity among AGYW, MSM, transgender women, injection drug users, and Black Americans, resulting in lowered health provider willingness to prescribe PrEP to these clients (49–54). More generally, in a systematic review of health care worker motivation, the construct of "moral norms" was found to be a significant determinant of intention, and intention predictive of provider's behavior (55, 56).

HCWs belong to multiple communities in their personal and professional capacities which may have different values and expectations related to PrEP provision. Although national guidelines and formal trainings (professional community) may clearly articulate expectations supporting integration of PrEP with other SRH services for young women, HCWs are also heavily influenced by their social worlds (extended family, neighbors, and faith communities) which may hold very different norms, expectations, and values (38, 39, 43, 56–58). The lack of congruence or alignment between personal and professional expectations and values may add a psychological burden as health providers exert effort to resolve the tension between the two,

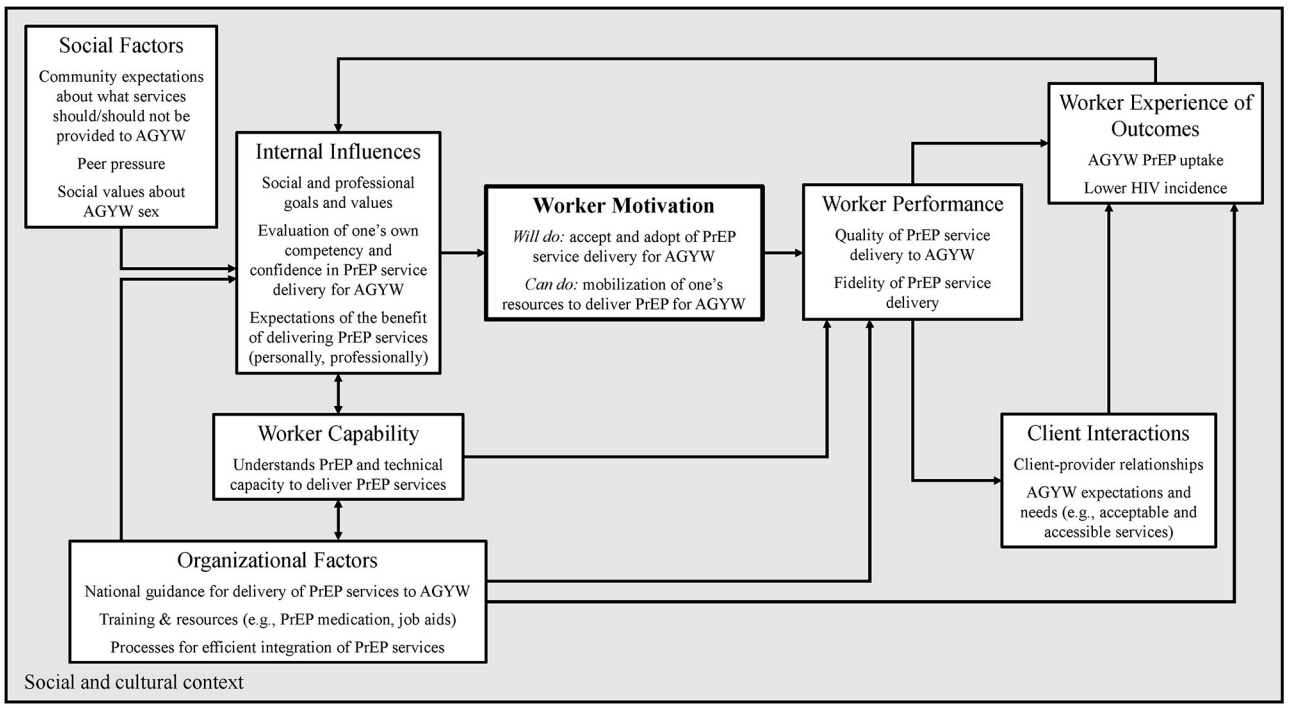

FIGURE 2 | Health care worker motivation and values alignment. Figure adapted from Franco, Bennet, Kanfer, Social Science & Medicine 54 (2002).

serving as a demotivating influence on the task-focused work of PrEP and SRH integration (45, 59). While individuals can hold multiple beliefs about a behavior or an intervention, the psychological principle of *salience* suggests one can attend to a relatively small number of beliefs at any given moment (60, 61). Our study participants described several strategies of persuasion they used to help co-workers resolve this tension, either through encouraging alignment between the personal and professional or be encouraging the salience of professional values as they tasked with integrating PrEP and SRH for AGYW.

First, they urged colleagues to prioritize their professional identities and the associated vocational responsibilities of keeping young women healthy. The construct of "professionalism," i.e., how closely health care providers identify with the values and expectations associated with their profession, has been documented as an important motivator to implementing evidence-based practices (56, 62). Second, our study participants described entreating their colleagues to recognize AGYW's disproportionate HIV risk and societal norms which often constrain a young woman's ability to keep herself HIV-free, either via abstinence or the use of condoms, and highlighted the potential of PrEP to empower women to protect themselves. Health care worker belief that an intervention is well-placed to meet a client's specific needs has been identified as an important facilitating factor in intervention implementation (27). Finally, our study participants sought to strengthen their colleagues' motivation through appealing to their empathy, urging them to imagine they or their female relatives needed PrEP. The more closely HCWs can align their own perceived risks and needs with those of their client population and their community, the more highly motivated they may be to provide the intervention (41, 63, 64). All of these strategies may contribute to HCWs developing a sense of "coherence" around PrEP and SRH service integration for AGYW. Coherence has been described as a set of beliefs drawing from professional, social, and personal identities, which facilitate actionable meaning-making about an intervention [(45, 56, 62, 65); **Figure 2**]. The more frontline HCWs perceive a service or practice as meaningful and useful, the more highly motivated they will be and the more likely they are to expend the necessary energy for its implementation (41, 63).

Moral concerns around women's sexual activity are not unique to PrEP delivery (66, 67). HCW judgmental and censoring attitudes, especially toward sexual activity of adolescent and unmarried women, have been identified as discouraging the provision and use of contraceptive services by these populations (68–76). Although the WHO and national governments have called attention to the need for adolescent-friendly reproductive health services, progress in public clinics has been slow, though moving in the right direction (77). In spite of natural synergies across the provision of PrEP and other SRH services to AGYW, the success of such planned integration will be limited if moral reservations around family planning are amplified by similar reservations about PrEP among frontline health workers.

There is some evidence that formal training can facilitate changes in HCW attitudes to SRH services to be more client centered, although the outcomes vary greatly depending on

training methodologies and content (78, 79). For example, using participatory methods and/or the inclusion of adolescent "standard patients" during training may facilitate shifts in provider attitudes (79–81). Targeted recruitment and use of AGYW as local "PrEP champions" or opinion leaders as trainers, colleagues, or supervisors, may also positively influence shifts in provider attitudes and subsequent practice (82–84). Although widespread positive attitudes about SRH for AGYW, including PrEP, will not in themselves be sufficient for scaled integration and implementation, these will be foundational to a facilitative context (76, 85).

Maximizing the synergistic potential of SRH and PrEP should also consider services integration *outside* of health facilities. In many countries, policy shifts and product innovations are enabling increased access to SRH services without increasing patient volume at SRH clinics. For example, pharmacies and drug shops are important sources for oral contraceptive pills, emergency contraceptives, and condoms (86). In recent years, a subcutaneous contraception injection product containing medroxyprogesterone acetate (DMPASC) has been developed and shown it can be safely used by both community health workers and via self-injection (87). Well-designed digital health applications providing educational information can be highly acceptable to clients for accessing reproductive health information (88). Innovations such as these should also be considered for PrEP as a means toward broadening access for AGYW (89).

An important limitation of our analysis is that it was conducted within the context of two studies, with more resources and training available than in purely programmatic settings. Both PrIYA and POWER hired health care providers as study staff to provide technical assistance and some direct support for integrated PrEP/SRH services. HCW descriptions of workload and motivational challenges could be different outside of a research context. However, all of our study participants had extensive experience with public health clinics in their countries, and not all of the providers interviewed in this project were directly employed by POWER and PrIYA. Motivational issues are likely to be even more important outside of a research context.

CONCLUSION

While policies, guidelines, and facility-specific protocols are certainly essential tools to guide the integration of PrEP into other SRH services for AGYW, frontline health care workers must be motivated to implement them. HCWs individually and collectively must see the value of and find positive meaning in an intervention such as PrEP for it to become embedded into routine services and practice. Meaning is motivating, and motivation is crucial for the reflexive monitoring and feedback necessary to integrate, modify to evolving context, and hence scale interventions. Decades of family planning research have identified health care worker moral reservations or opposition to providing contraception to adolescents and young women as having a negative impact on the delivery and uptake of contraceptive services. As efforts move forward to integrate PrEP into family planning services for African AGYW, programs should anticipate and proactively work toward overcoming these same concerns.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because request for data sets will require approval of partners in South Africa and Kenya. Requests to access the datasets should be directed to Gabrielle O'Malley, gomalley@uw.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committees at the University of Cape Town, the University of the Witwatersrand in Johannesburg, the Kenya Medical Research Institute (KEMRI), the Kenyatta National Hospital Ethics and Research Committee and the University of Washington Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KB-S, SR, GB, and JD organized the database. GO'M, GB, SR, KB-S, and AW coded the data. GO'M wrote the first draft of the manuscript. All authors contributed to conception and design of the study, manuscript revision, read, and approved the submitted version.

FUNDING

This PrEP Implementation for Young Women and Adolescents (PrIYA) study was funded by the US National Institutes of Health (R01HD094630, R01HD100201, and R01AI125498) and by the United States Department of State as part of the DREAMS Innovation Challenge (Grant # 37188-1088 MOD01), managed by JSI Research & Training Institute, Inc. This study was supported via the University of Washington's Global Center for Integrated Health of Women, Adolescents, and Children (Global WACh). The Prevention Options for Women Evaluation Research (POWER) study was funded by the United States Agency for International Development (USAID) (Grant # AID-OAA-A-15-00034) and supported via University of Washington Department of Global Health's International Clinical Research Center. This PrEP for POWER was donated by Gilead Sciences. Data analysis was also supported by the National Institutes of Health (NIH) via the University of Washington's Center for AIDS Research (CFAR) Behavioral Sciences and Implementation Science Cores (Grant #AI027757).

ACKNOWLEDGMENTS

We thank the entire PrIYA and POWER study teams and clients for their time and contributions. Additional PrIYA and

POWER team study team members: Jaclyn Escudero, Harrison Lagat, Nancy Mwongeli, Winnie Owade, Merceline Awuor, Felix Abuna, Kenneth Mugwanya, Felix Mogaka, Josephine Odyoyo, Nomhle Khoza, Lara Kidoguchi, Ariane van der Straten, Ariana Katz, and Jessica Haberer. We also thank the Kenyan Ministry of Health, the Kisumu County Department of Health, the South Africa National Department of Health, the Gauteng of Department of Health, City of Cape Town Health Department, as well as the facility heads and in-charge for their collaboration.

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Disclaimer: The opinions, findings, and conclusions stated herein are those of the authors and do not necessarily reflect those of the United States Department of State, JSI, USAID, NIH, or Gilead Sciences.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX

Table A1 | Additional illustrative quotations.

Themes	Illustrative quotations
Learning by doing—facility context	When we went to those facilities, what we had in mind changed because each facility is unique (PrIYA FGD 5, participant 4). Judging by our clinic flow currently and how it's working, I think sitting down and discussing how best we can also make it work for PrEP. So we will have to redesign some of the things because we go back and see is this working, is this working…. So how can we best accommodate them [PrEP clients] into the clinic that is already in existence (POWER Johanessburg, IDI 3).
Learning by doing—dispensing	Initially when we started, we would write the prescription, and then we let them go and pick the medication from the pharmacy. But being a facility that was seeing so many patients and [because] that pharmacy was the pharmacy where we also had people living with HIV [getting ARVs]... most of the time the queues would be long. And when you sent the young woman for PrEP there, they would, like, take more time. … The second [issue] is that the staff … in the pharmacy felt like by them dispensing PrEP, we were adding them more work, and they were not really comfortable to dispense the PrEP. And so we decided that we'd let the nurse or the clinician prescribe the medication and also dispense the medication....[W]e would keep the drugs in the pharmacy, but in the morning when we open the clinic, we would take enough for that day (POWER, Kisumu IDI 17).
Learning by doing—counseling on risk assessment	The feedback we were getting was that people were quite resistant to being told they were at risk. And that is something I can totally relate to. I would hate it if I went somewhere and someone told me I was at risk based on my behavior. Like, "Excuse you?"…. But I think that we spent a lot of time thinking about how to change that narrative…. And so I think we learned a lot about how to talk about risk (POWER, Johannesburg IDI 10).
Concerns with PrEP encouraging promiscuity	Because PrEP is associated with issues of sexuality, there is always this concern about how we are promoting promiscuity. "Are we encouraging people to have sex?" (POWER, Kisumu IDI 13). And to many people, they are thinking if you are making this PrEP available and so effective in preventing HIV, you are saying to these women to be promiscuous. … But we try by all means to advise or show them that … we are not saying people should be reckless because they are on PrEP (POWER, Johannesburg IDI 11).
Concerns with PrEP encouraging promiscuity negatively impacting service provision	[W]e find some clinics where ...we have .. staff who believe strictly that some things are meant to be done when people are adults or when people are in marriage and should [not] be done at some other time—so for this kind of staff, they will not be open to giving the young women whatever they need. If they see a young woman coming maybe for family planning, they will be like "Why are you here? You are supposed to be in school. You are supposed to doing something else." And that discourages young women from interacting with them (POWER, Kisumu IDI 17). …[L]ike I have seen whereby a nurse…a female nurse, now feels like she is the mother to this girl and she is seeing this girl is now promiscuous, she becomes so annoying, shouts at her and when such a thing happens you find that the girl is scared and tends to stop opening up anymore (PrIYA, FGD 2 participant 5).
Conflicting personal and professional values and beliefs	To some of us health workers we tend to believe that sex should begin at a given age such that when we encounter maybe an adolescent who is 15 years of age in need of PrEP, we start doubting whether it is true or not, we tend to [project] our own beliefs on that client. So it is high time we need to change our attitude so that we get to know that some of the adolescents, actually they have early sexual activity, their sexual activeness starts very early (PrIYA, FGD 6 participant 2). Some staff have values, you know, "Maybe I'm not supposed to offer family planning because I'm a Catholic. Catholics are against this" (POWER, Kisumu IDI 8).
Fostering motivation: focusing on the longer term	I even say to them [providers], 'You remember we are trying to curb the spread of HIV, and people you are seeing for ART, you know, the number would be less if we now had this prevention option of PrEP. So we are working toward the same goal (POWER, IDI Johannesburg 11).
Fostering motivation: professional expectations	I started going [to trainings] with the policies, so I could be like, 'This is a policy. It's just not widely disseminated yet.' … [Providers] often say they want to see the research, but that's not quite what they mean. They want to see the legitimacy. … This is approved by government. This is something that we're now providing that's been legitimately approved, like it's been regulated by SAPRAA [Southern African Pharmaceutical Regulatory Affairs Association]. …. There have been studies that shown us this, and it's been regulated and approved by government and regulatory bodies around the world (POWER, Johannesburg IDI 10). …. [I]t comes down to things like personal motivation…. I think there are other staff motivational issues that can be put into place even if you can't influence the actual salary change. So that even if they provide this additional service that they may feel is onerous and is taking up our time and is an additional responsibility for which I'm not paid, then it's looking at "what are you here for?" You're here to provide a service. Now what is that service? That service could range from PrEP, to contraception, to ARV treatment, to putting plaster of Paris on broken bones, to whatever else. So helping them appreciate what they are doing and then helping them recognize they're appreciated for what they are doing. So that they also feel that they are important and that what they are doing is contributing the overall goals of the country, of the region, in achieving better health (POWER, Kisumu IDI 13).
Fostering motivation through seeing value to the community	People would argue, "Why give the medication? That one is promotion for promiscuity." But it reached certain levels where people were seeing the importance [of PrEP] because the clients themselves were coming for it… And when we saw them coming, we got to know, "Oh! So this thing is very important to the people." It is not important to the providers themselves. Those who consume it are now coming more and more, and they were really in good numbers. So that is the time we realized

(Continued)

Table A1 | Continued

Themes	Illustrative quotations
	this is very important. …. [W]hen we were in training, we were also worried…. "What will people perceive about the PrEP?" But we came to realize that people are in need of it fully (POWER, Kisumu IDI 9).
	I'm sure at some point for them [HCW], they felt quite helpless as a helping professional. You know, you're trying to bring about a positive change in this person and to decrease the amount of risk that they are faced with. But there's really not that much that you can do. But PrEP sort of gave them another gateway, you know, to help these patients to take PrEP (POWER Johnaessburg, IDI 6).
Fostering motivation through continuing medical education	At initial stages people were a bit skeptical [about providing PrEP] and I think it was mainly with relation to what …they thought, that this would lead to more maybe promiscuity and you know the reserved cultures that maybe the hospital is [in], the catchment area, so they thought maybe it would lead to promiscuity. But again after the sensitization and the CMEs, they discovered that that is not the case, yeah so they gained a better reception after they got the information, yeah (PrIYA, FGD 8, participant 1).
Fostering motivation through highlighting professional values	[E]ven if it is an adolescent and the rest of the age groups we should treat them as clients so we should not impose our values on the patients and then as health care workers we should think that this is a preventing measure so what if you don't give this patient the preventive measure then now the client turns to be positive so it is better to prevent than to treat yes (PrIYA, FGD 6, participant 1).
	…[I]t is up on us as the health workers who are at those various stations [FP/MCH clinics] because the reason as to why we are here is to give quality service to our clients and all of us want to help in reduction of HIV prevalence in our country isn't it? So it is up on us to change our attitude and maybe not to wait for support supervision [laughter] because you know we always know the right thing that we should be doing there yeah… So it is upon us to embrace the new intervention that has come and give good services to our clients (PrIYA FGD 06, participant 2).
	My advice to them [reluctant HCW]is that they should just call a spade a spade and because they are tasked with the duty of giving service to mankind, they should just talk about PrEP, talk about sex and talk about everything, not hiding any information from the young women so that they see the light and follow the light (PrIYA, FGD 1, participant 4).
Fostering motivation through emphasizing social realities and professional role	The thing I'm seeing is that sometimes it's difficult for them to negotiate condom use. It's also difficult for them to say "no" to sex because sometimes they are forced into it. So I thought it [PrEP] was a really good idea (POWER, Johannesburg IDI 05).
	The thing that had the nurses embrace [PrEP] is just because we were dealing with the same group of people, because there is no way a girl can come for family planning and you are offering PrEP at the same time and not talk to her about PrEP. That was not fair because this girl has come to see me, so a girl has come to seek family planning and also she wants to test for pregnancy …. So it is just unfair that I will go, provide her with the [family planning] methods and not talk to her [about PrEP]. …..if someone is coming for contraception, it means that they are sexually active. She does not want to get pregnant, but what about HIV? So it puts you in a situation where you really need to talk to her about the need for her to be protected against HIV, and protecting yourself against HIV, that is giving PrEP (POWER, Kisumu IDI 01).
	My [initial] concern was that it [giving PrEP to AGYW] was like we were promoting promiscuity, like we were giving them a room. But later I realized that it [risk behavior] is still there, despite the fact that we are denying them [PrEP] … They will not stop [change their risk behavior] because you think they should be stopping (POWER, Kisumu IDI 5).
	It's mostly, the decision of a partner more than their decision, to use it [condoms] or not to use it. Because, if the male partner doesn't feel like using it, that means that the condom won't be used even though sex is gonna be happening…..So it was quite a nice thing to hear about, and then I strongly felt that it's a good thing for them to have power on their hands as well so that they can their own informed decisions…and be in charge of their sexuality or sexual life as well (POWER, Cape Town IDI 3).
Fostering motivation through empathy	Because if you have people that pull in a different direction, that makes things difficult for you. But once people [are] of one in mind, and one in, "this needs to be done", then it can be done. Most of them [HCW in our studies] are living in the townships.... So they knew also the risks in the townships. For me coming in to the township, and my findings as in, so many girls testing positive and so many girls [are] coming for contraceptives, and so many stories we hear. That was for me a driving force. So it was really, we can actually save someone here, that was the thing, we can actually save someone. …..So the reality for me was also evident, I could see that this can make a difference into someone's life (POWER, Cape Town IDI 10).
	What I know about PrEP now has really changed my—is it attitude. The way I viewed PrEP before is not the way I view it now, because now I understand we don't want our young people to get infected because they are the future generation. HIV has been like "God, so what do we do?" So if something can be done to protect this young generation, to me it is a plus. … I am happy, and now I can be more involved because now I understand what it is all about, and I cannot be judgmental. You know, before I was like, "You are giving [PrEP to] which people?" But now [I feel] it can even help your own child (POWER, Kisumu IDI 04).
	… I have family members who are HIV positive, that also has an influence of me, making things easy for myself to actually deliver PrEP because, my goal is to have an HIV-free generation…. I always tell stories that are happening because I am part of the community. I've been in the township; I know exactly what is happening there. …I always reference from what's happening in the township, and then uhm I think also they can relate to that, and uhm, it kind of flows. …And nobody wants to have HIV so, people want anything that is going to prevent them from getting HIV. And for now we have PrEP and it works (POWER Cape Town IDI 6).

frontiers in Reproductive Health

PERSPECTIVE
published: 14 June 2021
doi: 10.3389/frph.2021.680046

Missed Opportunities for HIV Prevention in Perinatal Care Settings in the United States

Lealah Pollock[1*†], *Marliese Warren*[1†] *and Judy Levison*[1,2*†]

[1] National Clinician Consultation Center, Department of Family and Community Medicine, University of California, San Francisco, San Francisco, CA, United States, [2] Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, United States

Universal opt-out HIV screening in pregnancy is an essential intervention toward eliminating perinatal HIV transmission in the US. However, it fails to identify pregnant people who are HIV negative at the time of testing but are at ongoing risk for HIV acquisition. Those of us involved in caring for women living with HIV are acutely aware of the many diagnoses of HIV that might have been prevented if only a partner had been tested for HIV or preexposure prophylaxis (PrEP) had been offered to a patient. This perspective article will review current recommendations and evidence-based interventions to evaluate missed opportunities for HIV prevention in US perinatal care settings. We identified three barriers to implementation of HIV prevention strategies during pregnancy and breastfeeding: (1) HIV risk for women is underestimated and poorly defined in clinical practice; (2) Partner testing is challenging and implementation studies in the US are lacking; and (3) PrEP remains underutilized. In March 2020, the National Perinatal HIV Hotline convened a group of clinicians and researchers specializing in perinatal HIV care to a case-based discussion of missed opportunities in perinatal HIV prevention. From our review of the literature via PubMed search as well as expert opinions gathered in this discussion, we make recommendations for addressing these barriers.

Keywords: hiv prevention, pregnancy, breastfeeding, HIV self-testing, partner testing, pre-exposure prophylaxis

OPEN ACCESS

Edited by:
Thesla Palanee-Phillips, Wits Reproductive Health and HIV Institute, South Africa

Reviewed by:
Kenneth Mugwanya, University of Washington, United States
Akon Emmanuel Ndiok, University of Calabar, Nigeria

***Correspondence:**
Lealah Pollock
Lealah.Pollock@ucsf.edu
Judy Levison
jlevison@bcm.edu

† These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *13 March 2021*
Accepted: *17 May 2021*
Published: *14 June 2021*

Citation:
Pollock L, Warren M and Levison J (2021) Missed Opportunities for HIV Prevention in Perinatal Care Settings in the United States. Front. Reprod. Health 3:680046. doi: 10.3389/frph.2021.680046

INTRODUCTION

Universal HIV testing in pregnancy is an essential step in preventing perinatal HIV transmission. However, testing only the pregnant patient fails to identify people at risk for HIV acquisition during pregnancy and breastfeeding and misses opportunities to interrupt sexual and perinatal transmission of HIV (1). Risk for HIV acquisition per receptive vaginal condomless sex act increases substantially during pregnancy and in the postpartum period (2, 3). In addition, seroconversion during pregnancy and breastfeeding carries a high risk of HIV transmission to the baby and is an ongoing obstacle to the goal of eliminating perinatal HIV transmission in the US. A PubMed search of articles from 2006–2021 was conducted using key words pre-exposure prophylaxis and HIV and (women or pregnancy or pregnant or conception or preconception or postpartum or breastfeeding) as well as pre-exposure prophylaxis and (peri conception or peri-conception or periconception). We reviewed the citations in relevant articles in order to identify additional literature for inclusion. This perspective article will review current

recommendations and evidence-based interventions to evaluate missed opportunities for HIV prevention in US perinatal care settings. We will also present opinions generated from a gathering of perinatal HIV experts convened in March 2020.

EVIDENCE-BASED INTERVENTIONS

Recommended and tested interventions generally fall into two categories: increasing provision of preexposure prophylaxis (PrEP) during pregnancy and breastfeeding, and offering HIV testing to sexual partners of pregnant people.

Provision of PrEP During Pregnancy and Breastfeeding

PrEP is a highly effective HIV prevention method in which an HIV-negative individual takes antiretroviral medications in order to prevent HIV acquisition. The only medication that is currently approved for HIV prevention among cisgender women in the United States is tenofovir disoproxil fumarate 300 mg-emtricitabine 200 mg (TDF-FTC), in the form of a daily oral pill. Other medications and routes of administration are under investigation.

TDF and FTC have been shown to be safe during many years of use as part of an antiretroviral regimen for pregnant women living with HIV and, more recently, as PrEP for HIV-negative women (4, 5). When used during breastfeeding, breast milk concentrations of tenofovir are low, and infant plasma concentrations are <1% of pediatric therapeutic levels (6, 7). Despite being highly efficacious and safe, PrEP remains underutilized during pregnancy and breastfeeding (8).

A "PrEP care continuum" has been proposed as a framework to understand PrEP implementation and dissemination in at-risk populations (9). The first step in the PrEP care continuum is generally defined as PrEP awareness, which has three components: identifying individuals at highest risk for contracting HIV, increasing HIV risk awareness among those individuals, and enhancing PrEP awareness (10). This framework is particularly helpful in thinking about PrEP implementation in populations with low HIV risk awareness, such as pregnant and breastfeeding individuals.

Providers Unaware of HIV Risk

In 2017, the Centers for Disease Control (CDC) (11) identified indications for PrEP use by heterosexually active men and women, including HIV-negative women not in a monogamous relationship with a recently tested HIV-negative partner who also have at least one of the following risk factors: infrequent condom use with one or more partners of unknown HIV status who are known to be at substantial risk of HIV infection, in an ongoing sexual relationship with an HIV-positive partner, or infection with syphilis or gonorrhea diagnosed or reported in the last 6 months. Using these criteria, Fruhauf and Colemen (12) estimated that 10% of their pregnant population in Baltimore were eligible for PrEP. However, this list is somewhat unwieldy for the busy practicing clinician.

Women and Partners Unaware of HIV Risk

Studies in the US suggest that women may underestimate their HIV risk and the HIV risk status of their male partners (13, 14). Women may be unaware that their male partners have risks for HIV. Partner characteristics that present a risk for HIV include concurrent partnerships with women and/or men, untreated sexually transmitted infections (STIs), injection drug use, prior incarceration, and undisclosed or undiagnosed HIV infection (15). Relying on a biological marker of HIV risk, such as diagnosis of a bacterial STI, also fails to identify a significant number of women who will later acquire HIV (16). In one survey of African American women, age over 35, being recently homeless, being on Medicaid, and last sex partner characteristics (crack cocaine use and being a transactional sex partner) were more strongly associated with a new HIV diagnosis than any individual risk factor (17).

A history of trauma, including intimate partner violence (IPV) and substance use, including non-injection substance use, are additional risk factors for HIV (18, 19). One study showed women experiencing IPV were more worried about getting HIV in the next 6 months, but their PrEP awareness and intentions were the same as women without these experiences (20). Engaging in transactional sex in exchange for drugs as well as loss of inhibitions can be seen with both injection and non-injection drug use. Substance use clinics have therefore been suggested as ideal sites for offering PrEP (21).

Patient Awareness of PrEP and Provider Willingness to Prescribe

Studies of at-risk women have demonstrated a low public awareness of PrEP, although this awareness appears to be increasing over time and likely varies by location, with 6–44% of women reporting having heard of PrEP (13, 22, 23). Even using existing guidelines to identify women at risk of acquiring HIV, there are huge gaps in implementation. An analysis of nationwide insurance claims data from 2017 found that only 6–12% women diagnosed with gonorrhea or syphilis were tested for HIV and none of these patients were prescribed PrEP (24). Studies assessing PrEP awareness specifically among pregnant patients and prenatal providers are lacking at this time. Interviews with clinicians documented in two qualitative studies have elucidated conflicting perceptions about who should be responsible for prescribing PrEP (25, 26). Many primary care physicians believe that PrEP prescription is in the purview of specialists, while many specialists see it as the responsibility of primary care clinicians. In a survey of family planning providers in 2015, only about one-third answered basic knowledge questions about PrEP correctly (27). Some clinicians said they would consider prescribing if patients specifically requested PrEP, which assumes knowledge and high motivation on the part of patients (25, 26). The larger view of assessing all women for periconception, pregnancy, and postpartum risk has yet to be embraced on a national scale in the US and other countries (28).

HIV Testing for Partners of Pregnant and Breastfeeding People

US guidelines recommend that partners of pregnant women undergo HIV testing when their status is unknown. The goal is to facilitate linkage to care for partners with HIV and guide a discussion about prevention (8, 11). The challenges of following this recommendation have been highlighted in implementation studies in US settings.

There are two primary approaches to testing partners of pregnant women –offering testing for male partners, not tied to the prenatal HIV testing of the pregnant partner; or offering counseling, testing, and disclosure with a trained counselor to both partners as a couple. Both of these approaches can be carried out either in the clinic or at home. In Sub-Saharan Africa, study participants have expressed a variety of preferences about where and how HIV testing should occur; pregnant patients and their partners often have different preferences (29, 30).

Partner HIV Testing

We could identify no studies looking at home-based testing among pregnant women and their partners in the US. In Kenya and Uganda, home-based self-testing and home-based testing administered by trained personnel both resulted in two- to three-times higher uptake of male partner testing and couples' testing and higher rates of HIV status disclosure than inviting male partners to the clinic for HIV testing. However, linkage to care after HIV testing at home remains a challenge (30–33).

In one clinic in Chicago, two-thirds of participants were interested in knowing their partner's status and three-quarters of them believed their partner would like to know his status (34). However, only 39% of participants reported that their partner had insurance coverage for medical care or a primary care provider.

Another study invited HIV-negative pregnant women to bring their male partner to their next prenatal visit for a free HIV test, but only 20.6% of invited males underwent HIV testing (35). The authors found that decisions about testing were driven by perceptions about fidelity, male partner autonomy, fetal safety, ease of testing, and recency of prior HIV testing.

Couples' HIV Testing

Couples' HIV testing has been evaluated for its ability to increase condom use within a partnership, and is effective, but studies in the US have primarily been done outside of the context of pregnancy and prenatal care (36). In one urban academic antenatal care setting in the US, couples who received couples HIV testing and counseling reported a very high level of acceptability and increased ease in having conversations around safe sex (37). However, only 8% of eligible couples consented for the study. The most common reasons for declining participation were difficulty bringing a partner in for testing, including scheduling conflicts for the partner and the partner not being available or interested, and low perceived risk for HIV infection.

Addressing Community and Structural-Level Risk for HIV

In 2018, Blacks/African Americans made up 13% of the female population but accounted for 58% of new HIV diagnoses among women (38). Individual risk behaviors cannot explain the dramatic racial disparities in HIV rates (14, 15, 39). Non-Hispanic Black women are more likely to have concurrent sexual partners and to perceive their partners to be nonmonogamous. However, they are also more likely to use condoms than White women, suggesting that other social and structural factors likely contribute to HIV acquisition risk (40).

Multiple authors have highlighted the role that racial segregation, higher community baseline HIV and STD prevalence, poverty, gender inequality, mass incarceration, lack of access to healthcare, and racism play in driving racial disparities in HIV prevalence (14, 15, 39–41). Ojikutu (39) concludes that women at high risk may be "hidden in plain sight," to be found if clinicians would pay greater attention to sociodemographic factors than individual sexual behaviors. Assessing socioeconomic/contextual factors that increase HIV risk may be more helpful than individual behavioral risk factors or sex partner characteristics (14, 15, 17). However, these social and structural factors that continue to drive the HIV epidemic among women must primarily be addressed with structural interventions (42). While offering PrEP to pregnant patients who engage in transactional sex or have substance use disorder is important, offering economic opportunities, stable housing, non-stigmatizing mental health care, comprehensive syringe services programs, and access to substance use treatment may be far more effective in reducing their risk for HIV and improving health overall. Moreover, as women's HIV vulnerability is directly linked to community-level HIV prevalence and HIV viral load, interventions to decrease HIV stigma in the population and decrease bias and discrimination in health care will help to mitigate this vulnerability (43).

BEST PRACTICES AND FUTURE DIRECTIONS

The National Perinatal HIV Hotline (www.nccc.ucsf.edu) hosted roundtable discussion in 2020, *Preventing Maternal HIV Transmission during Pregnancy and Breastfeeding*, that coincided with the Conference on Retroviruses and Opportunistic Infections (CROI). Attendees were clinicians, HIV researchers, federal funders, and community members who discussed current practices and future directions. The discussion is summarized below.

HIV Risk Assessment: Pregnant Person's Risk

Participants identified prenatal care visits as an opportunity to discuss each patient's social and reproductive history, including previous STI diagnoses. This discussion can be framed as a routine part of care to ensure the pregnant person's and baby's health. Discussing HIV as one of many relevant infections and conditions can help normalize the condition, particularly when providers avoid using stigmatizing language. Providers can also routinely ask pregnant people whether they have new sexual partners without making assumptions about relationships or partner concurrency.

HIV Risk Assessment: Partner Risk

Among HIV providers, asking about partner HIV status and encouraging partner testing is often routine. However, in a general prenatal/clinical setting, it is not standard practice. The current American College of Obstetrics and Gynecology (ACOG) prenatal form includes questions that ask about patient and partner history of hepatitis, tuberculosis, and herpes as well as patient history of STIs including gonorrhea, chlamydia, human papilloma virus, and syphilis. The group suggested that ACOG include a question about the HIV status of sexual partner(s). If partner status is unknown, providers could offer partner HIV testing and discuss PrEP.

Couples' HIV Testing

Participants identified barriers to couples' HIV testing in prenatal care in the US, including wariness about deferring HIV testing of the pregnant person in order to test both partners simultaneously. One proposed solution focused on partner testing by linking pregnant people with partners of unknown HIV status to a PrEP coordinator and comprehensive services for partners (e.g., HIV and STI testing, vaccines like Tdap and influenza, and linkage to primary care).

Secondary Distribution of HIV Self-Tests for Partners

As discussed above and also noted by roundtable participants, HIV self-test dispensation within prenatal care is ongoing broadly in East and Southern Africa and seems to be acceptable to patients and their partners. In the UK, self-testing kits are available and free (44). HIV self-testing should be explored as a strategy for partner testing in the US.

Universal Education About HIV Prevention and PrEP

Participants noted that assessing risk in a low prevalence population remains an issue for evaluating PrEP eligibility. One proposed solution was universal education about HIV risk and PrEP. Anyone who requests PrEP should receive it, regardless of the clinician's assessment of risk. Participants in the group noted that pregnant people may not wish to discuss their HIV risk behaviors but may respond to being offered PrEP. Additionally, personal risk factors and behaviors often change over time. There are times when a woman might not be sexually active and might not want to remain on PrEP continuously but would like the option to return to PrEP.

DISCUSSION

We identified three areas that contribute to missed opportunities for HIV prevention in pregnancy and breastfeeding: (1) HIV risk awareness among women is low and HIV risk for women is challenging to identify and define in clinical practice; (2) Partner testing is far from routine and implementation studies in the US are lacking; and (3) PrEP remains underutilized among women, especially during pregnancy and breastfeeding. Utilizing our review of the literature, the views and opinions shared during the 2020 roundtable discussion, and our own experience and perspectives, we will share next steps and opportunities for addressing each of these gaps.

HIV Risk for Women Is Challenging to Identify and Define in Clinical Practice

Individual factors that should alert clinicians to HIV risk include a recent (and not so recent) STI diagnosis; infrequent condom use with one or more partners of unknown HIV status, especially within a high-prevalence sexual network; a history of intimate partner violence; engaging in transactional sex; substance use disorder and/or substance use associated with sex; having a partner with HIV without consistent virologic suppression; and having a partner with any of the factors listed here. Questions about these risks could be routinely assessed in perinatal care settings, using prenatal intake questionnaires or checklists. However, these checklists have been challenging to implement, partly because standardized HIV risk assessment tools for cisgender women in the US haven't been developed. Also, many of these factors, especially those involving partner characteristics, are often unknown to pregnant people themselves.

One question that is easy to implement is: "Are any of your sexual partners living with HIV?" This question has emerged as an important screening question for all people seeking preconception, pregnancy, and postpartum care, both in the literature and in our roundtable discussion (1, 27, 34). Even if the response is "I don't know my partner's HIV status," the question may lead to a discussion about partner testing and PrEP.

Being at risk is a function of both environment (e.g., living in a community with high underlying HIV incidence) and individual exposure to risk (e.g., having condomless sex with a partner with untreated HIV) (45). While individual- and partner-level risk factors for HIV are important to understand and assess, community- and structural-level factors play a very large role in individual HIV risk. Clinicians should understand the contextual risks of HIV acquisition, especially among low income or homeless women, women living in the South, and women of color, but should avoid profiling individual women based on poverty, geography, or race. Being aware of the HIV prevalence where one is practicing is crucial and could potentially be a point of discussion when talking to patients about their individual HIV risk (41). Interventions that target invidiuals should be grounded in principles of equity and evaluated based on their impact on health disparities, but structural-level interventions are needed in order to combat structural-level health determinants. Interventions aimed at reducing inequities and racism in policing, criminal justice, education, economic opportunity, physical and mental health care, and housing will likely have very real impacts on reducing HIV infections and should be included and evaluated as part of efforts to eliminate HIV transmission (42, 43, 46).

Population-based risk factors could be utilized to develop standardized risk assessment tools, none of which have been developed or validated for cis-female populations in the US. However, standardized risk assessment tools have their own

drawbacks: they can be challenging to validate in a low-prevalence region or population, they are not generalizable to other populations beyond the one in which they were validated, and they are likely to miss individuals who are high-risk but "screen out" by the tool (45). Additionally, development of risk assessments often occurs without community input and risks exacerbating rather than decreasing bias and stigma by creating a "profile" of a patient at risk (39). Clinicians and policy makers need to talk to community members, both those living with HIV and those who are at-risk, and incorporate their input when developing risk assessments. Discussing "risk" may not be the right approach at all. Dazón Dixon Diallo has pointed out that HIV "vulnerability" might better capture the life conditions and structural factors that create an opportunity for HIV acquisition (47).

Partner Testing Is Challenging and Implementation Studies in the US Are Lacking

Very few studies in the US have assessed attitudes toward or effectiveness of interventions to offer HIV testing to partners of pregnant people. The studies that have been done have demonstrated a desire for partner testing but have also highlighted low uptake of testing and multiple barriers to testing (34, 35, 37).

The fragmentation of the US healthcare system is an unfortunate barrier to partner HIV testing. How do you create an entry in the EMR for a male partner seen in a prenatal care setting? Who is responsible for tracking and following up on results? Outside of couples' testing, how and when and by whom does disclosure occur? Who pays for partner HIV testing? System changes, such as single payer healthcare, would allow partner and couples' HIV testing to support the health of pregnant people, their infants, and their partners. Despite these challenges, the perinatal period presents a potential opportunity to engage partners in their own healthcare by framing it as being in service to the birthing person and infant.

While HIV incidence, HIV stigma and attitudes toward HIV testing are likely different in the US than in other countries, and also differ among subpopulations within the US, we can still gain important knowledge and insights from studies of male partners testing in sub-Saharan Africa. In particular, the concept of offering different options for male partner testing and the increased uptake of home-based testing are important considerations to apply to future studies in the US. The US is not dispensing HIV self-tests to pregnant people for secondary distribution due to concerns of suicide/self-harm or lack of linkage to HIV care among those who test HIV-positive (48–50). However, the potential to use self-testing as a strategy to reach partners of pregnant and breastfeeding people was highlighted by our roundtable participants.

The CDC encourages the implementation of HIV self-testing programs to meet the ambitious goals of the federal Ending the HIV Epidemic (EHE) initiative[1]. Based on the success of the eSTAMP study (51), two EHE jurisdictions in California began utilizing self-testing kits and found that fears of self-harm and patients lost to follow up were not realized and were outweighed by the benefits of privacy. Test counselors and patient navigators were able to remain connected to their clients and all patients who received a preliminary positive HIV test received confirmatory tests and were successfully linked to care as needed (52).

PrEP Remains Underutilized Among Women, Especially During Pregnancy and Breastfeeding

National organizations, such as the CDC and ACOG, should more strongly endorse the use of PrEP in pregnancy and breastfeeding, beyond its use in serodifferent couples. These organizations can also help develop and promote tools to assist prenatal care providers in assessing HIV risk, promoting partner HIV testing, and offering PrEP to all pregnant and breastfeeding women who are interested. The ACOG obstetric patient record forms should include questions about partner HIV status and partner HIV risk and could include prompts for offering PrEP. Electronic medical record technology could be used to streamline the process of ordering baseline labs, ordering PrEP, planning timing of follow up labs and appointments, and obtaining approval for financial coverage of PrEP. Excitingly, current EHE efforts have eliminated the financial barrier to PrEP for people without insurance coverage[2].

Part of increasing PrEP uptake is also increasing community-level PrEP awareness, including awareness that PrEP can be used as an HIV prevention tool during pregnancy and breastfeeding. Community-based education programs can reach women who may not come to clinic and plant the seed for people before they become pregnant (5). Additionally, educational materials in clinic waiting rooms or examination rooms, and public messaging on television, radio, and social media can be used to disseminate information about PrEP more widely.

The Department of Health and Human Services (DHHS) Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission and the World Health Organization (WHO) agree that all viable HIV prevention options, including PrEP, should be encouraged for women at risk for HIV, especially during pregnancy and breastfeeding, given the increased risk of HIV acquisition during pregnancy and the potential for perinatal transmission with maternal seroconversion during pregnancy (8, 53). The DHHS Panel cites many indications for PrEP, including simply feeling at risk for HIV. While not the only method of HIV prevention, PrEP offers women a tool they can control to protect themselves without having to negotiate with a partner (54). Combined with routine opt-out HIV testing and assessment of partner HIV status, offering PrEP during pregnancy and breastfeeding has the powerful potential to eliminate perinatal HIV transmission. US clinicians interested

[1]https://www.cdc.gov/hiv/testing/self-testing.html

[2]https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/prep-program

in learning more about prescribing PrEP to their patients can call the PrEPline toll free and speak with an expert clinician consultant: nccc.ucsf.edu.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession numbers can be found below: https://nccc.ucsf.edu/wp-content/uploads/2017/08/2020NatlPeriHotline_CROIRoundtableSummary_10.08.pdf.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

A cooperative agreement from US Department of Health and Human Services, Health Resources and Services Administration, HIV/AIDS Bureau grant number U1OHA30039 supported the development of the 2020 National Perinatal HIV Roundtable. Opinions expressed in this article do not necessarily reflect the views of HRSA.

ACKNOWLEDGMENTS

The authors want to acknowledge the contributions of Deborah S. Storm for her help with editing and identifying citations. We also want to thank the participants of the 2020 National Perinatal HIV Roundtable especially Dawn Averitt, Lynn T. Matthews, Pooja Mittal, Renee Heffron, Nelly Mugo, Betty Njoroge, Jullian Pintye, Randy Statler, and Anjuli Wagner.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

ORIGINAL RESEARCH
published: 18 June 2021
doi: 10.3389/frph.2021.667823

Integrating Oral PrEP Into Family Planning Services for Women in Sub-saharan Africa: Findings From a Multi-Country Landscape Analysis

*Neeraja Bhavaraju[1], Rose Wilcher[2], Regeru Njoroge Regeru[3], Saiqa Mullick[4], Imelda Mahaka[5], Jessica Rodrigues[6], Jennifer Mason[7], Jane Schueller[8] and Kristine Torjesen[2]**

[1] Afton Bloom, Washington, DC, United States, [2] Global Health, Population and Nutrition, FHI 360, Durham, NC, United States, [3] LVCT Health, Nairobi, Kenya, [4] Wits Reproductive Health and HIV Institute, Faculty of Health Science, University of the Witwatersrand, Johannesburg, South Africa, [5] Pangaea Zimbabwe AIDS Trust, Harare, Zimbabwe, [6] AVAC, New York, NY, United States, [7] Office of Population and Reproductive Health, United States Agency for International Development, Washington, DC, United States, [8] Office of HIV/AIDS, United States Agency for International Development, Washington, DC, United States

OPEN ACCESS

Edited by:
Renee Heffron, University of Washington, United States

Reviewed by:
Jillian Pintye, University of Washington, United States
Flavia Matovu Kiweewa, MU JHU Research Collaboration, Uganda

***Correspondence:**
Kristine Torjesen
ktorjesen@fhi360.org

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *14 February 2021*
Accepted: *26 May 2021*
Published: *18 June 2021*

Citation:
Bhavaraju N, Wilcher R, Regeru RN, Mullick S, Mahaka I, Rodrigues J, Mason J, Schueller J and Torjesen K (2021) Integrating Oral PrEP Into Family Planning Services for Women in Sub-saharan Africa: Findings From a Multi-Country Landscape Analysis. Front. Reprod. Health 3:667823. doi: 10.3389/frph.2021.667823

Integration of HIV and family planning (FP) services is a renewed focus area for national policymakers, donors, and implementers in sub-Saharan Africa as a result of high HIV incidence among general-population women, especially adolescent girls and young women (AGYW), and the perception that integrating HIV pre-exposure prophylaxis (PrEP) into FP services may be an effective way to provide comprehensive HIV and FP services to this population. We conducted a focused desk review to develop a PrEP-FP integration framework across five key categories: plans and policies, resource management, service delivery, PrEP use, and monitoring and reporting. The framework was refined via interviews with 30 stakeholders across seven countries at varying stages of oral PrEP rollout: Kenya, Lesotho, Malawi, South Africa, Uganda, Zambia, and Zimbabwe. After refining the framework, we developed a PrEP-FP integration matrix and assessed country-specific progress to identify common enablers of and barriers to PrEP-FP integration. None of the countries included in our analysis had made substantial progress toward integrated PrEP-FP service delivery. Although the countries made progress in one or two categories, integration was often impeded by lack of advancement in other areas. Our framework offers policymakers, program implementers, and health care providers a road map for strategically assessing and monitoring progress toward PrEP-FP integration in their contexts.

Keywords: HIV prevention, PrEP, PrEP-FP integration, SRH-HIV integration, AGYW

INTRODUCTION

The region of East and southern Africa is the most affected by HIV, with over 700,000 new infections in 2019 (1). Women are disproportionately affected, as demonstrated by 2018 HIV prevalence rates among young women (15–24 years), which are more than double the rates seen among young men (1). Oral pre-exposure prophylaxis (PrEP) and the future introduction of new

biomedical products—such as the dapivirine vaginal ring, long-acting injectable cabotegravir, and multipurpose HIV prevention and contraceptive technologies—have the potential to substantially reduce new HIV infections if these products can be accessed and effectively used by those at risk of HIV (2–4).

However, the rollout of oral PrEP has been confronted with many challenges, including difficulties translating policy into practice and optimizing access, uptake, and effective use among populations at risk of acquiring HIV in sub-Saharan Africa (5). PrEP uptake and use among adolescent girls and young women (AGYW), in particular, have been impeded by barriers including low perceived HIV risk, pill burden, limited private storage space, fear of inadvertent disclosure to family and partners, intimate partner violence, stigma associated with an antiretroviral-based product, and negative attitudes among healthcare providers toward adolescent sexuality and PrEP use (6–8). In addition, although some decentralized, community-based models of PrEP delivery are emerging, PrEP services have largely been provided through specialized HIV or STI clinics, where AGYW do not routinely seek care and that primarily target key populations, such as female sex workers, men who have sex with men, and transgender women (9).

A potential solution for increasing access to and uptake of oral PrEP among women is to integrate oral PrEP counseling and delivery in family planning (FP) services, which are well-established and well-utilized by sexually active women in many settings. More than one-quarter (28.5%) of women in sub-Saharan Africa of reproductive age (15–49 years) use a modern contraceptive method, including 24.7% of AGYW (15–24 years) (10). Contraceptive prevalence among AGYW is even higher in high HIV burden countries such as Lesotho (59.2%), Zimbabwe (50.7%), and Kenya (36.8%) (10). Half of modern contraceptive users use short-acting methods, such as the daily pill or 3-month injection, both of which typically require the same clinic visit schedule as oral PrEP (11). As a result, integration of FP and oral PrEP services have potential for alignment. Service integration has also received increased attention following the results of the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial, which found high HIV incidence among women accessing contraceptive services in three high HIV burden countries, with HIV risk greatest among women younger than 24 years (12). These results prompted the World Health Organization and other stakeholders to endorse providing HIV prevention options, including PrEP, in FP services in high HIV burden settings, asserting that scale-up of oral PrEP and other future HIV prevention products in these settings may more effectively reach priority populations such as AGYW where they already receive preventive health services (13, 14).

The attention being given to integrating PrEP into FP services (referred to as PrEP-FP integration henceforth) builds on more than two decades of advocacy, programmatic efforts, and research aimed at strengthening the integration of sexual and reproductive health (SRH) and HIV services more broadly. These efforts, which embrace a woman-centered, choice-based, and rights-based approach to service delivery, have introduced a range of service integration models for different combinations of services, all with the goal of achieving better SRH and HIV outcomes. Although studies suggest that clients have a preference for integrated SRH-HIV services, the evidence of the effects of integrated services on service quality and client outcomes is mixed (15–19). Moreover, these efforts have suggested that achieving service integration requires overcoming challenges to integration throughout the health system, including in policies and guidelines, financing mechanisms, demand creation, monitoring and evaluation, supply chains, and human resource capacity (16). However, the non-integration of some of these health system "hardware elements" (primarily related to structure and resources) may be mitigated by strong "software elements," such as leadership, management, and provider motivation, agency, and relationships, all of which are essential enablers of effective SRH-HIV integration (20).

The evidence base pertaining to PrEP-FP integration specifically is limited, in part because PrEP is relatively new to the market, with the first African regulatory approvals in 2015. Early demonstration projects suggest that PrEP delivery in FP settings is feasible; however, uptake of PrEP by screened and eligible AGYW in these studies was low, ranging from 4 to 16% (21, 22).

To unlock the potential to meet the HIV prevention needs of women by integrating PrEP delivery into FP services, programs need practical guidance on how to overcome challenges to PrEP-FP integration throughout the health system and achieve sustainable integration of these two services at scale. Drawing on an existing product introduction framework developed to support national rollout and scale-up of oral PrEP (23), a desk review of relevant SRH-HIV integration literature and policy documents, and interviews with an expert panel, we proposed and applied a PrEP-FP integration framework that delineates the systems issues that must be addressed for effective integration, particularly for AGYW.

MATERIALS AND METHODS

This programmatic analysis involved three steps. First, we conducted a desk review of published reviews and policy documents related to HIV-FP service delivery integration and oral PrEP introduction to inform the development of a PrEP-FP integration framework. Next, we conducted interviews with 30 experts at the global level and across East and southern Africa to further refine the framework. Finally, we applied the framework to seven countries with high levels of HIV burden and at varying stages of PrEP rollout—Kenya, Lesotho, Malawi, South Africa, Uganda, Zambia, and Zimbabwe—identifying barriers to and enablers of PrEP-FP integration along the framework.

The desk review included five global review articles purposively selected to provide context on the current state of evidence regarding HIV and FP integration (15–18, 24). The desk review for Lesotho, Malawi, South Africa, Uganda, and Zambia included 61 policy and program sources (11–14 per country) related to country plans and policies, integration information (site audits and reports), and demographic information (25). For Kenya and Zimbabwe, information was sourced from the HIV Prevention Market Manager reports on

integration of HIV prevention and SRH services in each country, which were based on policy reviews, expert interviews, facility assessments, and youth consultations (26, 27).

The interviews were conducted with a convenience sample of 30 experts, including six of the authors, who were engaged in programmatic and technical support for PrEP and/or FP implementation and represented both global and country perspectives. They included seventeen national implementers (3 from Kenya, 2 from Lesotho, 2 from Malawi, 4 from South Africa, 1 from Uganda, 2 from Zambia, 3 from Zimbabwe), one national policymaker (from Uganda), seven global implementers, and five staff from the United States Agency for International Development (USAID) (25). Interviews were conducted virtually with individuals or in small groups of two to three persons. The interviews were recorded with each participant's verbal permission, and notes were transcribed into a Word document. Prior to the interviews, the draft PrEP-FP integration framework was shared with participants. During the interviews, participants were asked to provide input on the framework components, as well as country-specific feedback on activities related to PrEP-FP integration. Interview discussion themes were structured around five health system domains: plans and policies, resource management, service delivery, PrEP use, and monitoring and reporting.

Based on the desk review and expert interviews, the components of the PrEP-FP integration framework were refined and a general assessment of progress toward integration was mapped across the seven countries, including identifying common barriers to and enablers of PrEP-FP integration.

RESULTS

The analysis identified 17 essential elements to support PrEP-FP integration across five major health system domains: plans and policies, resource management, service delivery, PrEP use, and monitoring and reporting. These elements formed the foundation of the PrEP-FP integration framework (see **Figure 1**) (25).

During the assessment based on this framework, consistent patterns emerged across the seven countries that highlighted barriers to and enablers of integration (see **Figure 2**) (25). The key findings for each category are presented in sections Plans and policies, Resource management, Service delivery, PrEP Use, and Monitoring and reporting.

Plans and Policies

Leadership and dedicated human and financial resources are essential to support PrEP-FP integration. Across the countries included in this analysis, policymakers and donors consistently supported integrated service delivery, and every country had national policy documents promoting the delivery of integrated health services, including HIV prevention and FP services. Several countries had also introduced national initiatives specifically focused on multisectoral approaches to AGYW well-being, such as the She Conquers (28) campaign in South Africa, which aimed to align services to reduce HIV incidence, unplanned pregnancy, and incidence of intimate partner violence, as well as school dropouts and unemployment. In practice, however, structures for coordinating services typically remained siloed. Across all the countries, HIV prevention, including PrEP, and FP were managed by different Ministry of Health departments and separate national-level technical working groups. A stakeholder in Malawi noted, "Integration is being discussed at a national level, but who really champions integration? A missing link is that there is no unit in charge of integration."

Few countries have tasked an individual or department with managing integration at the national and subnational levels, although both are critical to support implementation of integrated service delivery. For example, in Zimbabwe, a national HIV-SRH Integration Officer sits within the Family and Child Health Department of the Ministry of Health and Child Care (MoHCC), but provincial-level responsibilities are split between separate SRH and HIV focal persons. One potential exception is Kenya, where a renewed push to integrate HIV prevention and FP services is being led by a national subcommittee formed in July 2020 with joint membership from the National AIDS and STIs Control Programme (NASCOP) and the Department of Reproductive and Maternal Health, with an aim to replicate the structure at subnational levels in future years.

More specific policies can also enable or impede service integration. For example, guidelines that support differentiated service delivery and task-shifting are often different across PrEP and FP services. In contrast to a concentrated effort to ensure most FP services can be delivered by a range of providers, including community health workers, and across diverse channels, including community-based programs and pharmacies, PrEP is largely delivered via clinicians, including clinical officers, doctors, or nurses specifically trained in HIV care. Changes in policies on task shifting and expansion of the provider cadres that can deliver PrEP may be needed to enable and support PrEP-FP integration. Similarly, other policies on PrEP provision, including requirements for laboratory tests, multi-month dispensing, and age restrictions, also need to be considered to support alignment with provision of FP services. As noted by a stakeholder in Zambia, "Our public health FP facilities are very crowded. We need multi-month dispensing for both PrEP and FP and to think about what a community health worker can do. Without that, I don't know how we will manage it."

Resource Management

PrEP and FP funding for commodity procurement, distribution, and management also need to be considered to support integrated services. One of the largest challenges to effective PrEP-FP integration is a difference in financing for the two services. PrEP has largely been donor-funded, with extensive dedicated resources to support PrEP provider training, service delivery, and monitoring. FP services, on the other hand, have transitioned to being funded with a combination of domestic and dedicated donor funds. Separate funding streams often contribute to silos in planning, budgeting, and delivering PrEP and FP services. For example, a South Africa implementing partner noted the challenge that donors can pose to service integration: "Funding can be a real challenge. Within our work

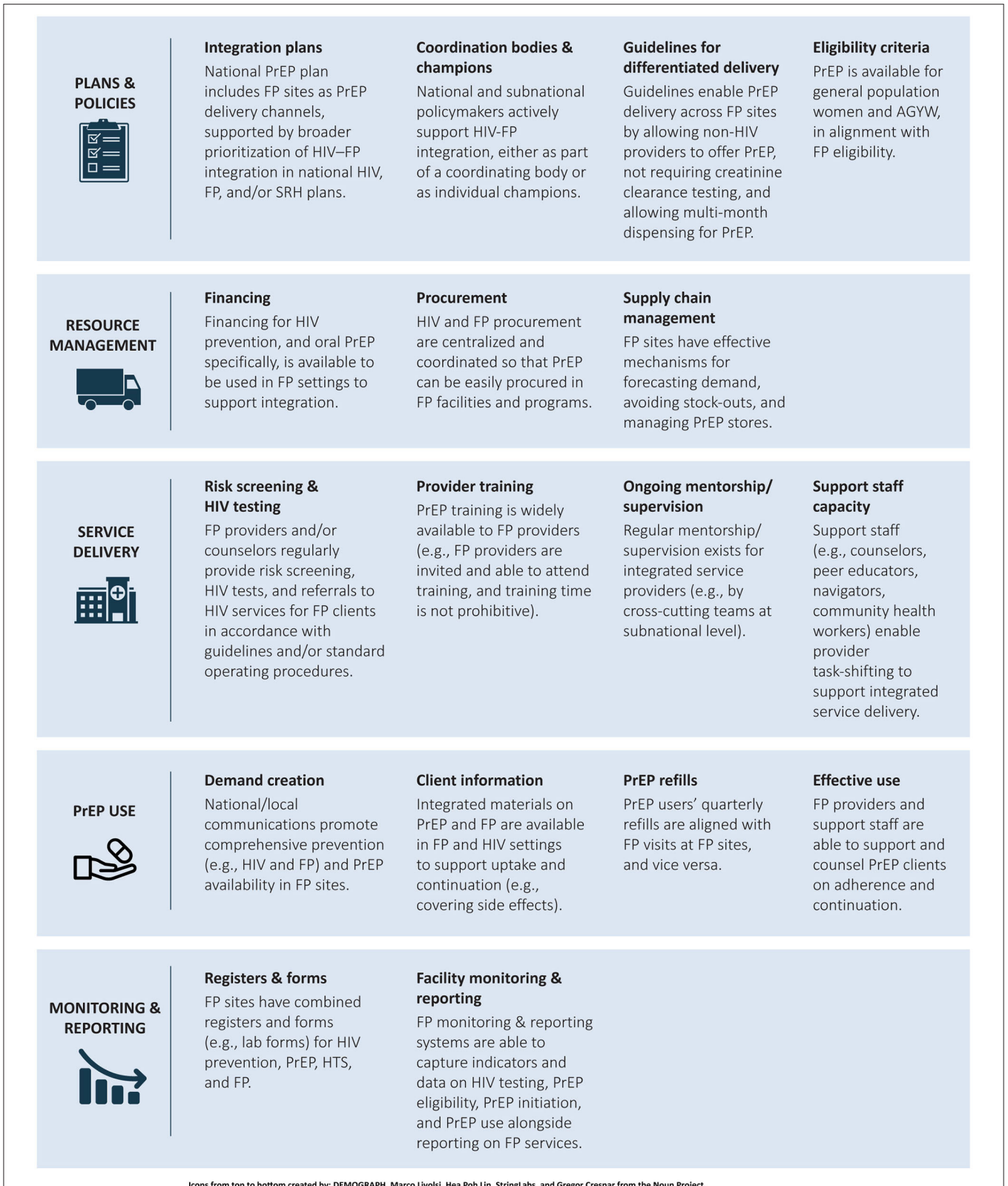

FIGURE 1 | PrEP–Family planning integration framework. PrEP, pre-exposure prophylaxis; FP, family planning; SRH, sexual and reproductive health; AGYW, adolescent girls and young women; HTS, HIV testing services.

	INTEGRATION ENABLERS	INTEGRATION BARRIERS
PLANS & POLICIES	• Many policymakers champion service integration. • National plans often cite service integration as a priority for the health system. • Most countries do not require laboratory testing beyond an HIV test.	• While plans cite integration, integration is typically not a core responsibility for any individual or coordinating body. • Dedicated resources for integrated processes/systems are limited.
RESOURCE MANAGEMENT	• Many countries have centralized procurement systems that support HIV and FP programs. • HIV programs are well-resourced and have the potential to support integrated service delivery.	• Separate funding streams for HIV and FP lead to siloed planning, budgeting, and service delivery. • Integrating PrEP into FP without additional resources risks reducing the quality of both services. • In some settings, both HIV and FP programs experience regular commodity stock-outs, which can hinder integration efforts.
SERVICE DELIVERY	• Several different models of service delivery are available that could be tailored to specific contexts. • Lay counselors, peer educators, expert clients, or navigators provide additional capacity for testing, counseling, and referrals to support integrated service delivery and alleviate provider burden. • HIV self-tests offer the potential to alleviate the additional burden on FP providers and streamline the client experience.	• Many FP providers are not trained to provide HIV services, including PrEP. • HIV risk screening, testing, and counseling (e.g., risk assessment, discussion of sexual partners) are not regular practices in FP services. • Providers in smaller clinics already provide integrated services, but many have not yet been trained in PrEP provision. • With any service delivery model, provider attitudes toward PrEP provision, especially for AGYW, will be a challenge for integrated services — as they are for independent services.
PrEP USE	• Demand creation considerations are similar across FP and HIV prevention (e.g., stigma, partner dynamics). • Visit schedules for PrEP and FP are aligned for the most common FP methods (e.g., quarterly).	• There are few examples of integrated demand creation.
MONITORING & REPORTING	• Many countries have centralized national monitoring and reporting systems that support HIV and FP programs.	• Provider and facility-level monitoring and reporting tools are often siloed, with different registers for each service. • HIV prevention and FP take different approaches to follow-up and monitoring.

Icons from top to bottom created by: DEMOGRAPH, Marco Livolsi, Hea Poh Lin, StringLabs, and Gregor Cresnar from the Noun Project.

FIGURE 2 | Summary of key findings: consistent patterns across seven countries. FP, family planning; PrEP, pre-exposure prophylaxis; AGYW, adolescent girls and young women.

on PrEP, we were trying to also improve access to FP for AGYW, because that is such a big gap. But every time we included FP elements, we had to justify how it helped to meet the 90-90-90 goals. It was an uphill battle."

In terms of resource management, most of the countries included in this analysis have centralized public procurement systems that manage both PrEP and FP commodity procurement. However, siloed funding results in parallel systems for commodity procurement and distribution, creating a barrier to integration. An implementing partner from Lesotho highlighted the challenges that siloed resource management systems can have throughout the supply chain: "Integration would be ideal, but commodities are our biggest challenge. In our area, we are responsible for PrEP implementation, and another NGO is responsible for FP implementation. So, the district manager will not allow us to get FP commodities. For now, we have trained providers to deliver both PrEP and FP, but we cannot get FP commodities. It requires coordination across multiple units within the Ministry of Health, and those silos then flow down to the service point." While this example focuses on the integration of FP into PrEP service delivery, it nonetheless offers insight into supply chain challenges faced when integrating HIV prevention and FP services.

Service Delivery

There are several models for PrEP-FP integration, each of which has benefits and challenges (see **Figure 3**) (25). One model is to equip FP providers to offer both FP and PrEP services in a single visit. This is the most streamlined model from the end-user perspective, because it requires only a single visit to a provider to access a complete range of services. In this model, however, FP providers must provide HIV testing services (HTS), carry out HIV risk assessment and PrEP baseline assessment, and provide PrEP counseling and services. To do so effectively, FP providers must have the necessary training, mentorship, and supervision on HIV prevention and PrEP specifically. HTS and PrEP services would also need to be included in job descriptions, standard operating procedures, and job aids for FP providers. In the high-volume facilities where PrEP is most likely to be available, this model carries a high risk of disrupting FP service delivery because it requires more time from FP providers, diverting their time from provision of contraceptive services. In low-volume or rural settings, where providers already provide a range of integrated services, including FP and HIV prevention, this model could be effective. However, it was rarely employed to support integrated PrEP-FP service delivery in the seven countries.

Another model is to offer both FP and PrEP services in a single facility or community-based setting, with systems of referrals between different providers and service delivery points. In this model, FP providers make referrals to PrEP providers for those who need both services. Referrals can be made early in the process—for example, a referral for HTS—or later, for example, with an FP provider conducting HTS and HIV risk assessment, and then making a referral to a PrEP provider for PrEP counseling, eligibility determination, commodity provision, records management, and follow-up care. One way many programs were operationalizing this model was to have a dedicated PrEP provider available to screen, counsel, and support PrEP clients in FP settings. This approach supports integrated service delivery for end users without requiring as much integration of back-end systems, including funding and monitoring and reporting. Some programs employing this second model were also using referrals with a "fast-track option" that allows clients to avoid waiting in multiple queues to help improve end-users' experiences.

While co-locating services offered by different providers and providing structured referrals is not as streamlined for end users as the first model, it is another way of operationalizing integration at the facility and provider levels. Elements of this second model are already in place in many of the countries included in this analysis: HTS is widely available in FP settings and HIV risk assessment is part of standard practice for FP visits in more than half of the countries. As such, this is the most commonly adopted integration model across countries, with a particular focus on reaching HIV-negative AGYW. As a stakeholder in Uganda noted, "Most FP providers have basic training on HCT [HTS], but it does not include PrEP yet. With limited resources, we are rolling out PrEP training in FP settings specifically in the facilities or geographies where we will get maximum benefit, with a focus on AGYW."

A third model is to offer both FP and PrEP services in the same facility or setting at the same time, but without a structured referral system. This approach could include, for example, coordinating dates and locations for community-based PrEP and FP services. Although this model might be the easiest to implement, it offers less efficiency from the end-user perspective. For example, a collaboration between two implementing partners to offer community-based PrEP and FP services in Lesotho demonstrates some of the challenges: "We are trying to collaborate to co-locate services so that clients can move from tent to tent, but we have not seen good results because clients do not want to go and join another queue and see a new face."

Some integration models may require significant changes at the point of service delivery, as is often seen in programs led by implementing partners or specific adolescent-friendly services that are designed to offer a "one-stop shop" approach. In these settings, programs and facilities were also testing approaches to minimizing burdens on providers and disruption of existing services, including shifting some tasks to cadres of lay healthcare workers or using self-administered risk assessments and HIV tests. As a stakeholder in Kenya noted, "FP services typically quickly dispense boxes of contraceptive pills. Incorporating something that takes 20 to 30 minutes per client is a lot. Having some way to do screening before getting to the provider helps. We are also looking to implement HIV self-testing, so that women can take an HIV test as they are waiting for FP services to reduce health personnel bottlenecks."

PrEP Use

Integrated demand creation for both PrEP and FP is critical, to build awareness of PrEP as an intervention and a component of an integrated service package, and to foster awareness of its availability in FP settings. Integrating demand creation efforts

MODEL 1 : One provider provides a range of FP and HIV services

- In the **high-volume, Tier I, or central hospitals or NGO-run programs** where PrEP is most often available, HIV or FP providers receive support to transition to integrated service delivery, with integrated training, job aids, risk screening and counseling, and monitoring; task-shifting and other methods are leveraged to reduce the burden on providers. This model is not frequently seen in practice.
- In **low-volume clinics, at the district or community level**, clinicians typically cover a broad range of healthcare services, including HTS and FP. Low access to laboratories for testing limits the ability to add PrEP services, especially if creatinine tests are required.

MODEL 2 : One facility provides a range of FP and HIV services with strong referral mechanisms

A more common model of integrated service delivery at **larger health facilities** is when specialized service providers continue to provide separate HIV or FP services (e.g., a PrEP provider is "embedded" in FP services or facilities offer multiple services), but investments are made to support effective referrals (e.g., FP providers conducting HIV risk-screening, lay counselors supporting counseling, counselor-accompanied referrals, and/or fast-track mechanisms).

MODEL 3 : Separate but co-located FP and HIV services are offered simultaneously

A good first step is to ensure services are offered in the same place at the same time (e.g., at the **same facility and/or coordinated community-based programs**); however, experience suggests this model requires strong referrals and/or fast-track mechanisms to effectively support clients to take up multiple services.

Icons from top to bottom created by Wilson Joseph from the Noun Project, Zaenul Yahya from the Noun Project, and public domain.

FIGURE 3 | PrEP-FP integration models. PrEP, pre-exposure prophylaxis; NGO, nongovernmental organization; FP, family planning; HTS, HIV testing services.

can also be cost-effective and mutually beneficial for PrEP and FP goals, because both services reach similar populations and seek to expand access to and use of preventive health services, often with a lens to strengthening women's empowerment and health autonomy. South Africa, for example, has established the B-Wise (29) platform focused broadly on AGYW health, which could serve as a platform for both FP and PrEP. As a stakeholder from South Africa shared, "On the 'B-Wise' site, people can come with questions and talk to a chatbot or a helpline, and then get linked to a healthcare provider. The whole approach is to promote self-care around different needs. Not just a pregnancy test, but also STI screening and HIV prevention, so that young people can understand their comprehensive needs." Although all the countries included in this analysis had some demand creation investments for PrEP or FP, integrated approaches to demand creation were rare.

Several projects offering integrated PrEP-FP service delivery allow for multi-month dispensing of PrEP so users can align clinic visit schedules for quarterly HIV tests and PrEP and short-acting FP refills. This approach is particularly helpful for those who use contraceptive pills or injections but is less useful for those who use long-acting methods, such as an implant or intrauterine device. Across the seven countries, more than 50% of women and girls of reproductive age used the contraceptive pill or injection; however, to fully support women's needs for integrated services, PrEP-FP integration models must develop an efficient approach to follow-up for women using long-acting or permanent contraception.

Monitoring and Reporting

Differences in the nature of PrEP and FP service delivery are also reflected in monitoring and reporting for these services. None of the seven countries had a fully integrated monitoring and reporting system for PrEP and FP services. At the facility level, this means that providers offering integrated services must complete multiple, separate registers during a single visit to

account for the different services provided. As a stakeholder in Zimbabwe noted, "The registers should be integrated so that providers can complete one register across all services. As long as they are separate, healthcare providers will continue to see different activities [PrEP provision] as add-ons and not core to their work." Some programs did record a limited number of indicators on integrated services, such as tracking FP users who received HTS at their last visit.

This challenge is amplified within national health information systems, where PrEP and FP services are monitored and assessed very differently. PrEP programs aim to track clients through individual client records, and follow-up is managed to achieve quantitative site-level targets for initiation and continuation. Due to the emphasis on the voluntary nature of FP services, contraceptive clients are rarely monitored, and programs use aggregate metrics to track overall numbers of FP users and contraceptives dispensed rather than progress toward site-level targets. As a global expert noted, "There is generally little data or recordkeeping for FP services. FP clients may have a services card and FP sites have registers, but there are no individual client files. On the PrEP side, there is a lot of paperwork. How can these be accommodated in FP services? In FP rooms? Who will be responsible? PrEP may provide an opportunity to improve monitoring of integrated services, but it will require a lot of support." Stakeholders noted that emerging investments in individual-level electronic medical records will help support monitoring and recordkeeping across services in the future.

DISCUSSION

Integrated service delivery is a complex, multifaceted undertaking that requires a system-wide approach (15). This paper describes a PrEP-FP integration framework that delineates enablers of and barriers to PrEP integration with FP services across five domains. When the framework was applied as a matrix across seven countries in East and southern Africa, patterns emerged revealing critical gaps that may hinder progress toward PrEP-FP integration. For example, many of the countries had established policy frameworks to support integrated service delivery, but areas such as coordination, resource management, provider training, demand creation, and monitoring and reporting had yet to be addressed. While support for PrEP-FP integration was strong, implementation examples were limited to a few programs, many of which were funded through research programs or non-governmental organizations (NGOs) rather than the public sector. Given the relative newness of PrEP, few studies evaluating the integration of oral PrEP with FP services in Africa have been published (21, 30). Further research is needed to determine whether PrEP-FP integration can help overcome barriers to PrEP uptake and continuation, and whether integrated delivery impacts the quality of care for FP and HIV prevention services.

Plans and Policies

Despite PrEP being a relatively new service, many countries are moving forward with national policies and guidelines to support PrEP-FP integration, building on broader efforts to promote HIV-SRH integration across services and populations. However, as highlighted in the PrEP-FP integration framework, efforts are still needed at the policy level to ensure coordination and collaboration between HIV/PrEP and SRH/FP departments, along with identifying which national body or bodies will be responsible for PrEP-FP integration. Given the decentralization of services to the district level in most countries, and even to the facility level in some countries, it is critical that any integration efforts reach the subnational level. Without the constructive engagement of local government officials, health providers, and community stakeholders, it is unlikely integration will succeed.

Resource Management

Resource management is a more challenging domain because investments are needed for commodities and integration of supply chains, training, demand creation, and monitoring and evaluation systems. HIV programs are generally better funded than SRH/FP programs, and government and donor funding for these programs is often siloed; hence, coordination across donors, ministries of health, and subnational actors is essential to support PrEP-FP integration. Recent experience with the integration of HIV testing into FP services suggests that integration of HIV services with FP is feasible, and governments should consider building on these efforts to support PrEP-FP integration (18).

Service Delivery

Similar to broader SRH-HIV integration efforts, PrEP-FP integration will likely rely on a variety of integration models ranging from one-stop shops to enhanced referrals (17). Determining which model fits best in a given context will require the thoughtful engagement of policymakers, service providers, program managers, and clients, together with consideration of other FP integration priorities beyond PrEP (e.g., STI screening) and population-specific needs. Most countries in our analysis had made progress integrating HIV testing into FP services, which provides a natural link to then provide counseling and offer PrEP to those who test negative. Previous efforts at SRH-HIV integration found that providers miss opportunities to integrate care and programs face challenges to maintaining quality of care with integrated service delivery (24). As identified in the PrEP-FP integration framework, critical areas that need to be addressed to overcome these pitfalls include provider training, ongoing mentorship, and capacity building for ancillary staff (i.e., lay counselors, peer navigators, and community health workers). Care must be taken to ensure that the large majority of women of reproductive age who seek FP services—who may not need PrEP services—are not disenfranchised by the inclusion of the new service or subjected to a lower quality of care due to increases in client volume or provider workloads.

PrEP Use

To support PrEP use for those accessing PrEP in FP settings, engagement with clients must be integrated across the client journey—starting with demand creation efforts and continuing through to follow-up care. While integrated messaging has the potential to be more cost-effective and mutually beneficial for

both HIV prevention and FP goals, the challenge remains that demand creation efforts are not well-funded or sustained in either health area. Nevertheless, governments can influence a more integrated effort, as evidenced in the South Africa B-Wise example described above. Additional efforts are needed to align PrEP refill schedules with FP services and to integrate outreach (e.g., by peer ambassadors) and counseling to support informed decision making and help reduce discontinuation of both PrEP and contraception.

Monitoring and Reporting

The difference in intensity of data reporting requirements (e.g., PEPFAR requirements for PrEP compared to demographic and health management information system requirements for FP) and the common use of separate registers for different services makes it difficult to integrate monitoring and reporting. Initially, the PrEP monitoring approach in sub-Saharan Africa mirrored that of HIV treatment services rather than those of comparable prevention models such as FP. Shifting this mindset will require intentional effort by governments and donors to consider alternative requirements for and methods of PrEP reporting. At the same time, many unanswered questions about PrEP remain, particularly as new products come on the market and as PrEP-FP integration efforts are nascent. Early PrEP-FP integration should be assessed to inform ongoing efforts, and investments will be necessary to support the additional data collection needed to monitor PrEP-FP delivery. A recent review highlights the potential of electronic health information systems to facilitate coordination across services, which may be an effective solution for monitoring and reporting of integrated health service delivery (31).

LIMITATIONS

The PrEP-FP framework described in this paper is limited by the fact that it was a high-level programmatic effort, with a focused desk review and expert interviews in a select group of countries in East and southern Africa. The experts consulted were a small, convenience sample including varied representation across seven countries, only one national policymaker, no providers, and six of the authors, which limits the generalizability of this programmatic effort. The framework focuses specifically on integrating PrEP into FP services and does not examine barriers and enablers associated with integrating PrEP into other areas, such as maternal health and child health services. It also does not address whether PrEP-FP integration can increase PrEP uptake. The framework was developed with a lens on general-population women and AGYW; specific integration needs for key populations, such as female sex workers, deserve further attention. Finally, while the experts interviewed reflected on a wide range of service delivery approaches, the primary emphasis was on facility-based rather than community-based delivery, given that most PrEP is currently provided through health facilities. However, community-based delivery of PrEP is expanding, and further exploration of the enablers of and barriers to PrEP-FP integration in these settings is warranted.

CONCLUSIONS

While there is broad interest in integrating PrEP into FP services, there are key differences between these services that manifest not only at the site of service provision but also throughout different elements of the health system. The PrEP-FP integration framework we developed highlights the multiple system factors that need to be in place to facilitate integrated service delivery. The HIV prevention field is expanding rapidly, with new products on the near horizon and the potential for at least one antiretroviral-contraceptive multipurpose technology (MPT) to enter the market in the next 5 years. Addressing PrEP-FP integration now will facilitate the introduction of MPT products in the future. At the same time, focusing these efforts on achieving a "win-win" for both FP and PrEP (HIV) is a key consideration in moving integration beyond the conceptual level to full implementation. Evidence demonstrating that client use of both services increased, client satisfaction improved, and efficient and feasible approaches to service management and provision were identified would make the path to wider-scale adoption of PrEP-FP integration more likely.

The full PrEP-FP integration framework and matrix, publicly available on the PrEPWatch website, is a programmatic tool that may be adapted to different settings, be these country-specific or other types of HIV-SRH integration efforts (25). Our hope is that the framework can help policymakers and program managers take a comprehensive, systems approach to integrated PrEP-FP delivery, assess opportunities for progress, and anticipate key challenges in their settings.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.prepwatch.org/wp-content/uploads/2020/07/OPTIONS_PrEP_FP_IntegrationAnalysis.pdf.

AUTHOR CONTRIBUTIONS

NB conceptualized the framework, conducted the desk review, interviews and analysis, contributed to writing the manuscript, and interpretation of the findings. KT, RW, RR, SM, IM, JR, and JM contributed to the adaptation of the framework, the writing of the manuscript, and interpretation of the findings. JS contributed to the writing of the manuscript and interpretation of the findings. All authors contributed to the article and approved the submitted version.

FUNDING

This work was made possible by the generous support of the American people through the U.S. Agency for International Development (USAID) and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). It is the result of a collaboration between the Optimizing Prevention Technology

Introduction On Schedule (OPTIONS) Consortium and the Collaboration for HIV Prevention Options to Control the Epidemic (CHOICE). Financial assistance was provided by USAID (https://www.usaid.gov/) to FHI 360 under the terms of Cooperative Agreement no. AID-OAA-A-15-00035 and Cooperative Agreement no. 7200AA19CA00002.

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Disclaimer: The contents of this document are those of the authors and do not necessarily reflect the views of USAID or the U.S. Government.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

PERSPECTIVE
published: 23 June 2021
doi: 10.3389/frph.2021.682689

The Promise of the Dual Prevention Pill: A Framework for Development and Introduction

Barbara A. Friedland[1*†], *Sanyukta Mathur*[2†] *and Lisa B. Haddad*[1]

[1] Population Council, Center for Biomedical Research, New York, NY, United States, [2] Population Council, HIV and AIDS Program, Washington, DC, United States

Women of reproductive age need multipurpose prevention technology (MPT) products to address two overlapping health risks: unintended pregnancy and HIV. Currently, condoms are the only available MPT, however male condoms are not within the control of a woman, and the use of female condoms has been limited by low acceptability and cost. Oral pre-exposure prophylaxis (PrEP) is highly effective for HIV prevention, yet uptake and adherence among women have been low to date. Women globally need more options for HIV and pregnancy prevention. Several MPTs for simultaneous HIV and pregnancy prevention are in various stages of development and clinical testing, although most are many years away from market launch. A dual prevention pill (DPP), a daily oral pill combining oral contraceptives and PrEP, both of which are licensed, approved products in many low- and middle-income countries (LMIC), is likely to be the fastest route to getting an MPT product into the hands of women. The DPP is one option that could enhance method choice, particularly for women who are already using oral contraceptives. By leveraging the oral contraceptive market and reaching women currently using condoms or with an unmet need for contraception, the DPP has the potential to increase the uptake of PrEP. The successful rollout of the DPP will require careful consideration of user-, provider-, and product-centered factors during product development and introduction. Early attention to these interrelated factors can help ensure that the DPP has the ideal characteristics for maximum product acceptability, that effective and quality services are designed and implemented, and that users can make informed choices, demand the product, and use it effectively. The proposed framework outlines key considerations for the effective development and introduction of the DPP, which could also facilitate integration models for future MPTs.

Keywords: HIV prevention, multipurpose prevention technologies, PrEP-FP integration, integrated healthcare, oral contraceptives, PrEP, dual prevention pill, informed choice

OPEN ACCESS

Edited by:
Renee Heffron, University of Washington, United States

Reviewed by:
Lisa Lazarus, University of Manitoba, Canada
Kathryn Therese Mngadi, Aurum Institute, South Africa

***Correspondence:**
Barbara A. Friedland
bfriedland@popcouncil.org

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *19 March 2021*
Accepted: *25 May 2021*
Published: *23 June 2021*

Citation:
Friedland BA, Mathur S and Haddad LB (2021) The Promise of the Dual Prevention Pill: A Framework for Development and Introduction. Front. Reprod. Health 3:682689. doi: 10.3389/frph.2021.682689

INTRODUCTION

Women worldwide are confronted with two significant, overlapping health risks: unintended pregnancy and HIV/sexually transmitted infections (STIs). More than 218 million women in low- and middle-income countries (LMICs), including 26% of women in sub-Saharan Africa (SSA), have an unmet need for contraception (1). Although, significant advances have been made in HIV treatment and prevention over the last decade, HIV/AIDS continues to be a leading cause

of death among women of reproductive age globally (2). Nearly 800,000 women aged 15 and above were newly infected with HIV in 2019 (2). In SSA, women and girls accounted for 59% of all new HIV infections, and adolescent girls and young women (AGYW) aged 15–24 years old were twice as likely to be living with HIV compared to their male counterparts (2). Despite substantial efforts by the global health community to integrate HIV and family planning service delivery, given the simultaneous risks of HIV infection and unintended pregnancy (3–7), for most women in LMICs, these services remain siloed (8).

Multipurpose prevention technology (MPT) products offer the potential to integrate sexual and reproductive health services and meet the diverse health needs of women over their reproductive lifespans (9–13). A growing body of literature indicates that a majority of women would be more interested in using an HIV-prevention method that also prevents pregnancy since preventing unintended pregnancy is often their primary concern (14–16). In a recent study from South Africa, significantly more women were interested in using the SILCS diaphragm together with a vaginal microbicide as an MPT (68%) vs. SILCS alone for contraception (17%) or a microbicide alone for HIV prevention (14%) (17). In the Share.Learn.Shape global internet survey, 83% of women preferred an HIV/STI prevention method that also prevented unintended pregnancy vs. a product for disease prevention alone (14). In the same survey, there was high interest in a range of MPT products, including on-demand, daily, and long-acting methods. Furthermore, family planning is more acceptable than disease prevention in many communities. For example, some participants in the ASPIRE trial evaluating the safety and efficacy of the dapivirine intravaginal ring (IVR) reported telling their partners that they were using a new contraceptive vs. a product for HIV prevention (18). Currently, condoms are the only available MPT, yet male condoms are not within the control of a woman, and many women risk gender-based violence by merely suggesting condom use (19). The uptake of female condoms has been limited by cost, access, and acceptability issues (including the objections of male partners) (20, 21). MPTs could help to overcome barriers to negotiating HIV prevention and adherence issues related to stigma and gender dynamics seen in trials of microbicides and oral pre-exposure prophylaxis (PrEP). Several MPTs for simultaneous HIV and pregnancy prevention are in various stages of development, however, most are likely to be many years away from market launch (22, 23). A dual prevention pill (DPP) containing PrEP co-formulated with a combined oral contraceptive (COC) is likely to be the fastest route to the introduction of a female-initiated MPT because PrEP and generic COCs are both licensed, marketed products that are widely available in many LMICs (24).

THE PROMISE OF THE DPP

We believe that the DPP could vastly increase the number of women protected by PrEP as well as potentially increase the number of women using contraception. In the family planning arena, COCs continue to be the first-choice method for many women, despite the availability of longer-acting formulations. COCs are currently used by 151 million women worldwide (25), and over 5 million women in 15 SSA countries with a significant HIV epidemic (26). Oral PrEP, however, has had poor uptake and adherence among women to date, despite being highly effective for HIV prevention (27–29). Stigma is often cited as a reason for non-use of PrEP (30–33); women fear being regarded as HIV-positive or promiscuous if they are seen taking Truvada®, the same antiretroviral (ARV) drug that is used for HIV treatment. Many women have voiced concerns about the consequences PrEP will have on their sexual relationships, as PrEP use often signals mistrust and infidelity, which can potentially result in relationship dissolution or violence (33, 34). We hypothesize that the DPP has the potential to reduce the stigma associated with PrEP-only products by adding the justification of providing contraception, as many women find it easier to negotiate contraception vs. HIV/STI prevention with their partners or have a shared desire for pregnancy prevention. Furthermore, we believe women's motivation to prevent pregnancy may drive adherence to PrEP when combined in a DPP. We estimate that by leveraging the COC market and reaching women currently using condoms or with an unmet need for contraception, between 250,000 and 1.25 million women per year in 15 SSA countries might choose to switch to the DPP, which could increase the number of women using PrEP by up to 10 times (26).

DPP DEVELOPMENT PATHWAY

The first generation DPP in development combines the active pharmaceutical ingredients (APIs) in a generic COC [150 mcg levonorgestrel (LNG), 30 mcg ethinyl estradiol (EE)] with the APIs in Truvada® [300 mg tenofovir disoproxil fumarate (TDF), 200 mg emtricitabine (FTC)] or generic equivalents (35). The DPP regimen is intended to align with a 21/7 COC regimen containing 21 tablets with active COCs and PrEP, and 7 tablets containing only PrEP (vs. placebo pills in current 21/7 COC regimens). Because PrEP and COCs are already licensed, marketed products, the development pathway (**Figure 1**) is streamlined, requiring only a bioequivalence (BE) study rather than long, expensive Phase 3 safety and efficacy trials. In a standard BE study, healthy volunteers are enrolled in a crossover design to compare and ensure that the pharmacokinetic profile of the new drug (the DPP in this case) matches that of the reference products (Truvada and COC). Ideally, the DPP will be marketed in blister packaging to look as similar as possible to a contraceptive regimen (recognizing that Truvada is a much larger tablet than any COC). Both Viatris and the Population Council are developing DPP formulations, with potential approval as early as 2023. Given the short timeline for development, preparing for an introduction now is critical to maximizing the potential reach of the DPP.

FRAMEWORK TO GUIDE DPP PRODUCT DEVELOPMENT AND INTRODUCTION

The development of new technology in and of itself does not imply demand, access, or use (36). The social and structural context of product provision can have an outsized influence on

FIGURE 1 | DPP Development Pathway.

informed choice, product uptake, and effective and sustained use. Furthermore, there has been a growing recognition that end-user perspectives are important in the product development cycle and can help identify modifiable factors to inform formulation scientists about product attributes that may need optimization to enhance uptake, acceptability, and effective use (37–39). We propose a conceptual framework for DPP development and introduction in which user-, provider- and product-centered factors interact to influence user acceptability, intention-to-use, and, ultimately, product use (**Figure 2**). We used Ajzen's Theory of Planned Behavior (TPB) to guide the outcome of interest, the behavioral intention to use the DPP, as well as the framing of user-centered factors (40). We used previous frameworks on MPT development (10), PrEP introduction (41, 42), and contraceptive development and introduction (36, 43) to articulate the provider- and product-centered factors. The user-, provider- and product-related factors are situated within their socio-ecological levels, which interact to influence the intention of women to use the DPP.

In our framework, the aim is for the ***individual user*** to be enabled ***to make informed choices for HIV and pregnancy prevention*** options in choosing the DPP. According to the TPB, attitudes, subjective norms, and perceived behavioral control of an individual influence their behavioral intentions. In our framework, the characteristics of women, as well as their partnership dynamics, and their broader family and community context shape these intentions. ***The characteristics of women*** include life stage (such as age, marital status, and parity), knowledge (such as awareness of PrEP efficacy), perceived risk of acquiring HIV or having an unintended pregnancy, attitudes (about COCs/PrEP, perceived impact of acquiring HIV or having an unintended pregnancy), and experiences (such as contraceptive/PrEP use history). ***Partner dynamics*** that are likely to influence DPP use include the type of partner(s) that women have; the HIV status of the partner, risk behaviors, awareness, and approval of the DPP or other prevention products; interpersonal power and communication within relationships; and perceived or actual impact of the DPP on sexual activity and sexual pleasure (for women and their partners). Finally, in most settings, ***family and community context*** and prevailing social and gender norms (such as community perception of fertility, childbearing, and family size), perceptions of the DPP and other prevention products, norms about contraceptive and PrEP use, and HIV-related stigma will likely influence an individual user's intention to use the DPP.

Provider-centered factors include elements that are important for ensuring the effective provision of quality services for the DPP. These include the ***healthcare providers*** and their knowledge about the DPP (such as indications, dosing regimen, counseling on side effects), attitudes, perspectives, and biases (such as frowning upon adolescent sexuality or favoring long-acting contraceptive methods for their clients), and experiences (such as the prior provision of PrEP or contraception, counseling users on adherence). Additionally, ***the service delivery setting and broader health system infrastructure*** within which healthcare providers operate are likely to influence client-provider interactions and the equitable access of women to the DPP. For example, it is critical to consider the type of training and support available to healthcare providers, their actual and perceived workload and responsibilities, product availability, and client flow at the ***service delivery setting***. Similarly, at the ***health system*** level, product costs and financing, delivery platforms, task shifting (such as from clinicians to nurses or paramedical professionals, increased emphasis on self-care to lessen the burden on the health system), and demand generation for the DPP are just some of the key factors to consider for effective provision of the DPP.

Finally, we consider the ideal characteristics for DPP acceptability, centered around three key ***product attributes***, the dosing regimen (daily), the APIs (including contraindications and side-effect profiles of the contraceptive hormones and ARVs), and the physical properties (tablet size). Layered on top of the product attributes are the ***policies and regulations*** (such as consent laws, regulatory approvals, and financing considerations) and the broader ***scientific landscape*** (such as product effectiveness relative to other products, medical screening and monitoring, and outcomes research) that are likely to influence DPP acceptability.

The three factors outlined in the framework are interrelated and dynamic; a shift in any single factor is likely to influence the intention to use the DPP by the individual user. For example, as next-generation DPPs are considered with different formulations or with different dosing regimens, service provision and user perspectives may also shift. Further, the actual use of the DPP and the subjective evaluation of that experience by an individual, the risks and benefits, will in turn influence behavioral intentions to continue using the DPP.

DISCUSSION

After decades of efforts to better integrate HIV and reproductive health services, the advent of novel MPTs that help women avoid unintended pregnancy and HIV may pave the way for providing more comprehensive care for individuals. The DPP offers one such potential for rapid development, introduction to the market, and expanding the method mix and choice for individual users.

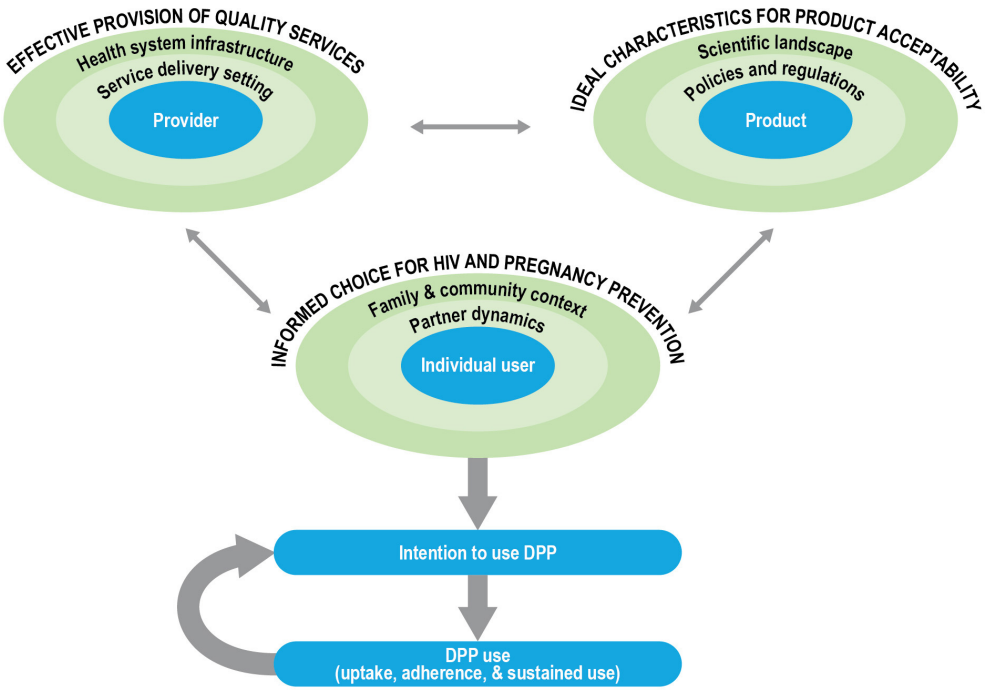

FIGURE 2 | Framework for DPP development and introduction.

At the same time, a systematic and coordinated approach to evidence generation is needed across product developers, socio-behavioral researchers, program developers, end-users, healthcare providers, and key stakeholders to maximize the potential impact of the DPP (44, 45). As we lay out in the proposed framework, critical questions must be assessed for user-, provider-, and product-centered factors to facilitate the effective, efficient, and equitable introduction of the DPP.

End-User Research

Evidence shows the importance of early engagement with potential end-users to identify facilitators and barriers to product acceptability, intention to use, product uptake, and effective use. For example, while it is assumed that combining HIV prevention with contraception will reduce the stigma associated with PrEP, empirical data will be needed to demonstrate that this is the case. Further, it will be important to ensure that rates of unintended pregnancy do not increase among COC users who switch to the DPP. For example, women taking COCs are advised to take two pills if they miss a dose; however, that is not the recommendation for PrEP and guidelines will need to be developed regarding missed doses. Counseling messages will need to be developed to position the DPP within the contraceptive method mix and ensure shared decision-making between providers and users for women to select the method that best matches their prevention priorities. Further, as with other PrEP products, women will need counseling on how to avoid STIs. Appropriate tools will need to be adapted and developed, including interactive client pre-counseling self-assessments to educate and counsel women about the anticipated side effects, risks, and benefits of the method to support effective and sustained use. Additional efforts will be needed to strategically engage male partners without diminishing women's autonomy (33, 46–48). End-user engagement will be key to inform demand creation, branding and marketing strategies, tools to support end-users, and implementation plans.

Engaging Providers

Providers play an instrumental role in influencing the demand, uptake, and effective use of new products. From the perspectives of reproductive health/family planning providers, the DPP or similar technologies introduced through family planning clinics could enhance integration but could also be a burden. The DPP may require additional HIV- or PrEP-related medical screening, testing, and monitoring that may be perceived to be outside of the scope of or burdensome to many family planning and primary healthcare providers. Concerns that the introduction of the DPP could influence client uptake of long-acting contraceptive methods need to be mitigated by developing guidance for healthcare providers on how to support their clients to effectively meet their HIV and pregnancy prevention goals through a shared decision-making model of counseling and provision that maximizes client autonomy and informed choice to alleviate the potential for coercion. In particular, it will be important to explore the knowledge and attitudes of providers about the DPP, which will influence the access of women and the messages regarding the DPP. Mechanisms to effectively engage and support healthcare providers, including additional

training and resources, within their eco-system will be critical to informing service delivery points about the need for the DPP.

Policy and Regulatory Considerations

Finally, to better understand how this new technology will be integrated within healthcare systems, further elucidation will be needed on product financing, market shaping and sizing, and value for money analyses. For the product developers, expanding beyond the current formulations of the DPP may help to further expand the market. Creating a co-formulated DPP with Descovy® [tenofovir alafenamide (TAF) and FTC], once it is approved for use as PrEP in heterosexual women, may be more appealing to women because of its smaller size. Alternative contraceptive regimens, such as extended cycles or progestin-only pills, may simplify the DPP regimen, offer more options, including for those with contraindications to estrogen-containing products (such as post-partum women) or those who desire amenorrhea (49, 50), and address challenges in counseling messages around missed doses for COCs vs. PrEP. Incorporating end-user preferences for the ideal DPP characteristics into the product development process is likely to enhance uptake.

Conclusion

We have laid out a broad scope of work, yet experience has shown us that asymmetric attention to any of these factors can lead to ineffective product uptake (36, 51). The proposed framework for guiding DPP development and introduction will continue to be important after the initial phases of product introduction to ensure that women can safely choose, access, and use the DPP. The DPP framework could serve as a model for the integration of future MPTs, including next-generation DPP products and other formulations like intravaginal rings and implants. Lessons learned from the DPP can pave the way for new technologies that best meet the needs of women, effectively destigmatize HIV as a general aspect of comprehensive reproductive health services, and lead to efficient integration of HIV and reproductive health services.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BAF and SM conceptualized the DPP development and introduction framework and jointly drafted the manuscript. LBH is the senior author and provided strategic guidance on the development of the manuscript and the framework. All authors contributed to the writing and review of the manuscript.

FUNDING

This research was made possible by the support of the Children's Investment Fund Foundation (CIFF) (R-1903-03681) and the US National Institutes of Mental Health (NIMH) (1R34MH119982-01).

ACKNOWLEDGMENTS

We are grateful to our Population Council colleagues for their support of the DPP development work, in particular, Dr. George Creasy for spearheading the development of the DPP, Drs. Nanlesta Pilgrim and Eileen Yam for their contribution to the development of this conceptual framework, Sherry Hutchinson for graphics support, and Rebecca Brodsky for her review of the manuscript. We also want to thank our research partners at the University of Zimbabwe Clinical Trials Research Centre (Dr. Nyaradzo Mgodi, PI) and at Wits Reproductive Health and HIV Institute (Dr. Thesla Palanee-Phillips) for their collaboration on pilot DPP acceptability and adherence studies, and the members and advisors of the CIFF DPP Consortium who have contributed to our thinking about the value of this technology.

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Disclaimer: The views and opinions expressed in this paper are those of the authors and not necessarily the views and opinions of CIFF or NIMH.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

COMMUNITY CASE STUDY
published: 13 July 2021
doi: 10.3389/frph.2021.684717

Integration of HIV Prevention With Sexual and Reproductive Health Services: Evidence for Contraceptive Options and HIV Outcomes Study Experience of Integrating Oral Pre-exposure HIV Prophylaxis in Family Planning Services in Lusaka, Zambia

Margaret Phiri Kasaro[1], Ntazana Sindano[1], Manze Chinyama[1], Mayaba Mudenda[1], Florence Chilaisha[1], Joan T. Price[1,2] and Modesta Chileshe[1]*

[1] University of North Carolina Global Projects Zambia, Lusaka, Zambia, [2] Division of Global Women's Health, Department of Obstetrics and Gynecology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

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***Correspondence:**
Margaret Phiri Kasaro
margaret.kasaro@unclusaka.org

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *23 March 2021*
Accepted: *04 June 2021*
Published: *13 July 2021*

Citation:
Kasaro MP, Sindano N, Chinyama M, Mudenda M, Chilaisha F, Price JT and Chileshe M (2021) Integration of HIV Prevention With Sexual and Reproductive Health Services: Evidence for Contraceptive Options and HIV Outcomes Study Experience of Integrating Oral Pre-exposure HIV Prophylaxis in Family Planning Services in Lusaka, Zambia. Front. Reprod. Health 3:684717. doi: 10.3389/frph.2021.684717

The WHO guideline on the integration of family planning (FP) and pre-exposure HIV prophylaxis (PrEP) to enhance the health of women and adolescent girls is reflected in the Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection, 2020. There is however a dearth of data on the integration of PrEP and FP in Zambia. We describe the integration of oral PrEP in FP services using the Evidence for Contraceptive Options and HIV Outcomes (ECHO) study experience at Kamwala District Health Center in Lusaka, Zambia. The provision of oral PrEP at Kamwala started in October 2017, lasting for ∼11 months, and utilized the model where initial processes to offer PrEP were on-site followed by off-site referral to laboratory and PrEP provider services. The characteristics of 658 women who enrolled in ECHO at Kamwala are representative of women accessing FP services in Lusaka. About 644 of the enrollees were offered oral PrEP. The proportion of women accepting PrEP was low at 1.08% and the proportion of study visits at which PrEP was requested was also low at 0.57%. Those who accepted PrEP were above 20 years old, married, with at least primary education, sexual behavior, and risk comparable to decliners. The ECHO study experience indicates that the setup and integration of oral PrEP and FP services are feasible in the setting. However, uptake of PrEP was very low. Possible contributory factors were as follows: (1) timing of introduction of PrEP midway in the study, (2) PrEP being a new intervention, (3) challenges of autonomy of young women to include a daily pill into their lives and anticipated challenges to adherence because of fear of adverse events, (4) possible underdetermined risk due to use of an unvalidated risk assessment tool and assessment by health care provider vs. self-assessment, and (5) extra layer of challenges to negotiate due to needing for

off-site referrals. Following these findings, we conclude that further research through demonstration projects of integration of oral PrEP and FP may provide solutions to low uptake. This information is critical for scaling up of integration HIV prevention services and sexual and reproductive health (SRH) services.

Keywords: family planning, integration, sexual and reproductive health, oral pre-exposure prophylaxis, HIV prevention

INTRODUCTION

African women are disproportionately affected by HIV infection. Sub-Saharan Africa carries more than 70% of the global burden of infection with women bearing the brunt of this burden. In particular, adolescent girls and young women aged 15–24 years have up to eight-fold higher incidence of HIV infection compared to their male peers (1). In Zambia, the 2,018 numbers indicate that 11.3% of adults were living with HIV out of which 14.3% are women compared to 8.8% men. Adolescent girls and young women are four times at higher risk with the prevalence of 5.7% compared to their male peers at 1.8% (2).

The need for contraceptive services in Zambia is high with a total fertility rate (TFR) of 4.7 births per woman, the contraceptive prevalence rate (CPR) standing at 50%, and unmet need of 20% for married women (3). The need for contraception is likely to be underestimated as this information excludes unmarried women. Efforts to both increase provision of contraception and reduce HIV transmission among women can be delivered in one stop. Family planning (FP) clinics provide services to women at risk for acquiring HIV and could be a vehicle for providing both contraceptive and HIV prevention services (4, 5).

The HIV prevention "toolkit" comprises both behavioral and biomedical approaches. Behavioral approaches focus on reducing high-risk practices including non-condom protected sexual encounters. Biomedical HIV prevention approaches encompass a diverse array of strategies including HIV counseling and testing, linkage and retention in HIV care (test and treat), post-exposure prophylaxis (PEP), and medical male circumcision and enhanced ARV adherence among HIV seropositive individuals (treatment as prevention) (6). A recently added tool to this arsenal is pre-exposure prophylaxis (PrEP) (7, 8). Oral PrEP is the use of oral ARV medications by HIV-uninfected individuals before HIV exposure. The efficacy of oral PrEP in studies with different populations indicates higher efficacy in studies with high adherence, 42% in MSM, 62 and 75% in discordant couples, and undetermined efficacy due to low adherence in women-only studies, Fem PrEP and VOICE (9–13). Oral PrEP is, therefore, a recommended user-controlled HIV prevention strategy that has the potential to reduce new HIV infections if delivered with high coverage and if used with sufficient adherence (6, 14, 15). Interpersonal relationships and power dynamics may present challenges for women to visit health care facilities for HIV prevention services only. FP clinic visits would be acceptable reasons, and therefore, the FP clinic could be a vehicle to deliver this HIV prevention strategy to women.

The WHO has identified populations with a background HIV incidence of >3% as being at substantial risk of HIV acquisition. Other factors considered high risk include self-assessed or partner risk and being a young woman. Therefore, WHO guidance on FP and PrEP integration are that FP and HIV prevention integration is essential if the health of women and adolescent girls is to be improved (16). The National HIV/AIDS Strategic Framework (NASF) 2017–2021 of Zambia acknowledges the potential impact of PrEP particularly as an additional option in the context of combination prevention. The NASF 2017–2021 targets the prevention of HIV infection in discordant couples and key populations. This is to be achieved by implementing evidence-informed communication and advocacy strategies to increase both healthcare provider and public awareness of PrEP without stigmatizing the intervention and its potential users, nor increasing risky sexual behavior. Further, the NASF proposes integrating PrEP into other HIV prevention programs and sexual and reproductive health (SRH) services including fertility planning services and antenatal care (17). In the 2020 Consolidated Zambia HIV guidelines, scale-up and provision of PrEP are outlined. With regards to the integration of HIV prevention and FP, it states that PrEP should be provided as part of a comprehensive package that includes contraception choices (18). There is however a dearth of data on the integration of PrEP and FP in Zambia. This, therefore, is a narrative of the integration of oral PrEP in FP services using the Evidence for Contraceptive Options and HIV Outcomes (ECHO) study experience at a district health center in Lusaka, Zambia. We will describe the step-by-step processes that were followed to make oral PrEP available in the study, summarize the characteristics of all the participants on the study, characteristics of participants who were offered PrEP, those who accepted PrEP, and finally show uptake of PrEP.

CONTEXT

Setting

The oral PrEP/FP integration experience of the ECHO study described here was at the research site at the Kamwala Health Center (KHC) in Lusaka urban district. KHC is one of the 23 centers in Lusaka urban that provide primary health care to a population of over 2.7 million. These facilities provide health care services including Maternal and Child Health (MCH) and HIV prevention, treatment, and care. FP services and HIV prevention are provided in MCH and antiretroviral therapy (ART) departments, respectively, with guidance to provide choices for contraception in the ART department and offer a comprehensive

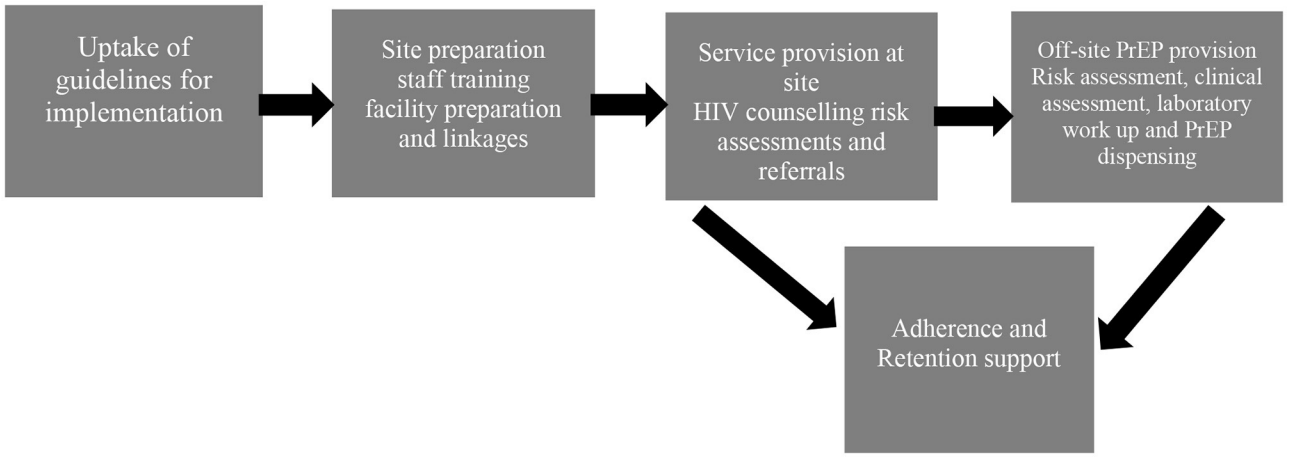

FIGURE 1 | Process of implementation of the provision of Oral PrEP in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) study at Kamwala.

HIV prevention package including PrEP to women who perceive HIV risk in the MCH department. KHC was one of the sites in the ECHO trial, a large multicenter, open-label, randomized clinical trial comparing HIV incidence among women randomized to intramuscular depot medroxyprogesterone acetate (DMPA-IM), a copper intrauterine device (IUD), and a levonorgestrel (LNG) implant (19).

Population

Lusaka is the capital city of Zambia and has a population of 2.7 million and women of the reproductive age group account for about 50% of that. KHC provides primary health services to a catchment area serving ∼100,000 population. The ECHO study recruited 658 HIV-negative women aged between 18 and 45 years old seeking effective contraception. About 644 out of the 658 women were offered oral PrEP.

Methods

The oral PrEP/FP integration process is described by a detailed account of steps taken to implement the provision of PrEP and with aid of secondary data to show characteristics of study participants, acceptors of PrEP, and uptake of PrEP. At Kamwala, PrEP was included in the HIV prevention package on October 11, 2017, after adoption as the national standard in Zambia in 2017. Risk assessment for PrEP was conducted at each visit or contact with the participant using an HIV testing counseling and risk reduction script (**Data Sheet 1**) was modified to include information on oral PrEP as per study SOP (**Data Sheet 2**).

The detailed methods of the ECHO trial have been described previously (19). Briefly, between December 2015 and September 2017, 7,829 sexually active women aged 16–35 years from four countries (Eswatini, Kenya, South Africa, and Zambia), who desired effective contraception and consented to be randomized to any of the three trial contraceptive methods were enrolled. The trial assessed HIV risk acquisition of three contraceptive methods by comparing HIV incidence among women randomized to DMPA-IM, an IUD, and an LNG implant. During the trial, the HIV prevention package provided to all women included HIV risk reduction counseling; HIV counseling and testing; sexually transmitted infection (STI) testing, treatment and partner notification of STIs; condom provision; partner HIV counseling and testing, and referral for ART in discordant couples. Oral PrEP was included in the HIV prevention package in 2016–17 following WHO recommendation in 2015. Women were followed every 3 months for a maximum of 18 months, and the study ended in October 2018. Ethics review committees provided approval for the study; written informed consent was obtained from each woman prior to commencement of study procedures.

RESULTS

The ECHO site at Kamwala commenced providing oral PrEP on October 11, 2017, up to the exit of the last participant in October 2018. **Figure 1** is showing the activities and processes for implementation of the provision of PrEP in the ECHO study at KHC:

Step 1

Adoption of WHO guidelines by ECHO study management team and uptake by the research site. The ECHO study management team repackaged the WHO recommendations so that evidence, rationale, and steps to implementation were used by ECHO sites successfully. The research sites were engaged regularly during this planning phase.

Step 2

Site preparation was the next step and involved facility readiness and staff training. In this step, we took stock of the available space, structures, and resources to allow the introduction of PrEP. The existing facilities were identified and planned for dual-use if necessary. There were no extra facilities built or renovated to provide oral PrEP. Staffing needs were assessed, and it was determined that the same study staff who were conducting research procedures that included the provision of

TABLE 1 | Characteristics of evidence for contraceptive options and HIV outcomes (ECHO) participants, of those offered oral PrEP, and of those who accepted.

	All ECHO participants (*N* = 658)	ECHO participants offered PrEP (*N* = 644)	ECHO participants accepted PrEP (*N* = 7)
Age			
Over 25 years	35.41% (*N* = 233)	35.87% (*N* = 231)	42.9% (*N* = 3)
20–25 years	50.91% (*N* = 335)	50.62% (*N* = 326)	57.1% (*N* = 4)
<20 years	13.37% (*N* = 88)	13.20% (*N* = 85)	-
Unknown	0.30% (*N* = 2)	0.31% (*N* = 2)	-
Marital status			
Married (monogamous)	90.3% (*N* = 594)	90.53% (*N* = 583)	100% (*N* = 7)
Married (polygamous)	0.15% (*N* = 1)	0.16% (*N* = 1)	-
Divorced	0.46% (*N* = 3)	0.47% (*N* = 3)	-
Never married	7.14% (*N* = 47)	6.99% (*N* = 45)	-
Separated	1.98% (*N* = 13)	1.86% (*N* = 12)	-
Education			
College degree or higher	2.89% (*N* = 19)	2.8% (*N* = 18)	-
Secondary school	52.58% (*N* = 346)	52.5% (*N* = 338)	14.3% (*N* = 1)
Primary school	38.60% (*N* = 254)	39% (*N* = 251)	85.7% (*N* = 6)
No education	5.93% (*N* = 39)	5.75% (*N* = 37)	-
Earns income			
Yes	29 % (*N* = 191)	29.35% (*N* = 189)	42.9% (*N* = 3)
No	71% (*N* = 467)	70.65% (*N* = 455)	57.1% (*N* = 4)
Sexual behavior assessment (past 3 months)			
Had a sex partner (yes)	100% (*N* = 658)	100% (*N* = 644)	100% (*N* = 7)
Had new sex partner (yes)	0.15% (*N* = 1)	0.16% (*N* = 1)	-
Had new sex partner (no)	99.85% (*N* = 657)	99.84% (*N* = 643)	100% (*N* = 7)
Had sex for money (no)	100% (*N* = 658)	100% (*N* = 644)	100% (*N* = 7)
Had anal sex (no)	100% (*N* = 658)	100% (*N* = 644)	100% (*N* = 7)
Frequency of condom use			
Always	12% (*N* = 79)	12% (*N* = 75)	42.9% (*N* = 3)
Never	24.2% (*N* = 159)	24.4% (*N* = 157)	-
Often	6.84% (*N* = 45)	6.83% (*N* = 44)	28.6% (*N* = 2)
Rarely	12.2% (*N* = 80)	12.42% (*N* = 80)	-
Sometimes	44.8% (*N* = 295)	44.8% (*N* = 288)	28.6% (*N* = 2)
Participant reported partner HIV Status			
Partner HIV negative	90.12% (*N* = 593)	89.9% (*N* = 579)	28.6% (*N* = 2)
Partner HIV positive	1.37% (*N* = 9)	1.4% (*N* = 9)	71.4% (*N* = 5)
Partner HIV status unknown	8.51% (*N* = 56)	8.7% (*N* = 56)	-
Partner has sex with others by participant report			
Yes	10.79% (*N* = 71)	10.87% (*N* = 70)	14.3% (*N* = 1)
No	34.80% (*N* = 229)	34.63% (*N* = 223)	85.7% (*N* = 6)
Don't know	54.41% (*N* = 358)	54.41% (*N* = 358)	-

HIV prevention package would be trained to provide initial steps for oral PrEP provision. The training included content on what PrEP is, requirements for the successful provision, and addressed the attitudes of the health care provider and perceptions on the use of ART to prevent HIV.

The next part was the creation of linkages by identification and partnering with PrEP providers. The facilities for pharmacy, laboratory, and clinical staff to provide PrEP were determined to not be available and not feasible to be developed at the research site. It was, therefore, decided to utilize off-site providers. This step involved the identification of providers within the government and the private sector. Although PrEP was already part of HIV management services within the government facilities, it was not yet fully implemented. At this point, a PrEP demonstration project at a health facility about 3 km from the research site was identified. Prior to the initiation of participant referrals, there were multiple communications for introductions, sharing objectives, and establishing agreements between the research site and the PrEP demonstration project.

TABLE 2 | Oral PrEP uptake.

By proportion of participants ever accepting PrEP	By repeat acceptance of PrEP
Total offered PrEP	Study visits where PrEP was offered
644 participants	2,438 visits
Participants accepting Oral PrEP	Visits with PrEP accepted
7 participants (1.08%)	14 visits (0.57%)

Step 3

Planning for activities for adherence, safety monitoring, and retention support. The staff was trained to provide information and support so that participants would adhere to PrEP as per instructions from the off-site provider, report any adverse events and continue to take PrEP as long as they needed it.

Step 4

PrEP provision steps at the research site and off-site. At the research site, HIV counseling, risk assessment, and referral steps in the cascade of PrEP provision were conducted. Referral to providers was made using a referral letter in a format that is used by the district health referral system. In addition, the research staff was able to access the medical records of the participants by using the existing permissions obtained from the District Health Office for the ECHO study in general. The participants were provided information on what to expect at the off-site provider i.e., risk assessment, clinical eligibility assessment, counseling for safety monitoring, dispensing of PrEP, adherence, and retention.

Table 1 shows the characteristics of all participants of the ECHO study at Kamwala, characteristics of those who were still on the study when PrEP was included in the HIV prevention package and, therefore, offered PrEP, and those who accepted PrEP. Among all ECHO participants, 97% (644/658) were offered PrEP. Over 80% of these were over 20 years old, 90% were in monogamous marriages, and 90% comprised those with primary and secondary education. In terms of sexual behavior and risk, all participants reported one current sexual partner, all reported no transactional sex, and 88% reported inconsistent use of condoms. The seven participants who accepted PrEP were all above 20 years old, married, with at least primary education, and sexual behavior and risk similar to decliners.

Uptake was assessed by determining the proportion of acceptors of PrEP out of all participants who were offered PrEP and the proportion of visits when PrEP was requested out of all visits after PrEP provision was implemented. **Table 2** shows that PrEP uptake by participants was low at 1.08% and the proportion of study visits at which PrEP was requested was also low at 0.57%.

DISCUSSION

The 2020 Zambia HIV guidelines for the prevention of HIV within contraceptive context are in sync with the WHO recommendation. The ECHO study experience at KHC has shown that with available internal resources and creating linkages with external resources, integration of oral PrEP and FP is feasible in our setting. However, although the process was successfully set up, uptake of oral PrEP in the study was very low and the possible explanations include individual, community, and structural factors.

The demographic characteristics and sexual behavior of women who were offered oral PrEP in ECHO at KHC were young, married, with at least primary education, and reported sexual behavior and risk included having one current sexual partner and inconsistent use of condoms. This profile of women who participated in ECHO is similar to that of women who participated in the Zambian Demographic and Health Survey, 2018 (18).

The feasibility of integration has been demonstrated within this ECHO study experience and other studies (5, 20, 21). The first step in the implementation of PrEP at KHC is representative of strong political will. There was step-by-step support from the ECHO leadership team to the ECHO sites during the process. The implementation model that we used was to maximize available internal resources and create linkages with external providers for components of the cascade that we could not provide. The internal resources include space and staff who were already providing FP and HIV risk-reduction counseling. The research site was able to initiate processes to offer and assess risk and need for PrEP by providing the relevant training to the staff. There were no changes to the physical facilities. Linkages were identified and created with providers who could assess, provide PrEP and monitor for safety. In addition to the participant report on accessing and experience of PrEP, the agreement with the external partner allowed us to access participant medical records, and therefore, we were able to provide safety monitoring, adherence, and retention support to the participants. Other researchers have described models of integration that have a PrEP-dedicated nurse stationed in the FP clinic to lead the delivery of counseling about HIV risk and provision of PrEP. Women accessing FP services would first complete other services, including HIV testing, and then referral to the PrEP-dedicated nurse would be done. PrEP visit schedules would mirror approaches used in FP clinics (5). Lessons from the contraception world emphasize that introduction of PrEP should be strategic to include a focus on the interface between PrEP and users, method mix, and delivery methods (22). In the US, strategies to increase uptake of PrEP in SRH services have been proposed in a call for leadership in the provision of PrEP to women and these include: identifying a clinic champion to motivate and lead by example, encouragement to use the many existing resources to train staff and educate clients about PrEP, utilizing PEP transition to PrEP opportunities, coupling PrEP visits with contraceptive visits, using phone contact for visits that may not require in-person visits, and engaging the community to increase demand and knowledge of PrEP (4).

Although we were able to setup the machinery to provide oral PrEP, uptake in the ECHO study at KHC was very low, lower than any uptake recorded so far. Other researchers have shown uptake between 22% within the FP context (5) and 95% within a clinical trial setting for young women (23). Assessment of risk in both studies indicated that there were high levels of self-perceived risk of acquiring HIV because of unknown HIV status of partner,

partner having other sexual partners, and inconsistent condom use (5, 23). Other factors that these studies indicate contributed to the uptake of PrEP, are the impact of community education and raising awareness of HIV prevention including PrEP done through the combined effort of study staff, community outreach teams, and advisory boards (5, 20). In the ECHO study as a whole, 622 out of 7,829 women reported using PrEP with a median duration of use at 85 days (IQR 39–96) before study exit (19).

The very low uptake could be attributed to several factors including the timing of PrEP introduction into the study, and it is a new intervention. PrEP was introduced about midway into the study after participants had "settled down" with the study procedures and interventions. This was compounded by the fact that PrEP is a new intervention. There could have been a lack of knowledge and skepticism to try the new intervention both of which could have led to low demand. However, a more compelling reason for low demand could have been because the majority of women enrolled on ECHO at KHC were young and that this age group lack gender autonomy and may be faced with challenges of incorporating a daily intervention into their lives (24, 25). Further hesitancy may have been caused by anticipated challenges of adherence such as fear of adverse reactions.

We also think that because we did not use a validated risk assessment tool that this could have led to the poor determination of risk perception. Several risk assessment tools have been developed for use with various at-risk populations including one developed and validated by Balkus et al. (26) to predict HIV acquisition among African women. The tool was based on data from trials of biomedical HIV prevention interventions (VOICE, HPTN 035, and FEM-Oral PrEP). Such tools help to accurately identify individual risk so that PrEP is offered to those who can benefit the most (27). In addition, risk assessment may also have been underdetermined due to assessment by health care workers rather than by self-assessment.

Finally, low uptake of PrEP at KHC could also be attributed to the need for off-site referral. These referrals may have presented another layer of barriers such as distance and transport costs, meeting different providers, and the need for further assessments including laboratory testing.

This work had some limitations. Although the feasibility of integrating PrEP and FP services was demonstrated, uptake was very low with only seven women accepting to use PrEP. The data presented in this study is as collected in the original study design and no further in-depth qualitative data were collected to investigate why women would decline PrEP. In addition, other measures of success of implementing PrEP in FP settings such as adherence and retention were not determined. The implementation process, successes, and challenges described here are specific to Lusaka and may not apply to different geographical settings.

This analysis joins the first few assessments of integration of oral PrEP in FP services in the setting and can be part of the evidence for conducting larger implementation projects. Following these findings, we conclude that further research through demonstration projects of integration of oral PrEP and FP is needed, and this may provide insights into low uptake. This is critical for scaling up of integration HIV prevention services including oral PrEP and SRH services.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The parent study, Evidence for Contraceptive Options and HIV Outcomes (ECHO) involving human participants was reviewed and approved by University of Zambia Biomedical Research Ethics Committee and University of North Carolina Institutional Review Board. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK drafted the initial manuscript. NS analyzed the data. All the authors have read the manuscript, provided critical review, and approved the final manuscript.

FUNDING

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial was funded by Bill and Melinda Gates Foundation (Grant Number INV-006860), US Agency for International Development and the President's Emergency Plan for AIDS Relief, Swedish International Development Cooperation Agency, South African Medical Research Council, and UN Population Fund.

ACKNOWLEDGMENTS

We also thanks to the members of staff who worked hard and contributed to the integration of Oral PrEP and family planning (FP) in the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial at Kamwala Health Center (KHC).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2021.684717/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

ORIGINAL RESEARCH
published: 14 July 2021
doi: 10.3389/frph.2021.684114

Uptake of Contraception Among Adolescent Girls and Young Women PrEP Clients: Leveraging the Opportunity to Strengthen HIV and Sexual and Reproductive Health Integration

Melanie Pleaner[1], Zukiswa Fipaza[1], Khuthala Mabetha[1], Letitia Greener[1], Sydney Ncube[1], Vusile Butler[1], Mags Beksinska[2] and Saiqa Mullick[1]*

[1] Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa, [2] MatCH Research Unit, Department of Obstetrics and Gynecology, Faculty of Health Sciences, University of the Witwatersrand, Durban, South Africa

OPEN ACCESS

Edited by:
Renee Heffron, University of Washington, United States

Reviewed by:
Maria Pyra, Howard Brown Health Center, United States
Daniel Were, Jhpiego, Kenya

***Correspondence:**
Melanie Pleaner
mpleaner@wrhi.ac.za

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *22 March 2021*
Accepted: *10 June 2021*
Published: *14 July 2021*

Citation:
Pleaner M, Fipaza Z, Mabetha K, Greener L, Ncube S, Butler V, Beksinska M and Mullick S (2021) Uptake of Contraception Among Adolescent Girls and Young Women PrEP Clients: Leveraging the Opportunity to Strengthen HIV and Sexual and Reproductive Health Integration. Front. Reprod. Health 3:684114. doi: 10.3389/frph.2021.684114

The introduction of oral pre-exposure prophylaxis (PrEP) for HIV prevention was a major breakthrough in South Africa (SA). While the initial introduction focused on issues such as the development and implementation of new guidelines, supply, and the development of demand creation strategies, the need to integrate PrEP services with sexual and reproductive health (SRH) services has gained traction both globally and locally. Project PrEP was implemented in eight healthcare facilities and four mobile clinics in three provinces in SA. Using monitoring data from across the four project clusters, and 4,949 clients, over a 21-month period, we conducted an analysis of baseline routine monitoring data to examine contraceptive uptake in adolescent girls and young women (AGYW) initiating PrEP at project sites. Two-thirds of women (62.3%, $n = 3,083$) reported the current use of contraception at baseline, with the most commonly used methods being hormonal injectables (61.9%, $n = 1,829$) and male condoms (19.4%, $n = 575$). A third (32.3%, $n = 603$) of the non-contraceptive users accepted a method at PrEP initiation. From a total of 1,007 (32.7%) current contraceptive users at baseline, 865 (85.9%) chose the same or a different method at this visit. The method uptake at PrEP initiation increased the overall contraceptive prevalence by 12.2 to 74.5%. Data indicated that over a third (38.8%, $n = 725$) who were not using a method at baseline described themselves as consistent condom users. Although a major focus of the project was on PrEP service provision, all women were counseled and offered contraceptive services. The acceptance of a method by a third of non-users was promising; however, more understanding of those who did not take up a method is required. The need to leverage opportunities for the promotion of the integration of HIV and family planning at all levels of PrEP provision was highlighted.

Keywords: pre-exposure prophylaxis, contraception, integration, HIV prevention, South Africa, adolescent girls and young women, sexual and reproductive health

INTRODUCTION

South Africa (SA) has the largest HIV epidemic in the world. In 2019, there were 7.5 million people living with HIV and 200,000 new infections (1). Adolescent girls and young women (AGYW) aged 15–24 are particularly affected, with HIV prevalence among young women nearly four times greater than that of young men (1, 2). Oral pre-exposure prophylaxis (PrEP), comprising the antiretrovirals emtricitabine and tenofovir disoproxil fumarate (TDF), has been a game changer in HIV prevention, with over 90% prevention of HIV when used correctly (3, 4).

Oral pre-exposure prophylaxis was initially introduced into SA *via* several research and demonstration projects, focusing initially on key populations, including men who have sex with men, sex workers, and AGYW (5, 6). The launch of the SA national PrEP guidelines in 2016 (7) was combined with a nationally coordinated training and implementation program, and access to PrEP expanded in a phased approach to include a range of target populations and public sector health facilities, educational institutions, and non-governmental organizations (8). As the availability of PrEP increased, so there was a concomitant interest in exploring different models to improve both access and utilization for AGYW. In addition, there was growing recognition of the need to leverage opportunities to combine HIV services with complementary sexual and reproductive health (SRH) services, with contraception forming an important component of this service delivery package (9–11).

Contraception is identified as a priority strategy in both global and national strategies to improve the health and well-being of AGYW (12, 13). In spite of an enabling contraceptive policy in SA, there are still challenges in contraceptive utilization with young women (14). The 2016 South African Demographic and Health Survey (SADHS) reported that the contraceptive prevalence rate (CPR) in sexually active young women aged 15–19 in the SADHS was 60.4% and slightly higher in females aged 20–24 at 61.3% (15). Despite these rates being one of the highest in Africa, there remains a high rate of adolescent pregnancy and the same survey indicated that 16% of SA adolescent females aged 15–19 have begun childbearing: 1% have given birth, and another 3% were pregnant with their first child at the time of interview (15). Recent data from the national HSRC Youth Survey indicate an unmet need for contraception among young people in SA (14). Among the women who reported being pregnant in the past 5 years, only 10.1% of women aged 15–19 years and 20.9% of those aged 20–24 years desired to get pregnant. Of those who had been pregnant in the past 5 years, only 12.8% in 15- to 19-year olds and 19.7% in 20- to 24-year olds had been using contraception. Although adolescent pregnancy has been a public health challenge in SA for many years, the prevalence of overwhelmingly unintended pregnancies among females aged 15–19 has remained unchanged for the past 20 years (15).

The arguments for integrated SRH and HIV services are supported by the benefits accrued by both clients and healthcare providers in terms of improvements in access, efficient use of resources, comprehensive client-centered quality care, and health outcomes. The interrelationship between HIV and unintended pregnancy particularly underpins this need for integration (16, 17). From a global perspective, this is deemed necessary to attain global development targets, the sustainable development goals (18), as well as the provision of SRH services within a rights-based framework (19, 20).

The literature makes a distinction between linkages and integrated care. Linkages refer to a bidirectional relationship between SRH and HIV embracing policy, programs, services, and advocacy. Integration, a subset of linkages, refers to the combining of several services at the operational or programmatic level, with the provision of combined services occurring at the place, or through a process of structured referrals, usually at the same site (18, 21).

The relative benefits of the bidirectional integration of contraception into HIV services (17, 21–24), and HIV into contraceptive services (18, 23, 25), are well-described and highlight cross-cutting issues such as health system-related issues, improved health outcomes, cost-effectiveness as well as the benefits for the end-user.

Initially, the integration of HIV into family planning services emphasized the promotion of core HIV services such as HIV testing, PMTCT, and antiretroviral treatment (25). More recently, as HIV prevention options have expanded, we have seen the emergence of research and discussion focusing on the potential of the integration of SRH and oral PrEP. An important issue emphasizing the need to include contraceptive services with PrEP provision relates to concern about inconsistent condom use among some PrEP users, and the consequent increased risk of unintended pregnancy (26).

The need to ensure contraceptive services form an intrinsic part of PrEP services for AGYW is particularly important given the range of challenges facing young women with regard to condom use (14), accessing contraception, method utilization, and method continuation (14). The potential of PrEP services being a gateway to access contraceptive services is therefore particularly relevant (5). In addition to the potential benefits of integration, the need to develop the health systems to support integration has also been identified—this includes cross-cutting items across the value chain, including planning and budgeting, supply chain for contraceptive and PrEP commodities, provider training and support, service delivery strategies, end-user support, monitoring and evaluation as well as community engagement and demand creation, framed by youth-friendly service provision (27, 28).

The convergence of the need to improve HIV prevention plus SRH services for AGYW in SA informed the design and implementation of Project PrEP, a comprehensive, real-world HIV prevention program, funded by Unitaid. Initiated in 2018 in SA, the project aimed to improve access, demonstrate service delivery, and provide evidence to guide appropriate and effective models for PrEP delivery framed by comprehensive, quality SRH health services. As a part of this process, we conducted an analysis of baseline routine monitoring data to examine contraceptive use and uptake in AGYW accessing PrEP in the project sites, and how the monitoring and evaluation data can further be improved to capture the bidirectional nature of integration.

MATERIALS AND METHODS

Study Setting and Design

The goal for Project PrEP is to contribute to a decrease in the incidence of HIV in AGYW of age 15–24 years in SA with a primary aim to inform evidence on the appropriate and most effective models for PrEP delivery, in the context of comprehensive integrated SRH and HIV prevention services to AGYW.

Project PrEP is structured around three objectives: (1) to increase accessibility of PrEP (within a comprehensive SRH service package) for the eligible adolescent population in the project implementation areas; (2) to identify and develop effective delivery model and appropriate use of PrEP among adolescents; and (3) to provide evidence (as a country as well regionally and globally) on the use of PrEP in adolescents which is generated and disseminated. The project is working to increase demand for PrEP in high-priority communities where clinics are located by implementing targeted and specially designed demand creation activities. Those interested are linked to care for testing and those negative and at risk offered and provided PrEP as part of a comprehensive SRH package through fixed and mobile facilities.

The service package includes HIV combination prevention options, such as condom promotion, HIV testing, PEP and oral PrEP, and SRH services with a focus on contraception, sexually transmitted infections, and gender-based violence. As PrEP is a relatively new HIV prevention method in SA and is one of the primary objectives for the project, young people may be attracted to the service because of their interest in PrEP. This has the potential of leveraging the opportunity for SRH service integration, such as the promotion of and improved access to contraceptive services. While demand generation activities for the project promoted both HIV prevention and SRH, this was an opportunity to engage on issues such as risk, sexually transmitted infections (STIs), and the prevention of unintended pregnancies in those interested in PrEP.

This implementation science project was undertaken in eight fixed and four mobile healthcare facilities in three provinces in SA (Eastern Cape, KwaZulu-Natal, and Gauteng Provinces). The Eastern Cape included two districts with each district hosting two fixed and one mobile clinic ($n = 6$). KwaZulu-Natal and Gauteng had two fixed and one mobile clinic ($n = 3$, respectively) participating in the project. The study sites were selected to participate in collaboration with the National Department of Health, and in consultation with provincial and district DOH officials. Key factors for facility selection included population density (urban, peri-urban, or rural), client volume at the PHC facility, availability of SRH services within and in the area surrounding the health facility, and geographic size of the catchment area of the health facility. They were selected as facilities in priority areas, which had high HIV prevalence, high rates of teenage pregnancy, and several secondary and tertiary learning institutions in the catchment and so had easy access and the potential to attract young people.

Demand creation activities targeted both communities and health facilities. The youth-friendly services were promoted in the community to encourage AGYW to come to facilities to hear more about what was available. At the facilities and mobile sites involved in the project, health talks and other demand creation activities targeted AGYW. All the staff were trained to provide integrated messages on SRH including PrEP. AGYW who were interested in PrEP or other services were managed according to DoH guidelines (6), and on presentation for a service, the AGYW was asked by the data capturer what services they would like to know more about. The HIV counselor discussed HIV and SRH as part of the risk reduction discussion. The healthcare provider (nurse) discussed risk, PrEP, and HIV prevention, plus assessed which other services are required. Monitoring data were collected *via* a short questionnaire administered by project staff and included demographic characteristics and sexual behaviors, PrEP initiation screening required, HIV prevention service uptake such as HIV testing and counseling, pregnancy testing, and screening services—for example, tuberculosis (TB), gender-based violence (GBV), mental health, and STIs and hepatitis B. This was combined with referrals for any additional services not available on the mobiles. This information was stored in a central health information system for reporting and tracking health service delivery.

Contraceptives available in the fixed sites varied according to commodity supply and staff capacity, but in the main, included injectables [3-monthly intramuscular depot medroxyprogesterone acetate (DMPA-IM), 2-monthly noristerat (norethisterone enanthate/NET-EN], subdermal contraceptive implant, oral contraceptive pills, copper intrauterine device (IUCD), and male and female condoms as per the National Contraceptive Guidelines (29). The mobile sites had injectables, oral contraceptive pills, and male and female condoms; in addition, two of the four mobiles were able to insert implants. Clients were referred to the fixed sites for implant and IUCD insertions. Women were counseled about the different methods during their visit regardless of contraceptive use status and could choose to stay on their existing method or initiate a new method. The non-users of contraception category included a combination of AGYW who had never used contraception and those who had used contraception before but were not currently using a method on the day of their PrEP initiation.

The specific objectives for this analysis were first to examine the level of integration of contraceptive uptake among AGYW users and non-contraceptive users in the sites at first visit. The second objective was to look at patterns of contraceptive uptake, and the third was to reflect on how this data can contribute to improved access and strengthen integration and improve monitoring data to capture integration at service delivery level.

Study Population and Sample Size

The services in Project PrEP focused on AGYW (<25 years), but women aged 25 years and older and males were able to access the same services. In this analysis, we looked at AGYW (aged 15–24 years), comprising those who were eligible for PrEP services at the 12 project sites between December 2018 and September 2020.

Data Management and Analysis

The monitoring and evaluation data were collected on hard copy along the client pathway—by the intake data capturer, by the HIV testing counselor, and then the nurse. This is then entered into REDCAP by the data capturer, which is overseen by the data quality monitor. The REDCap (Research Electronic Data Capture) is hosted at the University of the Witwatersrand. REDCap is a secure, web-based software platform designed to support data capture for research studies (30). Data were exported to STATA 15 (StataCorp 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP) for analysis. Data presented are a secondary cross-sectional descriptive analysis of routine monitoring data.

Ethical Considerations

This project was approved by the University of Witwatersrand Human Research Ethics Committee (M180860), the World Health Organization Ethics Research Committee (ERC) protocol ID: Wits PrEP-AGYW-Main protocol 0003088, and was approved by the Department of Health at the national, provincial, district, municipal, and facility level.

RESULTS

The overall sample size of AGYW who had visited a facility for any service between December 2018 and September 2020 was 5,376. In this analysis, we looked at those AGYW (aged 15–24), who were HIV-negative, and were offered and accepted oral PrEP at the 12 project sites during this period ($n = 4, 949$). Clients who tested HIV-positive, and who were referred for HIV counseling and antiretroviral treatment, or after HIV testing who did not express an interest in initiating PrEP were excluded ($n = 427$).

Baseline characteristics were collated (**Table 1**) and showed that two-thirds of women (62.3%, $n = 3,083$) reported the current use of contraception, while a third (27.7%, $n = 1,866$) were non-users. Just under two-thirds (58.7%) were aged 20–24 years, and over two-thirds were learners (still at school) or in post-school education (further education). The proportion in each age category, relationship, and other characteristics were similar across contraceptive users and non-users.

Table 2 shows the different methods that the current contraceptive users were utilizing on the day of their PrEP initiation visit. Injectables were used by two-thirds of AGYW (61.9%, $n = 1,829$) and a fifth (19.4%, $n = 575$) reported male condoms. Similar proportions used oral pills and implants. A small number of contraceptive users ($n = 6$) used contraceptive patches. This method is not available in the public health sector, and these users would have obtained them from the private sector or elsewhere. Condom use consistency was asked in a different section of the questionnaire, and in both user and non-user categories, it was approximately a third in both categories. Among AGYW reporting male condoms for contraception, almost half (47.8%) reported that they were consistent users.

In total, 1,007 (32.7%) of current contraceptive users at PrEP initiation visit chose the same or a different method at this visit. Of these, 865 (85.9%) continued on their current method, while some used the opportunity to change their method.

Table 2 shows the methods accepted by the non-users of contraception at baseline on the same day of PrEP initiation. A third (32.3%, $n = 603$) of the non-contraceptive users accepted a contraceptive method at this visit. The methods chosen by the AGYW were similar in proportion to the current users with the largest proportion (42%) choosing injections. However, although injectables were the most used method, the proportion choosing this method was lower compared to the current users. Oral contraceptive pills accounted for almost a fifth (19.7%) of uptake, 10% higher than the current users. Similarly, 34.6% of those not initiating PrEP accepted a method.

TABLE 1 | Baseline characteristics of adolescent girls and young women (AGYW) initiated on pre-exposure prophylaxis (PrEP) ($n = 4,949$).

Demographic characteristics	Contraceptive users at first visit ($n = 3,083$) % *N*	Non-contraceptive users at first visit ($n = 1,866$) % *N*
Age		
15–19	41.3 (1,272)	43.4 (810)
20–24	58.7 (1,811)	56.6 (1,056)
Relationship status		
Partner (not cohabiting)	75.4 (2,325)	72.0 (1,343)
Single	17.2 (529)	19.8 (370)
Casual partners	1.8 (57)	3.3 (62)
Open relationship	2.4 (73)	2.5 (47)
Cohabiting	0.6 (20)	1.1 (21)
Married	0.8 (24)	0.3 (6)
Divorced	0.1 (2)	0.1 (1)
Widowed	0.2 (7)	0.1 (1)
Missing	1.5 (46)	0.8 (15)
Occupational status		
Learner-primary	0.3 (9)	0.4 (8)
Learner-secondary	32.6 (1,007)	33.3 (622)
Student (post school)*	31.6 (975)	36.6 (683)
Student (Other)	5.1 (157)	2.5 (46)
Employed	10.1 (313)	10.2 (191)
Unemployed	18.2 (560)	15.6 (291)
Missing	2.0 (62)	1.3 (25)
Type of facility		
Fixed site	61.3 (1,890)	68.0 (1,269)
Mobile	38.7 (1,193)	32.0 (597)
Population group		
African	99.5 (3,069)	99.4 (1,855)
Other	0.2 (7)	0.3 (5)
Missing	0.2(7)	0.3 (6)
Ever engaged in transactional sex	1.1 (31)	1.3 (24.0)
Self-reported STI in past 6 months	3.3 (101)	2.3 (43)
Always using condoms	42.0 (1,295)	38.8 (725)

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TABLE 2 | Contraceptive method type currently used at PrEP initiation.

	Current users ***n* = 3,083*** **% (*N*)**	**Method accepted by non-users**** ***n* = 1,866** **% (N)**
Injectables	61.9 (1,829)	42.7 (260)
Male condoms	19.4 (575)	23.3 (142)
Oral contraceptive pills	9.0 (266)	19.7(120)
Implant	8.5 (250)	3.1 (19)
IUCD	0.8 (24)	0.7 (4)
Patch	0.2 (6)	0.0 (0)
Female condoms	< 1.0 (2)	0.0 (0)
No method accepted	N/A	67.6 (1,262)

**131 AGYW reported to be using a method but method not recorded.*
***58 New acceptors but method not documented.*

The method uptake at PrEP initiation increased the overall contraceptive prevalence by 12.2 to 74.5%. Two-thirds of the non-contraceptive users (67.6%, $n = 1,262$) did not commence on a method, of which 856 indicated they had no demand, while there were no data available on the remaining 406. The monitoring data indicated that over a third (38.8%, $n = 725$) who were not using a method at baseline described themselves as consistent condom users (used a condom every time they had sex).

In addition to contraceptive services, additional health services were offered to AGYW as part of PrEP initiation and integrated service delivery, including HIV testing and screening for STIs and TB. Although not always documented, 3,947 (79.7%) of AGYW were screened verbally for STI symptoms and 2,460 (50%) were documented to have been screened for TB using a checklist. AGYW were screened for hepatitis B and 185 women positive for hepatitis B were referred for the assessment. A further 15.7% ($n = 779$) were screened for mental health well-being if indicated following a checklist. A total of 73 AGYW received a Pap smear.

DISCUSSION

The CPR of 62.3% in the group of PrEP initiating AGYW was aligned with that seen in the SADHS 2016 (64% prevalence rate for sexually active, unmarried women) (31). Similarly, the method mix among AGYW aged 15–24 years using contraception mirrored that seen in the SADHS with the injectables being the most common method used at baseline and accepted by the new users, and male condoms the second most utilized method. Although SA has the largest female condom program globally (32), only two AYGW reported being current users and no new user accepted female condoms although they were available at the sites. While it is encouraging to see condoms being reported as a method of contraception, we know that condoms can be less reliable as a method of contraception particularly if used inconsistently and that consistent and correct condom use is a challenge, particularly for AGYW (14, 33). The proportion of AGYW using implants in the AGYW is similar to that reported in the SADHS.

Although a major focus was on PrEP service provision, contraceptive prevalence increased by 12.2–74.5% in the PrEP acceptors. However, all non-users of contraception were offered a method as part of the service package; two-thirds declined. This is potentially a missed opportunity. Unfortunately, the monitoring data did not collect specific information as to the reason for the lack of demand, and reasons for this would require more intensive exploration. The women were, however, given information and could have taken up a method at subsequent visits. Similar numbers of contraceptive users and non-users at baseline reported always using condoms. Condom use was mentioned in both user and non-user contraceptive groups. In the group who did not accept a method at baseline, 38.8% reported always using condoms, indicating that a consistent condom use may not have been perceived as a "contraceptive method" by some AGYW. However, a fifth (19.4%) in the contraceptive user category cited condom use as their method. Condom use continues to be viewed as a STI/HIV prevention strategy rather than a dual method of contraception and STI/HIV prevention (34). This information indicates the need to clarify condom use with AGYW as this method may be under-reported as a contraceptive method. Male and female condoms are available at no cost in all public sector facilities and many non-governmental organizations and community venues. AGYW with access to condoms from non-health facility venues may have not needed to request them from a provider during their consultation, thus reporting no demand. Condoms carried by women remain stigmatized in SA, and AGYW may rely on the provision of condoms by their partners and require partner cooperation for their use (34).

Despite the uptake of hormonal contraceptive methods in the non-users at baseline and the number of consistent condom users, there was still a substantial number of AGYW who did not take up the opportunity to accept an effective method of contraception. Their acceptance of PrEP indicates that they perceived themselves to be at risk of HIV infection and wanted to protect themselves yet may have remained at risk of pregnancy. Despite these youth-friendly services addressing health service-level barriers related to non-use of contraception, there are numerous and multilevel factors at other levels that may be contributing to the lack of demand. At the individual level, factors contributing to risk of pregnancy in AGYW include the lack of knowledge about sex and contraception, young age at first sex, low education, and being out of school (35, 36). Partner-level factors include age disparate relationships ($\geq$5 or more years older) and gender power (in)equity in relationships (37–39). These barriers will need to be addressed to optimize contraceptive acceptability and uptake.

It was encouraging to see that a third of the contraceptive users at baseline chose to use the services available and either continued on the same method or chose a different method on the day they initiated PrEP. We do not know how many of these users had previously used the mobile or fixed service they attended but these data are important as it not only shows that two different services can be accessed in one visit but also that it can be documented. However, challenges arose in collecting follow-up data for each individual as PrEP visits are not necessarily aligned with contraceptive visits, and ensuring that AGYW were tracked

across different health facilities where records were not electronic was complex.

Discussing eligibility for PrEP automatically triggers a range of other services that are required in the SA PrEP guidelines, including HIV testing, STI, and hepatitis B and TB screening. This opens the opportunity for discussion of other services, including the need for contraception, TB, and mental health screening. Project PrEP offered the option of PrEP to AGYW regardless of the service they had originally presented for. AGYW who specifically came for PrEP were offered other services. This bidirectional approach ensured that regardless of service, the package was offered.

Although able to provide PrEP, the mobile services are not able to provide the full range of contraceptive methods for several reasons, including the infrastructure to conduct IUCD insertions and only some nurses were trained and able to insert implants. However, they still were able to provide a range of methods and were able to counsel, educate, and refer to fixed facilities. Mobile facilities are important to ensure that the hard-to-reach communities are served with SRH options that are accessible.

Contraception is identified as a priority strategy in both global and national strategies to improve the health and well-being of AGYW (12, 13). This is well-recognized and is reflected as a goal in several regional AGYW programs (DREAMS) and national campaigns (She Conquers) (40, 41), both focusing on contraception and prevention of teenage pregnancy being one of its primary objectives (40). However, there are barriers to young women accessing contraception, and this impacts on effective use and continuation rates on methods (33). Project PrEP sought to improve access to both PrEP and SRH services through integrated service provision, and we looked specifically at how this service provided an opportunity for improved access to contraception for young women.

Emergency contraception is an important intervention to prevent unintended pregnancy for AGYW (42, 43), especially at the community level (44); however, there are no reported monitoring data to report on its use in this project. This needs to be reinforced and brought into the contraceptive method mix as well as capturing this method in routine data collection tools.

The opportunities afforded by strategic and appropriate integration of HIV and contraceptive services are multifold (23): From a service and rights perspective, the integration supports the rights of women to control their own fertility whether HIV-positive or HIV-negative; both provide the opportunity to reinforce discussions about risk, prevention, and options for the combined prevention of HIV prevention and unintended pregnancy, thereby improving health outcomes.

This project focused on the use of PrEP as a potential hook and platform for improving access to contraception. The opportunities presented for integration need to be leveraged and maximized—including finding more effective ways to monitor and measure integration and ensuring that key SRH services such as contraception are combined at all levels of demand creation and that counseling about contraception and contraceptive choices are part of the core PrEP package. Further analysis needs to be undertaken to look at the factors influencing contraceptive use—such as commodity supply and availability, staff training, and harnessing opportunities for integration such as demand creation and risk assessment—and how to ensure these strategies mirror HIV prevention and SRH integration.

LIMITATIONS

There are several limitations to our analysis. The data source was restricted to routine monitoring service data, and there were also changes in the monitoring and evaluation collection tools during the period under discussion, resulting in some data that were missing while more in-depth information such as exact reasons for non-use is not collected routinely. The data do not record the primary service that AGYW came for and other services utilized as a result. Follow-up for PrEP and contraception was challenging for a number of reasons. COVID-19 lockdowns restricted mobile clinics entering communities while repeat contraception, PrEP, and other services were available in the Department of Health Clinic cluster where clients may not have had project data collected.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because: The project is still ongoing but data will be available at a later date on reasonable request to the principal investigators. Requests to access the datasets should be directed to smullick@wrhi.ac.za.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Witwatersrand Human Research Ethics Committee (M180860), the World Health Organisation Ethics Research Committee (ERC) protocol ID: Wits PrEP-AGYW-Main protocol 0003088 and approved by the Department of Health at national, provincial, district, municipal and facility level. This study used monitoring data and so no parental or guardian consent was required. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: The data used was from facility monitoring data used by the Department of Health. It was anonymous and not collected for any specific research purpose.

AUTHOR CONTRIBUTIONS

SM, MP, LG, ZF, SN, and VB contributed to conception and design of the study. ZF and SN organized the database. KM and MB and MP performed the statistical analysis and data interpretation. MP wrote the first draft of the manuscript. MP, MB, SM, and KM wrote sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

FUNDING

Project PrEP was funded by Unitaid, award number 2017-21-Wits-PrEP.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

ORIGINAL RESEARCH
published: 16 July 2021
doi: 10.3389/frph.2021.668685

Prevalence and Incidence of Sexually Transmitted Infection in Injectable Progestin Contraception Users in South Africa

Lisa M. Noguchi[1], Jeanne M. Marrazzo[2], Barbara Richardson[3], Sharon L. Hillier[4], Jennifer E. Balkus[5], Thesla Palanee-Phillips[6], Gonasagrie Nair[7†], Ravindre Panchia[8], Jeanna Piper[9], Kailazarid Gomez[10], Gita Ramjee[11‡] and Z. Mike Chirenje[12]*

[1] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [2] Division of Infectious Diseases, School of Medicine, The University of Alabama at Birmingham, Birmingham, AL, United States, [3] Department of Biostatistics, University of Washington, Seattle, WA, United States, [4] Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh and the Magee-Womens Research Institute, Pittsburgh, PA, United States, [5] Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA, United States, [6] Wits Reproductive Health & HIV Institute, University of the Witwatersrand, Johannesburg, South Africa, [7] CAPRISA, Durban, South Africa, [8] Perinatal HIV Research Unit, Johannesburg, South Africa, [9] Division of AIDS, NIAID, U.S. National Institutes of Health, Bethesda, MD, United States, [10] FHI 360, Durham, NC, United States, [11] South African Medical Research Council, Durban, South Africa, [12] University of Zimbabwe Clinical Trials Research Centre, Department of Obstetrics and Gynaecology, Harare, Zimbabwe

OPEN ACCESS

Edited by:
Marissa L. Becker,
University of Manitoba, Canada

Reviewed by:
Lyle McKinnon,
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Flavia Matovu Kiweewa,
MU JHU Research Collaboration, Uganda

***Correspondence:**
Lisa M. Noguchi
lnoguch1@jhu.edu

†Present address:
Gonasagrie Nair,
Centre for Medical Ethics and Law, Stellenbosch University, Stellenbosch, South Africa

‡Deceased

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: 17 February 2021
Accepted: 17 May 2021
Published: 16 July 2021

Citation:
Noguchi LM, Marrazzo JM, Richardson B, Hillier SL, Balkus JE, Palanee-Phillips T, Nair G, Panchia R, Piper J, Gomez K, Ramjee G and Chirenje ZM (2021) Prevalence and Incidence of Sexually Transmitted Infection in Injectable Progestin Contraception Users in South Africa. Front. Reprod. Health 3:668685. doi: 10.3389/frph.2021.668685

Introduction: Whether intramuscular depot medroxyprogesterone acetate (DMPA-IM) and norethisterone enanthate (NET-EN) have a differential impact on the incidence of sexually transmitted infection (STI) remains unclear. In the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial, HIV-1 acquisition was higher for DMPA-IM users vs. NET-EN users. We compared DMPA-IM and NET-EN users with regard to chlamydia, gonorrhea, trichomoniasis, syphilis, and herpes simplex virus type 2 (HSV-2) infection.

Materials and Methods: Prospective data were analyzed from VOICE, a randomized trial of HIV-1 chemoprophylaxis. Participants were evaluated annually and as indicated for chlamydia, gonorrhea, trichomoniasis, and syphilis. Stored specimens were tested for HSV-2. Proportional hazards models compared the risk of STI between DMPA-IM and NET-EN users.

Results: Among 2,911 injectable contraception users in South Africa, 1,800 (61.8%) used DMPA-IM and 1,111 used NET-EN (38.2%). DMPA-IM and NET-EN users did not differ in baseline chlamydia: 15.1 vs. 14.3%, $p = 0.54$; gonorrhea: 3.4 vs. 3.7%, $p = 0.70$; trichomoniasis: 5.7 vs.5.0%, $p = 0.40$; or syphilis: 1.5 vs. 0.7%, $p = 0.08$; but differed for baseline HSV-2: (51.3 vs. 38.6%, $p < 0.001$). Four hundred forty-eight incident chlamydia, 103 gonorrhea, 150 trichomonas, 17 syphilis, and 48 HSV-2 infections were detected over 2,742, 2,742, 2,783, 2,945, and 756 person-years (py), respectively (chlamydia 16.3/100 py; gonorrhea 3.8/100 py; trichomoniasis 5.4/100 py; syphilis 0.6/100 py; HSV-2 6.4/100 py). Comparing DMPA-IM with NET-EN users, no difference was noted in the incidence of chlamydia, gonorrhea, trichomoniasis, syphilis, or HSV-2 infections, including when adjusted for confounders [chlamydia (aHR 1.03, 95% CI 0.85–1.25), gonorrhea (aHR 0.88, 95% CI 0.60–1.31), trichomoniasis (aHR 1.07, 95% CI 0.74–1.54), syphilis (aHR 0.41, 95% CI 0.15–1.10), and HSV-2 (aHR 0.83, 95% CI 0.45–1.54, $p = 0.56$)].

Discussion: Among South African participants enrolled in VOICE, DMPA-IM and NET-EN users differed in prevalence of HSV-2 at baseline but did not differ in the incidence of chlamydia, gonorrhea, trichomoniasis, syphilis, or HSV-2 infection. Differential HIV-1 acquisition, previously demonstrated in this cohort, does not appear to be explained by differential STI acquisition. However, the high incidence of multiple STIs reinforces the need to accelerate access to comprehensive sexual and reproductive health services.

Keywords: depot medroxyprogesterone acetate, norethisterone enanthate, chlamydia, gonorrhea, contraception, trichomoniasis, syphilis, HSV-2

INTRODUCTION

Uptake of injectable progestin contraception, particularly the progestogen derivative, intramuscular depot medroxyprogesterone acetate (DMPA-IM), and the synthetic progestin norethisterone enanthate (NET-EN), has increased substantially over the past several decades (1). These two methods differ in duration of contraceptive effectiveness and administration schedule (every three months for DMPA-IM vs. every two months for NET-EN) but have otherwise been treated similarly in terms of clinical guidance (2). Results from multiple observational studies previously suggested that DMPA-IM might increase the risk of women acquiring sexually transmitted HIV, although findings have been inconsistent (3). Evidence has also conflicted regarding the potential impact of injectable progestin contraception on sexually transmitted infections (STIs), including *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), *Trichomonas vaginalis* (TV), syphilis, and herpes simplex virus type 2 (HSV-2) infections (4–7).

The Evidence for Contraceptive Options in HIV Outcomes (ECHO) trial (8) found no difference in risk for HIV acquisition among those randomized to DMPA-IM, a copper intrauterine device (IUD), or a levonorgestrel (LNG) implant. A subsequent analysis of data from ECHO noted that prevalent CT at the final visit did not differ between the DMPA-IM and copper IUD groups, and the DMPA-IM group had a significantly lower risk of CT compared with the LNG implant group [prevalence ratio (PR) 0.83, 95% CI 0.72–0.95] (9). At the final visit, the prevalence of NG in the same study differed between the DMPA-IM and copper IUD groups (PR 0.67, 95% CI 0.52–0.87). These results suggest that women randomized to DMPA did not have a higher risk of CT or NG compared with users of LNG implants or copper IUD. However, the ECHO trial lacked a randomization arm for NET-EN, which has been noted as a gap in understanding the potentially complex relationship between contraceptive method of choice and risk for HIV and STI acquisition (10).

Following the results of the ECHO trial, a guidance statement from WHO reiterated that women at high risk of HIV infection are eligible to use all progestogen-only contraceptive methods without restriction (MEC Category 1) (11). While global guidance has treated DMPA-IM, DMPA-SC, and NET-EN similarly, a recent review of pharmacokinetic, biologic, and epidemiologic differences in MPA- and NET-based progestin-only injectable contraceptives concluded that they are likely to act differently relative to potential HIV acquisition in women, based on most of the available biological activity and epidemiological data (12). Recent findings from the Zim-CHIC study suggest that women who initiate DMPA and NET-EN exhibit some differences in genital tract immune mediators (both soluble and cellular) (13). However, changes were limited compared to those observed among women initiating the use of a copper IUD. Differential impact on the vaginal epithelium, genital microenvironment, and/or local immune response have been proposed as potential mechanisms for differences in STI acquisition among users of different contraceptive methods. However, until recently, relatively few studies have reported whether NET-EN users differ from DMPA-IM users with respect to the acquisition of HIV and STI, although analysis of available data suggests a lower risk for HIV-1 infection associated with NET-EN compared with DMPA-IM (3).

Among South African participants who used injectable progestin contraception in the VOICE study, DMPA-IM users had ∼50% increased risk of HIV-1 acquisition, compared with NET-EN users (14). In this cohort, HIV-1 infection was strongly associated with the history of CT, NG, or TV infection at screening (HR 2.15, 95% CI 1.66–2.79, $p < 0.001$). Users of DMPA-IM tended to be slightly older compared with users of NET-EN (14), a finding consistent with historic trends in South Africa (15), but suggesting a comparatively lower risk for many STIs (16). However, in a secondary analysis of data from a randomized trial of the dapivirine vaginal ring for HIV-1 prevention, investigators found no statistically significant differences in HIV-1 incidence by contraceptive method, including DMPA-IM, NET-EN, implants, or copper IUD (17). Additional analyses from the same dapivirine ring study found that incidence of CT and NG was not significantly different between DMPA-IM and NET-EN users; however, the incidence of TV was lower among DMPA-IM compared with copper IUD users (18).

Thus, the extent to which DMPA-IM and NET-EN users may differ in their risk for HIV and STI acquisition remains unclear, particularly for STI other than CT and NG. In this analysis, the prevalence and incidence of CT, NG, TV, syphilis, and HSV-2 infections were compared between DMPA-IM and NET-EN users enrolled at VOICE sites in South Africa.

MATERIALS AND METHODS

This analysis included prospective data from participants at 11 South African sites in VOICE, a Phase 2B, randomized trial of the safety and effectiveness of tenofovir-based HIV-1 chemoprophylaxis (**Figure 1**) (19). Details of the VOICE trial have been described in Marrazzo et al. (20). Diagnostic tests for STI were chosen based upon sensitivity, specificity, and feasibility, among those that were available at the time VOICE was implemented. Women were screened for CT and NG infection by using nucleic acid amplification testing (Becton Dickinson ProbeTec ET®, Franklin Lakes, NJ, USA) of urine samples at study screening, annually, and at the end of study product use, with additional testing performed as clinically indicated. Routine screening and clinically indicated testing for TV were performed using the OSOM Rapid Trichomonas® test (Genzyme, Cambridge, MA, USA). Specimens were collected from the lateral vaginal wall or posterior fornix using a Dacron® swab (Genzyme, Cambridge, MA, USA). Testing was performed during participant visits, when possible, but storage at room temperature for 24 h or refrigeration for 36 h was permitted before testing. Due to low sensitivity, wet prep data were not used to define TV infection outcomes in this analysis. Syphilis testing was performed at study screening of participants, annually, as clinically indicated, and at study exit using a rapid plasma reagin (RPR) screening test, followed by a confirmatory microhemagglutinin assay for *Treponema pallidum* (MHA-TP) or *T. pallidum* hemagglutination assay (TPHA) for reactive samples.

Participant sera were tested for HSV-2 (HerpeSelect enzyme immunoassay, EIA) at enrollment and were determined to have a pre-existing infection if the titer result was $\geq$ 3.5. Quarterly EIA results were available for participants in the two VOICE gel study arms, due to a planned, separate comparison between tenofovir gel and placebo gel arms. At study exit, repeat EIA was conducted for samples of susceptible participants, using a seroconversion cut-off of $\geq$ 3.5. Confirmation was performed using Western blot on samples from enrollment and exit visits for the subset of participants in study gel arms.

Results, counseling, and treatment were provided on-site. Single-dose, directly observed STI therapy for CT, NG, and TV infections, was encouraged across sites but not required. Syphilis was treated with three doses of benzathine penicillin. While local guidelines advised syndromic management for genital tract infections, sites used protocol-specific guidance for laboratory assay-based STI screening and treatment (21). Consistent with local standards of care, sex partners of women with STI diagnoses were not routinely offered presumptive therapy but were referred to local facilities. Asymptomatic women, who had completed treatment for CT, NG, TV, and/or syphilis, diagnosed at screening were permitted to enroll.

Contraception was provided on-site at all study sites and methods obtained off-site were transcribed from family planning records of participants. Exposure lengths per injection [17 weeks (DMPA-IM) and 10 weeks (NET-EN)] were based on WHO guidelines for the duration of contraceptive coverage (22). Exposure was further categorized to distinguish periods where combined oral contraceptive (COC) and injectable exposure overlapped, for example, to treat breakthrough vaginal bleeding. Distinct segments of exposure were estimated representing days that each woman used each method. Participant-years of contraceptive exposure include all segments of use.

This secondary analysis of data from the VOICE study excluded those participants who enrolled in countries not using NET-EN, were HIV-infected at enrollment, never used injectable contraception, were missing data on injectable contraceptive type, switched between the two injectable types during follow-up, or initiated injectable contraception following censoring (**Figure 1**). Participants were not excluded for injections that were not received on schedule. Baseline demographic, sexual behavior, and partner characteristics were compared between participants using DMPA-IM and NET-EN as their first injectable method on the study, using Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables. Prevalence for each STI was calculated and compared between DMPA-IM and NET-EN users using Pearson's chi-squared test. Incidence rates for each STI were calculated per 100 person-years (py) follow-up with 95% confidence intervals overall and separately for person-time specific to DMPA-IM and NET-EN exposure. Recent partner change was measured as a binary variable. The frequency of vaginal sex was measured as a number of vaginal sex acts in the past week. The additional partners of primary partners were reported categorically ("yes," "no," and "don't know"). Condom use was a binary variable indicating condom use at last vaginal intercourse.

Andersen-Gill proportional hazards models, which allow for multiple individual failure events per participant, were used to investigate the potential association between injectable contraceptive type and acquisition of CT, NG, TV, and syphilis during follow-up (23). Cox proportional hazards models were used to investigate the potential association between injectable type and HSV-2 acquisition and were restricted to VOICE study gel arms, as noted above. As participants may have missed injections or switched to contraceptive methods other than injectables, exposure was treated as time-varying. As routine STI screening occurred on an annual basis following enrollment, analysis was restricted to women who did not switch injectable contraceptive types during follow-up. Follow-up time began after enrollment, with first injectable use during the study used as the time origin for all models. Observations were censored at the estimated date of HIV-1 infection, pregnancy detection, or last test (for particular STI) during follow-up. The date of HIV-1 infection was estimated using the midpoint between the last negative and first confirmed positive test. Censoring at the time of HIV-1 infection and pregnancy was undertaken because of the likelihood of differential STI screening and treatment following diagnosis. Hazard ratios were recalculated comparing DMPA-IM with NET-EN use for all infections, adjusting for potential confounding variables, which were chosen a priori by consensus of the authors based on their potential to impact study endpoints [time-fixed age and marriage/cohabitation, and time-varying oral contraceptive pill (OCP) use, frequency of sex, and condom use]. Power calculations were not undertaken prior to analyses.

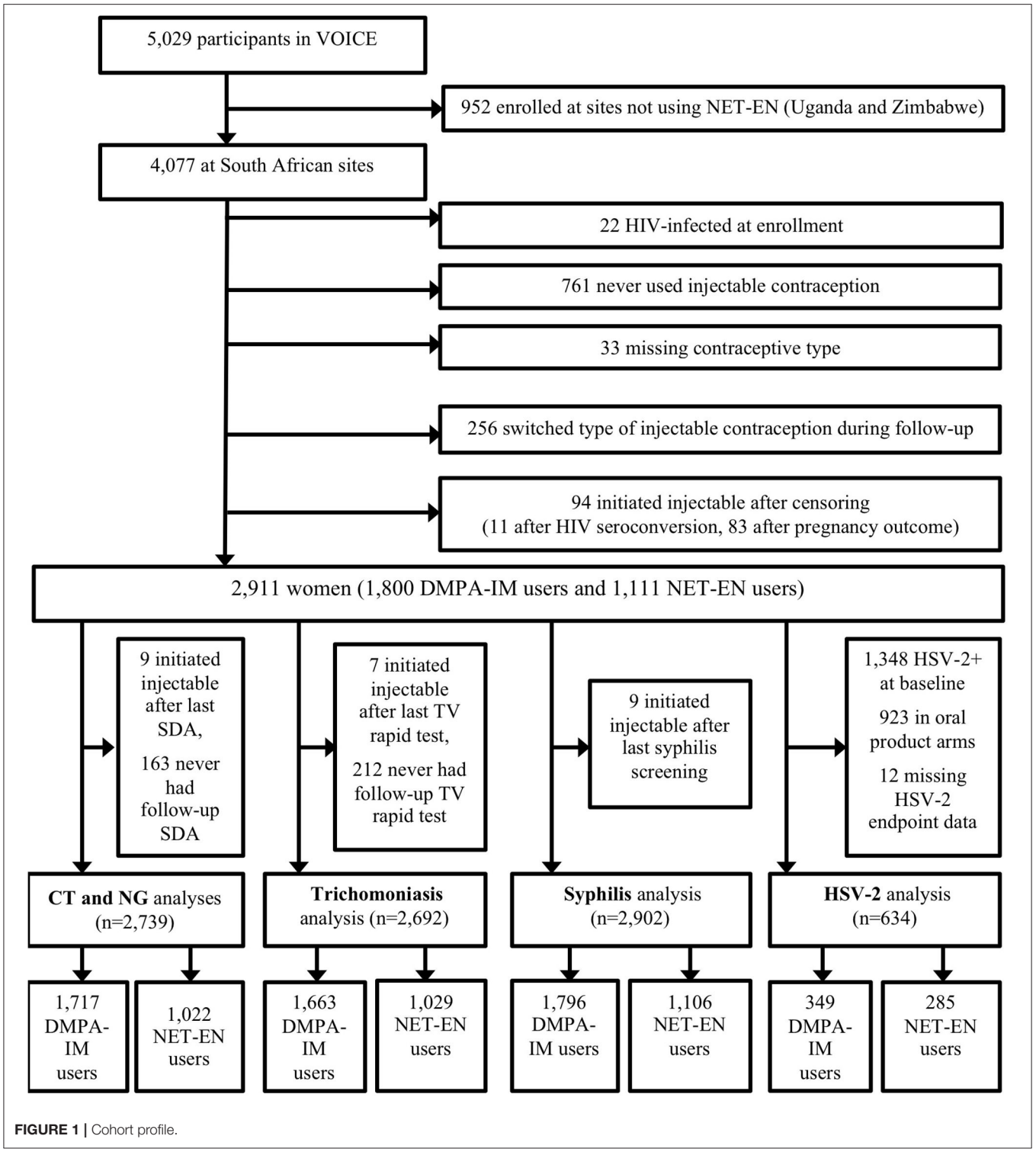

FIGURE 1 | Cohort profile.

These analyses did not include comparisons with non-injectable methods of contraception or those who reported using no contraceptive method. While VOICE study procedures included verification of injectable contraceptive use, this same level of verification was not available for OCPs. Additionally, it is likely that adherence to OCPs as a method of contraception in the VOICE study was poor, given the incidence of pregnancy in this group. Recent evidence from other studies that included assessment of hormone levels indicates that self-reported data on contraceptive use may be misreported, suggesting that studies that rely on self-report to identify contraceptive hormone exposure could suffer from significant misclassification (24).

These analyses did not estimate the impact of each injectable or the pooled impact of injectable progestin contraceptive use compared with non-use on acquisition of the acquisition of STI for several reasons. First, the VOICE study did not include many women who did not use hormonal contraception. Second, guidance on design and analysis of observational studies such as this one recommends more precise characterization of contraceptive exposure, in part by disaggregating hormonal contraceptive type in analyses (25). As confidence intervals for incidence rates of STI overlapped substantially across sites, a site-stratified hazard ratio was not calculated for unadjusted or adjusted models. Additional analyses were calculated for the subgroups of women reporting no condom use at baseline and those <25 years old. No adjustments were made for VOICE study arm due to generally low VOICE study drug adherence across participants, or additional analyses among those with higher levels of detectable study drug, due to small numbers of endpoints. In addition, no impact was anticipated for oral study drugs on bacterial and protozoal infections. As noted above, only data for study gel arms were included for analyses of HSV-2 endpoints.

The comparison of DMPA-IM with NET-EN users to examine risk of STI was not pre-specified in the VOICE trial but was designed prior to knowledge of final VOICE results, with the hypothesis of no difference in incident STI between DMPA-IM and NET-EN users. Statistical tests used a two-sided alpha of 0.05. Analyses were conducted using Stata version 13.1 (StataCorp, Inc, College Station, TX). All participants provided written informed consent. The VOICE study underwent all required institutional review board (IRB) reviews and is registered with Clinicaltrials.gov (NCT00705679). The Johns Hopkins Bloomberg School of Public Health IRB provided additional approval for this secondary data analysis.

RESULTS

Among 4,077 women enrolled for the VOICE trial in South African sites, 3,316 (81.3%) used injectable progestin contraception during follow-up. Of these, 2,911 (87.8%) were included in these analyses; 1,800 (61.8%) used DMPA-IM and 1,111 used NET-EN (38.2%) (**Figure 1**). The exclusion of those who switched injectable contraceptive type during follow-up or who initiated injectable progestin contraception following last STI testing (for each STI) means that this cohort differed slightly in composition from the VOICE cohort previously analyzed for the difference in HIV-1 acquisition. A non-significant increased risk for HIV-1 acquisition persisted in this smaller cohort for DMPA-IM compared with NET-EN users (aHR 1.30, 95% CI 0.96–1.77). The median follow-up duration was 15.6 months (IQR, 12–18.5 months), which did not differ significantly by injectable type ($p = 0.54$). **Table 1** includes demographic and behavior characteristics of participants at baseline for each analysis.

Chlamydial Infection

Among 2,739 participants included in the analysis of CT infection, the overall prevalence of CT infection at baseline was 14.8% (**Table 1**). Users of DMPA-IM and NET-EN did not differ in the likelihood of diagnosis at baseline ($p = 0.54$). Over 2,742 py of follow-up, the number of CT infections occurred was 448 for an overall incidence of 16.3/100 py (**Table 2**), which did not differ significantly by injectable type [DMPA-IM 15.6/100 py, 95% CI (13.9–17.6/100 py) vs. NET-EN 17.5/100 py, 95% CI (15.2–20.3/100 py) (HR 0.91, 95% CI 0.75–1.10, $p = 0.32$)]. Adjustment for potential confounding variables (time-fixed age and marriage/cohabitation, and time-varying oral contraceptive use, frequency of sex, and condom use) did not qualitatively change this estimate (adjusted HR [aHR] 1.03, 95% CI 0.85–1.25, $p = 0.77$). Among women who disclosed at baseline that they did not use condoms, no significant difference was detected between DMPA-IM compared with NET-EN users in acquisition of CT (HR 0.82, 95% CI 0.44–1.55, aHR 0.78, 95% CI 0.41–1.50). Restricting analyses to women <25 years old did not qualitatively change findings (HR 1.07, 95% CI 0.86–1.32, aHR 1.08, 95% CI 0.87–1.35).

Gonorrheal Infection

The overall prevalence of NG infection among South African users of injectable progestin contraception at baseline was 3.5% (**Table 1**). Users of DMPA-IM and NET-EN did not differ in the likelihood of diagnosis at baseline ($p = 0.70$). Among injectable progestin contraceptive users overall, 103 NG infections occurred over 2,742 pys of follow-up for an overall incidence of 3.8/100 pys (**Table 2**). Incidence of NG infection did not differ significantly by injectable progestin type (DMPA-IM vs. NET-EN: 3.6/100 py, 95% CI 2.8–4.6/100 py, vs. 4.0/100 py, 95% CI 2.9–5.4/100 py) (HR 0.88, 95% CI 0.60–1.31, $p = 0.54$). Adjustment for potential confounding variables did not qualitatively change this estimate (aHR 1.06, 95% CI 0.70–1.59, $p = 0.79$). Among women who disclosed at baseline that they did not use condoms, too few NG endpoints ($n = 7$) were available for analysis. Restricting analyses to women <25-years-old did not qualitatively change findings (HR 0.99, 95% CI 0.64–1.55; aHR 1.03, 95% CI 0.65–1.62).

Trichomonas Infection

The overall prevalence of TV infection was 5.4% (**Table 1**). Users of DMPA-IM and NET-EN did not differ in the likelihood of diagnosis at baseline ($p = 0.40$). Among injectable progestin contraceptive users overall, 150 TV infections occurred over 2,783 pys of follow-up for an overall incidence of 5.4/100 pys (**Table 2**). Incidence of TV infection did not differ significantly by progestin type (DMPA-IM vs. NET-EN: 5.6/100 py, 95% CI 4.6–6.8/100 py, vs. 5.1/100 py, 95% CI 3.9–6.7/100 py) (HR 1.09, 95% CI 0.78–1.52, $p = 0.62$). Adjustment for potential confounding variables did not qualitatively change the estimate for the difference in hazard of TV (aHR 1.07, 95% CI 0.74–1.54, $p = 0.72$). Among women who disclosed at baseline that they did not use condoms, no significant difference was observed when comparing DMPA-IM vs. NET-EN users in TV acquisition (HR 0.87, 95% CI 0.29–2.53; aHR 0.81, 95% CI 0.28–2.43). Restricting analyses to women <25-years-old also did not qualitatively change findings (HR 1.10, 95% CI 0.71–1.70, aHR 1.17, 95% CI 0.73–1.87).

TABLE 1 | Baseline characteristics of women on using injectable progestin contraceptive type.

	Chlamydia and gonorrhea analyses			Trichomonas analysis			Syphilis analysis			HSV-2 analysis		
	Total	**DMPA-IM**	**NET-EN**	**Total**	**DMPA-IM**	**NET-EN**	**Total**	**DMPA-IM**	**NET-EN**	**Total**	**DMPA-IM**	**NET-EN**
Characteristic	*n* = 2,739	*n* = 1,717	*n* = 1,022	*n* = 2,692	*n* = 1,663	*n* = 1,029	*n* = 1,560	*n* = 878	*n* = 682	*n* = 634	*n* = 349	*n* = 285
Demographic												
Median age, years (IQR)	23 (21–27)	24 (21–27)	23 (20–26)	23 (21–27)	24 (21–28)	23 (20–26)	23 (21–27)	24 (21–27)	23 (20–26)	22 (20–25)	23 (20–26)	22 (20–24)
Married/cohabitating	517 (18.9)	360 (21.0)	157 (15.4)	517 (19.2)	358 (21.5)	159 (15.5)	551 (19.0)	380 (21.2)	171 (15.5)	104 (16.4)	69 (19.8)	35 (12.3)
Parous	2,301 (84.0)	1,595 (92.9)	706 (69.1)	2,255 (83.8)	1,549 (93.1)	706 (68.6)	2,423 (83.5)	1,670 (93.0)	753 (68.1)	479 (75.6)	311 (89.1)	168 (59.0)
Any secondary education	2,628 (96.0)	1,635 (95.2)	993 (97.2)	2,583 (96.0)	1,582 (95.1)	1,001 (97.3)	2,788 (96.1)	1,713 (95.4)	1,075 (97.2)	615 (97.0)	335 (96.0)	280 (98.3)
Formal employment	264 (9.6)	162 (9.4)	102 (10.0)	259 (9.6)	158 (9.5)	101 (9.8)	278 (9.6)	168 (9.4)	110 (10.0)	54 (8.5)	23 (6.6)	31 (10.9)
Home owned self/family	2,264 (82.7)	1,420 (82.7)	844 (82.6)	2,217 (82.4)	1,369 (82.3)	848 (82.4)	2,383 (82.1)	1,476 (82.2)	907 (82.0)	541 (85.3)	295 (84.5)	246 (86.3)
Sexual behavior												
Has >1 sexual partner	89 (3.3)	40 (2.3)	49 (4.8)	95 (3.5)	45 (2.7)	50 (4.9)	104 (3.6)	47 (2.6)	57 (5.2)	23 (3.6)	8 (2.3)	15 (5.3)
Median vag. sex past wk (IQR)	2 (1–3)	2 (1–3)	2 (0–3)	2 (1–3)	2 (1–3)	2 (0–3)	2 (1–3)	2 (1–3)	2 (0–3)	1 (0–3)	2 (0–3)	1 (0–3)
Condom at last sex	1,845 (74.3)	1,145 (73.9)	700 (75.0)	1,822 (74.4)	1,120 (74.2)	702 (74.7)	1,959 (74.5)	1,204 (74.1)	755 (75.0)	418 (72.8)	226 (72.2)	192 (73.6)
Any anal sex past 3 months	546 (20.3)	324 (19.2)	222 (22.1)	529 (20.0)	316 (19.3)	213 (21.1)	571 (20.0)	333 (18.8)	238 (22.0)	122 (19.5)	52 (15.1)	70 (24.9)
Sex for money past year	132 (4.9)	80 (4.7)	52 (5.2)	132 (5.0)	81 (4.9)	51 (5.0)	143 (5.0)	84 (4.7)	59 (5.4)	31 (4.9)	17 (4.9)	14 (5.0)
Primary partner												
Any secondary education	2,520 (92.7)	1,570 (91.9)	950 (94.0)	2,479 (92.8)	1,522 (92.1)	957 (94.0)	2,669 (92.7)	1,643 (92.0)	1,026 (93.8)	594 (94.6)	325 (93.7)	269 (95.7)
Has other partners												
Yes	239 (9.0)	145 (8.6)	94 (9.7)	239 (9.2)	144 (8.8)	95 (9.8)	255 (9.1)	152 (8.6)	103 (9.9)	55 (9.0)	23 (6.7)	32 (11.9)
Don't know	1,725 (65.1)	1,116 (66.3)	609 (62.9)	1,681 (64.6)	1,077 (66.1)	604 (62.2)	1,811 (64.6)	1,166 (66.2)	645 (61.8)	371 (60.7)	211 (61.5)	160 (59.7)
Genital tract infection												
Chlamydia	406 (14.8)	260 (15.1)	146 (14.3)	401 (14.9)	253 (15.2)	148 (14.4)	431 (14.9)	269 (15.0)	162 (14.7)	100 (15.7)	54 (15.5)	46 (16.1)
Gonorrhea	97 (3.5)	59 (3.4)	38 (3.7)	96 (3.6)	56 (3.4)	40 (3.9)	103 (3.6)	61 (3.4)	42 (3.8)	19 (3.0)	8 (2.3)	11 (3.9)
Trichomoniasis	154 (5.6)	101 (5.9)	53 (5.2)	146 (5.4)	95 (5.7)	51 (5.0)	161 (5.6)	107 (6.0)	54 (4.9)	29 (4.6)	18 (5.2)	11 (3.9)
Syphilis	34 (1.2)	26 (1.4)	8 (0.72)	34 (1.2)	26 (1.4)	8 (0.7)	34 (1.2)	26 (1.5)	8 (0.7)	4 (0.6)	2 (0.6)	2 (0.7)
Herpes simplex virus type 2	1,277 (46.6)	875 (51.0)	402 (39.3)	1,251 (46.5)	850 (51.1)	401 (39.0)	1,345 (46.4)	919 (51.2)	426 (38.5)	NA	NA	NA

DMPA-IM, depot medroxyprogesterone acetate; NET-EN, norethisterone enanthate; IQR, interquartile range. Characteristics are n (%), unless otherwise indicated.

TABLE 2 | Acquisition of sexually transmitted infection (STI) among users of injectable progestin contraception.

			Unadjusted model		Adjusted model*	
	Cases/py	Incidence/100 py (95% CI)	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Chlamydial infection						
NET-EN	180/1,025.9	17.5 (15.2–20.3)	REF		REF	
DMPA-IM	268/1,715.7	15.6 (13.9–17.6)	0.91 (0.75–1.10)	0.32	1.03 (0.85–1.25)	0.77
Total	448/2,741.7	16.3 (14.9–17.9)				
Gonorrheal infection						
NET-EN	41/1,025.9	4.0 (2.9–5.4)	REF		REF	
DMPA-IM	62/1,715.7	3.6 (2.8–4.6)	0.88 (0.60–1.31)	0.54	1.06 (0.70–1.59)	0.79
Total	103/2,741.7	3.8 (3.1–4.6)				
Trichomonas infection						
NET-EN	53/1,037.4	5.1 (3.9–6.7)	REF			
DMPA-IM	97/1,745.8	5.6 (4.6–6.8)	1.09 (0.78–1.52)	0.62	1.07 (0.74–1.54)	0.72
Total	150/2,783.2	5.4 (4.6–6.3)				
Syphilis infection						
NET-EN	10/1128.2	0.9 (0.5–1.6)	REF		REF	
DMPA-IM	7/1816.3	0.4 (0.2–0.8)	0.44 (0.17–1.16)	0.10	0.41 (0.15–1.10)	0.08
Total	17/2944.5	0.6 (0.4–0.9)				
Herpes simplex virus (HSV-2) infection						
NET-EN	21/328.4	6.4 (4.2–9.8)	REF		REF	
DMPA-IM	27/427.2	6.3 (4.3–8.4)	1.01 (0.57–1.79)	0.98	0.83 (0.45–1.54)	0.56
Total	48/755.6	6.4 (4.8–8.4)				

py, person-years; CI, confidence interval; NET-EN, norethisterone enanthate; DMPA-IM, depot medroxyprogesterone acetate; REF, reference; HSV-2, herpes simplex virus type 2.
**Adjusted for baseline age and marriage/cohabitation, and time-varying oral contraceptive use, frequency of intercourse, and condom use at last vaginal sex.*

Syphilis Infection

The overall prevalence of syphilis among South African users of injectable progestin contraception at baseline was 1.2% (**Table 1**). Users of DMPA-IM and NET-EN did not differ in their likelihood of diagnosis at baseline ($p = 0.08$). Among injectable progestin contraceptive users, 17 syphilis infections were detected over ∼2,945 pys of follow-up for an overall incidence of 0.6/100 pys (**Table 2**), which did not differ significantly by progestin type (DMPA-IM vs. NET-EN: 0.4/100 py, 95% CI 0.2–0.8/100 py, vs. 0.9/100 py, 95% CI 0.5–1.6/100 py) (HR 0.44, 95% CI 0.17–1.16, $p = 0.10$). Adjustment for potential confounding variables did not qualitatively change the estimate for the difference in hazard of syphilis infection (aHR 0.41, 95% CI 0.15–1.10, $p = 0.08$). Among women who disclosed at baseline that they did not use condoms, estimates were not calculated, due to an inadequate number of endpoints ($n = 1$). Restricting analyses to women under 25 years old did not qualitatively change findings (HR 0.63, 95% CI 0.19–2.08, aHR 0.60, 95% CI 0.18–2.01).

Herpes Simplex Virus Type 2 Infection

The overall prevalence of HSV-2 among all South African users of injectable progestin contraception at baseline was 46.5%. Among the subset of participants who had HSV-2 outcome data during follow-up, HSV-2 prevalence at baseline was 46.3%. Users of DMPA-IM had a higher likelihood of diagnosis at baseline compared to NET-EN users (51.3 vs. 38.6%, $p < 0.001$). Among those injectable progestin contraceptive users who were negative for HSV-2 at baseline ($n = 634$), 48 HSV-2 infections occurred over 756 pys of follow-up for an overall incidence of 6.4/100 pys (**Table 2**), which did not differ significantly by progestin type (DMPA-IM vs. NET-EN: 6.3/100 py, 95% CI 4.3–9.2/100 py, vs. 6.4/100 py, 95% CI 4.2–9.8/100 py) (HR 1.01, 95% CI 0.57–1.79, $p = 0.98$). Adjustment for potential confounding variables did not qualitatively change the estimate for the difference in hazard of HSV-2 infection between DMPA-IM and NET-EN users (aHR 0.83, 95% CI 0.45–1.54, $p = 0.56$). Estimates were not generated for the subgroup of women who disclosed at baseline that they did not use condoms, due to a small number of endpoints ($n = 3$). Restricting analyses to women < 25 years old did not qualitatively change findings (HR 0.73, 95% CI 0.37–1.42, $p = 0.35$; aHR 0.58, 95% CI 0.28–1.20, $p = 0.14$).

DISCUSSION

In this analysis of 2,911 women who used injectable progestin-only contraception at South African VOICE sites, DMPA-IM and NET-EN users differed in their likelihood of HSV-2 diagnosis at baseline. However, no difference was observed between DMPA-IM and NET-EN users for the acquisition of CT, NG, TV, syphilis, or HSV-2 infection during follow-up. Findings were not modified when adjusted for potentially confounding variables. Similar estimates were found among women who disclosed a recent history of unprotected sex and women under 25 years old.

This analysis included 448 incident CT infections, 103 incident NG infections, 150 incident TV infections, 17 incident

syphilis infections, and 48 incident HSV-2 infections detected over approximately 2,700 person-years of follow-up, constituting one of the largest datasets for observational analyses of hormonal contraceptive use and STI acquisition in a single study. Characterization of exposure for the model was strengthened by frequent measurement and on-site provision of contraception throughout study participation. Endpoints for CT and NG were measured with high sensitivity and specificity *via* DNA amplification assay performed on urine.

This analysis focused on the comparison between two different injectable methods, with the goal of decreasing (but not necessarily eliminating) confounding related to condom use, coital frequency, and/or partner selection. Such differences were anticipated to be lesser between DMPA and NET-EN users as compared with those between hormonal and non-hormonal methods of contraception. Comparisons between injectable methods also have a greater utility for women who want to avoid pregnancy and for contraceptive providers.

Several studies have investigated whether HC use increases the risk of contracting STIs in women. However, most findings are from observational analyses, such as this one, and few have compared injectable methods with each other. The VOICE study was not designed to investigate the association between contraceptive types and the acquisition of STIs. Thus, this study design, like all observational designs is subject to bias, and results must be interpreted cautiously. In this analysis, the observed difference in HSV-2 at baseline between DMPA-IM and NET-EN users is likely related to differences in age. Compared to NET-EN users, DMPA-IM users reported higher numbers of sex acts per week and were more likely to be married or cohabitating, suggesting potentially more opportunities for incident infections. Having more than one partner was more frequently reported by NET-EN users compared with DMPA-IM users. Reported condom use at last sex appeared similar between the two groups, although it was likely over-reported, given the high incidence of STI observed during the study. While analyses adjusting for potential confounders did not show differences between DMPA-IM and NET-EN users for the acquisition of STI during follow-up, residual confounding in these results cannot be ruled out.

More frequent assessment of STI outcomes may have been more informative. As sub-clinical STI are common, contraceptive exposure contemporaneous with STI diagnosis may not correspond with contraceptive exposure at the time of true STI acquisition. It is unknown if partner treatment differed between DMPA-IM and NET-EN users. As single-dose directly observed therapy (for CT, NG, and TV) was encouraged but not required, it is possible that some STI treatment was not completed between tests. However, the investigators have no reason to suspect under-treatment, if it occurred, differed by exposure of interest. If women received STI treatment off-site without study staff knowledge, this may have impacted results; a substantial impact is unlikely, though, as women received monthly care at sites, accessed free STI testing there, and were asked about medical care and medications taken between visits. If this did occur, it may have been more likely for symptomatic infections. Lastly, participants were South African women participating in HIV prevention research, potentially limiting generalizability.

Had this analysis estimated more incident STIs in DMPA-IM compared with NET-EN users, it might have suggested that the previously observed difference in HIV-1 incidence between these groups was related either to differences in behavioral risk or a biological mediating effect of these STIs between injectable progestin contraception exposure and HIV-1 acquisition. However, such a trend was not observed. Strong evidence supports the role of both ulcerative and non-ulcerative STI in promoting HIV-1 transmission by increasing HIV-1 infectiousness and susceptibility through various biological mechanisms (26). Increased STI risk has also been proposed as a mechanism of mediation by which HC could increase the risk of HIV-1 infection in women (27). These results do not rule out the possibility that higher acquisition of HIV-1 in DMPA-IM compared with NET-EN users, previously observed in this cohort, is related to unmeasured confounding. In part, comparisons between DMPA-IM and NET-EN users were undertaken with the hypothesis that restriction to a single contraceptive delivery system (injection) might reduce behavioral confounding potentially associated with comparison of injectable contraceptive use to no HC use. However, unmeasured differences in behavioral risk for STI may still be present between DMPA-IM and NET-EN users and could explain differential HIV-1 acquisition. Exposure to STIs analyzed in this study may or may not overlap with HIV-1 exposure in sexual networks of the study participants. Thus, DMPA-IM and NET-EN users may have similar exposure risk for these STIs and differential exposure risk for HIV-1 infection. The exclusion of those who switched injectable contraceptive type during follow-up, or who initiated injectable progestin contraception following last STI testing (for each STI) means that this cohort differed slightly in composition from the cohort previously analyzed for difference in HIV-1 acquisition. However, a non-significant increased risk for acquisition of HIV-1 persisted in this smaller cohort for DMPA-IM compared with NET-EN users.

The incidence of STI was unfortunately high in this cohort, as has been noted in other estimates from South Africa (9, 16, 28). Results of this analysis suggest that DMPA-IM and NET-EN users have a similar risk of incidence of CT, NG, TV, syphilis, and HSV-2 infection. While the ECHO trial was not able to address outstanding questions about potential differences in STI or HIV risk associated with DMPA-IM compared with NET-EN use, results from secondary analyses of data from several HIV prevention trials suggest that this risk is not likely to be substantially different by injectable type. Such analyses, including this analysis on STI outcomes from the VOICE trial, largely support current WHO guidance recommending no restriction of use for injectable progestogen contraception, based on their risk of STI or HIV acquisition (11, 29).

Sufficient data support the widespread acceptability of the injectable route of delivery for contraception, which remains a significant proportion of family planning uptake in areas simultaneously impacted by the HIV epidemic and high rates of maternal mortality. Despite many years of controversy regarding potential risks associated with injectable contraception, particularly DMPA-IM, the available evidence does not suggest a clear benefit for individual users of injectable contraception to switch from DMPA-IM to NET-EN use, based on their

risk for STI or HIV acquisition. However, the evidence clearly supports benefits at individual and public health levels of contraceptive access and informed choice, which still lag in many areas impacted by high rates of STI and maternal mortality. Reproductive health services as currently designed and implemented have unfortunately been inadequate to address gaps in knowledge and practices leading to a reduction in STI. A recent report from UNFPA notes that ∼65% of reproductive age women in South Africa are able to make their own decisions regarding sexual and reproductive health and rights, including deciding on their own health care, the use of contraception, and saying no to sex, suggesting that efforts to curb STI rates must address a range of underlying drivers. Thus, while the high incidence of multiple STIs in this cohort points to the critical need for expanded access to comprehensive, integrated, sexual and reproductive health services, including prevention and treatment of STIs, results in this study also reflect a larger public health crisis that cannot be addressed by modifications to service delivery alone.

DATA AVAILABILITY STATEMENT

The datasets generated for this article are not readily available because data requests are subject to review by MTN. Requests to access the datasets should be directed to MTN Regulatory, mtnregulatory@mtnstopshiv.org.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins Bloomberg School of Public Health. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LN, BR, and JM conceptualized the article and analysis plan. LN did the analyses in collaboration with BR. LN drafted the initial report. BR, SH, JB, ZC, GN, TP-P, JP, and JM contributed to the content and revisions. GR, GN, TP-P, and RP contributed to data collection. KG contributed to study operations. All authors contributed to article content.

FUNDING

LN, BR, SH, JB, ZC, GN, TP-P, RP, KG, and JM report support from the National Institutes of Health (NIH). LN reports support from the Johns Hopkins Training Program in Sexually Transmitted Infections (T32-AI050056). The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, and UM1AI106707) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the NIH. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official views of the NIH.

ACKNOWLEDGMENTS

The authors thank all team members and participants in the VOICE study, with special gratitude for the contributions of the late GR, whose dedication to advancing the reproductive health of women lives on. LN additionally thanks Dr. Taha E. Taha of the Johns Hopkins Bloomberg School of Public Health.

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Conflict of Interest: TP-P is the co-editor of the 'Integration of HIV Prevention with Sexual and Reproductive Health Services' special issue to which this manuscript is submitted.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

BRIEF RESEARCH REPORT
published: 21 July 2021
doi: 10.3389/frph.2021.667413

Contraceptive Method Mix and HIV Risk Behaviors Among Kenyan Adolescent Girls and Young Women Seeking Family Planning Services: Implications for Integrating HIV Prevention

*Edward Nyaboe[1], Anna Larsen[2], Joseph Sila[3], John Kinuthia[3,4], George Owiti[3], Felix Abuna[3], Pamela Kohler[4,5], Grace John-Stewart[2,4,6,7] and Jillian Pintye[8]**

[1] Kenya Medical Research Institute, Nairobi, Kenya, [2] Department of Epidemiology, University of Washington, Seattle, WA, United States, [3] Department of Research and Programs, Kenyatta National Hospital, Nairobi, Kenya, [4] Department of Global Health, University of Washington, Seattle, WA, United States, [5] Department of Child, Family, and Population Health, University of Washington, Seattle, WA, United States, [6] Department of Medicine, University of Washington, Seattle, WA, United States, [7] Department of Pediatrics, University of Washington, Seattle, WA, United States, [8] Department of Biobehavioral Nursing and Health Informatics, University of Washington, Seattle, WA, United States

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Edited by:
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***Correspondence:**
Jillian Pintye
jpintye@uw.edu

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: 13 February 2021
Accepted: 22 June 2021
Published: 21 July 2021

Citation:
Nyaboe E, Larsen A, Sila J, Kinuthia J, Owiti G, Abuna F, Kohler P, John-Stewart G and Pintye J (2021) Contraceptive Method Mix and HIV Risk Behaviors Among Kenyan Adolescent Girls and Young Women Seeking Family Planning Services: Implications for Integrating HIV Prevention. Front. Reprod. Health 3:667413. doi: 10.3389/frph.2021.667413

Background: Understanding HIV risk behaviors among adolescent girls and young women (AGYW) seeking contraception could help inform integrating HIV prevention services within family planning (FP) clinics.

Methods: From 10/2018 to 04/2019, we conducted a survey at 4 FP clinics in Kisumu, Kenya to evaluate risk behaviors among AGYW without HIV infection seeking contraception. All AGYW aged 15–24 were invited to participate following receipt of FP services. Adolescent girls and young women initiating or refilling contraception were included in this analysis. Long-acting reversible contraceptives (LARC) included intrauterine devices, implants, or injectables. Non-LARC methods included oral contraceptive pills (OCP) or condoms. We used an empiric risk score to assess HIV risk behaviors; HIV risk scores of ≥5 (corresponding to 5–15% HIV incidence) defined "high" HIV risk.

Results: Overall, 555 AGYW seeking FP were included. Median age was 22 years [interquartile range (IQR) 20–23], median completed education was 12 years (IQR 10–12); 23% of AGYW had HIV risk scores of ≥5. The most frequent form of contraception was injectables (43%), followed by implants (39%). After adjustment for education, prior pregnancy, and marital status, LARC users more frequently engaged in transactional sex than non-LARC users [6 vs. 0%, adjusted prevalence ratio (PR) = 1.17, 95% CI 1.09–1.29, $p < 0.001$]; LARC use was not associated with HIV risk scores ≥5. Among LARC users, AGYW using injectables more frequently had condomless sex compared to AGYW using other LARC methods (85 vs. 75%, adjusted PR = 1.52, 95% CI 1.09–2.10, $p = 0.012$); injectable use was not associated with HIV risk scores ≥5.

Conclusions: Adolescent girls and young women seeking contraception frequently had high HIV risk, emphasizing the importance of integrating HIV prevention within FP. Multipurpose technologies for contraception and HIV prevention could particularly benefit AGYW.

Keywords: contraceptive use, LARC, HIV prevention, adolescents, Africa

INTRODUCTION

Long-acting reversible contraceptives (LARCs) have the potential to reduce unintended pregnancy and associated morbidity and mortality, particularly in high HIV prevalence settings of sub-Saharan Africa where 47% of women have an unmet need for modern contraception (1, 2). Following goals set out by the Family Planning 2020 (FP2020) initiative, LARC access is expanding in sub-Saharan Africa, with younger and less educated women reached through demand generation approaches and service delivery mechanisms (3, 4). Results from the recent ECHO (Evidence for Contraceptive Options in HIV Outcomes) randomized trial among women recruited through family planning (FP) clinics in eSwatini, Kenya, South Africa, and Zambia provide strong evidence that HIV acquisition risk does not substantially differ between LARC methods commonly used in African settings (5). However, ECHO found an alarmingly high HIV incidence rate (4.3%) among adolescent girls and young women (AGYW) despite an individualized HIV prevention package provided to all participants and country-wide HIV treatment and prevention programs (5). These findings highlight a gap in integration of HIV prevention services for AGYW into routine FP care.

Behavioral risks for HIV acquisition may differ among AGYW who self-select certain FP methods over others in real-world settings. Understanding behavioral profiles among AGYW seeking contraception could help inform integration of tailored HIV prevention counseling and interventions within FP clinics. We evaluated the contraceptive method mix and HIV behavioral risk factors among AGYW seeking FP services at routine clinics in Kisumu County, Kenya.

METHODS

Study Setting and Design

The PrIYA Program, a collaboration with the Department of Health and Sanitation, Kisumu County, and the National AIDS and STI Control Programme (NASCOP), was a 2-year implementation project which integrated delivery of PrEP into routine maternal child health and FP systems (6–8). The program aimed to reach AGYW at high risk for HIV acquisition and was implemented from June 2017 to October 2018 in 16 facilities in Kisumu County, Kenya, which has an adult HIV prevalence of 19.9%. (9–11). We conducted a survey at a subset of former PrIYA sites to evaluate behavioral characteristics and HIV risk factors among AGYW in FP clinics (12, 13). Four public-sector facilities were selected based on having the highest monthly enrollment of new FP clients.

Study Population

All HIV-negative women at the four facilities were approached after receipt of routine FP services, including HIV testing, from October 2018 to June 2019. Those between 15 and 24 years and who received FP services at the facility, including confirmation of HIV-negative status via routine HIV testing, were eligible for enrollment. All eligible women interested in participating were enrolled upon provision of written informed consent. Adolescent girls and young women were included in the current analysis if they initiated or refilled an FP method, including injectables, implants, IUDs, oral contraceptive pills (OCP), or condoms. We excluded AGYW who were removing a contraceptive method or seeking other non-contraceptive services (e.g., cervical cancer screening) at the FP clinics.

Data Collection

Trained study nurses administered surveys in Kiswahili, Dholuo, or English using tablets. Surveys were field-tested and included questions about demographics, partnership characteristics, sexual and reproductive behaviors, perceived HIV risk, and HIV risk behaviors. Long-acting reversible contraceptive was defined as IUDs, implants, or injectables. Non-LARC methods included OCP or condoms. Contraceptive type was mutually exclusive and defined as the primary method used for contraception (e.g., no dual methods).

Behavioral HIV Risk Assessment

We evaluated participants for HIV behavioral risk factors using a standardized risk assessment tool used by the Kenya Ministry of Health to screen for PrEP which includes the following behavioral characteristics: partner HIV status, condomless sex, engagement in transactional sex, experiencing intimate partner violence, and being forced to have sex in the last 6 months (14). We used an empiric risk score to further assess HIV risk behaviors which was validated to predict risk of HIV acquisition among young women in sub-Saharan African settings (15). Characteristics included in the risk score were age <25 years old (risk score of 2), not living with a spouse/partner (1), any alcohol use within the past 30 days (1), receiving financial support from a partner (1), and having a partner with other sexual partners (2) or not knowing if a partner has other sexual partners (1, 15). "High" HIV risk is defined by an HIV risk score of ≥5 (corresponding to 5–15% HIV incidence in cohorts of African women) (15). Risk scores of ≤4 correspond to HIV incidence of 0–5% and are considered "low" HIV risk. We also assessed self-perceived risk for HIV acquisition on a four-point Likert scale by asking participants "*What is your gut feeling about how likely you are*

to get infected with HIV?," with possible responses of very likely, somewhat likely, very unlikely, or extremely unlikely (16).

Statistical Analysis

We used descriptive statistics to determine the frequency of demographic characteristics, pregnancy history and FP use, HIV risk perception, and HIV risk behaviors (15). We used Poisson regression models, clustering by facility, to calculate prevalence ratios (PRs) for HIV risk factors by LARC use status. Potential correlates of LARC use identified in univariable models were adjusted for years completed education, having at least one prior pregnancy, and marital status in multivariable models; adjustment variables were determined *a priori* because of their known association with LARC use based on prior studies. We used similar models to calculate PRs for HIV risk factors by injectable use status among LARC users. Analyses were performed in STATA 15.0.

Considerations for Human Subjects

The Kenyatta National Hospital-University of Nairobi Ethics Research Committee and University of Washington Human Subjects Review Committee reviewed and approved the study protocol, informed consent forms, and data collection tools. We also obtained approval by the Kisumu County Department of Health and health administrators within the health facilities involved.

RESULTS

Overall, 555 AGYW seeking FP services (initiating or refilling an FP method) completed the survey, and were included in this analysis (**Figure 1**). Median age was 22 years [interquartile range (IQR) 20–23], median completed education was 12 years (IQR 10–12), 24% of women were currently in school, and 59% were married. The majority 464 (84%) of AGYW had a current primary partner, of whom 87% reported their partner was HIV-negative and 12% reported not knowing their partner's HIV status; 4 (1%) AGYW reported having a partner known to be living with HIV. Approximately one-fourth (23%) of AGYW had HIV risk scores ≥5.

The most frequent form of contraception was injectables (43%), followed by implants (39%), pills (12%), intrauterine devices (3%), and condoms alone (3%). Long-acting reversible contraceptive use was associated with years of completed education and having a prior pregnancy (**Table 1**). There were no differences in frequency of HIV risk scores ≥5 between AGYW using LARC compared to those using non-LARC methods. Adolescent girls and young women who used LARC more frequently reported engaging in transactional sex in the last 6 months compared to non-LARC methods users (6 vs. 0%, adjusted PR = 1.17, 95% CI 1.09–1.29, $p < 0.001$). There were no differences in other behavioral risk factors for HIV between LARC and non-LARC users.

Among AGYW using LARC ($n = 460$), injectable users were less frequently to report being currently in school and a prior pregnancy (**Table 2**). There were no differences in frequency of HIV risk scores ≥5 between AGYW using injectables compared to those using other LARC methods. Among other individual HIV risk behaviors, AGYW using injectables more frequently had condomless sex in the last 6 months compared to AGYW using other LARC methods (85 vs. 75%, adjusted PR = 1.52, 95% CI 1.09–2.10, $p = 0.012$), yet less frequently had ≥4 lifetime sexual partners (12 vs. 20%, adjusted PR = 0.75, 95% CI 0.64–0.88, $p < 0.001$). There were no other differences in HIV risk behaviors between AGYW using injectables compared to those using other LARC methods.

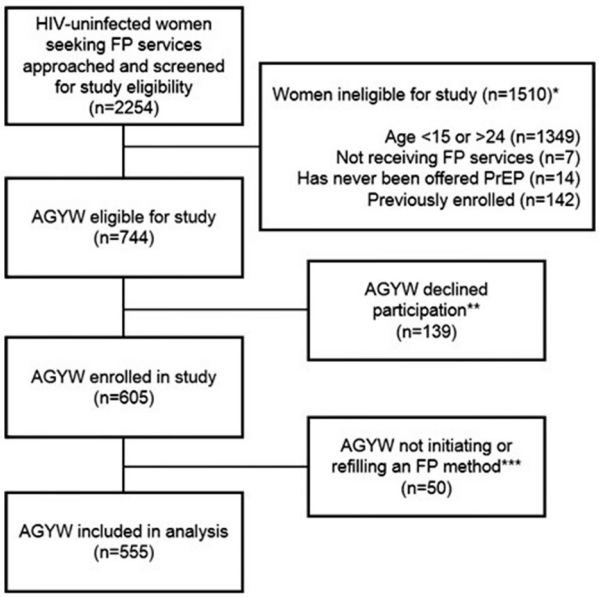

FIGURE 1 | Flow chart of participant inclusion in the present analysis among HIV-uninfected AGYW seeking family planning services in Western Kenya. AGYW, adolescent girls and young women. *Categories describing reasons for ineligibility are not mutually exclusive. **Reasons for declination were not captured systematically. Anecdotally, the most common reason for declining was lack of time. Other common reasons included infant crying/fussing and male partner refusal. ***Fifty women were not initiating or refilling a family planning method, thus were excluded from the present analysis.

Overall, 14% of AGYW reported that they felt acquiring HIV in the next year was very likely. AGYW with partners of unknown HIV status or who were known to be living with HIV were more likely to report high self-perceived HIV risk than AGYW with HIV-negative partners (42 vs. 8%, PR = 1.31, 95% CI 1.24–1.39, $p < 0.001$). There were no differences in high self-perceived HIV risk among AGYW with risk scores ≥5 compared to those with scores <5 (18 vs. 12%, PR = 1.05, 95% 98–1.13, $p = 0.166$). There were also no appreciable differences in HIV risk perception across contraceptive methods (data not shown).

DISCUSSION

In this survey among Kenyan AGYW within routine FP settings, LARC use was frequent with >80% of AGYW using either injectables or implants. Nearly one-quarter of AGYW had HIV risk scores ≥5, indicating high behavioral risk for HIV

TABLE 1 | Demographic characteristics and HIV behavioral risk factors among LARC and non-LARC contraceptive users ($n = 555$)[a].

Characteristic	Overall ($n = 555$)	Contraceptive type		Univariate Poisson regression		Multivariate Poisson regression	
		LARC ($n = 475$)	Non-LARC ($n = 80$)	Unadjusted PR (95% CI)	*p*-value	Adjusted PR (95% CI)	*p*-value[b]
DEMOGRAPHIC CHARACTERISTICS							
Age ≥22 years	285 (51.4%)	253 (53.3%)	32 (40.0%)	1.08 (0.99–1.17)	0.066		
Completed education ≤12 years	423 (76.2%)	355 (74.7%)	68 (85.0%)	1.08 (1.03–1.14)	0.002	1.08 (1.01–1.16)	0.020
Currently in school	121 (21.9%)	98 (20.7%)	23 (28.7%)	0.93 (0.85–1.02)	0.136		
Regularly employed	80 (14.5%)	73 (15.5%)	7 (8.8%)	1.08 (1.06–1.10)	<0.001	1.00 (0.93–1.07)	0.962
Currently has primary partner	464 (83.6%)	394 (82.9%)	70 (87.5%)	0.96 (0.85–1.08)	0.446		
At least one prior pregnancy	446 (80.4%)	402 (84.6%)	44 (55.0%)	1.35 (1.23–1.47)	<0.001	1.34 (1.20–1.48)	<0.001
BEHAVIORAL HIV RISK FACTORS							
Total lifetime sexual partners (≥4)	83 (15.0%)	74 (15.6%)	9 (11.3%)	1.05 (1.00–1.10)	0.044	0.99 (0.92–1.07)	0.885
Partner HIV status unknown or positive	62 (13.4%)	50 (12.8%)	12 (17.1%)	0.94 (0.87–1.01)	0.128		
Condomless sex (last 6 months)	437 (78.7%)	380 (80.0%)	57 (71.3%)	1.08 (1.02–1.15)	0.012	1.02 (0.98–1.06)	0.422
Transactional sex (last 6 months)	28 (5.0%)	28 (5.9%)	0 (0.0%)	1.18 (1.04–1.34)	0.009	1.17 (1.09–1.24)	<0.001
Forced sex (last 6 months)	38 (6.8%)	35 (7.4%)	3 (3.8%)	1.08 (0.94–1.25)	0.275		
Intimate partner violence[c]	12 (2.6%)	11 (2.8%)	1 (1.4%)	1.08 (1.01–1.16)	0.031	1.04 (0.93–1.15)	0.481
High self-perceived HIV risk[d]	76 (13.7%)	65 (13.7%)	11 (13.8%)	1.00 (0.93–1.07)	0.990		
EMPIRIC HIV RISK SCORE FACTORS							
Unmarried/Not living with partner	228 (41.1%)	180 (37.9%)	48 (60.0%)	0.94 (0.88–0.99)	0.026	0.99 (1.20–1.48)	0.573
Alcohol use (past 30 days)	75 (13.5%)	65 (13.7%)	10 (12.5%)	1.01 (0.95–1.08)	0.655		
No financial support from partner	12 (2.2%)	10 (2.1%)	2 (2.5%)	0.97 (0.66–1.43)	0.890		
Primary partner has other partners	203 (36.6%)	174 (36.6%)	29 (36.3%)	1.00 (0.98–1.03)	0.929		
High HIV risk (risk score: ≥5)[e]	125 (22.5%)	99 (20.8%)	26 (32.5%)	0.91 (0.86–0.86)	0.001	0.98 (0.93–1.02)	0.326

LARC, long-acting reversible contraception.

[a] *Other LARC methods include implants and intrauterine devices.*

[b] *Prevalence ratios adjusted for years completed education, having at least one prior pregnancy, and marital status.*

[c] *Intimate partner violence defined as Hurt-Insult-Threaten-Scream (HiTS) score ≥10 (32).*

[d] *High self-perceived HIV risk, Somewhat/very likely to acquire HIV; Low self-perceived HIV risk, Extremely/very unlikely to acquire HIV.*

[e] *VOICE risk scoring (16): Age < 25 = 1 (all participants in this analysis are <25, thus we have excluded age from the table but included the age score in the risk score calculation), Married = 2, any alcohol = 1, partner provides financial support = 1, partner has other partners: yes = 2, do not know = 2.*

acquisition (15), though only 14% of AGYW felt acquiring HIV in the next year was very likely. Our results add to recent data underscoring that AGYW seeking FP services frequently have behavioral risks for HIV acquisition and that differences between AGYW who self-select certain FP methods are important considerations for HIV prevention interventions. Our findings support the need to integrate HIV prevention services within FP with tailored counseling for AGYW. Given the high frequency of LARC methods observed in our study population, long-acting PrEP agents and multipurpose technologies may be particularly attractive in this setting (17).

In our study, report of condomless sex in the last 6 months was high (80%), similar to the ECHO trial in which 73% of participants recruited from FP clinics reported condomless sex in the last 3 months (5). We found that AGYW using injectables more frequently reported condomless sex than AGYW using other LARC. Prior to the ECHO trial, observational studies evaluating the causal relationship between DMPA and HIV risk were prone to concerns about confounding factors, such as underreported condomless sex (18). Studies evaluating biomarkers of condomless sex among women in Zimbabwe demonstrated that misreporting of condom use does not differ between injectable, OCP, or non-hormonal contraception users, though implants users were not evaluated (19). Our results suggest that AGYW who self-select injectable contraception may be more likely to have condomless sex and subsequently higher HIV risk in real-world settings. Adolescent LARC users may no longer perceive a need for condoms if the likelihood of pregnancy

TABLE 2 | Demographic characteristics and HIV behavioral risk factors among injectable and other LARC users ($n = 475$)[a].

Characteristic	Overall ($n = 475$)	Contraceptive type		Univariate Poisson regression		Multivariate Poisson regression	
		Injectable ($n = 240$)	Other LARC ($n = 235$)	Unadjusted PR (95% CI)	*p*-value	Adjusted PR (95% CI)	*p*-value[b]
DEMOGRAPHIC CHARACTERISTICS							
Age ≥22 years	253 (53.3%)	124 (52.8%)	129 (53.8%)	1.01 (0.89–1.16)	0.766		
Completed education ≤12 years	355 (74.7%)	181 (75.4%)	174 (74.0%)	0.96 (0.71–1.31)	0.814		
Currently in school	98 (20.7%)	43 (18.1%)	55 (23.4%)	0.84 (0.79–0.90)	<0.001	0.72 (0.64–0.80)	<0.001
Regularly employed	73 (15.5%)	41 (17.2%)	32 (13.7%)	1.14 (1.05–1.24)	0.002	1.21 (0.97–1.50)	0.095
Currently has primary partner	394 (82.9%)	200 (83.3%)	194 (82.6%)	1.03 (0.79–1.33)	0.835		
At least one prior pregnancy	402 (84.6%)	193 (80.4%)	209 (88.9%)	0.75 (0.67–0.83)	<0.001	0.63 (0.53–0.74)	<0.001
BEHAVIORAL HIV RISK FACTORS							
Total lifetime sexual partners (≥4)	74 (15.6%)	28 (11.7%)	46 (19.6%)	0.72 (0.57–0.89)	0.003	0.75 (0.64–0.88)	<0.001
Partner HIV status unknown or positive	50 (12.8%)	42 (19.0%)	32 (14.6%)	1.25 (0.93–1.69)	0.133		
Condomless sex (last 6 months)	380 (80.0%)	205 (85.4%)	175 (74.5%)	1.46 (1.06–2.03)	0.022	1.52 (1.09–2.10)	0.012
Transactional sex (last 6 months)	28 (5.9%)	12 (5.0%)	16 (6.8%)	0.84 (0.73–0.96)	0.013	0.93 (0.74–1.16)	0.523
Forced sex (last 6 months)	35 (7.4%)	17 (7.1%)	18 (7.7%)	0.96 (0.85–1.08)	0.475		
Intimate partner violence[c]	11 (2.8%)	5 (2.5%)	6 (3.1%)	0.89 (0.64–1.24)	0.497		
High self-perceived HIV risk[d]	65 (13.7%)	33 (13.8%)	32 (13.6%)	1.01 (0.82–1.24)	0.940		
EMPIRIC HIV RISK SCORE FACTORS							
Unmarried/not living with partner	180 (37.9%)	89 (37.1%)	91 (38.7%)	0.98 (0.92–1.05)	0.630		
Alcohol use (past 30 days)	65 (13.7%)	36 (15.0%)	29 (12.3%)	1.11 (0.87–1.42)	0.384		
No financial support from partner	10 (2.1%)	235 (97.9%)	230 (97.9%)	0.99 (0.61–1.61)	0.966		
Primary partner has other partners	174 (36.6%)	88 (36.7%)	86 (36.6%)	1.00 (0.95–1.06)	0.979		
High HIV risk (risk score: ≥5)[e]	99 (20.8%)	51 (21.3%)	48 (20.4%)	1.02 (0.93–1.12)	0.603		

LARC, long-acting reversible contraception.

[a]Other LARC methods include implants and intrauterine devices.

[b]Prevalence ratios adjusted for years completed education, having at least one prior pregnancy, and marital status.

[c]Intimate partner violence defined as Hurt-Insult-Threaten-Scream (HiTS) score ≥10 (34).

[d]High self-perceived HIV risk, Somewhat/very likely to acquire HIV; Low self-perceived HIV risk, Extremely/very unlikely to acquire HIV.

[e]VOICE risk scoring (16): Age <25 = 1 (all participants in this analysis are <25, thus we have excluded age from the table but included the age score in the risk score calculation), Married = 2, any alcohol = 1, partner provides financial support = 1, partner has other partners: yes = 2, do not know = 2.

is minimal, even if they have other HIV risk behaviors (20). As uptake of LARC increases among AGYW, there is an urgent need to incorporate HIV prevention services like PrEP within FP settings (7). Multipurpose prevention technologies (MPTs) in the pipeline for prevention of HIV and unintended pregnancy in one formulation could be particularly useful for AGYW who may benefit from HIV prevention tools and for whom condoms are not preferred (21).

Similar to previous studies, we found that only a small proportion of AGYW in FP settings self-perceive high HIV risk, despite frequently reporting HIV risk behaviors (7, 22). Family planning providers are well-positioned to counsel AGYW on HIV risk behaviors and to ensure AGYW are aware of and offered comprehensive HIV prevention options (23). In the PrIYA Program (7, 8, 24), 16% of AGYW with HIV risk factors accepted PrEP (7, 8) and low perceived HIV risk was the primary reason for declining PrEP. Among the current study population, we previously reported PrEP uptake was 4% overall under programmatic conditions and 78% of AGYW with high behavioral HIV risk declined PrEP due to low perceived risk of HIV (13). To date, studies evaluating integrated delivery of FP with HIV prevention services primarily focus on provision of biomedical interventions such as PrEP and HIV testing (7, 25, 26). Interventions promoting confidentiality, supportive provider interaction, specialized provider training, and the removal of logistic barriers have positive effects on reproductive health outcomes among AGYW (27), though more rigorous research is needed. One ongoing study tests a standardized patient actor-based provider training to improve PrEP counseling for AGYW in Kenya and case scenarios include navigation of HIV risk assessment (28). Our findings support that counseling on HIV prevention within FP settings should consider how risk perception influences uptake of HIV prevention services among AGYW. More research is needed on that moves beyond

provision of HIV prevention interventions to address factors influencing uptake within FP settings such as low risk perception.

Our study has limitations. We ascertained the primary FP method being initiated or refilled during the participant's clinic visit and did not assess dual use of condoms with other methods. However, condomless sex was very frequently reported in our study. Frequency of some HIV risk behaviors was rare (e.g., transactional or forced sex) and therefore our statistical power was limited to detect some associations. Our data are limited to AGYW seeking contraception at public sector facilities and may not be representative of AGYW who seek contraception elsewhere (e.g., retail pharmacies).

In conclusion, our results support that approaches currently in development to concurrently prevent HIV and unintended pregnancy may be particularly beneficial for AGYW, especially those who prefer injectable contraception and report condomless sex. Counseling on behavioral risks and HIV prevention tailored to AGYW could be useful within FP settings. More implementation research is needed on integrating HIV prevention services into FP to address other factors influencing uptake.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Kenyatta National Hospital-University of Nairobi Ethics Research Committee and University of Washington Human Subjects Review Committee reviewed and approved the study protocol, informed consent forms, and data collection tools. We also obtained approval by the Kisumu County Department of Health and health administrators within the health facilities involved. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GJ-S and JP designed the study. EN, JS, and AL analyzed the data. EN, JP, and AL drafted the manuscript. JK, GO, FA, PK, and GJ-S contributed to the interpretation of the results and critically revising the manuscript for important intellectual content, and all authors approved the manuscript for publication. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the US National Institutes of Health (R01HD094630, R01HD100201, R01NR019220, and R01AI125498). During manuscript development, EN was a scholar in the International AIDS Research and Training Program, supported by the Fogarty International Center (D43TW009783). The PrEP Implementation for Young Women and Adolescents (PrIYA) Program was funded by the United States Department of State as part of the DREAMS Innovation Challenge (Grant # 37188-1088 MOD01), managed by JSI Research & Training Institute, Inc. The PrIYA Team was supported by the University of Washington's Center for AIDS Research Behavioral Sciences Core (CFAR BSC) (P30 AI027757) and the Global Center for Integrated Health of Women, Adolescents, and Children (Global WACh).

ACKNOWLEDGMENTS

We thank the PrIYA study team and clients for their time and contributions. We thank the Kenyan Ministry of Health nationally and the Kisumu County Department of health, as well as the facility heads and in-charges for their collaboration.

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Disclaimer: This work was funded by a grant from the United States Department of State as part of PEPFAR's DREAMS Partnership, managed by JSI Research & Training Institute, Inc. (JSI). The opinions, findings, and conclusions stated herein are those of the authors and do not necessarily reflect those of the United States Department of State or JSI.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

OPINION
published: 06 September 2021
doi: 10.3389/frph.2021.704841

Multipurpose Prevention Technologies: Opportunities and Challenges to Ensure Advancement of the Most Promising MPTs

Bethany Young Holt[1]*, *Jim A. Turpin*[2] and *Joseph Romano*[3]

[1] Initiative for Multipurpose Prevention Technologies, CAMI Health, Public Health Institute, Sacramento, CA, United States, [2] Howpin Consulting, Frederick, MD, United States, [3] NWJ Group, LLC, Wayne, PA, United States

Keywords: multipurpose prevention technologies, hiv prevention, STI prevention, contraception, MPTs, sexual and reproductive health

OPEN ACCESS

Edited by:
Renee Heffron, University of Washington, United States

Reviewed by:
Dvora Joseph Davey, University of California, Los Angeles, United States

***Correspondence:**
Bethany Young Holt
byh@cami-health.org

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *04 May 2021*
Accepted: *12 August 2021*
Published: *06 September 2021*

Citation:
Young Holt B, Turpin JA and Romano J (2021) Multipurpose Prevention Technologies: Opportunities and Challenges to Ensure Advancement of the Most Promising MPTs. Front. Reprod. Health 3:704841. doi: 10.3389/frph.2021.704841

INTRODUCTION

The HIV/sexually transmitted infection (STI) syndemics and the unmet need for modern contraceptive methods continue to pose significant health risks for women worldwide (1). Women are at high risk of HIV in many regions of the world, particularly young women and girls in Sub-Saharan Africa where 71% of all new infections are among adolescents (2–4). The risk of HIV acquisition and transmission through mother-to-child transmission (MTCT) and among pregnant and breastfeeding women are significant contributors to the HIV epidemic (5). Rates of STIs, such as gonorrhea, chlamydia, syphilis, and herpes are rising and compounding the risk of HIV acquisition (6, 7). At the same time, an estimated 218 million women in lower- and middle-income countries (LMICs) have an unmet need for contraception (8), and 817 women die each day from preventable causes related to pregnancy or child-birth (7). As awareness of the need to address these interlinked risks has increased, the need for new technologies that combine protection against unintended pregnancy, HIV and other STIs is a growing research priority (9). Addressing these interlinked risks also aligns with the goals of the WHO-led initiative for the elimination of maternal-to-child transmission (EMTCT) of HIV and syphilis as a public health priority (5).

Multipurpose Prevention Technologies (MPTs) are products that simultaneously prevent HIV, other STIs, and/or unintended pregnancy. They have power to revolutionize women's health by providing prevention for multiple indications (10). Additionally, MPTs that combine HIV prevention and contraception may improve uptake of and adherence to HIV pre-exposure prophylaxis (PrEP) by offering streamlined product delivery and eliminating the need for multiple, separate clinic visits to address family planning and other sexual and reproductive health (SRH) needs (11). Given the urgent need to reduce HIV infection in pregnant and breastfeeding women, MPTs that allow for contraception and prevent HIV and other STIs may benefit women who wish to conceive as well as pregnancy and breast feeding women who are not using contraceptives. A study among pregnant women of the dapivirine ring and the Truvada oral tablet aims to assess the safety, adherence and acceptability of these HIV prevention approaches when used during pregnancy which can inform MPT development (12). Yet, even with the potential of MPTs to transform the lives of women everywhere, especially those in LMICs, MPT development is scientifically and logistically complex. The resources critical for transitioning promising pre-clinical product candidates and formulations into clinical evaluation remain limited despite intensified collaborations and investments between government and private sectors.

OPPORTUNITIES

Male and female condoms, when used properly through their multi-spectrum ability to block infection and transmission of HIV and other STIs and prevent pregnancy, are the only currently approved MPT products. The United Nations (UN) Department of Economic and Social Affairs recently reported a worldwide increase in condom use from 1994 to 2015 (13). The global condom market was valued at $6.76 billion in 2017 and is estimated to increase to $11.1 billion by 2023 (14). Yet, for many people condoms are not feasible for a variety of reasons. These include coital dependency, unequal power balance between male and female partners and other challenges that may arise in negotiating condom use in intimate relationships, and sexual preferences that play into condom disuse. Despite these many challenges, alternative contraceptive use and acceptability have markedly increased since the creation of various modern methods [such as the pill and the intrauterine device (IUD)] (13). However, the most commonly used contraceptive methods, namely sterilization, the pill, injectables and IUDs, do not protect against STIs. Thus, condoms are only a precursor to other successful MPTs, in which various drug delivery platforms (e.g., pills, injectables, vaginal rings, and subdermal implants etc) can be leveraged as more user-friendly options.

Over the past decade there has been a growing array of new MPT candidates proposed, with over two dozen in active development. These include intravaginal rings, vaginal and rectal gels, vaginal inserts and films, systemic delivery implants, subdermal microarray patches, and oral tablets containing contraceptives, anti-HIV and/or other STI prevention drugs (15) (**Figure 1**). The majority of MPT candidates are in early pre-clinical stages of development by small biotechnology companies and academic labs. These efforts are largely funded by the United States government, primarily the United States Agency for International Development (USAID) and the National Institutes of Health (NIH).

Multiple end-user preference studies are lending support to the potential reproductive health impact of MPTs, as well as informing on product design strategies. For example, an end-user study conducted in three sub-Saharan Africa countries indicates specific end-user preferences identifying preferred MPT product dosage forms (16). The TRIO Study explored user preferences after use of placebo formulations of oral tablets, intravaginal rings and injectables (17). Further insight into the potential success of long acting MPTs can also be inferred from a study of preference for long-acting injectable PrEP conducted among African and US women (18). In the US, several studies have specifically gauged women's preferences for MPTs (19, 20), including a cross-sectional national survey that assessed women's preferences for MPTs in the form of injectables, vaginal gels, intravaginal rings and diaphragms. Results from these studies indicate a high level of end-user preference for female controlled, discreet, long-acting products, such as injectables. These finding are harmonious with decades of research on contraceptive methods demonstrating use is greater when more method options are available (21). Providing women with an array of MPT method options must then be a goal of any long term MPT development efforts and is essential in creating an MPT product portfolio that realizes the reproductive health impact of MPTs.

Although a start has been made in creating a new generation of MPT products, significant funding is required to bring these MPTS to market. This includes funds to support pre-clinical research for translation to clinical testing, support of clinical testing and small- and large-scale manufacturing. Importantly, this also includes investments of funds, time and expertise to address the complex regulatory requirements that will enable multi-indication MTPs to advance to regulatory approval. Because of this complexity, public and private partnerships between academic researchers, small companies, big pharmaceuticals, the USG, and other supporting groups are needed to foster an end- to-end approach while promoting the advancement of economically viable end-user friendly MPT products. Although resources remain limited, support for MPTs is growing within the U.S. Health and Human Services (22) as well as among European funders and life science investors. Many funding agencies that support MPTs are working to leverage and optimize limited resources to address priorities and gaps to advance the most promising candidates; such strategic collaborations are essential.

The current MPT field is building upon lessons learned from decades of research in contraception, HIV topical microbicide development, systemic HIV prevention products and prevention of non-HIV STIs. A number of single indication contraceptive products are available to women (23–25) and new innovations are also underway for male contraception (25, 26). Single indication HIV-only prevention products are also in development. Importantly, after multiple clinical trials demonstrating efficacy, the dapivirine intravaginal ring for HIV prevention is in the process of gaining regulatory approval in individual countries (27–30). Furthermore, long-acting injectable cabotegravir (CAB-LA) has completed phase 3 trials in men who have sex with men, transgender women, and cisgender women, showing strong efficacy and safety results (31, 32). Likewise, a growing number of HIV prevention combination products are in development that include two oral PrEP compounds approved for use: Truvada® for use by men and women containing emtricitabine and tenofovir disoproxil fumarate (33, 34), and Descovy®, containing emtricitabine and tenofovir alafenamide, which currently is only approved for men who have sex with men (MSM) and transgender women (35). New approaches for prevention of non-HIV STIs include those which address growing concerns around the development of antibiotic resistant STI prevention (36, 37). These include agents which stimulate host immune responses as well as non-immune approaches, including vaginal barrier methods, vaginal biofilm inhibitors, and microbiome modulators (38–42). As with contraceptives, all of these single indication anti-infective products and combination HIV prevention products can be critical components of a future MPT strategy since they can serve as the building blocks for multi-indication MPTs.

CHALLENGES

The increasing number of technology options and new drugs entering the prevention pipeline will require proper

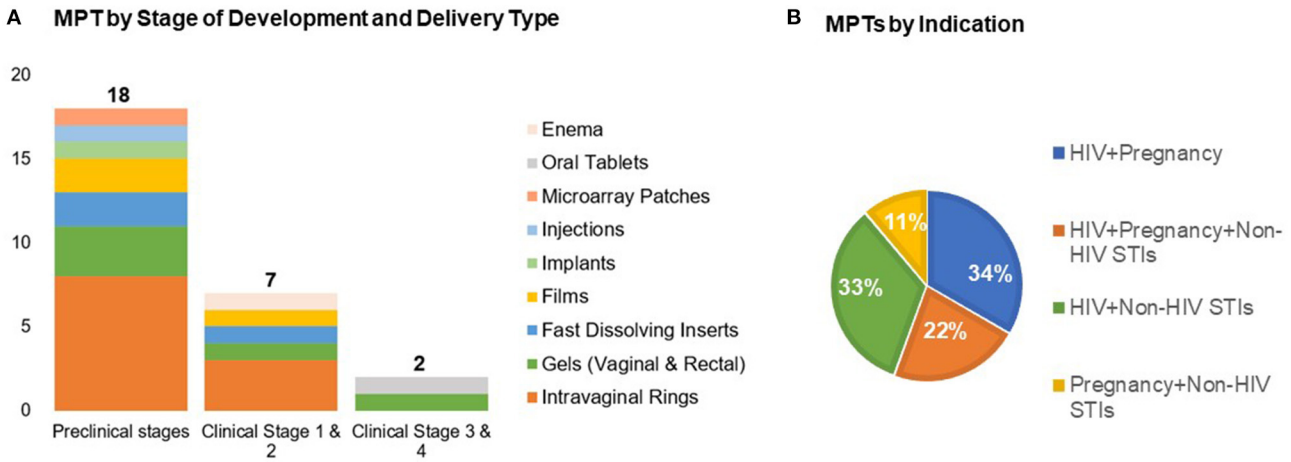

FIGURE 1 | Recent advances in MPTs development by **(A)** stage of development across delivery types and **(B)** indication ($n = 27$). Adapted from the Initiative for MPTs (IMPT) pipeline database (15).

investment to confirm that adequate resources are available to support potential high impact products through licensure and access needs. Challenges include obstacles to manufacturing (e.g., mixing of hormone and non-hormone drug substances/products), clinical trials (e.g., design of Phase 3 multi-indication trials) and other regulatory challenges (e.g., requirements for licensure of a combination dual indication long-acting product in a potentially novel drug-delivery system). Future trials will need to move beyond placebo-controlled designs toward superiority and non-inferiority trials that compare any new candidate against existing effective treatment options. As more single indication prevention products become available, the less likely it will be that regulatory bodies will approve efficacy studies that are placebo controlled. This approach will require larger more expensive trials with more challenging logistics, particularly if products like the CAB-LA HIV prevention injectable or EFDA implants become the standard of care (SOC) for HIV prevention (at least for LA systemic products) (42, 43). Further, although concurrent development of promising MPT candidates can accelerate progress for the field, available limited resources should be invested in a portfolio of diverse promising approaches for indication, mechanism of action and dosage form, and avoid developing nearly identical MPT products without strong justification for such an investment.

Promoting the development of a product pipeline that combines and optimizes the expertise currently associated with single indication products to create the desired multi-indication MPTs is key. This will require integration of the preclinical, clinical manufacturing and regulatory expertise associated with STI and contraceptive product development into a focused platform capable of supporting the development and licensure of multi-indication MPTs. This effort will require not only clarifying the complex manufacturing and regulatory challenges associated with combining multiple drugs and excipients, that may have incompatible biophysical, rheological and biochemical properties, but also the creation of multidisciplinary public/private partnerships to fund and guide this effort. Central, too, for the success of MPTs is the technical guidance required to evaluate and advance promising preclinical products into clinical formulations that can be advanced to human testing and ultimately licensure, particularly for groups with little experience in these areas (44, 45).

DISCUSSION

MPTs present significant reproductive health and general opportunities for addressing multiple indications in at-risk populations, particularly adolescent girls and young women in regions of the world where risk of HIV, other STIs and unintended pregnancies remains high. Given the current limited resources for expansion of MPT product development, ongoing strategic thinking and action is needed to optimize use of technical capacities, enhance collaborative approaches, identify resources to help fill gaps, and add rigor to the development process with the aim of advancing the most promising products.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

The authors declare that this work was made possible by the generous support of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) through an interagency agreement with the United States Agency for International Development (USAID), cooperative agreement number AID-OAA-A-16-00045. The funder had no involvement in this manuscript. The funder was not involved in the study design, collection, analysis, interpretation of data, and the writing of this article or the decision to submit it for publication.

ACKNOWLEDGMENTS

The authors would like to thank Anke Hemmerling (University of California San Francisco & University of California Berkeley), Katherine Yang (University of California San Francisco), Sharon Achilles (University of Pittsburgh), and Susanna Moore (IMPT| CAMI Health| Public Health Institute) for their valuable feedback on the ideas outlined in this commentary.

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Conflict of Interest: BYH was employed by the Public Health Institute. JT was employed by the company Howpin Consulting. JR was employed by the company NWJ Group, LLC.

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frontiers in Reproductive Health

PERSPECTIVE
published: 23 September 2021
doi: 10.3389/frph.2021.683415

Integrating Pre-Exposure Prophylaxis Delivery in Public Health Family Planning Clinics: Lessons Learned From a Programmatic Implementation Project in Kenya

Kenneth K. Mugwanya[1,2*†] *and John Kinuthia*[1,3‡]

[1] Department of Global Health, University of Washington, Seattle, WA, United States, [2] Department of Epidemiology, University of Washington, Seattle, WA, United States, [3] Kenyatta National Referral Hospital, Nairobi, Kenya

OPEN ACCESS

Edited by:
Thesla Palanee-Phillips, Wits Reproductive Health and HIV Institute, South Africa

Reviewed by:
Maria Pyra, Howard Brown Health Center, United States
Malgorzata Beksinska, University of the Witwatersrand, South Africa

***Correspondence:**
Kenneth K. Mugwanya
mugwanya@uw.edu

†First author

‡Senior author

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: 21 March 2021
Accepted: 23 August 2021
Published: 23 September 2021

Citation:
Mugwanya KK and Kinuthia J (2021) Integrating Pre-Exposure Prophylaxis Delivery in Public Health Family Planning Clinics: Lessons Learned From a Programmatic Implementation Project in Kenya. Front. Reprod. Health 3:683415. doi: 10.3389/frph.2021.683415

Sexually active African women are a priority population for HIV prevention due to the disproportionately high frequency of new HIV infections. Family planning (FP) clinics offer an already trusted platform that can be used to reach women for HIV prevention services, including pre-exposure prophylaxis (PrEP). In the recent PrEP Implementation in Young Women and Adolescent (PrIYA program), we piloted PrEP implementation in FP clinics in Kisumu, Kenya, and demonstrated that it was possible to integrate PrEP provision in FP systems with a program-dedicated staff. In this perspective, we describe experiences and strategies employed to introduce PrEP implementation in FP clinics and lessons learned. We identified the following lessons for PrEP introduction in FP clinics in Kenya: (1) possible to integrate and generate high enthusiasm for PrEP delivery in FP clinics but persistence on PrEP is a challenge, (2) involvement of national and regional stakeholders is critical for buy-in, contextualization, and sustainability, (3) delivery models that do not integrate fully with existing staff and systems are less sustainable, (4) creatinine testing at PrEP initiation may not be necessary, (5) fully integrated HIV and FP data systems need to be developed, and (6) incorporating implementation science evaluation is important to understand and document effective implementation strategies. In summary, integration of HIV prevention and FP services provides an opportunity to promote one-stop women-centered care efficiently. However, a broader focus on delivery models that utilize existing staff and novel strategies to help women identify their own risk for HIV are needed to ensure greater success and sustainability.

Keywords: family planning clinics, HIV prevention, implementation, pre-exposure prophylaxis (or PrEP), integrated services

INTRODUCTION

In HIV high burden settings, many women concerned about avoiding or postponing pregnancy are also at elevated risk for HIV. A recent landmark clinical trial in eastern and southern Africa (the ECHO Trial), designed to evaluate the risk of acquiring HIV in HIV-negative women who used depot medroxyprogesterone acetate-intramuscular, the copper intrauterine device, or

levonorgestrel found no substantial difference in the risk for acquiring HIV among women using any of the three common methods of contraception included in the study (1). However, the incidence of new HIV infections among the participants was very high, nearly 4%, with a higher rate among women under 25 years irrespective of the contraceptive method. These results have rightly spurred important discussions about the urgent need to strengthen the integration of reproductive health services with combination HIV prevention services, including pre-exposure prophylaxis (PrEP). PrEP as a recommended user-controlled strategy can play an important role in preventing HIV acquisition, especially for women. In many settings in Africa family planning (FP) clinics provide broad coverage for women in their reproductive years. In Kenya, 65% of sexually active unmarried women use a modern contraceptive and a substantial proportion (69%) access it through public health FP settings (2). Thus, integrating PrEP in FP clinics where women already trust providers could allow for one-stop comprehensive healthcare services for women. However, there is limited experience from real-world settings on approaches and strategies to best deliver PrEP in African public health settings. In the recent PrEP Implementation in Young Women and Adolescent (PrIYA) program (funded through PEPFAR DREAMS innovation challenge) (3, 4), we piloted the implementation of PrEP in FP clinics in Kisumu, Kenya, and demonstrated that it was possible to integrate PrEP provision in FP systems with program-dedicated staff (3). In this report, we describe how we approached the introduction of PrEP implementation in FP clinics and lessons learned to facilitate dissemination of these learnings in other low-income settings.

OVERVIEW OF THE PRIYA PROGRAM

The project goal, methods, implementation, and primary quantitative results have been previously reported (3, 4). Briefly, PrIYA was a 2-year implementation project to reach adolescents and young women at high risk for HIV acquisition through integrated delivery of PrEP within routine maternal child health (MCH) and FP clinics in Kisumu, Kenya. PrIYA was part of the larger DREAMS Innovation Challenge funded by the President's Emergency Plan For AIDS Relief (PEPFAR). The overall goal of the project was to demonstrate the feasibility of integrating PrEP delivery in 16 public MCH and FP clinics. The project M & E Logic Model is provided in **Supplementary Figure 1**. The program was implemented between July 2017 and June 2018 as a collaborative effort between the University of Washington, the Kisumu County Department of Health, and 16 health facilities in Kisumu, Kenya. FP clinics at eight of the 16 facilities participated as a delivery point for PrEP. The implementation strategies to promote PrEP screening and provision in FP clinics included: training of existing health providers, stakeholder engagement, technical assistance, and demonstration of clinical PrEP provision by project-supported nurses embedded within FP clinics. Project-supported nurses performed only HIV risk counseling and provision of PrEP but did not participate in the delivery of FP services. At nearly all the eight clinics, women first completed other services including HIV testing and were then referred to a PrEP-dedicated nurse. Specifically, women of reproductive age accessing FP services were universally counseled by a PrEP program dedicated nurse for HIV behavioral risk factors and willingness to consider PrEP for HIV prevention. The screening was conducted according to the Kenya National Guidelines (5), guided by the Ministry of Health (MOH) risk assessment tool (RAST) that was used to initiate conversions with women about HIV risk and HIV prevention but not as a scoring tool for ruling in or out potential PrEP users. Kenya PrEP guidelines identified the presence of any of the following behavioral factors in the last 6 months as an indication for substantial ongoing risk of acquiring HIV include the following: inconsistent or no condom use; having a high-risk sex partner(s) and of unknown HIV status; engaging in transactional sex; history of ongoing intimate partner and gender-based violence; recent sexually transmitted infections self-reported or etiologically diagnosed; recurrent use of post exposure prophylaxis; recurrent sex under the influence of alcohol/recreational drugs; injecting drug with shared needles and/or syringes; and having an HIV positive partner.

PROCESS AND LESSONS LEARNED

Moving novel interventions to scaled implementation requires adaptations to better fit within complex contexts, needs of the local target population, or to respond to unanticipated challenges (6, 7). Due to restrictions on the use of funds on research-related activities, the PrIYA program did not embed rigorous implementation science research, including the application of qualitative interviews with health providers or individual women that would have provided important insights into the implementation process and relevant contextual factors for integrated delivery. Nonetheless, we used multiple sources to document and understand the process of integrating PrEP provision in FP clinics in Kenya. The sources included: abstraction of program data, technical assistant reports, debrief reports from clinical training and stakeholder engagement, and observations. In this narrative, to supplement our published quantitative analysis, we describe our experiences and lessons learned that are organized under 10 themes: (1) Data collection and systems; (2) Demand creation, initiation, and continuation; (3) Service delivery models; (4) Stakeholder engagement and facility preparation; (5) Training and capacity strengthening for PrEP implementation; (6) PrEP commodity supply chain; (7) PrEP laboratories; (8) New clients to FP clinics; (9) Consent for programmatic and research activities; and (10) Importance of integrating rigorous implementation science evaluation.

Data Collection and Systems

In this perspective, we present how the program and clinical data were obtained. The lack of robust data systems to track clients longitudinally is a key challenge in many FP clinics in low-income settings. For the PrIYA project, we used MOH/NASCOP data collection tools for HIV risk assessment and initiation of clients, which included RAST tool to guide PrEP eligibility and

a clinical encounter form (PrEP card) for those who initiated PrEP. Program data including demographics, behavioral-risk characteristics, reported partner HIV status, PrEP uptake, self-reported adherence to PrEP, and adverse events were abstracted daily by program nurses and entered daily into tablets for upload to a server. Continuation and adherence to PrEP were assessed by self-report and PrEP refill records at the clinic and through follow-up phone calls to ascertain PrEP continuation status and reasons for discontinuing PrEP. In addition, we used MOH daily activity registers and drug accountability registers. For project-specific activities, referral books were used to document and track clients referred for services to relevant departments, including referral for other gender-based violence and treatment of sexually transmitted infections. Of note, although service provision for PrEP and FP was integrated, data tools remained mostly vertical with RAST, PrEP card, and M & E registers for PrEP services completed separately from the FP register for FP services. This unintegrated data system meant that staff had to complete duplicate forms and registers. Thus, robust and fully integrated data systems to monitor PrEP clients that align with other databases in FP clinics need to be developed to streamline longitudinal tracking of clients. We found that simple CME-liked training of health providers on proper documentation and reporting procedures helped to streamline reporting of MOH/NASCOP-mandated PrEP indicators.

Demand Creation, Initiation, and Continuation on PrEP

Methods and analysis for quantitative data from the project have been previously reported. Briefly, we found high enthusiasm for PrEP from women accessing FP clinics. Overall, 1,271 were screened for HIV risk of whom 42% were $<$ 24 years (3). The majority of women who reported were using injectable (56%) or implant (31%) methods for contraception, with only 5% reporting to be on oral contraception pills. Although in a community online survey $>$87% of women had heard about PrEP and 75% clearly understood who could be eligible for PrEP (8), demand for PrEP was mostly provider-driven through counseling by healthcare providers and facility-based healthcare talk in the waiting areas. More than one-third of women did not know the HIV status of their male partners.

Nearly 22% (278) of all women screened for HIV risk accepted PrEP with acceptance $>$ 90% among women with at least one risk factor for HIV as per the Kenya PrEP guidelines (3). A higher proportion of women not on any contraception at the screening visit (39%) and those on the oral contraceptive pill (28%) initiated PrEP compared with only 24% of women on the implant and 15% on injectable contraception (**Figure 1**). Women $\geq$ 24 years more frequently elected to initiate PrEP compared to women $<$ 24 years (69 vs. 31%) and were more likely to perceive or self-assess to be at risk for HIV than women $<$ 24 years. Overall, among women screened and elected not to initiate PrEP ($n = 987$), 45% reported to have the low-perceived risk for HIV, and more than one-third (427/1,271) reported partners of unknown HIV status. We found that a substantial proportion of these women with partners of unknown HIV status ($>$ 40%) still felt that they needed to consult their male partners before they could consider PrEP (**Figure 2**). This was a surprising observation given that PrEP as a user-controlled prevention option is expected to empower young at-risk women to have control of their own HIV prevention choices. Because we did not do any qualitative research, we were unable to gain important insights into this emergent theme. Of note, there were no important variations in reasons for no acceptance of PrEP by contraception method used (**Supplementary Figure 2**).

As observed in most PrEP studies in women, continuation was a challenge with sharp declines in use within months of initiation—and often within the first month. Overall, 41% returned for their first refill visit; there were variations by contraception method used: 56% for those not initially on any contraption method, 39% for injectable, 35% for oral contraception pill, 30% for an implant, and 20% for women IUD (**Supplementary Figure 3**). Awareness of PrEP and perceived risk of individuals for HIV were main drivers of continuation, with higher continuation rates observed among women who reported an HIV-positive male partner or those who were self-assessed to be at risk of acquiring HIV. Thus, in addition to advancing more prevention methods to provide more options and choices to address varying experiences and preferences of women, defining strategies that support women to better evaluate their own risk for HIV is equally important. In the program, we promoted male partner testing through distribution of HIV self-test kits that allowed some women with male partners of unknown HIV status to make informed decisions about their risk for HIV and needs for PrEP (9).

Service Delivery Models

The primary strategy to integrate PrEP delivery in FP clinics was a program-supported nurse-led delivery of HIV risk counseling and provision of PrEP for women accessing routine FP services. New nurses hired specifically for the project and embedded into FP clinics were trained on screening and PrEP provision using a 2-day case-based interactive Kenya MOH PrEP curriculum. Project nurses only performed HIV risk counseling and provision of PrEP but did not participate in the delivery of FP services. Medically eligible women who wanted to initiate PrEP received same-day PrEP. As previously reported, across clinics, two main delivery services models for PrEP delivery were implemented: (1) codelivery where FP and PrEP services were delivered by the same FP nurse or (2) sequential services in which PrEP services by a PrEP-dedicated project nurse were offered after the client had completed their routine FP services (10). Common reasons for using a co-delivery approach instead of a sequential approach included not having a separate space allocated for PrEP services and having the high client to provider ratio, making it infeasible to allocate a nurse specifically for PrEP services. Screening for HIV risk was conducted according to the Kenya PrEP national guidelines (5), guided by a Kenya MOH RAST that was modified to include self-assessed reasons of women for choosing or declining PrEP. Provision of PrEP was subsequently transferred to the facility staff after projected funding had ended. Importantly, we found that PrEP uptake declined substantially when program-dedicated staff left after the project ended, demonstrating the need for PrEP delivery

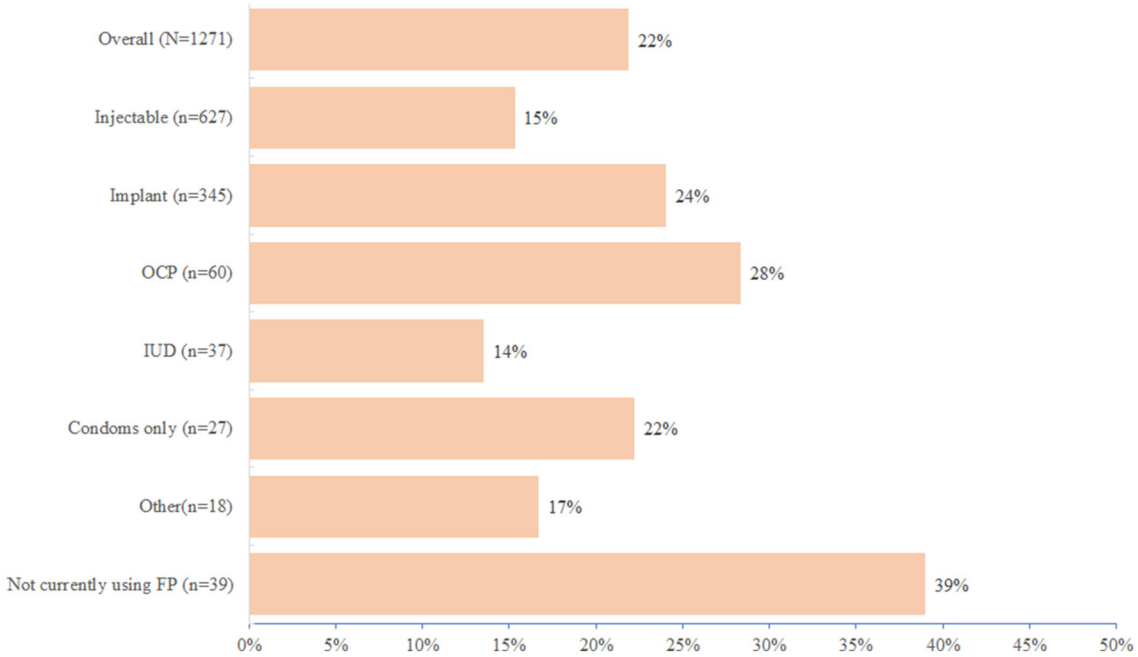

FIGURE 1 | Frequency of PrEP initiation by contraception method used.

models that integrate fully with existing service delivery models and staffing.

Stakeholder Engagement and Facility Preparation

Government support and program ownership is the key to the success and sustainability of African PrEP programs. PrEP roll-out nationally in Kenya was officially launched in May 2017, making it the first African national PrEP program and delivery and is slowly expanding (11). In the devolved government structure of Kenya, the MOH sets and guides national policy and guidelines, development of tools, and convenes implementation partners while County governments are responsible for service delivery. The PrIYA program worked closely with the Kisumu County government in planning the project and ensuring that PrEP medications were available at the healthcare facilities. The selection of clinics was conducted in consultation with the County-Government-based clinical volume and geographical location. The PrIYA project team was part of the Kenya national and County PrEP Technical Working Groups (TWG, which is charged with guiding PrEP implementation) but no direct financial support was provided to MOH or the County. Importantly, the project used the TWG platform to offer guidance and technical support needed to deliver PrEP in FP clinics on a national level.

Training and Capacity Strengthening for PrEP Implementation

At the start of the project, 40 program-dedicated newly hired nurses were trained by the project leadership team on clinical PrEP delivery per national guidelines and subsequently deployed at the 16 MCH and FP clinics; eight nurses were deployed in FP clinics. Program nurses thereafter worked with the Kisumu County Health authorities to support the readiness of clinics to deliver PrEP in FP clinics in a combination HIV prevention package. At each of the implementing clinics, program nurses conducted sensitization sessions to introduce the program and seek advice on the best ways to integrate PrEP delivery at the facility. Six months prior to the end of the study project, we conducted facility-wide training (i.e., to train other providers beyond FP clinics). The purpose of this effort was to coach and mentor existing healthcare providers as a sustainability plan to transfer the provision of PrEP services from project-dedicated nurses after project funding had ended. Overall, a total of 554 existing MOH healthcare providers (an average of 34 per facility) from MCH and FP clinics were trained in competencies in the following domains: (1) HIV risk assessment, counseling on PrEP initiation, discontinuation, adherence, and interpretation of PrEP-related laboratory tests, (2) Sensitization of women about PrEP in FP and MCH clinics, (3) Standardized clinical tools for promoting engagement of their male partner for HIV testing, and (4) Interpretation and use of clinical-level data to monitor women on PrEP. Subsequently, at the request of the Kisumu County government, we expanded our training and mentorship to an additional 21 ministry of health facilities where we trained 160 health providers on PrEP delivery. At these clinics, mentorship training was separated into short didactic and practical modules covered over 3–5 days at the facility. We found that this modular training provided flexibility and an effective format to provide on-job PrEP training for healthcare workers in public healthcare facilities without requiring them to leave the facility or disrupting other service provisions.

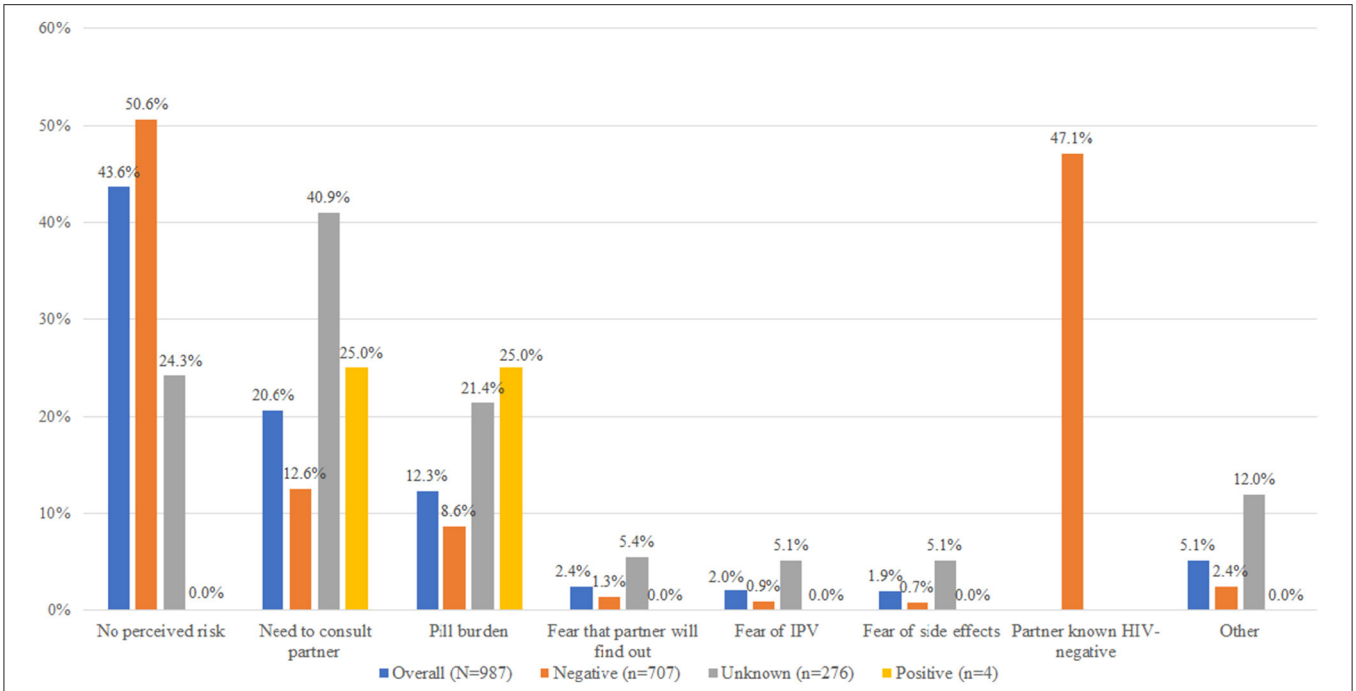

FIGURE 2 | Reasons for declining PrEP by reported male partner HIV status.

PrEP Commodity Supply Chain

Pre-exposure prophylaxis commodities, including PrEP medications and HIV testing kits, were provided from the national program and supplied by the Kenya Medical Supplies Agency at no cost to women. HIV uninfected women at substantial risk for HIV infection who chose to initiate PrEP received PrEP as part of the Kenya National PrEP Program. Prior to starting, program staff worked with clinic staff, county-level health officials, and the Kenya Medical Supplies Agency to make PrEP commodities available within FP clinics. Because the national PrEP program was in the startup phase, cases of commodity stockouts were frequent in the early phase (first 6 months) mostly resulting from under projection of the required quantities. When stock-outs of PrEP commodities occurred, the program worked closely with the County and Sub-County pharmacists to redistribute PrEP drugs from healthcare facilities with adequate stock to those who had stock-outs which ensured continuity of services at the affected clinics.

PrEP Laboratories

The Kenya PrEP guidelines recommend creatinine testing at baseline to evaluate kidney function but advise that the absence of test results should not delay PrEP initiation (5). In the Health system of Kenya, the cost of most laboratory testing including creatinine is met by the user, and mandating creatinine before PrEP initiation has the potential to be a significant barrier to access to PrEP services. Previous studies of PrEP safety found the risk of suboptimal kidney function to be very rare and no more frequent among PrEP users compared to non-PrEP users (12–17). In a subsect of the utility of point-of-care (POC) creatinine testing at PrEP initiation nested within the PrIYA project (18), we found that implementation of POC creatinine testing was feasible and performed more conservatively than laboratory-based testing (Roche Cobas c111 Analyzer; Roche Diagnostics, Indianapolis, IN). Importantly, POC testing results were available in a median of 1 min at a cost of $4.5 per test compared to 3.5 h at $5 per test for the standard laboratory testing. We found that in our project population of young healthy women, PrEP ineligibility due to suboptimal kidney function was very rare (only 0.02%) (18), suggesting that not requiring creatinine testing at PrEP initiation will generally be a safe decision (18). For those who sustain PrEP use annual testing may be adequate.

New Clients to FP Clinics

To advance comprehensive HIV prevention services, the PrIYA project actively promoted knowledge of male partners with partner invitation and secondary distribution of HIV self-test kits (results presented elsewhere) (9). We observed that offering PrEP services and promotion of male partner testing attracted new clients to FP and MCH clinics that included women who came to FP clinics solely for PrEP services and some male partners who responded to clinic-based partner testing invitations. FP settings are traditionally not set for male partners but as efforts to integrate comprehensive HIV prevention services in FP settings take effect, it is imperative that providers prepare to serve clients across the gender spectrum.

Consent for Programmatic and Research Activities

An early phase of implementation of a new biomedical intervention like PrEP is associated with uncertainties about requirements for consenting and how to manage priority

populations that may not have been included in efficacy clinical trials. For PrEP, important populations excluded from efficacy trials included individuals younger than 18 years, pregnant and lactating women. In this project, we learned that it is possible to work with oversight ethical authorities to define and separate research procedures from program activities. In the PrIYA project, research procedures were defined as those activities not required for the clinical provision of PrEP but are important to understand how the overall program works, for which written informed consent was required. Written informed consent was obtained for all research procedures, for example, dried blood spots for tenofovir levels to evaluate adherence to PrEP. For program procedures related to standard procedures for PrEP counseling and provision of (i.e., HIV testing and counseling, PrEP prescription, and dispensing), the local IRB determined them to be of minimal risk for which only oral consenting was obtained, which helped to overcome an important barrier to access PrEP in this population.

Incorporating Implementation Science Evaluation Is Important to Understand Delivery

Moving novel interventions from research into real-world settings presents challenges on how to adapt and fit the novel intervention or practice into complex contexts. Incorporating implementation science studies is important to document and understand what works for whom and under what circumstances and determining the best strategies for successful implementation interventions in real-world settings. Restrictions on the use of funds for certain research activities prohibited the PrIYA program to conduct rigorous process evaluation research, including qualitative interviews that would have provided additional insights into the implementation process and relevant contextual factors. Despite the limitations, triangulation of multiple data sources permitted the project to document and learn important lessons to the extent possible about working in public health FP clinics in this setting.

CONCLUSION

Ensuring that African young women have access to effective contraception and are also able to protect themselves from HIV is critical to optimize their health and ending the HIV epidemic. The PrIYA program pioneered the implementation of PrEP delivery in real-world African FP settings, demonstrating that it is feasible and practical to gain efficiencies with a one-stop station for HIV prevention and FP services using existing public health FP infrastructure. Because of the strong support of the Kenyan Ministry of Health for PrEP as an important HIV prevention intervention, Kenya is an incubator for research on innovative PrEP delivery models, and lessons learned have the potential to inform and guide the expansion of PrEP delivery in other African settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Human Subjects Division of the University of Washington and the Kenyatta Nation Hospital Ethical Review Committee approved the project and approval was obtained from the Kisumu County administration and facility in charges. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

KM was supported by funding from the US National Institute of Health Grant # R00MH118134 and R01MH123267.

ACKNOWLEDGMENTS

We thank the PrIYA program team and clients for their time and contributions. We thank the Kenyan Ministry of Health nationally and in Kisumu County and the facility heads and in-charges for their collaboration.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2021.683415/full#supplementary-material

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Author Disclaimer: The parent PrIYA Program was funded by the United States Department of State as part of the DREAMS Innovation Challenge (Grant # 37188-1088 MOD01), managed by JSI Research & Training Institute, Inc. (JSI). The opinions, findings, and conclusions stated herein are those of the authors and do not necessarily reflect those of the United States Department of State or JSI.

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frontiers in Reproductive Health

ORIGINAL RESEARCH
published: 04 November 2021
doi: 10.3389/frph.2021.693429

Experiences With Safer Conception Services for HIV-Serodiscordant Couples at a Referral Hospital in Nairobi, Kenya

Anne Kaggiah[1], Grace Kimemia[2], Hellen Moraa[3], Peter Muiruri[4], John Kinuthia[1] and Alison C. Roxby[5]*

[1] Department of Research and Programs, Kenyatta National Hospital, Nairobi, Kenya, [2] African Population and Health Research Center, Nairobi, Kenya, [3] Pediatrics Department, University of Nairobi, Nairobi, Kenya, [4] CoEHM Project, Kenyatta National Hospital, Nairobi, Kenya, [5] Departments of Medicine and Global Health, University of Washington, Seattle, WA, United States

Human immunodeficiency virus-serodiscordant couples are an important source of new HIV infections in Africa. When trying to conceive, uninfected partners may be at high risk of infection if the infected partner is not virally suppressed. Multiple strategies targeting safer conception exist, but these services are limited. However, when services are available and used, serodiscordant couples can be protected from HIV transmission, and safe to have children if desired. To successfully introduce, integrate, promote, and optimize the service delivery of safer conception with HIV care, it is crucial to understand how HIV-serodiscordant couples perceive and experience these services. Further, viral load monitoring can be critical to safer conception, but there is limited literature on how it informs the decision of the partners about conception. This qualitative study describes the knowledge, perceptions, and experiences of both safer conception services and viral load monitoring among 26 HIV-serodiscordant couples seeking safer conception care at a referral hospital in Nairobi, Kenya. In-depth interviews of HIV-serodiscordant couples were conducted from April to July 2017, and transcripts were analyzed to identify the themes central to the experience of safer conception services of couples and viral load monitoring. Serodiscordant couples reported success in using some of the safer conception methods and had positive experiences with healthcare providers. However, despite using the services, some were concerned about HIV transmission to the seronegative partner and baby, while others faced challenges when using pre-exposure prophylaxis (PrEP) and vaginal insemination. Overall, their motivation to have children overcame their concern about HIV transmission, and they welcomed discussions on risk reduction. Moreover, supportive clinic staff was identified as key to facilitating trust in safer conception methods. Furthermore, viral load monitoring was identified as integral to safer conception methods, an emerging theme that requires further evaluation, especially where routine viral load monitoring is not performed. In conclusion, healthcare providers offering safer conception services should build trust with couples, and recognize the need for continual couple counseling to encourage the adoption of safer conception services.

Keywords: HIV, serodiscordant couple, safer conception, HIV viral load, pregnancy, Kenya

OPEN ACCESS

Edited by:
Thesla Palanee-Phillips, Wits Reproductive Health and HIV Institute, South Africa

Reviewed by:
Akon Emmanuel Ndiok, University of Calabar, Nigeria
Jennifer Ann Smit, University of the Witwatersrand, South Africa

****Correspondence:***
Anne Kaggiah
akaggiah@gmail.com

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *10 April 2021*
Accepted: *04 October 2021*
Published: *04 November 2021*

Citation:
Kaggiah A, Kimemia G, Moraa H, Muiruri P, Kinuthia J and Roxby AC (2021) Experiences With Safer Conception Services for HIV-Serodiscordant Couples at a Referral Hospital in Nairobi, Kenya. Front. Reprod. Health 3:693429. doi: 10.3389/frph.2021.693429

INTRODUCTION

Human immunodeficiency virus-serodiscordant couples are estimated to represent 2–8% of the HIV-affected couples in Africa and 4.8% in Kenya (1, 2), and are an important source of new HIV infections in Africa (3, 4). Serodiscordant couples often desire fertility, leading them to practice unprotected sex where the uninfected partner may be at high risk of HIV infection if the infected partner is not virally suppressed (5, 6). In the era of undetectable = untransmittable (U=U), it is important to note that viral load monitoring is not always available in a timely manner to these couples. Fortunately, multiple strategies for safer conception exist (7). These include vaginal insemination (4), male circumcisions, *in-vitro* fertilization (IVF) (4), sperm washing (4, 8), antiretroviral therapy (ART) for viral suppression of the seropositive partner (4, 8), pre-exposure prophylaxis (PrEP) for the seronegative partner to prevent HIV transmission, timed unprotected intercourse (4, 8, 9), and the diagnosis and treatment of sexually transmitted infections (STIs) (7). Serodiscordant couples who were offered and used safer conception services felt safe and protected from HIV transmission and empowered to have children (4, 10). Evidence shows that HIV-serodiscordant couples are able to discuss and use available safer conception services (4, 11).

However, the uptake of safer conception services is affected by various concerns. These include the integrity of sperm during home vaginal insemination, conflicting religious beliefs (4, 12), costs associated with sperm washing and IVF (3, 4, 12), difficulties in identifying the fertile period, perceived risk of HIV transmission during timed unprotected intercourse (4), poor adherence or perceived adverse events regarding ART or PrEP use, and beliefs about condoms as the primary prevention for HIV transmission (4, 13). While couples are eager to learn from healthcare providers about safer conception services (8, 10), the lack of support (8, 11), perceived judgment (8, 14), and stigma (13, 14) from providers can result in the reluctance of couples to initiate conversations of fertility desires and seek safer conception services (3, 8).

To successfully introduce, sustain integration, and optimize service delivery of safer conception services with HIV care it is crucial to understand how HIV-serodiscordant couples perceive and experience these services (15). Further, there is limited literature on how viral load results inform the decision of partners to conceive yet HIV viral load monitoring can be a critical part of safer conception. This qualitative study aimed to describe the knowledge, perceptions, and experiences of both safer conception services and viral load monitoring among HIV-serodiscordant couples seeking care at a referral hospital in Nairobi, Kenya.

METHODOLOGY

Study Design, Population, and Setting

Serodiscordant couples were eligible if they expressed fertility desire and were receiving HIV care at the Couple Counseling Center, Comprehensive Care Clinic, and Reproductive health clinics at the Kenyatta National Hospital (KNH) in Nairobi, the largest national referral and teaching hospital offering specialized health care services. Accordingly, we conducted qualitative in-depth interviews of couples from April to July 2017 to explore the knowledge, perceptions, and experiences of couples with safer conception services and viral load monitoring.

Recruitment and Consenting Procedures

Site sensitization was conducted at the Couple Counseling Center, Comprehensive Care Center, and Reproductive health clinic in the KNH by the study team. The healthcare workers providing care to HIV-serodiscordant couples were informed about the study and requested to refer serodiscordant couples who wanted to conceive and were receiving safer conception services for study participation. Serodiscordant couples presenting in these clinics were recruited if they wanted to conceive and were receiving safer conception services. In addition, both members of the couple should have been available and willing to provide written informed consent.

Five couples receiving safer conception services were recruited and data analyzed, additional couples who had received at least two sessions of safer conception counseling, where the female partner was within the fertile age and had one or no children, were identified and invited to participate. These factors were considered because couples attending multiple counseling sessions were a rich source of information (16), while the age and number of children influence decisions about conception among HIV-serodiscordant couples (10, 17, 18).

Those willing to participate were informed about the study objectives and procedures and written informed consent was obtained from all the participants prior to study participation. If a couple was found ineligible, refused to participate, or was unavailable, the study staff would approach a subsequent couple from the same recruitment site. All interviews were conducted in a private room, and all study participants were reimbursed Ksh.500 ($5) for their time and transport expenses.

Development of Interview Guides

Employing the grounded-theory methodology, we did not define *a priori* hypotheses. A structured interviewer guide inquiring about sociodemographic characteristics was utilized. The first section asked participants with fertility desire about their knowledge, perceptions, and experiences with safer conception services, whilst the second assessed their knowledge, perceptions, and experiences with HIV viral load monitoring as part of these services. These questions were developed from previous studies conducted among HIV-serodiscordant couples seeking safer conception services (19), and refined after pilot testing.

Data Collection

Face-to-face audio-recorded semi-structured in-depth interviews were conducted by experienced social scientists trained on the protocol for 1 week prior to data collection. The training included a review of the semi-structured interview guides, informed consent, and qualitative data collection procedures. The in-depth interviews were conducted in the language preferred by the participants, either English or Kiswahili. The interviews focused on the knowledge, perceptions, and experiences with safer conception services and viral load monitoring. To better

understand their knowledge, perceptions, and experiences, the HIV-serodiscordant couples were separated for individual in-depth interviews. This was to avoid the effect of the response of one partner on the other and prevent the dominance of the opinion of an individual.

Data Analysis

The audio-recorded interviews were translated into English and transcribed. All the transcripts were independently reviewed and coded by three investigators, using a constant comparative approach (20, 21).

The data from the initial participants that were recruited was first analyzed and coded. These codes subsequently guided additional data collection and analysis. New data was constantly compared with the previous data for consistencies and differences. Additionally, emerging themes from the transcript of an individual were compared to that of their partner for consistency or variance and subsequently grouped into categories for research team discussion to ensure validity. To check for the consistency of text interpretation, coding was compared across the coders using an agreed-upon codebook. Those with discrepancies were discussed by the research team until resolution. After all the interviews were coded, the dominant themes were organized and representative quotes were chosen to illustrate the themes in the words of the participants. Two coders (AK and HM) met weekly to discuss the emerging themes, and codes applied. Any differences in coding were discussed with the third coder (GK), in consultation with other members of the investigating team (JK and AR), until consensus was achieved. DEDOOSE Software Version 8.0.35, was used for data management and organization (22).

The study was approved by the Kenyatta National Hospital/University of Nairobi Ethical Research Committee (KNH/UON ERC) (Ref: P4/01/2017) and the University of Washington Institutional Review Board (Ref: STUDY00000953).

RESULTS

A total of 31 couples were approached to participate, of whom 4 couples declined to participate, while one couple was not eligible because they were not fluent in English or Kiswahili. New topics ceased to emerge after 26 couples were interviewed, and the data saturation was deemed to have been reached (23). The mean age among the members of the HIV serodiscordant couples was 39 (23–43) and 35 (23–56) years, for males and females, respectively. Slightly more women than men had more than 8 years of formal education (21, 40.3 vs. 18, 34.6%). The average duration of partnership was 5.4 years, and the average number of children was 1. There were more female (18, 69.2%) than male partners (8, 30.2%0) who were HIV-seropositive. Pre-exposure prophylaxis (8, 30.8%) was the most commonly used method of safer conception, while sperm wash (1, 3.8%) was the least used. However, while few couples used both PrEP and ART (2, 7.7%) as methods of safer conception, others have not used (4, 15.4%) the method. The majority (17, 69.2%) of couples were recruited from the Couple Counseling Center, while the least (3, 11.5%) were recruited from the Reproductive Clinic (**Table 1**).

TABLE 1 | Baseline characteristics of the study sample ($N = 26$ HIV-serodiscordant couples).

Sociodemographic characteristics	Mean or *n* (%)
Age in years	
Male	39 (23–56)
Female	35 (23–43)
Education > 8 years	
Male	18 (34.6)
Female	21 (40.3)
Number of years in partnership	5.4
Number of children	1
HIV-seropositive partners	
Male	8 (30.8)
Female	18 (69.2)
Method of safer conception	
ART	4 (15.4)
PrEP	8 (30.8)
Vaginal Insemination	4 (15.4)
Timed unprotected intercourse	3 (11.5)
ART and PrEP	2 (7.7)
Sperm wash	1 (3.8)
None	4 (15.4)
Recruitment clinics	
Couple counseling center	17 (65.4)
HIV Comprehensive care center	6 (23.1)
Reproductive Clinic	3 (11.5)

Several key themes related to the experiences of HIV-serodiscordant couples with safer conception methods and HIV viral load monitoring emerged from this study. An important theme was that couples had often been discouraged from attempting pregnancy at other sites, and were relieved to find a clinic that was interested in assisting them to achieve safe pregnancy. Overall, the couples described positive experiences with the services provided and the staff. Other notable themes included the challenges of accessing specialist fertility services, difficulties in adhering to some of the safer conception protocols, concerns about the effectiveness of PrEP, and continuing misinterpretation of viral load test results. Though the couples were interviewed separately, gendered differences in the experience of receiving safer conception services were not found, and couples greatly appreciated that these services were offered to them as a unit. The differences found were based on the serostatus of the partner, with seronegative partners expressing less knowledge about HIV and viral load testing. To fully describe the experiences of couples in our study, we report the key themes here for each step of the safer conception process.

Referral for Care Was Welcomed by Couples Seeking Fertility

Some partners from other clinics within and without KNH reported that they were referred for safer conception services when these services and expertise were perceived as unavailable during their routine care. The Comprehensive Care Center

within KNH offers routine HIV services such as the provision of ART, psychosocial support, and counseling services.

Based on the description of the participant, the Comprehensive Care Center offered limited counseling services and support to serodiscordant couples with fertility desires. Outside KNH, the health facilities that offer HIV services had little or no experience in supporting HIV-serodiscordant couples with fertility desire.

Couples who expressed fertility desire were mostly referred to the Couple Counseling Center at KNH, as described by an HIV-seronegative female partner who sought services at Comprehensive Care Center at KNH:

> "*Yes, she was going there [Comprehensive Care Center]…, then we were advised to come to this clinic [Couple Counseling Center] so that we can get the right assistance…they said this [Couple counseling Center] was the right place for the two of us because there are things that are accommodated here [Couple counseling center]…*" Couple 13 HIV-seronegative male partner

The couples were grateful for the option of a specialty clinic focusing on their fertility concerns, enabling them to access an expert understanding of HIV and its implications.

Couples Had Prior Negative Experiences With Community Providers and More Positive Experiences With Specialized Safer Conception Services

During the routine clinic visits, the couples would talk to their health providers about their fertility desires. This topic was met by mixed reactions from the providers who either showed empathy or outright displeasure toward the couple due to the perceived risk assessment of their health providers. There was a perception that HIV-serodiscordant couples should not have children because of possible HIV transmission to the seronegative partner and unborn child. In such instances, the participants reported that the health care providers from other facilities discouraged them from having children:

> "*...she (healthcare provider) told us that getting a second child is just risking, so she made us scared and we knew there was no way of getting a baby.*" Couple 11 HIV-seronegative male partner

> "*…She was afraid and she said that according to how the doctor tested her, he [the doctor] told her that she cannot have a baby.*" Couple 9 HIV-seronegative male partner

In addition, the HIV-serodiscordant couples were worried about conceiving naturally with their HIV status. When the couples were referred to the Couple Counseling Center, they learned about safer conception services, rejuvenating their fertility desires, as well as their hope and motivation toward having seronegative children, and maintaining their serodiscordant relationships:

> "*We had not tried (to have a baby). In fact, we had abstained from intercourse for a year…Because of that state of…one person has HIV and the other does not… We came here [Couple Counseling Center] for counseling, their services were good, they counseled us, and we saw that since we can get another child, we can stay as a couple.*" Couple 2 HIV-seropositive female partner

> "*They [safer conception services] are very important because they bring hope and light to some couples because at least now you know that I can still have a baby naturally.*" Couple 16 HIV-seronegative female partner

Further, the couples who accessed safer conception services felt that the services were important for the protection of the seronegative partner and unborn child from HIV transmission. The benefits of the services were highlighted by couples during the in-depth interviews.

> "*Yes, they [safer conception services] are beneficial because ….one partner is positive and the other one is negative. In order to protect the other one from being infected we need to use the safer methods. This is for the future of us and of the child that will be born.*" Couple 9 HIV-seronegative male partner

> "*The services [safer conception] offered are not bad rather they are helping us. They help protect our partners who are HIV negative from being infected. If they are on medication and we have intercourse normally, using the medicine they have already protected themselves.*" Couple 5 HIV-seropositive female partner

The couples who visited the Couple Counseling Center encountered health providers that are knowledgeable about safer conception services. The couples reported that it was easy to speak about their fertility intentions where healthcare providers reacted positively to their concerns. Moreover, the participants appreciated the services offered as described by the following excerpts:

> "*……The ones providing the services here are good-hearted compared to other places I have been. When I come here [Couple Counseling Center] I always feel at home. I respect this place.*" Couple 9 HIV-seronegative male partner

> "*If you want to get a baby it is not a must you struggle, you just come…..and inform the doctors that you want to conceive……. They [healthcare providers] received us well……*" Couple 25 HIV-seropositive female partner

For many partners, coming to the safer conception clinic was the conclusion of a multistep journey toward fertility, including coming to terms with their serodiscordant status, learning to hope that fertility would be possible, seeking correct expertise to guide their fertility journey, and self-education to understand and weigh competing options. The couples were grateful for the positive experiences of the safer conception clinic, despite carrying the emotional weight of the journey to arrive at this place of support and hope.

Couples Described High Levels of Knowledge of Safer Conception Services

While conducting in-depth interviews with different partners, we noted that the female participants were more knowledgeable than the male participants about safer conception methods such as

TABLE 2 | Excerpts describing couples' knowledge of safer conception methods.

Method	Quote
Timed unprotected intercourse	"*We started with my cycle, …we had to go through and see the most proper… date that I could conceive…..I was actually told that from the 10th day that is probably the time when I am fertile……that is the time we should have sex without protection*." Couple 24 HIV-seropositive female partner
PrEP	"…. *We were told that PrEP is of help because we have used [it] for 3 months and he has come for the test and he is negative….It helps the person who is HIV-seronegative not to be infected…….*" Couple 22 HIV-seropositive female partner
Vaginal insemination	*…….*"*Ejaculate in the condom and ……remove it and……. deposit [in the vagina] it [semen] using the syringe….*" Couple 22 HIV-seronegative male partner
ARVs	"*They told us of the methods of how we can do it….My partner was introduced to ARVs, he was not taking them before because the CD4 count was still ok, but he was told now he has to start using them…. his viral load was checked and we were told it is ok and we were just given a go ahead to just try….without the condom, to try you count the safer days and you just try naturally.*" Couple 10 HIV-seronegative female partner

timed unprotected intercourse, use of PrEP, vaginal insemination, and use of ARVs. The female partners provided detailed descriptions of the safer conception methods as informed by healthcare providers. **Table 2** above shows some of the methods partners were knowledgeable about:

The knowledge of these methods was very specialized, as none of them are commonly used in Kenya and therefore showed the investment of the couples in the process of pursuing safer conception services, as well as demonstrating that the clinical education process was effective at improving knowledge of different safer conception options.

Couples Reported Diverse Sources of Information

The sources of information about safer conception methods varied based on the exposure to different health facilities and mass media. One of the participants reported learning about safer conception services from health care providers during routine visits at the Couple Counseling Center or while attending support groups organized by the center.

> "*…We had a meeting on Saturday [at the clinic]....The (safer conception) methods were explained in that meeting.…*" Couple 5 HIV-seropositive female partner

> "*When my wife heard that I was using drugs, she … wondered what the drugs [were] for… I told her they [were] for prevention. She asked about what am preventing [HIV transmission]…..so today we came to the clinic together……and she was told that they are for prevention because I am positive and she is negative. So she heard that from doctor and that was affirmed.*" Couple 23 HIV-seropositive male partner

In addition to the use of ARVs by the HIV-seropositive partner as a method of safer conception, some partners heard about PrEP from televised mass media during its launch by the Kenyan Government. In other cases, as narrated by an HIV-seropositive female partner during an in-depth interview, the participants would explore the internet for information on how to protect the negative partner:

> "*On television, is it the one [PrEP] that was being launched just the other day.… I just heard it; it protects you from getting infected.…the negative partner.*" Couple 6 HIV-seronegative male partner

> "*….It is Google that told me that there is a drug [PrEP] that I can use that can protect the negative partner.*" Couple 14 HIV-seropositive female partner

Furthermore, some participants received information from friends or peers, to whom they have disclosed their HIV status. In one of the interviews, a participant reported that a friend, concerned about her not having another child, informed her about how she could safely conceive.

> "*…..From a man who questioned me on why I had stayed for long without getting another [child].……The man explained to me that there was a method of putting the sperms in the condom and I would be injected in the womb and I would conceive.*" Couple 5 HIV-seropositive female partner

Overall these experiences demonstrated that people sought information from diverse sources, and found it hard to determine the reliability of some of the information. The clinic provided a place to query experts, evaluate diverse information and make an informed decision about fertility and safer conception.

Successes and Challenges With Using Some Safer Conception Methods

After receiving detailed information about the available safer conception methods from healthcare providers, some participants reported success in using some such as PrEP, and reported they felt safe and protected from HIV transmission:

> "*…..My husband will be using those medications (PrEP) that will protect him from getting HIV, I feel safe.*" Couple 3 HIV-seropositive female partner

> "*…. I know… the PrEP that I was given.… protects me.*" Couple 12 HIV-seronegative male partner

> "*…….So as he uses that drug [PrEP], as we meet without condoms there is no way he can be [infected]……*" Couple 12 HIV-seropositive female partner

However, one couple reported that adherence and adverse events made it difficult to take PrEP, though they understood the benefits of using PrEP to reduce HIV transmission to the negative partner.

"*Taking medication [PrEP] every day, to some of us is so tricky. I wish it could be for a shorter period, if at all you take and conceive…..*" Couple 16 HIV-seronegative female partner

"*….with PrEP my partner was always complaining because of the reaction of the drugs.*" Couple 16 HIV-seropositive male partner

Though vaginal insemination was a preferred safer conception method among couples with an HIV-seronegative male partner, several couples reported it to be challenging due to the processes involved. Some female partners intimated that they found semen insertion *via* a syringe uncomfortable, while others doubted the effectiveness of the method because of semen spillage, and others found touching the genitalia uncomfortable:

"*The syringe method……it was a challenge, it was really a big challenge because… from school I learnt that sperms only survive outside for…I don't know how many hours. So, I was like… is it really going to work, you ejaculate then you put it in the syringe. It was a process, it is challenging.*" Couple 6 HIV-seropositive female

"*…like ejaculating in the condom and then you remove it and you deposit [semen] using the syringe… I didn't find it more effective for me, because when you are doing all that, you will lose some [semen]…Then putting [semen into the vagina] then… Waiting…an hour or 30 minutes.*" Couple 21 HIV-seronegative female partner

Furthermore, some participants expressed concerns about sperm washing, citing specialist providers who they felt were indifferent or unprofessional. Others were concerned that the method was ineffective and costly:

"*It is quite a lot of money for consultation and…...inserting the washed sperms… that process of taking the sperms you go to the clinic in town you are told to wait… I found that unprofessional, I said I wouldn't want to go through it.*" Couple 10 HIV-seropositive male partner

"*….For sperm wash you must be financially stable, and it is not 100% guarantee that it will work, if it fails that means you are going to repeat again…*" Couple 16 HIV-seropositive male partner

In general, having so many methods of safer conception was perceived by couples to be another challenge to navigate and another barrier to having a baby. While some were successful, overall, the process of safer conception was felt to be more complicated than natural conception and required a significant investment of time and energy.

Perceptions of Safer Conception

The study participants had varied perceptions of the different types of safer conception methods. During the interviews, some participants expressed that vaginal insemination was artificial and the sperms would not be viable:

"*If you take the syringe out of the condom you never know if …… the sperms are already dead because of the air.*" Couple 6 HIV-seronegative male partner

"*Artificial……..That is just what I think because just like in cows, they go to the veterinary and they conceive.*" Couple 8 HIV-seropositive male partner

Further, couples explained how they tracked their menstrual periods to identify fertile days, noted as important especially if the couples chose timed unprotected sex. However, based on the interviews, the couples displayed minimal understanding on how to count days and identify fertile days:

"*…… I am beginning my periods today, so from today I shall count 8 days, during those days we can have sex, after 8 days we have to skip 3 days and we meet on the 4 day and we alternate 4 times for 4 days the alternation is to make the sperms be strong.*" Couple 12 HIV-seropositive female partner

"*You know when women have had their periods after that the chances of getting a child are high or slightly before, so you should [have intercourse] in those 3 days continually.*" Couple 11 HIV-seronegative male partner

This theme showed that couples took the need to acquire specialized knowledge seriously on their path to fertility.

Concern for HIV Transmission Despite Safer Conception Methods

Although the concern for HIV transmission was the greatest motivator for clinic attendance, some participants expressed their ongoing concern about HIV infection despite being offered safer conception methods. For instance, in one couple, the HIV-seronegative male partner doubted the effectiveness of PrEP and the low viral load of his HIV-seropositive partner.

"*The hardest part was, are these drugs…. [PrEP] effective? Suppose they don't [work], whom do you blame, do you blame these professionals or do you blame your wife?*" Couple 22 HIV-seronegative male partner

"*He cannot accept even when we were being told that for example if my viral load is low you can risk having sex without the condom because it is not easy…. to infect him, he said never.*" Couple 22 HIV-seropositive female partner

This theme underlined the fear of HIV acquisition and transmission that was a great barrier to overcome to achieve safer conception. Despite the counseling and training that couples had received during safer conception services, the fear of HIV remained. In addition, some seropositive partners seemed more concerned about HIV transmission than their seronegative partners.

"*I……heard…….. we can stay together without him being [infected]. I was very happy because I……did [not] want to infect him.*" Couple 12 HIV-seropositive female partner

"*I am [on] medication [and] she is not [on] medication….[when] we have [unprotected] sex…..she is going to get [HIV infection]……*" Couple 16 HIV-seropositive male partner

On the other hand, the seronegative partners were supportive and motivated to get a baby using these services.

> "……*She was found to be [HIV] positive and I was [HIV] negative…….The doctor asked [us] how shall [we live]?……I told him that I…[will not] abandon her just because she is [HIV] positive.*" Couple 12 HIV-seronegative male partner

> *"[Safer conception services]….are very important because they bring hope and light to….couples ……I can still have a baby naturally……."* Couple 16 HIV-seronegative female partner

These themes emphasize the importance of providing these services to couples rather than individual members of the couple so that concerns of HIV transmission can be addressed and spousal support can be encouraged.

Understanding of Viral Load as a Measure of Infectivity and a Means to Reduce HIV Transmission

The couples reported that, prior to discussing safer conception methods, healthcare providers required the viral load testing of the HIV-seropositive partner. In addition, they understood that high viral loads level would deter or derail their plans to have children:

> *"The first requirement was a viral load…so when my viral load was below 20 copies, they [healthcare provider] gave me a green light to go ahead."* Couple 1 HIV-seropositive female partner

> "*Yes, it is important, because during our meetings with [healthcare provider] he says that when the viral load is undetectable that is the right time to conceive. But when it's high it is risky to conceive.*" Couple 8 HIV-seropositive male partner

Some partners in serodiscordant relationships demonstrated knowledge about viral load, and understood that a low or undetectable viral load in the seropositive partner meant that HIV transmission to the seronegative partner and baby would be reduced:

> *"When the viral load is high the chances of infecting your partner are high unlike when it is low or undetectable." Couple.*" Couple 8 HIV-seropositive male partner

> "*…If your viral load is low, you can't infect your partner.*" Couple 9 HIV-seropositive female partner

In this case, the couple explored the use of ARVs to reduce the viral load of the HIV-seropositive partner to undetectable levels. This could only be achieved if the seropositive partner adhered to their ART medication:

> "*It is the measuring of the amount of virus in your body. It checks if the drugs are working, and if the amount of virus is reducing or they are multiplying.*" Couple 3 HIV-seropositive female partner

> "*…Viral load is like when she doesn't use her medication well so the HIV virus goes on higher levels, but when she does take her medication properly the virus goes completely down.*" Couple 7 HIV-seronegative male partner

Some seronegative partners lacked knowledge of the viral load test prior to attending the Couple Counseling Center, attributed to the fact that most of the HIV-seropositive partners would attend the HIV clinic alone for their routine checkups, medication, and viral load testing. However, both partners were expected to attend safer conception counseling where HIV-seronegative partners learned about viral load:

> "*I have not heard about such a thing [viral load]…. I heard her asking the doctor that she wanted to know her levels because I want us to have the baby…The doctor…checked and told her she is negative something… and told her that she can conceive because her health is good. ….. I did not understand.*" Couple 9 HIV-seronegative male partner

> "*I have never heard [of viral load] and I don't know if he has ever been tested, I don't know….*" Couple 21 HIV-seronegative female partner

In addition, a few participants did not understand how to use viral load monitoring as a method of safer conception. As described by one, she thought that she should try conceiving when the viral load was high.

> "……*They [healthcare providers] have to determine if I was able to get a baby because my status could be that the viral load is low and may not be able to carry the pregnancy……they [healthcare providers] will try to take it [viral load] high for me to be able to get pregnant…..*" Couple 12 HIV-seropositive female partner

Overall, the couples benefited from understanding the role of the HIV viral load as part of the path toward safer conception. However, it remained a concept that was better understood by the HIV-positive partners, and viral load testing was understood as a potential barrier or possible delay to fertility plans.

DISCUSSION

This qualitative research elicited the viewpoints of HIV-serodiscordant couples seeking safer conception. Despite the sensitive topic, the couples shared their challenges seeking safer conception services while protecting the seronegative partner.

Overall, the themes identified reinforced that safer conception services were appreciated by the discordant couples, and resulted in couples with knowledge of their fertility options, good comprehension of the methods to reduce risk as they pursued fertility, and a reasonable understanding of the role of viral load suppression in safer conception. While some safer conception methods were unpopular, such as sperm washing and self-insemination, others appeared acceptable and couples displayed a nuanced understanding of risks and benefits. Finally, couples appreciated safer conception education and counseling services at the specialty clinic.

This research showed that couples relied on healthcare workers and support groups as main sources of information

and media, the internet, and friends as other sources. This underscores the need for specialized or integrated clinics with providers who have specific training on safer conception methods, as well as integration of this training into clinics where couples seek HIV care. Despite the overall broad knowledge demonstrated by couples, we did identify some couples with incorrect or incomplete knowledge of some of the safer conceptions methods, as seen in other studies (24). Continuous counseling of couples about safer conception may be needed to reinforce novel concepts, especially for those with limited health literacy.

While we were pleased with the satisfaction expressed by couples regarding services at the safer conception clinic, there is likely a much greater need from outside the referral center, as many were unaware of the existence of these services before referral by a provider. Another study conducted among serodiscordant couples in Kenya noted missed opportunities to provide safer conception, which could be improved by integrating services and training all healthcare workers providing care to these couples (24).

Given the very real concerns expressed by couples about HIV transmission to their partner or infant, there is a need for comprehensive and trusted services targeting this very important life choice. Counseling couples seeking safer conception services on a regular basis can help alleviate such concerns, making these services acceptable to these couples (14). Viral load monitoring was required prior to offering safer conception methods, however, some seronegative partners had limited understanding of the implications of viral load testing results or were unaware of the viral suppression states of their partners. There is a need to incorporate seronegative partners during ART adherence counseling of the seropositive partners to achieve undetectable viral load. Programs should understand that couples seek expert advice and need reassurance from professionals about their choices given that there is a risk to their closest loved ones.

Some methods, particularly vaginal insemination and sperm washing, were unpopular among couples due to their complexity and expense. While PrEP may supplant these methods, the couples also reported mixed opinions about PrEP, with seronegative persons expressing unwillingness to take daily pills. Current safer conception practices have evolved to rely more heavily on PrEP as a safer conception method. However, this research showed that even when HIV-serodiscordant couples are motivated by fertility desire, they may still be unwilling to use PrEP.

Despite U=U dominating the discourse around HIV risk, some have asked if clinics such as this continue to be necessary. Our research shows that HIV-serodiscordant couples face many barriers to conception, and fear infecting their loved ones. Most participants felt that these services were important for serodiscordant couples because they motivated, gave hope, and kept them together as they sought children. In addition, motivated couples are likely to accept these services despite the challenges in using some of the methods. Thus, these services need to be integrated with HIV care, and healthcare providers need training so that they can initiate conversations on safer conception with HIV-serodiscordant couples expressing fertility desire (25).

As viral load testing becomes easier and more convenient in sub-Saharan Africa, our findings show that HIV-serodiscordant couples are able to integrate this knowledge into safer conception. Most couples were aware that HIV viral load testing for the seropositive partner was essential, and couples had good knowledge of reduced HIV transmission from a person with undetectable viral load, and acknowledge the need for the seropositive partner to be adherent to their ARV medication. However, we did identify couples who lacked knowledge on viral load testing, especially seronegative partners who may neither attend HIV clinics nor receive the information. It remains, then, a key tenet of safer conception care to ensure that prior to attempting conception, both members of the couple understand the role of viral load in HIV transmission and the importance of ART adherence and viral load suppression.

Strengths and Limitations

To our knowledge, this is the first study within a public clinic setting offering safer conception services in Kenya, as most studies have been conducted in research settings. In addition, there is limited research on viral load monitoring as part of safer conception services, and the findings from this study could be used to bridge some of the gaps in the literature. A limitation is that the research was conducted in an urban setting, which may not be representative of the experiences of couples in rural areas. The members of the couple were interviewed separately to encourage the perspective of each member; however, with this approach, we were not able to observe the couple dynamics. This research was conducted when both PrEP and viral load monitoring were relatively new in Kenya; therefore current perspectives may be different as these technologies are more widely adopted.

Conclusions

This qualitative study showed that the couples had positive experiences with safer conception, received counseling and education, and were motivated to attempt conception despite their discordant status. The couples endorsed safer conception services delivered by healthcare providers with positive attitudes toward the fertility intention of serodiscordant couples. Interviews revealed that serodiscordant couples remained concerned about HIV transmission, and faced challenges when using some safer conception methods. In addition, viral load monitoring was required prior to offering safer conception methods, an emerging theme that needs to be evaluated further in areas where routine viral load monitoring is not performed. Overall, their motivation to have children helped them overcome challenges and remain open to discussions on risk reduction. Finally, HIV-serodiscordant couples were enthusiastic about ART and PrEP as a way to protect seronegative partners and appreciated counseling and reassurance regarding unprotected sex in that setting. Providers should consider these needs when offering safer conception services, and consider that ongoing couple counseling may be needed to alleviate concerns and challenges, thus making these services acceptable.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kenyatta National Hospital/University of Nairobi Ethical Research Committee (KNH/UON ERC) (Ref: P4/01/2017) and the University of Washington Institutional Review Board (Ref: STUDY00000953). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AK contributed to the conceptualization, data curation, funding acquisition, investigation, methodology, reviewing, and editing of the manuscript. AR contributed to the conceptualization, data curation, funding acquisition, investigation, methodology, supervision, resources, reviewing, and editing of the manuscript. GK contributed to the methodology, data validation, writing original draft, reviewing, and editing the manuscript. HM contributed to the methodology, investigation, data validation, reviewing, and editing of the manuscript. JK contributed to the conceptualization, funding acquisition, investigation, methodology, supervision, resources, reviewing, and editing of the manuscript. PM contributed to the methodology, resources, reviewing, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was funded by the National Institute of Health Research Training Grant #R25TW009345 funded by the Fogarty International Center, the NIH Office of the Director Office of AIDS Research, the NIH Office of the Director Office of Research on Women's Health, the National Heart, Lung and Blood Institute, the National Institute of Mental Health, and the National Institute of General Medical Sciences. AR was supported by NICHD K23HD071788 and NIH-supported Centers for AIDS Research: AI027757.

ACKNOWLEDGMENTS

We would like to appreciate the study participants who graciously shared their personal experiences with us.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Reproductive Health

SYSTEMATIC REVIEW
published: 26 November 2021
doi: 10.3389/frph.2021.672446

Pooled Prevalence of Adverse Pregnancy and Neonatal Outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results From a Systematic Review and Meta-Analyses to Inform Trials of Novel HIV Prevention Interventions During Pregnancy

*Erica M. Lokken[1], Anya Mathur[1], Katherine E. Bunge[2], Lee Fairlie[3], Bonus Makanani[4], Richard Beigi[2], Lisa Noguchi[5] and Jennifer E. Balkus[1,6,7]**

[1] Department of Global Health, University of Washington, Seattle, WA, United States, [2] Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, PA, United States, [3] Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [4] Department of Obstetrics and Gynecology, College of Medicine, University of Malawi, Blantyre, Malawi, [5] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States, [6] Department of Epidemiology, University of Washington, Seattle, WA, United States, [7] Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, WA, United States

Background: Robust data summarizing the prevalence of pregnancy and neonatal outcomes in low- and middle-income countries are critically important for studies evaluating investigational products for HIV prevention and treatment in pregnant and breastfeeding women. In preparation for studies evaluating the safety of the dapivirine vaginal ring for HIV prevention in pregnancy, we conducted a systematic literature review and meta-analyses to summarize the prevalence of pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe.

Methods: Ten individual systematic literature reviews were conducted to identify manuscripts presenting prevalence data for 12 pregnancy and neonatal outcomes [pregnancy loss, stillbirth, preterm birth, low birthweight (LBW), neonatal mortality, congenital anomaly, chorioamnionitis, postpartum endometritis, postpartum hemorrhage, gestational hypertension, preeclampsia/eclampsia, and preterm premature rupture of membranes (PPROM)]. Studies included in the meta-analyses were published between January 1, 1998, and July 11, 2018, provided numerator and denominator data to support prevalence estimation, and included women of any HIV serostatus. Random-effects meta-analyses were conducted to estimate the pooled prevalence and 95% confidence interval (CI) for each outcome overall, by country, and by HIV status.

Results: A total of 152 manuscripts were included across the 12 outcomes. Overall, the frequency of stillbirth ($n = 75$ estimates), LBW ($n = 68$), and preterm birth ($n = 67$) were

OPEN ACCESS

Edited by:
Tivani Phosa Mashamba-Thompson, University of Pretoria, South Africa

Reviewed by:
Lyle McKinnon, University of Manitoba, Canada
Saheed Akinmayowa Lawal, Olabisi Onabanjo University, Nigeria
Buyisile Chibi, Centre for the AIDS Programme of Research in South Africa, South Africa

***Correspondence:**
Jennifer E. Balkus
jbalkus@uw.edu

Specialty section:
This article was submitted to HIV and STIs, a section of the journal Frontiers in Reproductive Health

Received: *25 February 2021*
Accepted: *01 October 2021*
Published: *26 November 2021*

Citation:
Lokken EM, Mathur A, Bunge KE, Fairlie L, Makanani B, Beigi R, Noguchi L and Balkus JE (2021) Pooled Prevalence of Adverse Pregnancy and Neonatal Outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results From a Systematic Review and Meta-Analyses to Inform Trials of Novel HIV Prevention Interventions During Pregnancy. Front. Reprod. Health 3:672446. doi: 10.3389/frph.2021.672446

the most often reported. However, fewer than 10 total manuscripts reported prevalence estimates for chorioamnionitis, endometritis, or PPROM. The outcomes with the highest pooled prevalence were preterm birth (12.7%, 95%CI 11.2–14.3), LBW (11.7%, 95%CI 10.6–12.9), and gestational hypertension (11.4%, 95%CI 7.8–15.7). Among the outcomes with the lowest pooled prevalence estimates were neonatal mortality (1.7%, 95%CI 1.4–2.1), pregnancy loss [1.9%, 95%CI 1.1–2.8, predominately studies (23/29) assessing losses occurring after the first trimester], PPROM (2.2%, 95%CI 1.5–3.2), and stillbirth (2.5%, 95%CI 2.2–2.7).

Conclusions: Although this review identified numerous prevalence estimates for some outcomes, data were lacking for other important pregnancy-related conditions. Additional research in pregnant populations is needed for a thorough evaluation of investigational products, including for HIV prevention and treatment, and to inform better estimates of the burden of adverse pregnancy outcomes globally.

Keywords: Malawi, Zimbabwe, Uganda, South Africa, pregnancy complications, pregnancy outcomes, neonatal outcomes

INTRODUCTION

In Sub-Saharan Africa, cisgender women of reproductive age represent the largest proportion of those with new HIV infections, making them a key focus for HIV testing, treatment, and prevention efforts (1). Pregnant and postpartum women, in particular, have higher rates of HIV acquisition compared with non-pregnant women (2–4). Yet, despite the potential increased susceptibility of HIV faced by women during these clinically complex periods of their lives, pregnant and postpartum women are frequently excluded from clinical trials evaluating investigational products for HIV treatment or prevention. This exclusion is not unique to the development of HIV-related interventions, but rather is due to paternalistic regulatory restrictions in place in many countries that aim to protect pregnant women and the fetus (5, 6). As a result of such restrictions, data on the safety of medications used in pregnancy are grossly limited, with the majority of the safety data collected through postmarketing surveillance (7).

There is a scientific and ethical imperative to responsibly include pregnant women in research evaluating the safety and efficacy of investigational products. In line with this imperative, the Microbicide Trials Network (MTN) is conducting the DELIVER study, a phase 3b, randomized, open-label safety trial of the dapivirine vaginal ring (25 mg), and oral preexposure prophylaxis (PrEP) (Truvada: 200 mg emtricitabine [FTC]/300 mg tenofovir disoproxil fumarate [TDF]) for HIV prevention in pregnant cisgender women (MTN-042; ClinicalTrials.gov Number: NCT03965923). The primary objectives of this study are to describe maternal and infant safety and pregnancy outcomes among women randomized to receive the dapivirine vaginal ring or oral Truvada. As all enrolled women will be using an HIV prevention product during pregnancy, the frequency of pregnancy complications, pregnancy outcomes, and neonatal outcomes will be compared with the rates in the general population in Malawi, South Africa, Uganda, and Zimbabwe, where the DELIVER study is being conducted.

Maternal and neonatal outcomes, such as stillbirth, preterm birth, low birthweight (LBW), neonatal mortality, and maternal mortality represent internationally recognized and monitored priority health indicators (8–11). In comparison, a lack of sufficient data has been noted for other important outcomes, such as hypertensive disorders of pregnancy, premature preterm rupture of membranes (PPROM), postpartum hemorrhage (PPH), and congenital anomalies. This presents a challenge not only for allocating resources to improve these outcomes but also for evaluating investigational therapeutics for pregnant women. Robust data summarizing the expected prevalence of these outcomes among women in low and middle income countries (LMICs) are critically important for these studies. To that end, the objective of this systematic literature review and meta-analyses was to estimate the prevalence of 12 pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe.

METHODS

Literature Search, Inclusion and Exclusion Criteria, and Data Abstraction

We conducted 10 individual systematic literature reviews to identify manuscripts presenting prevalence data for 12 pregnancy and neonatal outcomes of interest including pregnancy loss (<20 0/7 weeks), stillbirth (≥20 0/7 weeks), preterm birth, LBW, neonatal mortality, congenital anomaly, chorioamnionitis, postpartum endometritis, PPH, gestational hypertension, preeclampsia/eclampsia, and PPROM (Outcome definitions and outcome-specific exclusion critiera are described in **Table 1**). Gestational hypertension, preeclampsia, and eclampsia were combined into one search strategy,

TABLE 1 | Definitions of pregnancy outcomes, infant outcomes, and pregnancy complications for the DELIVER Study and this systematic review and meta-analysis.

Category	Outcome	DELIVER study definition	Outcome specific exclusion criteria for systematic review & analysis
Pregnancy Outcome	Pregnancy loss	Pregnancy loss ≥12 weeks and <20 0/7 weeks	• Includes induced abortions only or unable to exclude induced abortions from prevalence estimate
	Stillbirth	Pregnancy loss ≥20 0/7 weeks, including stillbirth and fetal demise	• Reports term stillbirths only • Includes deaths that occurred shortly after birth
	Preterm live birth	Birth before 37 0/7 weeks, live birth only	• Studies enrolling mothers/infants into prospective follow-up weeks after birth (survival bias)
Infant Outcome	Congenital anomaly	Major anomalies that would be detectable at birth or within the first 28 days, including but not limited to polydactyly, craniofacial defects, neural tube defects/hydrocephalus, anencephaly, heart defects, inguinal/umbilical hernia, micrognathia, and cleft lip/palate	n/a
	Low birthweight	<2,500g	• Only includes full-term infants • Different definition (ex: <2,000 g) or ascertainment (self-report, measurement of chest and head circumference) • Studies enrolling mothers/infants after birth (survival bias)
	Neonatal Mortality	Deaths in the first 28 days of life (Days 0–27)	• Studies that only reported perinatal (stillbirth + early neonatal deaths) or early neonatal deaths (ex: <7 days, <14 days) • Only enrolled and reported mortality among healthy newborns
Pregnancy Complication	Chorioamnionitis	Clinical diagnosis following the following grading criteria: Grade 1: Fever of 100.4°F–100.9°F with more than one of the following: FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions, purulent AF, or preterm labor Grade 2: Grade 1 plus fever of 101°F–104°F Grade 3: Grade 2 plus fetal distress or fever > 104°F Grade 4: Grade 3 plus fetal demise or maternal symptoms of shock	n/a
	Endometritis	Puerperal sepsis and endometritis following the following grading criteria: Grade 0: None Grade 1: Low grade fever and uterine tenderness, resolved with oral antibiotics Grade 2: Moderate symptoms, treated by ≤ 3 days of parenteral antibiotics Grade 3: Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin Grade 4: Severe infection or infection for which operative intervention is indicated	• Studies using the term "puerperal sepsis" unless further defined or included endometritis/clinical features in definition
	Postpartum Hemorrhage	Grade 1: EBL 500–1,000 mL for vaginal delivery or 1,000–1,500 mL for Cesarean section (CS) or reported as slightly increased Grade 2: EBL > 1,000 mL or vaginal delivery or > 1,500 mL for CS, with or without mild dizziness, no transfusion required Grade 3: Hemorrhage at a level for which transfusion of 1–2 units of packed cells, but no other blood products indicated Grade 4: Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated	• Studies with self-report of hemorrhage (applied at first round of inclusion/exclusion)
	Gestational hypertension	Gestational hypertension	• Studies reporting women with chronic hypertension or unspecified hypertension
	Preeclampsia/ Eclampsia	Preeclampsia or Eclampsia	n/a
	PPROM	PPROM	n/a

hypertensive disorders of pregnancy. We also conducted one search for all pregnancy losses, including spontaneous abortion and stillbirth/fetal demise. Maternal mortality, a key pregnancy outcome, was excluded from this review as these estimates are routinely tracked by government agencies and surveillance systems.

Detailed inclusion and exclusion criteria for the systematic review and meta analyses are provided in **Table 2** and

TABLE 2 | Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria round 1	Additional exclusions prior to meta-analyses
Population	• Pregnant individuals and their neonates • Any HIV serostatus, including not reported	• Studies including high-risk pregnant individuals only (ex: population of women with pre-eclampsia/eclampsia) • Studies of adolescent pregnancies only	• In cases of multiple manuscripts reporting on the same study population, citation reporting the most complete data for each outcome was selected.
Outcome	• Studies reporting prevalence of 12 pregnancy complications and outcomes (see **Table 1**)	• Unable to abstract or calculate the numerator and denominator data for prevalence estimates	• Outcome specific exclusion criteria (see **Table 1**)
Setting	• Malawi, South Africa, Uganda, and Zimbabwe (DELIVER Study countries) • Ethiopia, Kenya, Tanzania, Mozambique, Zambia, Botswana, Lesotho, eSwatini, Namibia (non-DELIVER Study countries)		• Studies from non-DELIVER study countries for outcomes with <10 total manuscripts eligible • If studies included data for a DELIVER study country and a country not included in the DELIVER study but was unable to be disaggregated by country, the study was excluded.
Study Design	• Cross-sectional (including surveillance) • Cohort (prospective or retrospective) • Randomized trial • Pre/post studies • Case-control (only if the overall prevalence of entire cohort outcomes were reported prior to selection of case-control population)	• Study designs not conducive to estimating population estimate of outcome prevalence including most case-control studies, case reports/series, commentaries, qualitative studies	• Studies utilizing data from Demographic and Health Surveys (DHS) or Multiple Indicator Cluster Survey (MICS) data • For randomized trials and pre/post studies, only the placebo or before/pre time period were included in analysis.
Years & Language	• January 1, 1998–July 11, 2018 • English		

summarized below. Due to concerns regarding the expected paucity of data for some outcomes, the searches included studies that occurred in the DELIVER study countries (Malawi, South Africa, Uganda, and Zimbabwe) and nine additional countries in eastern and southern Africa (Ethiopia, Kenya, Tanzania, Mozambique, Zambia, Botswana, Lesotho, eSwatini, Namibia). All studies reporting study outcome prevalence data were included in the initial data abstraction phase, regardless of how the pregnancy or neonatal outcome was defined. Studies of individuals with any HIV serostatus were included. Exclusion criteria included studies of pregnancy outcomes among high-risk individuals only (e.g., those with preeclampsia/eclampsia), studies including adolescent pregnancies only, and studies where it was not possible to abstract or calculate the numerator and denominator for prevalence estimates. This included studies where prevalence data were inconsistently presented in the tables and the text. For these cases, two reviewers discussed the data and if a consensus could not be made on the best estimate, the manuscript was excluded. We also excluded study designs that are not conducive to estimates of prevalence, including most case-control studies, case reports/series, commentaries, and qualitative studies. If a case-control study first reported the total population at risk and the total number affected with an outcome prior to identifying their case and control population, the study was included and overall prevalence estimate data were abstracted.

MEDLINE (PubMed) was searched for eligible manuscripts published in English between January 1, 1998, and July 11, 2018 (Search Strategies: **Supplementary Table A1**). Each of the 10 outcome searches was conducted and reviewed separately. One reviewer conducted the title and abstract review for each outcome. Two reviewers assessed all full-text manuscripts to determine inclusion. The references of published systematic reviews and meta-analyses identified in the searches were also reviewed for inclusion. All data were abstracted into a single spreadsheet. The primary reviewer conducted the initial data abstraction for each manuscript. The number of pregnancies or infants with the outcome and total sample size at risk were abstracted for each outcome. The sample at risk was defined as the number of pregnancies or the number of infants depending on the outcome under study. Where appropriate, the sample size at risk was adjusted to account for competing pregnancy outcomes. For example, spontaneous abortions were subtracted from the at-risk denominator for stillbirth and delivery-related outcomes since pregnant individuals who experience pregnancy loss are no longer at risk for these future outcomes. If a study did not report either the numerator or denominator but reported a prevalence estimate, the missing value (numerator or denominator) was calculated for inclusion in the meta-analyses. For studies reporting results for multiple countries, prevalence estimates were disaggregated by the country when possible. The main outcome for each independent search, as well as all other outcomes of interest (**Table 1**), were abstracted from each manuscript to capture all outcome prevalence data within and across the 10 reviews. Prevalence estimates for subgroups, such as HIV status or study arm for randomized trials, were also abstracted. Additional study characteristics including study design, inclusion and exclusion criteria, population characteristics, location, and methods for ascertaining each outcome were abstracted.

Prior to estimating outcome-specific pooled prevalence estimates, the second round of data review was conducted and additional exclusion criteria were applied. First, manuscripts reporting on duplicate study populations were assessed. For each outcome, only the citation reporting the most detailed outcome and prevalence data was included to minimize overrepresentation from the same study population. Second, studies utilizing demographic and health survey or multiple indicator cluster survey data were excluded as these data were aggregated through another project supporting the DELIVER study. Finally, outcome-specific exclusions were also made (exclusions outlined in **Table 1**), such as non-standard definitions of the outcome or its ascertainment (e.g., LBW defined as <2,000 g, LBW only among live-born infants). During this phase, a second reviewer reviewed the abstracted data against the original manuscript for all included manuscripts to identify errors. Disagreements were discussed between reviewers one and two, and in cases of non-agreement, JEB was consulted to make the final determination.

After completing the 10 literature reviews and data abstraction, sufficient data were available from studies conducted in the DELIVER study countries (Malawi, Uganda, South Africa, and Zimbabwe) for most outcomes. Therefore, outcome-specific meta-analyses only included studies in these countries. For outcomes with fewer than 10 manuscripts occurring in DELIVER study countries, manuscripts from all countries considered in the preliminary searches were included in the meta-analyses. If studies included data for a DELIVER study country and a country not included in the DELIVER study that was unable to be disaggregated by the country, the study was excluded. Some manuscripts reported prevalence estimates for multiple DELIVER study countries, and such prevalence estimates were disaggregated by country in the outcome-specific meta-analyses when possible.

Analytic Methods for Meta-Analyses

Meta-analyses were conducted using metaprop_one in Stata 15.1 to estimate the pooled prevalence for each outcome using random-effects weighting and exact methods for 95% confidence interval (CI) estimation (12). The Freeman–Tukey double arcsine transformation was utilized to stabilize variances and to include the studies with 0% prevalence estimates (12, 13). For randomized trials and pre-post studies, the prevalence for the control arm or pre-study period, respectively, were included where possible. If not possible, the overall prevalence estimate was included. Study-specific decisions are described in the **Supplementary Material**.

Forest plots were generated to summarize pooled prevalence estimates overall, by country, and by HIV status. We also conducted sensitivity analyses, which involved 1) excluding manuscripts with an unspecified definition of the outcome, 2) excluding studies utilizing a study definition that was not consistent with the DELIVER study protocol definitions and 3) excluding outliers. Outliers were defined as studies with a prevalence estimate that was >1.5 times the interquartile range of all included studies (14). Several additional outcome-specific sensitivity and subgroup analyses were conducted, which included restricting to studies of LBW and preterm birth when these outcomes were ascertained for live-births only, assessing antepartum vs. intrapartum stillbirth prevalence estimates, restricting to studies reporting congenital anomalies from randomized trials with rigorous assessment for anomalies, and restricting to studies reporting PPH defined as ≥500 ml of blood loss. Results of sensitivity analyses are provided in the **Supplementary Material**.

RESULTS

Overview of Search Results

Search and review results for the 10 literature searches are presented in **Table 3**. Across all outcomes, a total of 152 manuscripts were included in the meta-analyses (**Supplementary Table A2**). There were <10 manuscripts reporting prevalence estimates for chorioamnionitis, endometritis, and PPROM; therefore, studies from all queried countries (not just DELIVER study countries) were included in those meta-analyses. The fewest studies were identified for chorioamnionitis ($n = 6$) and the most for stillbirth ($n = 71$). Although pregnancies occur among cisgender women as well as gender minorities with reproductive potential, the studies included in this review were presumed to evaluate pregnancy outcomes and complications among cisgender women only. Therefore, we use the term "woman/women" when reporting the results. The number of pregnant women/infants included in the meta-analyses ranged from 2,086 for chorioamnionitis to 1,498,361 for stillbirth (**Table 4**). Results for all meta-analyses overall and by country are presented in **Table 4** and results by HIV status are presented in **Table 5**. Outcome-specific forest plots, results of sensitivity analyses, and citations for all included manuscripts are in the **Supplementary Material**.

Pregnancy Outcomes

Pregnancy Loss

Twenty-nine manuscripts, contributing 33 total prevalence estimates and 49,095 pregnancies, were included in the pregnancy loss meta-analysis (**Supplemental Material Section B**). In these studies, pregnancy loss was defined as miscarriage, spontaneous abortion, or pregnancy loss by a specific week of gestation (e.g., <20 or <28 weeks of gestation). A gestational age threshold was not defined for 31% (9/29) of the included studies (**Supplementary Table B15**). Among the included manuscripts, the majority (23/29) enrolled women predominately after the first trimester (**Supplementary Table B15**); subsequently, the pooled prevalence estimates reported here primarily reflect those occurring after the first trimester.

The overall pooled prevalence of pregnancy loss including all studies independent of pregnancy loss definition was 1.9% (95%CI 1.1–2.8, $I^2 = 92.2\%$) (**Table 4**). The pooled prevalence ranged from 1.0% (95%CI 0.0–3.8) in Zimbabwe to 2.5% (95%CI 1.1–4.3) in South Africa. When restricting to studies defining pregnancy loss as losses occurring at <20 or ≤20 weeks of gestation, the overall pooled prevalence was 0.5% (95%CI: 0.0–1.6). The pooled prevalence of pregnancy loss was lower

TABLE 3 | Results for 10 systematic reviews of pregnancy outcomes, pregnancy complications, and neonatal outcomes in 13 Eastern and Southern African countries to support the DELIVER Study (MTN-042), 1998–2018.

Review step	Chorio-amnionitis	Endometritis	PPROM	Postpartum hemorrhage	Hypertensive disorders of pregnancy*	Neonatal mortality	Low birth weight	Congenital anomaly	Preterm birth	Pregnancy loss & stillbirth
Titles reviewed	6	43	50	217	549	834	791	620	590	874
Abstracts reviewed	1	12	23	68	124	379	213	75	265	237
Manuscripts reviewed†	1	4	9	32	54	211	140	40	189	174
Manuscripts Included From Main Search‡	1	4	5	16	19	100	115	15	109	124
Manuscripts Added From Other Searches§	5	4	2	17	33	41	60	25	48	73
Total Manuscripts—Abstracted	6	8	7	28	52	141	175	40	157	197
Total Manuscripts Included-Analysis**	6	7	7	17	18	26	63	19	64	78

This search included gestational hypertension and preeclampsia/eclampsia.

† Does not include the number of references from systematic reviews that were reviewed.

‡ Including systematic review reference reviews.

§ Two recent MTN manuscripts were added to this review by study investigators (15, 16). These manuscripts were published after the searches were conducted.

*** There were fewer than 10 total manuscripts reporting chorioamnionitis, endometritis, or PPROM. Therefore, studies from all queried countries (not just DELIVER study countries) were included in the meta-analyses. Some manuscripts reported prevalence estimates for multiple DELIVER study countries; such prevalence estimates were disaggregated by country in the outcome specific meta-analyses.*

TABLE 4A | The pooled prevalence of pregnancy outcomes, pregnancy complications, and neonatal outcomes.

Outcome	Overall				
	N		%	(95% CI)	I^2
	Estimates*	At Risk†			
Pregnancy Loss	33	49,095	1.9	(1.1, 2.8)	92.2%
Stillbirth	75	1,498,361	2.5	(2.2, 2.7)	98.0%
Preterm Birth	67	134,763	12.7	(11.2, 14.3)	98.4%
Congenital Anomaly	22	402,215	0.4	(0.2, 0.7)	97.9%
Low Birthweight	68	117,578	11.7	(10.6, 12.9)	97.1%
Neonatal Mortality	26	342,853	1.7	(1.4, 2.1)	97.2%
Chorioamnionitis‡	6	2,086	16.2	(8.0, 26.7)	96.9%
Endometritis‡	7	12,653	3.3	(1.1, 6.6)	98.4%
Postpartum Hemorrhage	17	71,308	4.4	(3.0, 6.0)	98.7%
Gestational Hypertension	14	32,024	11.4	(7.8, 15.7)	99.1%
Preeclampsia/Eclampsia	9	50,234	4.0	(1.9, 6.8)	99.4%
PPROM‡	7	26,220	2.2	(1.5, 3.2)	93.3%

**Estimates refers to the number of prevalence estimates. Some included manuscripts reported prevalence estimates by study country and therefore contributed more than one prevalence estimate to outcome specific meta-analyses.*

† Women/pregnancies or infants depending on the outcome and the study.

‡ There were fewer than 10 total manuscripts reporting chorioamnionitis, endometritis, or PPROM. Therefore, studies from all queried countries (not just DELIVER Study countries) were included in the meta-analyses.

among women living with HIV (0.8%, 95%CI 0.3–1.5; $n = 8$ estimates) than HIV-negative women (3.6%, 95%CI 0.5–9.1; $n = 4$ estimates), although the confidence intervals overlap (**Table 5**).

Stillbirth or Fetal Demise

A total of 1,498,361 pregnancies/infants from 71 manuscripts (75 prevalence estimates) were included in the stillbirth meta-analysis (**Supplemental Material Section B**). The overall pooled prevalence of stillbirth was 2.5% (95% CI 2.2–2.7, $I^2 = 98.0\%$) (**Table 4**). The prevalence was similar in all four DELIVER study countries and was 2.3% (95%CI 1.8, 2.9) in Malawi, 2.0% (95% CI 1.7–2.4) in South Africa, 2.0% (95%CI 0.4–4.7) in Zimbabwe, and 3.0% (95%CI 2.1–4.1) in Uganda. When restricting to studies defining stillbirth as those occurring at >20 or ≥20 weeks of gestation, the pooled prevalence was higher at 3.7% (95%CI 1.4, 4.3; **Supplementary Table B11**). There was no difference in the

TABLE 4B | DELIVER study country.

Outcome*	Malawi				South Africa				Uganda				Zimbabwe			
	N		%	(95% CI)	*N*		%	(95% CI)	*N*		%	(95% CI)	*N*		%	(95% CI)
	Estimates†	At Risk			Estimates	At Risk			Estimates	At Risk			Estimates	At Risk		
Pregnancy loss	7	3,956	0.6	(0.2, 1,2)	14	30,080	2.5	(1.1, 4.3)	8	7,382	1.4	(0.7, 2.1)	3	7,520	1.0	(0.0, 3.8)
Stillbirth	18	536,079	2.3	(1.8, 2.9)	26	871,383	2.0	(1.7, 2.4)	23	66,533	3.0	(2.1, 4.1)	6	24,003	2.0	(0.4, 4.7)
Preterm birth	13	9,850	13.5	(9.1, 18.5)	28	85,559	12.6	(10.0, 15.5)	15	11,066	11.4	(9.0, 14.1)	10	28,063	14.6	(12.4, 16.9)
Congenital anomaly	4	27,951	0.2	(0.0, 0.6)	8	312,903	0.2	(0.1, 0.5)	7	60,997	0.6	(0.0, 1.5)	1	31	0.0	(0.0, 11.2)
Low Birthweight	17	14,827	10.4	(8.5, 12.5)	20	54,144	12.7	(10.9, 14.5)	20	19,760	11.9	(9.8, 14.2)	11	28,847	11.8	(8.0, 16.2)
Neonatal Mortality	8	22,030	2.4	(1.4, 3.4)	10	276,251	0.9	(0.6, 1.2)	7	40,616	2.6	(2.3, 3.0)	1	3,956	1.3	(0.9, 1.7)
Chorioamnionitis‡	1	676	30.6	(27.2, 34.2)	0	–	–	–	2	423	21.5	(17.7, 25.6)	0	–	–	–
Endometritis‡	1	2,791	0.8	(0.5, 1.2)	2	4,197	0.3	(0.2, 0.6)	2	4,428	1.6	(0.4, 3.4)	0	–	–	–
Postpartum Hemorrhage	2	5,875	2.0	(1.7, 2.4)	10	57,046	3.6	(2.0, 5.6)	3	3,564	8.8	(2.5, 18.3)	2	4,823	1.9	(1.5, 2.3)
Gestational hypertension	0	–	–	–	10	23,225	10.0	(5.8, 15.3)	1	418	11.5	(8.6, 14.9)	3	8,381	16.5	(6.5, 29.9)
Preeclampsia/Eclampsia	1	2,791	0.7	(0.4, 1.1)	5	37,650	6.2	(3.0, 10.3)	1	418	4.5	(2.8, 7.0)	2	9,375	1.3	(1.1, 1.5)
PPROM‡	0	–	–	–	1	421	0.7	(0.1, 2.1)	2	6,528	2.7	(2.3, 3.2)	0	–	–	–

** Country specific I^2 are in the **Supplementary Material**.*

† Estimates refers to the number of prevalence estimates. Some included manuscripts reported prevalence estimates by study country and therefore contributed more than one prevalence estimate.

‡ There were fewer than 10 total manuscripts reporting chorioamnionitis, endometritis, or PPROM. Therefore, studies from all queried countries (not just DELIVER Study countries) were included in the meta-analyses.

TABLE 5 | Pooled prevalence of pregnancy outcomes, pregnancy complications, and neonatal outcomes—By HIV status.

Outcome	Women living with HIV				HIV-negative			
	N		%	(95% CI)	*N*		%	(95% CI)
	Estimates	At Risk			Estimates	At Risk		
Pregnancy loss	11	5,255	0.8	(0.3, 1.5)	4	2,161	3.6	(0.5, 9.1)
Stillbirth	17	13,377	2.9	(2.0, 3.8)	9	9,510	1.9	(1.3, 2.5)
Preterm birth	21	18,592	14.1	(11.0, 17.6)	13	11,108	10.0	(5.7, 15.4)
Congenital anomaly	8	1,846	1.8	(0.5, 3.6)	2	739	0.7	(0.1, 1.6)
Low birthweight	18	17,181	13.7	(11.2, 16.3)	10	20,529	10.0	(7.7, 12.5)
Neonatal mortality	5	6,713	1.0	(0.5, 1.8)	1	11,053	0.5	(0.4, 0.6)
Chorioamnionitis*	4	1,171	18.7	(5.6, 36.9)	1	68	5.9	(1.3, 13.0)
Endometritis*	3	4,022	2.9	(0.3, 7.6)	1	2,916	0.2	(0.1, 0.4)
Postpartum hemorrhage	5	7,541	4.5	(1.3, 9.4)	4	11,650	5.2	(0.4, 14.0)
Gestational hypertension	3	3,201	9.6	(1.3, 24.3)	4	2,399	5.8	(0.9, 14.3)
Preeclampsia/Eclampsia	3	7,701	2.3	(0.6, 5.2)	3	4,910	5.2	(2.6, 8.4)
PPROM*	1	68	10.3	(4.2, 20.1)	2	489	0.9	(0.2, 2.1)

**There were fewer than 10 total manuscripts reporting chorioamnionitis, endometritis, or PPROM. Therefore, studies from all queried countries (not just DELIVER study countries) were included in the meta-analyses.*

prevalence of macerated (antepartum) stillbirth (1.7%, 95%CI 1.1–2.4) vs. fresh (intrapartum) stillbirth (1.8%, 95%CI 1.3–2.4) (**Supplementary Tables B9, 10**). The overall pooled prevalence of stillbirth was 2.9% (95%CI 2.0–3.8) in women living with HIV and 1.9% (95%CI 1.3–2.5) in HIV-negative women (**Table 5**).

Preterm Birth

Sixty-three manuscripts contributing 67 prevalence estimates and 134,763 pregnancies/infants were included in the preterm birth meta-analysis (**Supplemental Material Section C**). The overall pooled prevalence of preterm birth was 12.7% (95%CI 11.2–14.3, $I^2 = 98.4\%$) and ranged from 11.4% (95%CI 9.0–14.1) in Uganda to 14.6% (9%CI 12.4–16.9) in Zimbabwe (**Table 4**). The overall pooled prevalence of preterm birth was 14.1% (95%CI 11.0–17.6) in women living with HIV and 10.0% (95%CI 5.7–15.4) in HIV-negative women (**Table 5**).

Neonatal Outcomes

Congenital Anomalies

Nineteen manuscripts (22 prevalence estimates) and 402,215 infants were included in the congenital anomalies meta-analysis (**Supplemental Material Section D**). Forty-two percent (8/19) of manuscripts reported results of randomized controlled trials. In most studies (84.2%, 16/19), assessment for congenital anomalies was conducted at or near the time of birth only, which may contribute to an underestimate of the true congenital anomaly rate (**Supplementary Table D6**).

The overall pooled prevalence of congenital anomalies was 0.4% (95%CI 0.2–0.7, $I^2 = 97.9\%$) and was similar in all the countries (**Table 4**). However, when restricting to eight estimates from randomized trials, the prevalence increased to 1.5% (95%CI 0.2–3.6; **Supplementary Table D4**). The overall pooled prevalence of congenital anomalies among women living with HIV was 1.8% (95%CI 0.5–3.6; $n = 8$ estimates). This is higher than the pooled prevalence in HIV-negative women (0.7%, 95%CI 0.1–1.6), but there were few included manuscripts ($n = 2$) (**Table 5**). The frequencies of specific or system-specific anomalies are summarized in **Table 6** and **Supplementary Table D5**. The most common anomalies were umbilical and inguinal hernias (1.7%, 95%CI 0.7–3.8) and polydactyly and syndactyl (0.7%, 95%CI 0.3–1.2).

Low Birthweight

Sixty-four manuscripts contributing 68 prevalence estimates and 117,583 infants were included in the LBW meta-analysis (**Supplemental Material Section E**). The overall pooled prevalence was 11.7% (95%CI 10.6–12.9, $I^2 = 97.1\%$), ranging from 10.4% (95%CI 8.5–12.5) in Malawi to 12.7% (95%CI 10.9–14.5) in South Africa (**Table 4**). The prevalence of LBW among women living with HIV was 13.7% (95%CI 11.2–16.3) and 10.0% (95%CI 7.7–12.5) among HIV-negative women (**Table 5**).

Neonatal Mortality

A total of 342,853 pregnancies from 26 manuscripts were included in the neonatal mortality meta-analysis (**Supplemental Material Section F**). The overall pooled prevalence of neonatal mortality was 1.7% (95% CI 1.4–2.1, $I^2 = 97.2\%$). The country-specific pooled prevalence of neonatal mortality was 2.4% (95%CI 1.4–3.4) in Malawi, 0.9% (95%CI 0.6–1.2) in South Africa, 2.6% (95%CI 2.3–3.0) in Uganda, and 1.3% (95%CI 0.9–1.7) in Zimbabwe (**Table 4**). Few studies reported neonatal mortality by HIV status of the mothers (**Table 5**). The prevalence of neonatal mortality among women living with HIV and HIV-negative women was 1.0% (95%CI 0.5–1.8; $n = 5$ estimates) and 0.5% (95%CI 0.4–0.6; $n = 1$ estimate), respectively.

TABLE 6 | Overall pooled prevalence of specific and system-specific congenital anomalies.

Anomaly Type*	*N*			%	(95%CI)
	Manuscripts	Cases	At Risk		
Not defined	8	49	13,372	0.34%	(0.04, 0.82)
Cleft lip and/or palate	8	111	205,537	0.03%	(0.01, 0.05)
Neural tube defects and/or Hydrocephalus	3	182	153,535	0.11%	(0.08, 0.14)
Cardiovascular	3	8	3,502	0.23%	(0.01, 0.65)
Polydactyly and Syndactyly	6	43	4,668	0.70%	(0.30, 1.22)
Musculoskeletal†	5	14	5,855	0.20%	(0.07, 0.38)
Umbilical and Inguinal Hernia	4	79	3,609	1.73%	(0.40, 3.81)
Esophageal, gastrointestinal, or anorectal	3	47	182,745	0.02%	(0.0, 0.07)
Genitourinary	2	8	2,662	0.23%	(0.06, 0.48)
Trisomy	3	3	4,850	0.05%	(0.05, 0.15)
Multiple systems	1	10	2,365	0.42%	(0.20, 0.78)
Other§	6	123	130,916	0.40%	(0.06, 0.98)

Congenital anomalies were grouped into subtypes by common types (ex: neural tube defects) and by system (ex: musculoskeletal). A subgroup was created when there was more than one reported case or study reporting the type/system of the anomaly. When multiple anomalies were listed per infant, the infant was included as one overall infant but was included as a case in each of the anomalies sub-types. If specific anomalies were not specified, such infants were included in the "multiple systems" sub-group. Naevus/birthmarks were excluded when possible for the overall and type specific analyses.

† *Including talipes equinovarus.*

Systems not defined.

§ *Includes singular, or infrequent, reports of rare or non-specific anomalies that did not fit well into other defined sub-groups. Examples include natal tooth, anophthalmia, facial asymmetry, arachnoid cyst, hypopigmented skin, macrocephaly with brain defect, subtle dysmorphism, and plagiocephaly.*

Pregnancy Complications

Gestational Hypertension

Fourteen manuscripts including a total of 32,024 pregnancies were included in the gestational hypertension meta-analysis (**Supplemental Material Section J**). The overall pooled prevalence of gestational hypertension was 11.4% (95%CI 7.8–15.7, $I^2 = 99.1\%$). The pooled prevalence was 10.0% (95%CI 5.8–15.3) in South Africa, 11.5% (95%CI 8.6–14.9) in Uganda, and 16.5% (95%CI 6.5–29.9) in Zimbabwe (**Table 4**). No published data were identified for Malawi. Pregnant women living with HIV had a higher prevalence of gestational hypertension than HIV-negative women (9.6%, 95%CI 1.3–24.3, $n = 3$ vs. 5.8%, 95%CI 0.9–14.3, $n = 4$; **Table 5**).

Preeclampsia/Eclampsia

Nine manuscripts reported data on preeclampsia/eclampsia diagnoses and included 50,234 pregnancies (**Supplemental Material Section J**). The overall pooled prevalence was 4.0% (95%CI 1.9–6.8; $I^2 = 99.4\%$). Country-specific pooled prevalence was 0.7% (95%CI 0.4–1.1) in Malawi, 6.2% (95%CI 3.0–10.3) in South Africa, 4.5% (95%CI 2.8–7.0) in Uganda, and 1.3% (95%CI 1.1–1.5) in Zimbabwe (**Table 4**). Pregnant women living with HIV ($n = 3$ estimates) had a lower prevalence of preeclampsia/eclampsia compared with HIV-negative pregnant women ($n = 3$ estimates) (2.3%, 95%CI 0.6–5.2 vs. 5.2%, 95%CI 2.6–8.4; **Table 5**).

Postpartum Hemorrhage

Seventeen manuscripts including 71,308 pregnancies reported prevalence data on PPH and were included in the meta-analysis (**Supplemental Material Section I**). The overall pooled prevalence was 4.4% (95%CI 3.0–6.0, $I^2 = 98.7\%$). Country-specific pooled prevalence estimates were 2.0% (95%CI 1.7–2.4) in Malawi, 3.6% (95%CI 2.0–5.6) in South Africa, 8.8% (95%CI 2.5–18.3) in Uganda, and 1.9% (95%CI 6.5–29.9) in Zimbabwe (**Table 4**). The pooled prevalence of PPH was similar between women living with HIV and HIV-negative women (4.5%, 95%CI 1.3–9.4 vs. 5.2%, 95%CI 0.4–14.0) (**Table 5**). When restricting to studies defining PPH as ≥500 mL blood loss ($n = 7$), the pooled prevalence was 7.5% (95%CI 4.6–11.1, **Supplementary Figure 14**).

Chorioamnionitis

A total of 2,086 pregnancies from six manuscripts were included in the chorioamnionitis meta-analysis, including studies from Malawi ($n = 1$), Uganda ($n = 2$), Zambia ($n = 1$), and Kenya ($n = 2$) (**Supplemental Material Section G**). The pooled prevalence for all studies was 16.2% (95%CI 8.0–26.7, $I^2 = 96.9\%$) (**Table 4**). However, most of the studies diagnosed chorioamnionitis using histologic criteria, and 66.7% (4/6) of the studies included women living with HIV who had low CD4 cell count or advanced AIDS (**Supplemental Material Notes G1**); these study characteristics may result in a biased estimate for general population women. The pooled prevalence of chorioamnionitis in women living with HIV was 18.7% (95%CI 5.6–36.9), whereas it was 5.9% (95%CI 1.3–13.0) in the one study reporting the prevalence among HIV-negative women (**Table 5**). There was no study assessing chorioamnionitis by clinical criteria among HIV-negative women (**Supplemental Material Notes G1**).

Postpartum Endometritis

Few studies reported data on postpartum endometritis prevalence. This meta-analysis includes seven manuscripts including a total of 12,653 pregnancies from Malawi ($n = 1$), South Africa ($n = 2$), Uganda ($n = 2$), Kenya ($n = 1$), and Ethiopia ($n = 1$) (**Supplemental Material Section H**). The overall pooled prevalence was 3.3% (95%CI 1.1–6.6, $I^2 = 96.9\%$) (**Table 4**). The prevalence was 2.9% (95%CI 0.3–7.6, $n = 3$ estimates) in women living with HIV and 0.2% (95%CI 0.1–0.4, $n = 1$ estimate) in HIV-negative women (**Table 5**).

Premature Preterm Rupture of Membranes

A total of 26,220 pregnancies from seven manuscripts were included in the PPROM meta-analysis (**Supplemental Material Section K**). The included studies represent data from South Africa ($n = 1$), Uganda ($n = 2$), Ethiopia ($n = 2$), and Kenya ($n = 2$). The overall pooled prevalence was 2.2% (95%CI 1.5–3.2, $I^2 = 93.3\%$; **Table 4**). The prevalence was 10.3% (95%CI 4.2–20.1) in the one study reporting PPROM among women living with HIV and 0.9% (95%CI 0.2–2.1) in HIV-negative women ($n = 2$ estimates).

Review of Potential Study Bias

A qualitative assessment of these literature reviews highlighted the lack of standard outcome ascertainment and quality control procedures, which affect prevalence estimates. Given the expected paucity of data for numerous outcomes of interest, the inclusion criteria for the reviews and meta-analyses included few restrictions on outcome ascertainment methods (outlined in **Table 1**). Notably, there are data quality issues in studies relying on routinely collected health data and chart abstraction in LMICs, including missing data and underreporting of pregnancy complications and outcomes occurring outside of health facilities (17, 18). There are also known challenges with measuring many of the included outcomes in LMICs, which contribute to underestimates and misclassification. For example, there are numerous methods for estimating gestational age with variable sensitivity and specificity (e.g., ultrasound, last day of menstrual period, fundal height, Ballard score) (19, 20). LBW estimates are complicated by accuracy and precision errors such as poorly calibrated scales, missing data, and overreporting of infants weighing 2,500 g at delivery (21). Additionally, while we excluded self-reported PPH, accurately estimating blood loss quantity is challenging in most settings (22). There were also varying definitions for many outcomes, which reduces the ability to compare between studies. For example, there was significant variability in pregnancy loss and stillbirth definitions, both in terminology and in the gestational age cutoff for pregnancy loss vs. stillbirth (**Supplementary Tables B15, 16**). Specifically, while the WHO definition of stillbirth for international comparability is a "baby born with no signs of life at or after 28 weeks' gestation" (23), other organizations and numerous studies, including the DELIVER study, use ≥20 weeks of (or ≥24 weeks) gestation to classify stillbirth/fetal demise (**Supplementary Tables B15, 16**). In addition, in many cases, outcome definitions were not stated in the included papers.

DISCUSSION

These systematic literature reviews and meta-analyses assessed the prevalence of 12 pregnancy and neonatal outcomes and pregnancy complications in Malawi, South Africa, Uganda, and Zimbabwe. The preponderance of published manuscripts reported data on the frequency of stillbirth, LBW, and preterm birth, which was expected given their status as priority health indicators (8). However, few studies reported on the prevalence of important pregnancy complications such as chorioamnionitis, postpartum endometritis, and PPROM. In many settings, including in LMICs, diagnoses of pregnancy complications can be challenging to ascertain, resulting in a paucity of data to inform reproductive and perinatal health initiatives, clinical care, and in the evaluation of investigational therapeutics, including those for HIV prevention and treatment, and for pregnant and breastfeeding individuals.

Collectively, the variability in outcome definition and ascertainment across studies reduces the ability to precisely estimate the prevalence of these pregnancy and neonatal outcomes. To address this challenge in the context of evaluating vaccine safety among pregnant people, the Global Alignment of Immunization Safety Assessment in pregnancy project (GAIA) was established in 2015 to "improve the quality of outcome data from clinical vaccine trials in pregnant women with a specific focus on the needs and requirements for safety monitoring in LMICs" (24). As part of the GAIA project, standardized case definitions for common obstetric and neonatal outcomes were established to improve the comparability of adverse outcomes across studies (25). Although some data may not be available from participant medical records to appropriately categorize certain outcomes, it is critical that studies of other biomedical interventions in pregnancy begin to collect data in support of the GAIA definitions to facilitate comparability.

The frequent exclusion of pregnant people from clinical trials of investigational products has created an environment where evidence-based guidelines for medication use during pregnancy are lacking, leading to suboptimal treatment. Data on the effect of pregnancy on drug pharmacokinetics, pharmacodynamics, and safety profiles often do not exist or are collected postmarketing, leaving patients and providers wary of medication use during pregnancy and while breastfeeding (5, 26, 27). Clearly, there is an ethical and public health imperative to include pregnant and breastfeeding women in clinical research (28). This need certainly extends to purposefully establishing the safety and efficacy of new HIV treatment and prevention methods in pregnant individuals with or at risk for HIV (5, 29). This can be illustrated by the 2019 finding from the Tsepamo study in Botswana that periconceptual dolutegravir use by women living with HIV may increase neural tube defects (30, 31). Sequential product development strategies that include safety studies among pregnant people are critical for ensuring that initial safety data on use in pregnancy are available for patients and providers at or near the time of product licensure (32). Since many pregnancy and neonatal outcomes are rare, the collection of additional postmarketing safety data must continue to be an important part of monitoring use in pregnant people.

This project had several strengths. Since the original literature searches included studies from the 13 countries in Sub-Saharan Africa, we were able to generate prevalence estimates for less frequently reported pregnancy complications (e.g., PPROM). In addition, while the pregnancy and neonatal outcomes are explicitly defined for the DELIVER study, the inclusion criteria included studies with varying definitions of each outcome given the paucity of data on some pregnancy outcomes and the known challenges of measuring these outcomes in low-resource settings. The inclusion of a range of definitions allowed us to generate overall prevalence estimates and conduct sensitivity analyses that were restricted to studies that defined outcomes most similarly to the DELIVER study protocol. Finally, two independent reviewers assessed each potential full-text manuscript for inclusion, and all the manuscripts and abstracted data included in the meta-analyses were read and reviewed by a second reviewer to guarantee quality.

There were several limitations to these meta-analyses. First, there was heterogeneity in the study design, study objectives, study inclusion/exclusion criteria affecting the risk-level of the included pregnant population, methods of ascertaining outcomes, the underlying health status of included pregnant individuals, and prevalence estimates across the included manuscripts. Our analysis also excluded studies restricted to adolescents and was unable to include age-standardization due to limitations in the available data. Collectively, our findings should be interpreted with this context in mind. Second, the pooled prevalence estimates for rare outcomes and subgroup analyses were limited by the paucity of data. The confidence intervals are wide and country-specific estimates may rely on data from only a few studies. For example, these meta-analyses suggest that women living with HIV had a higher pooled prevalence for many of the included outcomes such as stillbirth, preterm birth, congenital anomalies, and LBW. However, a minority of included studies reported prevalence by HIV status, and so these results, especially for the rare outcomes, should be interpreted cautiously. Third, despite the robust search, the review was limited by how manuscripts are indexed in MEDLINE. Manuscripts were frequently identified for inclusion in the review during the search for a single outcome while also including data on multiple additional outcomes of interest. Often, these manuscripts were not subsequently identified through specific searches for those other outcomes despite providing relevant estimates; thus, their inclusion for certain outcomes in this project occurred as a result of chance findings in manuscripts identified for another outcome. In addition, only one database was searched. Therefore, it is certain that additional prevalence estimates for these outcomes from Malawi, South Africa, Uganda, and Zimbabwe were not included in these meta-analyses. Fourth, the search strategy only included English language manuscripts identified through one database, which may have contributed to missing some prevalence estimates. Fifth, having one reviewer conduct initial data abstraction with a second reviewing for accuracy (instead of independent data abstraction by two reviewers) could have introduced bias. However, a rigorous process for identifying and adjudicating any errors and disagreements in data abstraction that were identified was followed limiting our concern for bias from this approach. Finally, while these literature reviews were conducted systematically, this review intentionally varied from certain aspects of the PRISMA guidelines for systematic reviews to best address our research question about the prevalence of pregnancy and neonatal outcomes and in response to the available data (33). For example, eligible countries were modified after the initial development of the searches. In addition, because of the size and scope of the literature reviews and the goal of estimating general population prevalence (versus intervention effect), we elected to present a qualitative summary of potential bias as this better represented the range of important considerations for interpretation of these data.

The prevalence estimates generated by this literature review and meta-analyses will be compared with the results of a records review of pregnancy outcomes at primary care and referral facilities affiliated with the DELIVER study (34). Together, these results will be utilized to assess whether the frequency of pregnancy and neonatal outcomes among pregnant women randomized to the dapivirine vaginal ring or oral TDF are similar to those observed in the areas where the study will be conducted. Importantly, these prevalence estimates will be a valuable resource for future trials of investigational products in pregnancy, including several HIV prevention methods (e.g., long-acting injectable cabotegravir) and maternal immunizations that are in the process of development or newly approved (35–37), including COVID-19 vaccines. In addition, these estimates may inform the allocation of resources and policies to prevent adverse pregnancy outcomes and complications. While this review identified a robust volume of data for some outcomes, data were severely lacking for other important pregnancy-related conditions, the quality of outcome ascertainment was variable, and stratification by HIV status was not ubiquitous. Fundamentally, there is an urgent need for pregnant people to be included in clinical research to understand the safety and efficacy of investigational products. There is also an urgent need to routinely collect quality and standardized data as the current, unreliable estimates make it challenging to distribute resources and understand whether quality improvement efforts are effective. Understanding the true burden of adverse pregnancy outcomes and complications in LMICs is essential to better serve women and other individuals of reproductive potential globally.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JB, KB, LF, and BM conceived of this project. EL and AM conducted the systematic review and meta analysis under supervision by JB. EL, AM, and JB drafted the first version of the manuscript. EL, KB, LF, BM, RB, LN, and JB interpreted the results. All authors reviewed, commented on, and approved the final manuscript.

FUNDING

The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, and UM1AI106707), with cofunding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. EML was additionally funded by a National Institute of Child Health and Human Development fellowship (F32 HD100202). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank George Yu for his early data management and study review contributions.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2021.672446/full#supplementary-material

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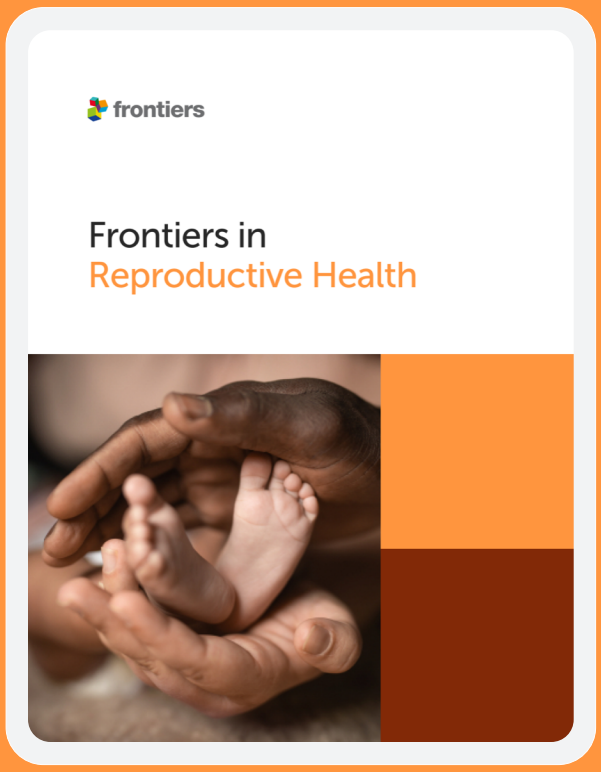

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