



Contribution of Sex Differences to HIV Immunology, Pathogenesis, and Cure Approaches

Jose A. Moran¹, Shireen R. Turner¹ and Matthew D. Marsden^{1,2*}

¹ Department of Microbiology and Molecular Genetics, School of Medicine, University of California, Irvine, CA, United States,

² Department of Medicine (Division of Infectious Diseases), School of Medicine, University of California, Irvine, CA, United States

Approximately 38 million people were living with human immunodeficiency virus (HIV) in 2020 and 53% of those infected were female. A variety of virological and immunological sex-associated differences (sexual dimorphism) in HIV infection have been recognized in males versus females. Social, behavioral, and societal influences play an important role in how the HIV pandemic has affected men and women differently. However, biological factors including anatomical, physiologic, hormonal, and genetic differences in sex chromosomes can each contribute to the distinct characteristics of HIV infection observed in males versus females. One striking example of this is the tendency for women to have lower HIV plasma viral loads than their male counterparts early in infection, though both progress to AIDS at similar rates. Sex differences in acquisition of HIV, innate and adaptive anti-HIV immune responses, efficacy/suitability of specific antiretroviral drugs, and viral pathogenesis have all been identified. Sex differences also have the potential to affect viral persistence, latency, and cure approaches. In this brief review, we summarize the major biological male/female sex differences in HIV infection and their importance to viral acquisition, pathogenesis, treatment, and cure efforts.

Keywords: HIV, sex differences, pathogenesis, persistence, latency, cure, sexual dimorphism

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*Correspondence:

Matthew D. Marsden
mdmarsde@hs.uci.edu

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INTRODUCTION

Human immunodeficiency virus (HIV) is a retrovirus that causes acquired immunodeficiency syndrome (AIDS) by infecting several important immune cell types including CD4+ T lymphocytes and macrophages (1, 2). Over 50% of people infected worldwide with HIV are female (3). While depletion of CD4+ T cells and progression to AIDS occurs in both males and females, there are significant sex-related differences in the course of infection. These “sex differences” have a biological origin, including hormonal or genetic. This is distinct from gender differences, which generally have a social or behavioral origin, including gendered socio-economic inequities such as unequal access to healthcare, financial resources, and education (4–8). While both sex and gender differences are

important in understanding the HIV pandemic, this review is focused on biological sex differences that affect HIV infection.

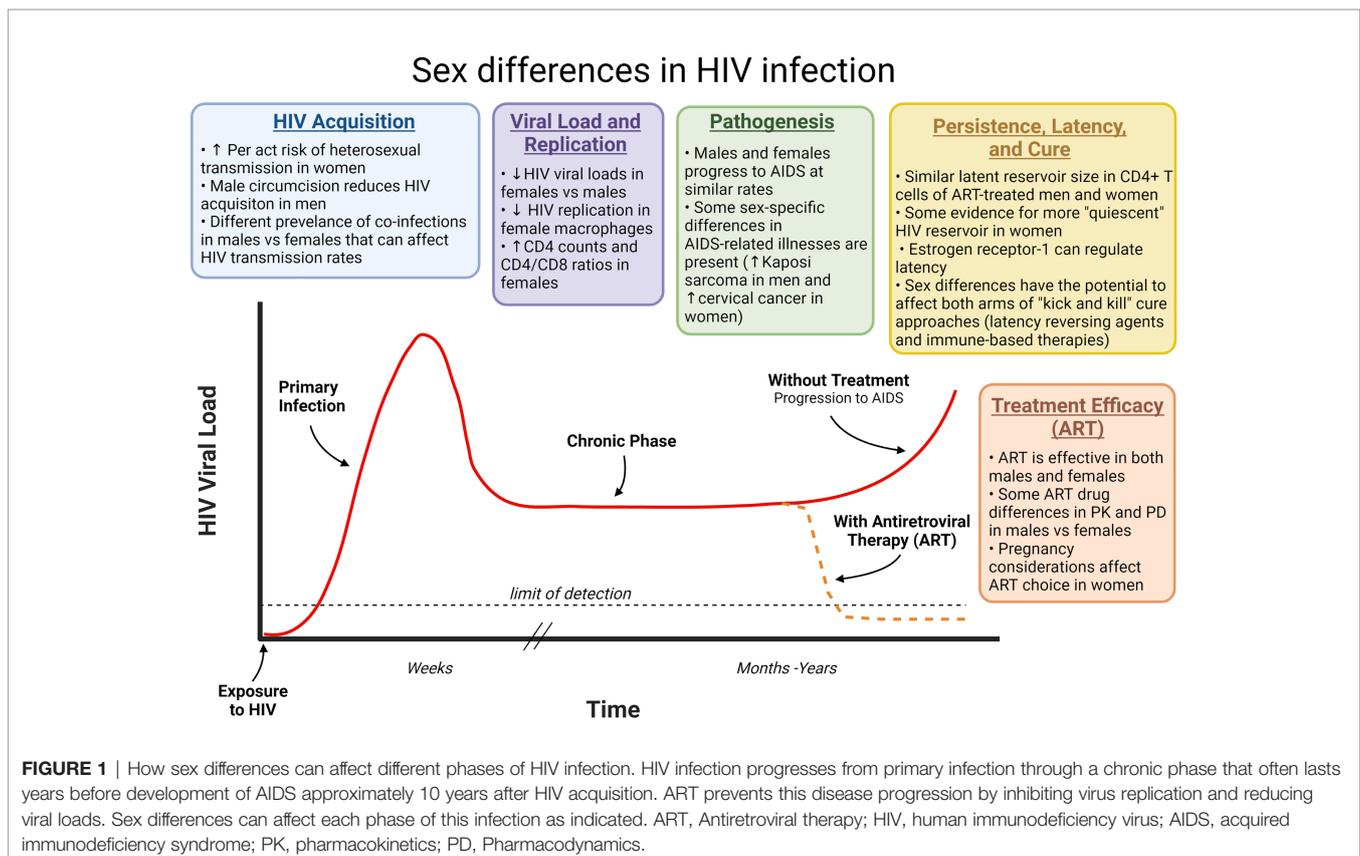
Sexual dimorphism in the mammalian immune system has long been recognized in the context of infection with many different pathogens, including influenza viruses, hepatitis B virus, and the parasite *Entamoeba histolytica* (9–11). Females often have more effective immune responses against pathogens but are also more prone to autoimmune diseases such as multiple sclerosis, scleroderma, and systemic lupus erythematosus (9, 12, 13). Many important aspects of the mammalian innate and adaptive immune response have been identified to vary in a sex-dependent manner, including the activity of key immune-related signal transduction pathways, the relative numbers of T cells, B cells and immunoglobulins, and the activation state of different immune cell subsets (9). Of particular interest, in the context of HIV, are the higher CD4+ T cell counts observed in both females compared to males. Females also have higher CD4/CD8 ratios and their macrophages have higher phagocytic activity and activation states than those from males (9). Therefore, in addition to broad immunological effects, sex differences directly influence the preferred target cells for HIV infection.

Sex differences in HIV infection have largely been attributed to anatomical, physiologic, hormonal, and genetic differences, including during pre- and post-adolescence, and in old age (14). This review will provide a brief overview of the main ways in which sex-based differences can affect HIV infection, including during initial acquisition, subsequent viral

replication, pathogenesis, treatment, and viral reservoirs/cure approaches (Figure 1).

SEX DIFFERENCES IN ACQUISITION OF HIV

With the widespread availability of ART, advent of pre-exposure prophylaxis (PrEP) and the continued education of HIV transmission risks, rates of HIV infection in the U.S. are declining (15). In 2019, the Center for Disease Control and Prevention (CDC) reported 19% of new HIV diagnoses in the US to be women (16), and worldwide over half of HIV infected people are female (6). Heterosexual HIV transmission is the main mode through which women become HIV-infected (84%) (16). Generally, receptive partners are at greater risk of contracting HIV during sexual intercourse due to large viral loads present in pre-seminal and seminal fluids from untreated HIV-infected insertive partners (17). Hence, transmission of HIV to women is more likely than the reverse during heterosexual intercourse when considering per-sexual-act risk. In higher-income countries, in the absence of antiretroviral therapy (ART), male-to-female transmission (0.08%) is double that of female-to-male (0.04%). In lower-income countries per-act male-to-female transmission (0.38%) was also higher than the reverse (0.30%) though this excludes transfer in commercial sex work (18). A similar trend is observed with insertive (0.17%) and receptive (1.25%) anal intercourse per-act risk, which may also be fueling heterosexual transmission (19).



HIV infects cells by binding to the CD4 receptor and a coreceptor (most commonly CCR5 or CXCR4) (20). CCR5 surface expression on CD4+ T cells is higher in men than women, potentially contributing to differences in HIV viral load in infected individuals (21). Langerhans cells are present in the vaginal mucosa and foreskin of uncircumcised men and have been shown to transport HIV to CD4+ T cells without becoming infected themselves (22–25). Hence, to lower heterosexual transmission, there has been a promotion of male circumcision, which reduces HIV acquisition in men by approximately 60% *via* several mechanisms including preventing the loss of epithelial barrier integrity and reducing the number of Langerhans cells present to transport the virus to T cells in draining lymph nodes (26–28).

Hormonal changes during menstruation have drastic effects on vaginal tissue physiology and immunologic characteristics, and on the vaginal microbiome (9, 29). Estrogen is protective against simian immunodeficiency virus (SIV) infection in rhesus macaques, though estrogen seems to have a more complex concentration-dependent role on inflammation in humans (30–32). At higher levels, estrogen is thought to be associated with lower HIV acquisition due to a decrease in migration of T cells and macrophages, and pro-inflammatory signal regulation (32, 33). Use of certain contraceptives, including injectable progestin-only contraceptives in women have also been associated with increased numbers of HIV target cells (CCR5+ CD4 T cells) in the cervix and an increased risk of HIV acquisition (34).

Systematic, meta-analysis, and longitudinal studies have shown that previous or concurrent infections with certain pathogens, including herpes simplex virus type two (HSV-2), *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, human papillomavirus (HPV), or general vaginal dysbiosis, can increase the risk of HIV acquisition (35–43). This is in part due to damage to the epithelia and mucosa caused by pre-existing infections, and also the associated immune inflammation, which increases the number of activated CD4+ T cells and macrophages present (the preferred host cells for HIV) (44). Many sexually transmitted infections increase HIV infection risk in both men and women, but some are more prevalent or affect one sex differently from the other. For example, *Trichomonas vaginalis* is 10-fold more prevalent and highly symptomatic in women but is largely asymptomatic (70%) in men (45). HSV-2 is also more prevalent in women, though HIV acquisition risk in HSV-2 infected women was comparable to men (37, 46, 47).

Development of a prophylactic vaccine to provide long-term protection from HIV infection or a therapeutic vaccine to suppress virus and prevent disease progression without ART is a major focus of the HIV field (48–50). Sexual dimorphism is also present in responses to vaccines, with women responding better to many vaccines, including influenza, hepatitis A, and hepatitis B (33, 51). Historically, females have been underrepresented in HIV vaccine trials which has complicated analysis of sex as a biological variable in these studies (52).

Together, these anatomic, physiologic, immunologic, and hormonal differences all contribute to observed differences in HIV acquisition dynamics in males and females.

SEX DIFFERENCES IN HIV VIRAL LOAD AND REPLICATION

Sex-related differences in the mammalian immune system often involve more frequent and severe infections in males and more efficient immune responses in females (14). This trend is also evident in viral infections, including HIV infection (13). Sexual dimorphism in the immune system is in part associated with intrinsic genetic differences observed prior to adult maturation and therefore before strong hormonal influences are widely evident (14, 53). Females have higher CD4+ T cell counts than their male counterparts and also have higher CD4/CD8 ratios (9). In HIV-infected children, females were shown to have lower HIV RNA levels than males in untreated infection (53). Women are also reported to have at least 40% lower HIV RNA compared to their male counterparts, which is most evident earlier in the course of infection (4, 9, 54, 55). Interestingly, CD4+ T cells do not show sex-biased differences in their capacity to support HIV infection *in vitro* (56). Female primary monocyte-derived macrophages, however, were shown to be less susceptible to HIV infection *in vitro* than male primary macrophages. This is believed to be dependent on sex differences in host anti-HIV restriction factor SAMHD1 (56). Although the genes for HIV entry receptors are not located on sex chromosomes, many immune genes do lie on the X chromosome, including certain toll-like receptors (TLRs) (33). Specifically, TLR-7 and TLR-8 are present in the X-chromosome and can recognize single-stranded viral RNA (ssRNA), including HIV genomic RNA (33, 57). Due to the presence of two X-chromosomes in females, one is normally inactivated during the embryonic stage. However, errors in this process can occur, with reports of 15–23% of X-linked genes escaping inactivation, including TLR-7 (58, 59). Biallelic expression of important X-chromosome genes, like TLR-7, leads to higher protein levels and might therefore lead to a more robust innate immune response (33, 59, 60). In female plasmacytoid dendritic cells, TLR-7 activation with HIV ssRNA led to the production of higher levels of IFN α , which is commonly observed in the first week of HIV infection (61–63). It has also been demonstrated that at low concentrations, estradiol, an estrogen sex hormone, and progesterone affect HIV replication by increasing HIV transcription but at high concentrations they reduce HIV integration (64), although another study indicates that 17 β -estradiol can inhibit HIV transcription by inducing a complex between β -catenin and estrogen receptor α on the HIV promoter (65). Hence, sex hormones can directly affect HIV replication, but their net effects can be complex and concentration dependent.

SEX DIFFERENCES IN HIV PATHOGENESIS

During the long “asymptomatic” phase of HIV infection, high levels of virus replication and CD4+ T cell killing occur, but this is counterbalanced by the host immune system replenishing

depleted CD4+ T cells *via* homeostatic proliferation. Eventually, this balance is lost and CD4+ T cell numbers decline to the point that effective immune responses against HIV and other pathogens can no longer be mounted, resulting in progression to AIDS (66). Women have higher CD4+ T cell counts, and lower HIV plasma RNA loads during the asymptomatic phase of infection, but both males and females progress to AIDS at similar rates (67–69). Females, however, progress to AIDS at higher rates when compared to males of equivalent HIV RNA load (67).

Examples of common infections during AIDS include candidiasis, both bacterial and *Pneumocystis jirovecii* pneumonia, cytomegalovirus (CMV), *Toxoplasma gondii* infections, and tuberculosis (70–72). Generally, these opportunistic infections do not have a sex-based bias to either male or female individuals (73, 74). Yet there are some exceptions, such as an increased risk of HSV-2 and toxoplasmosis infection in women (74–77). Certain viral pathogens can also cause cancer in immunodeficient individuals. One example is human herpesvirus-8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), which causes Kaposi sarcoma. There is a higher incidence of Kaposi sarcoma in men than women worldwide, and this trend is also evident when comparing HIV-infected men and women (78–80). HPV is common in both women and men but can cause cervical cancer at elevated rates in HIV-infected females (70, 74).

A very small subset of people are capable of naturally suppressing HIV to undetectable levels without ART treatment (elite controllers) (81, 82) or following cessation of ART (post-treatment controllers) (83). Women have been identified in some studies to be over-represented in each of these groups, which may be influenced by multiple genetic and immunologic factors but is broadly consistent with the enhanced immune responses against infectious diseases, including HIV, observed in females (9, 84–86).

In summary, differences in immune responses as well as exacerbation of infections and cancers that are also sex-biased in HIV uninfected individuals are features of HIV pathogenesis in males versus females.

SEX DIFFERENCES IN HIV TREATMENT

Modern ART regimens effectively suppress plasma viral loads and prevent progression to AIDS in both males and females (87). However, in some cases the pharmacokinetic and pharmacodynamic profiles and side effects of ART differ between males and females (88–91). This is driven by differences in body weight, body fat content, extracellular water content, and many other factors that together can influence drug efficacy or side effects in men and women (92). Even among women, plasma concentrations of some antiretroviral drugs may vary during pregnancy or during different menstrual cycle phases (88). Consideration of potential teratotoxic effects on the gestating fetus and efficacy in preventing mother-to-child transmission of HIV when selecting an ART regimen are also specific to women (93–95). The immunologic profile of men and

women can differ during ART. For example, after 48 weeks of combination ART qualitative and quantitative sex-associated differences in proinflammatory cytokines have been identified in plasma (96, 97).

Within the last decade, there have been major developments in a prophylactic approach to HIV infection. In 2012, the U.S. Food and Drug Administration (FDA) approved a daily tablet, which combined tenofovir disoproxil fumarate and emtricitabine as PrEP (98). This is effective in preventing infection in men and women (98–100). It does however take longer for women to achieve maximum protection for receptive vaginal intercourse (21 days) compared to receptive anal intercourse (7 days) due to lower concentrations of tenofovir in cervicovaginal tissues than in rectal tissues (101–103). The composition of the vaginal microbiome has also been shown to affect the efficacy of some PrEP approaches. For example, tenofovir gel was three times more effective at reducing HIV incidence in women with a vaginal bacterial community dominated by *Lactobacillus* versus those with *Gardnerella vaginalis*, potentially due to metabolism and inactivation of the drug by *Gardnerella vaginalis* (104). This may partially explain why PrEP with tenofovir was found to be more effective in men than women.

SEX DIFFERENCES IN PERSISTENCE, LATENCY, AND CURE APPROACHES

One of the primary reasons that HIV infection is not cured by ART alone is that HIV forms a latent reservoir in resting CD4+ T cells (105–109). These long-lived latently infected cells encode non-expressing HIV genomes in their chromosomes, which can reactivate to produce infectious virus years after they were initially infected. Depleting this latent reservoir is therefore a central goal of HIV cure efforts. However, the potential influence of biological sex has not been a major focus in HIV cure research, as evidenced by the significant underrepresentation of women in clinical HIV cure studies (52).

Several studies have evaluated the size of the latent reservoir in men versus women using different approaches. While total HIV DNA copy numbers in PBMC do not measure only activation-inducible, replication-competent, latent HIV reservoirs (due to the presence of defective or non-inducible proviruses) (110), HIV DNA levels at the time of treatment interruption has been shown to predict time-to-rebound upon cessation of ART in some cases (111). Cross-sectional studies have demonstrated lower HIV DNA copy numbers in PBMCs from women than men during ART (110, 112, 113). However, a prospective study of HIV-infected, ART-suppressed individuals consisting of 26 well-matched pairs of women and men did not show significant differences in the frequency of CD4+ T cells harboring total or integrated HIV DNA (114). Yet this study did identify increased HIV transcriptional activity in reservoir cells from men based on multiply spliced HIV transcripts and plasma viral loads measured by single-copy assays, suggesting the reservoir may be more quiescent in women. Another study investigated HIV reservoir size and other characteristics of

resting CD4+ T cells from matched ART-suppressed men and women (22 of each sex) with a comprehensive collection of analyses, including a quantitative viral outgrowth assay, intact proviral DNA assay, and total HIV DNA measures (115). They did not find significant differences in the frequency of latent HIV in resting CD4+ T cells between men and women. Hence, if sex differences in the size of the replication-competent latent reservoir in CD4+ T cells are present, they do not appear to be large enough to readily detect in these relatively small study populations.

One potential approach for eliminating latently infected cells is a “kick and kill” strategy, which involves inducing expression of the latent HIV genome to allow the host cell to be killed by viral cytopathic effects or the host immune response (105). To accomplish this, latency reversal agents (LRAs) that reactivate HIV expression are currently being explored. Interestingly, using a primary cell *in vitro* model of HIV latency, it was found that there were not sex-based differences in latency reversal using five different compounds (ingenol-3,20-dibenzoate, bryostatin-1, 3-hydroxy-1,2,3-benzotriazin-4[3H]-one [HODHBt], Pam3CSK4, and vorinostat) (116). However, comprehensive studies of different LRA classes in *ex vivo* latently-infected cells from ART-suppressed patients or *in vivo* models have not yet been performed. An additional study has demonstrated that the estrogen receptor acts as a potent repressor of latency reversal (117). This study showed in several model systems that selective estrogen receptor modulators including tamoxifen, raloxifene, and fulvestrant can weakly induce proviral reactivation but, importantly, can also sensitize cells to reactivation with other LRAs, including IL-15, vorinostat, and TNF α . Using primary cells from well-matched men and women, they also found that the total inducible RNA reservoir was smaller in women than men. These data suggest that targeting estrogen receptor signaling may be useful in augmenting latency reversal and depleting reservoir cells (117). As observed for other drugs, differences between men and women in the pharmacokinetic and pharmacodynamic properties of individual or combination LRAs may also occur (4, 92). Proposed “kill” approaches to eliminate virus host cells after latency reversal include anti-HIV envelope antibody or immunotoxin therapeutics, augmentation of immune responses, and cytotoxic T cells bearing chimeric antigen receptors (105). This “kill” arm of the “kick and kill” therapy may also be affected by sex differences *via* the same mechanisms that distinguish male from female immune responses in untreated HIV infection (9).

There have been three reported cases of apparent HIV cure through therapeutic interventions. This includes the two well-documented cases of the “Berlin Patient” and “London Patient” who received allogeneic hemopoietic stem cell transplants with

CCR5 Δ 32 mutations during their treatment for leukemia or Hodgkin lymphoma, respectively (118–120). Although the “Berlin Patient” passed away in 2020 of cancer after 13 years of undetectable plasma viral loads without ART, the “London Patient” has remained HIV undetectable since cessation of ART in 2017 (119–121). In early 2022, the first female patient was reported to have been potentially cured of HIV following transplant with cord blood encoding a similar mutation CCR5 Δ 32 for leukemia treatment. At that point she had undetectable viral loads for 14 months after discontinuing ART (118). The small number of these potential “cures” does not allow for systematic comparisons of sex differences, but they do provide a proof of concept for HIV cure in both sexes.

DISCUSSION

Intrinsic biological differences in males versus females can markedly influence the course of HIV infection (4, 5, 7). These sex-related factors affect acquisition of HIV, viral replication, pathogenesis, and the ART used in pre-exposure prophylaxis or treatment. The role of sex differences in HIV persistence and cure approaches is less well-defined. While there have been some important pioneering studies in this area, there is a pressing need to understand whether the characteristics or anatomic locations of persistent HIV reservoirs differ in males versus females during ART, and whether promising approaches for HIV cure behave similarly in both sexes. *In vivo* models (122–124) of HIV persistence and carefully planned clinical studies that specifically evaluate sex differences offer opportunities to achieve this goal and should be a focus of future work.

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JM, ST, and MM all contributed to literature searches and writing of the manuscript. All authors contributed to the article and approved the submitted version.

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