Supplementary Material

Comparison of interventions to improve long-term medication adherence across different clinical conditions: a systematic review with network meta-analysis

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**Supplementary Material**

1. Complete search strategy
2. Complete inclusion and exclusion criteria
3. Category definitions
4. Complete references
   1. Included meta-analyses
   2. Included primary studies
   3. Excluded primary studies
5. Risk of bias assessment
6. Studies included in the network meta-analysis
7. Node-splitting analyses
8. SUCRA analyses
9. **Complete search strategy**

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| **PubMed** | **#1** (“drug therapy”[Mesh Terms] OR “medication[Title/Abstract]) AND (“patient compliance”[Mesh Terms] OR “medication adherence”[Mesh Terms] OR “medication adherence”[Title/Abstract])  **#2** “systematic review”[Title/Abstract] OR “meta-analysis”[Publication type] OR “meta-analysis”[Title/Abstract]  **#1 AND #2** |

1. **Complete inclusion and exclusion criteria**

**Meta-analyses**

We are looking for meta-analyses focused on medication adherence interventions with adherence outcomes including: pill count, refill data, self-report, or electronic monitoring.

Excluded

1. Meta-Analysis not performed or studies in meta-analysis not listed
2. Only paediatric studies included (<18 years)
3. No medication adherence intervention studies included (i.e. only medication efficacy studies)
4. No medication adherence data reported
5. No outcomes of adherence reported including: pill count, refill data, self-report, and electronic monitoring (i.e. clinical outcomes only) or only includes outcomes that are not assessable (i.e. drug levels/depot medications/etc.)
6. Only provider/healthcare professional targeted interventions and outcomes

**Primary studies**

We are looking for experimental studies with interventions aimed at adult patients on prescription medications with adherence outcomes including: pill count, refill data, self-report, or electronic monitoring.

Exclusion criteria

1. Publications not subject to peer-review, conference posters/abstracts, dissertations, or unpublished data sets
2. Expert opinion pieces, economic analyses, single case reports, cross-sectional studies (i.e. retrospective data on once vs twice daily), medication efficacy studies with no adherence intervention, or cohort studies
3. Children < 18 years included in study or studies aimed at physicians/healthcare professionals
4. Over-the-counter medications, depot medications, vaccines, any medication without instructions or with “as needed” instructions where the patient decides the dose
5. Studies only measuring clinical outcomes, drug levels, undefined adherence outcomes, or initiation or discontinuation adherence
6. Treatment follow-up less than 10 months.
7. **Category definitions**

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| **Category** | **Definition** |
| Educational | Interventions providing information regarding the medication, disease state or importance of adherence, in any form (e.g. written, oral, in group, by telephone), to a patient with the aim of increasing a patient’s knowledge or skills that facilitate adherence. |
| Attitudinal | Interventions aiming to modify behavioral intention based on modifying patient’s attitudes, beliefs or subjective norm related to their disease state or medication (e.g. motivational interviewing, cognitive behavioral therapy, etc.), delivered in any form (e.g. written, oral, in group, by telephone). |
| Technical | Interventions providing any gadget, instrument, or system that facilitate the medication intake or increase convenience of the medication taking process, such as reminders, regime simplifications, telephone follow-ups, direction observation therapy, self-monitoring, cue-dose training, electronic monitoring feedback etc. |
| Rewards | Interventions that provide incentives, awards or penalties to facilitate medication adherence. |

1. **Complete references**
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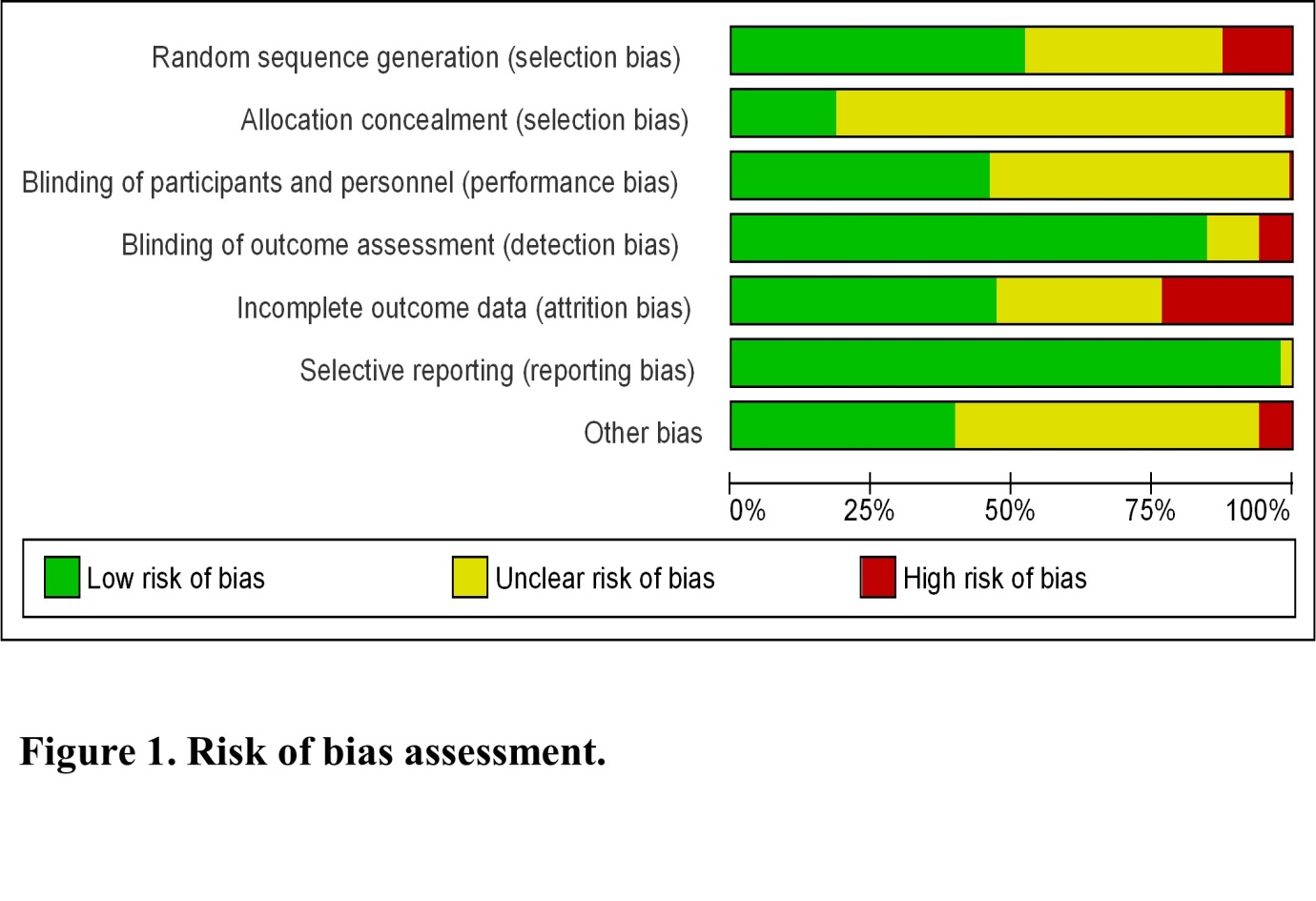
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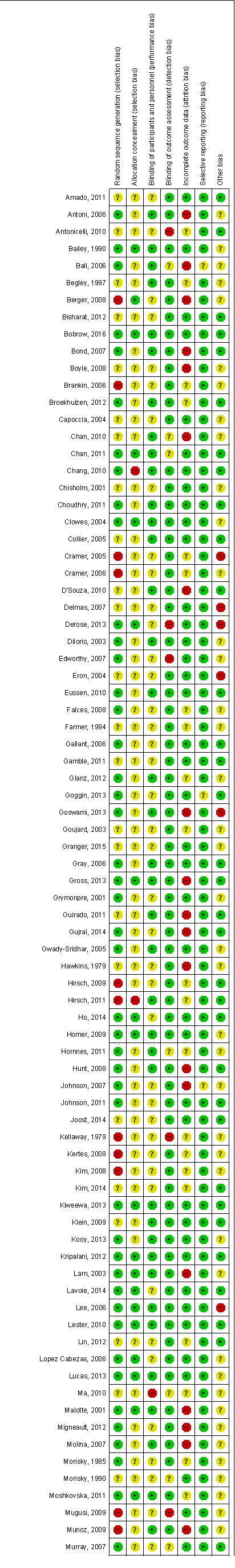
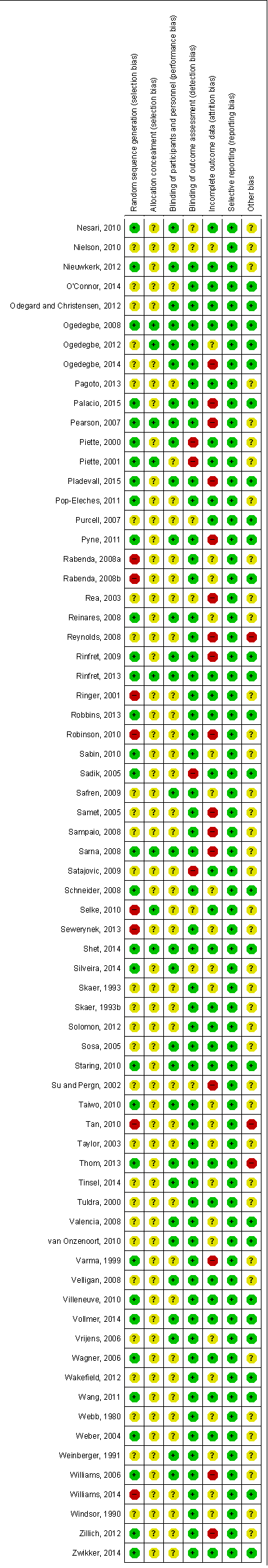
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     1. **Excluded primary studies**

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| **Meta-analysis** | **Original studies** |
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|  | Damrikarnlert, 2000 |
|  | Disney, 1990 |
|  | Edelstein, 1993 |
|  | Fyllingen, 1991 |
|  | Garcia Callejo, 1998 |
|  | Gehanno, 1994 |
|  | Gerber, 1985 |
|  | Gooch, 1993 |
|  | Gooch, 1997 |
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|  | Cordasco, 2009 |
|  | Fernandez, 2008 |
|  | Fisher, 2011 |
|  | Freedman, 2007 |
|  | Gazmararian, 2010 |
|  | Harper, 1984 |
|  | Laine, 1996 |
|  | Mann, 2001 |
|  | Martin, 2011 |
|  | McKenney, 1973 |
|  | McKenney, 1978 |
|  | Moitra, 2011 |
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|  | Gross, 2015 |
|  | Macalino, 2007 |
|  | Nachega, 2010 |
|  | Ruiz, 2010 |

1. **Risk of bias assessment**



**Figure 1. Risk of bias assessment.**



1. **Studies included in the network meta-analysis**
2. Cardiovascular and metabolic diseases

|  |  |  |  |
| --- | --- | --- | --- |
| **Study ID** | **Title** | **Study size** | **Interventions** |
| Antonicelli, 2010 | Impact of Home Patient Telemonitoring on Use of ß-Blockers in Congestive Heart Failure | 57 | Educational + Technical 4th, Standard care 4th |
| Broekhuizen, 2012 | Can Multiple Lifestyle Behaviours Be Improved in People with Familial Hypercholesterolemia? Results of a Parallel Randomised Controlled Trial | 224 | Educational + Attitudinal 4th, Standard care 4th |
| Choudhry, 2011 | Full Coverage for Preventive Medications after Myocardial Infarction | 5855 | Rewards 4th, Standard care 4th |
| Derose, 2013 | Automated Outreach to Increase Primary Adherence to Cholesterol-Lowering Medications | 5216 | Educational + Technical 4th, Standard care 4th |
| Edworthy, 2007 | Effects of an enhanced secondary prevention program for patients with heart disease: A prospective randomized trial | 2643 | Educational 4th, Standard care 4th |
| Eussen, 2010 | A Pharmaceutical Care Program to Improve Adherence to Statin Therapy: A Randomized Controlled Trial | 899 | Educational 4th, Standard care 4th |
| Falces, 2008 | [An educative intervention to improve treatment compliance and to prevent readmissions of elderly patients with heart failure] | 103 | Educational 4th, Standard care 4th |
| Goswami, 2013 | Impact of an integrated intervention program on atorvastatin adherence: a randomized controlled trial | 208 | Educational 4th, Standard care 4th |
| Gurjal, 2014 | Impact of community pharmacist intervention discussing patients’ beliefs to improve medication adherence | 200 | Attitudinal 4th, Standard care 4th |
| Hawkins, 1979 | Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients | 137 | Educational 4th, Standard care 4th |
| Ho, 2014 | Multifaceted Intervention to Improve Medication Adherence and Secondary Prevention Measures After Acute Coronary Syndrome Hospital Discharge A Randomized Clinical Trial | 241 | Educational + Technical 4th, Standard care 4th |
| Hornnes, 2011 | Blood Pressure 1 Year after Stroke: The Need to Optimize Secondary Prevention | 293 | Educational + Technical 4th, Standard care 4th |
| Hunt, 2008 | A Randomized Controlled Trial of Team-Based Care: Impact of Physician-Pharmacist Collaboration on Uncontrolled Hypertension | 272 | Educational + Technical 4th, Standard care 4th |
| Kooy, 2013 | Does the use of an electronic reminder device with or without counseling improve adherence to lipid-lowering treatment? The results of a randomized controlled trial | 381 | Technical 4th, Attitudinal + Technical 4th, Standard care 4th |
| Lopez Cabezas, 2006 | Randomized clinical trial of a postdischarge pharmaceutical care program vs. regular follow-up in patients with heart failure | 63 | Educational 4th, Standard care 4th |
| Morisky, 1985 | Evaluation of family health education to build social support for long-term control of high blood pressure. | 290 | Educational 4th, Standard care 4th |
| Ogedegbe, 2008 | A Practice-based Trial of Motivational Interviewing and Adherence in Hypertensive 065African Americans | 160 | Attitudinal 4th, Standard care 4th |
| Ogedegbe, 2012 | A Randomized Controlled Trial of Positive-Affect Intervention and Medication Adherence in Hypertensive African Americans | 256 | Educational 4th, Educational + Attitudinal 4th |
| Pagoto, 2013 | Can attention control conditions have detrimental effects in behavioral medicine randomized trials? | 235 | Educational 4th, Standard care 4th |
| Palacio, 2015 | Can Phone-Based Motivational Interviewing Improve Medication Adherence to Antiplatelet Medications After a Coronary Stent Among Racial Minorities? A Randomized Trial | 339 | Attitudinal 4th, Educational 4th |
| Piette, 2000 | Do Automated Calls with Nurse Follow-up Improve Self-Care and Glycemic Control among Vulnerable Patients with Diabetes? | 248 | Educational + Technical 4th, Standard care 4th |
| Piette, 2001 | Impact of Automated Calls With Nurse Follow-Up on Diabetes Treatment Outcomes in a Department of Veterans Affairs Health Care System A randomized controlled trial | 272 | Educational + Technical 4th, Standard care 4th |
| Rinfret, 2013 | Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation | 300 | Educational 4th, Standard care 4th |
| Sadik, 2005 | Pharmaceutical care of patients with heart failure | 208 | Educational + Technical 4th, Standard care 4th |
| Taylor, 2003 | Improving primary care in rural Alabama with a pharmacy initiative | 69 | Educational + Technical 4th, Standard care 4th |
| Thom, 2013 | Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients With or at High Risk of CVD The UMPIRE Randomized Clinical Trial | 1860 | Technical 4th, Standard care 4th |
| Varma, 1999 | Pharmaceutical Care of Patients with Congestive Heart Failure: Interventions and Outcomes | 49 | Educational + Technical 4th, Standard care 4th |
| Villeneuve, 2010 | A cluster randomized controlled Trial to Evaluate an Ambulatory primary care Management program for patients with dyslipidemia: the TEAM study | 225 | Educational 4th, Standard care 4th |
| Vollmer, 2014 | Improving Adherence to Cardiovascular Disease Medications With Information Technology | 21752 | Technical 4th, Educational + Technical 4th, Standard care 4th |
| Wang, 2011 | Effects of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China | 59 | Educational + Technical 4th, Standard care 4th |
| Zillich, 2012 | Evaluation of Specialized Medication Packaging Combined With Medication Therapy Management: Adherence, Outcomes, and Costs Among Medicaid Patients | 14621 | Educational 4th, Standard care 4th |

1. HIV

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| **Study ID** | **Title** | **Study size** | **Interventions** |
| Boyle, 2008 | Randomization to Once-Daily Stavudine Extended Release/Lamivudine/Efavirenz Versus a More Frequent Regimen Improves Adherence While Maintaining Viral Suppression | 300 | Technical 4th, Standard care 4th |
| Chang, 2010 | Effect of Peer Health Workers on AIDS Care in Rakai, Uganda: A Cluster-Randomized Trial | 1203 | Educational + Technical 4th, Standard care 4th |
| Collier, 2005 | A Randomized Study of Serial Telephone Call Support to Increase Adherence and Thereby Improve Virologic Outcome in Persons Initiating Antiretroviral Therapy | 101 | Educational + Attitudinal 4th, Standard care 4th |
| Eron, 2004 | Once-Daily versus Twice-Daily Lopinavir/Ritonavir in Antiretroviral-Naive HIV-Positive Patients: A 48-Week Randomized Clinical Trial | 38 | Technical 4th, Standard care 4th |
| Gallant, 2006 | Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV | 509 | Technical 4th, Standard care 4th |
| Gross, 2013 | Managed Problem Solving for Antiretroviral Therapy Adherence: A Randomized Trial | 180 | Educational + Attitudinal + Technical 4th, Standard care 4th |
| Hirsch, 2009 | Evaluation of the First Year of a Pilot Program in Community Pharmacy: HIV/AIDS Medication Therapy Management for Medi-Cal Beneficiaries | 7018 | Educational 4th, Standard care 4th |
| Hirsch, 2011 | Antiretroviral Therapy Adherence, Medication Use, and Health Care Costs During 3 Years of a Community Pharmacy Medication Therapy Management Program for Medi-Cal Beneficiaries with HIV/AIDS | 2234 | Educational + Technical 4th, Standard care 4th |
| Johnson, 2011 | Improving Coping Skills for Self-management of Treatment Side Effects Can Reduce Antiretroviral Medication Nonadherence among People Living with HIV | 249 | Educational + Attitudinal 4th, Standard care 4th |
| Kiweewa, 2013 | Noninferiority of a Task-Shifting HIV Care and Treatment Model Using Peer Counselors and Nurses Among Ugandan Women Initiated on ART: Evidence From a Randomized Trial | 85 | Educational 4th, Standard care 4th |
| Lester, 2010 | Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial | 538 | Technical 4th, Standard care 4th |
| Lucas, 2013 | Directly Administered Antiretroviral Therapy for HIVInfected Individuals in Opioid Treatment Programs: Results from a Randomized Clinical Trial | 107 | Technical 4th, Standard care 4th |
| Molina, 2007 | A Lopinavir/Ritonavir-Based Once-Daily Regimen Results in Better Compliance and Is Non-inferior to a Twice-Daily Regimen Through 96 Weeks | 190 | Technical 4th, Standard care 4th |
| Mugusi, 2009 | Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience | 621 | Technical 4th, Educational + Technical 4th, Standard care 4th |
| Munoz, 2009 | Community-based DOT-HAART Accompaniment in an Urban Resource-Poor Setting | 120 | Educational + Technical 4th, Standard care 4th |
| Pearson, 2007 | Randomized Control Trial of Peer-Delivered, Modified Directly Observed Therapy for HAART in Mozambique | 350 | Educational + Technical 4th, Standard care 4th |
| Pop-Eleches, 2011 | Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders | 428 | Technical 4th, Standard care 4th |
| Purcell, 2007 | Results From a Randomized Controlled Trial of a Peer-Mentoring Intervention to Reduce HIV Transmission and Increase Access to Care and Adherence | 408 | Attitudinal 4th, Educational 4th |
| Pyne, 2011 | Effectiveness of Collaborative Care for Depression in Human Immunodeficiency Virus Clinics | 178 | Educational + Technical 4th, Standard care 4th |
| Reynolds, 2008 | Telephone Support to Improve Antiretroviral Medication Adherence | 109 | Educational 4th, Educational + Attitudinal 4th |
| Sabin, 2010 | Using Electronic Drug Monitor Feedback to Improve Adherence to Antiretroviral Therapy Among HIV-Positive Patients in China | 64 | Educational + Technical 4th, Standard care 4th |
| Samet, 2005 | A randomized controlled trial to enhance antiretroviral therapy adherence in patients with a history of alcohol problems | 94 | Educational + Attitudinal + Technical 4th, Standard care 4th |
| Selke, 2010 | Task-Shifting of Antiretroviral Delivery From Health Care Workers to Persons Living With HIV/AIDS: Clinical Outcomes of a Community-Based Program in Kenya | 208 | Educational 4th, Standard care 4th |
| Shet, 2014 | Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India | 631 | Technical 4th, Standard care 4th |
| Silveira, 2014 | Randomized Controlled Trial to Evaluate the Impact of Pharmaceutical Care on Therapeutic Success in HIV-Infected Patients in Southern Brazil | 332 | Educational 4th, Standard care 4th |
| Sosa, 2005 | Abacavir and Lamivudine Fixed-Dose Combination Tablet | 236 | Technical 4th, Standard care 4th |
| Taiwo, 2010 | Assessing the Viorologic and Adherence Benefits of Patient-Selected HIV Treatment Partners in a Resource-limited Setting | 499 | Technical 4th, Standard care 4th |
| Tuldra, 2000 | Prospective Randomized Two-Arm Controlled Study To Determine the Efficacy of a Specific Intervention To Improve Long-Term Adherence to Highly Active Antiretroviral Therapy | 116 | Attitudinal 4th, Standard care 4th |
| Wagner, 2006 | Cognitive-behavioral intervention to enhance adherence to antiretroviral therapy: a randomized controlled trial (CCTG 578) | 199 | Attitudinal 4th, Standard care 4th |
| Weber, 2004 | Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial | 60 | Attitudinal 4th, Standard care 4th |
| Williams, 2006 | Home Visits to Improve Adherence to Highly Active Antiretroviral Therapy: A Randomized Controlled Trial | 171 | Educational + Attitudinal 4th, Standard care 4th |
| Williams, 2014 | Efficacy of an Evidence-Based ARV Adherence Intervention in China | 110 | Educational + Attitudinal 4th, Standard care 4th |
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1. Musculoskeletal diseases

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| **Study ID** | **Title** | **Study size** | **Interventions** |
| Brankin, 2006 | The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases | 15330 | Technical 4th, Standard care 4th |
| Clowes, 2004 | The Impact of Monitoring on Adherence and Persistence with Antiresorptive Treatment for Postmenopausal Osteoporosis: A Randomized Controlled Trial | 48 | Technical 4th, Standard care 4th |
| Cramer, 2005 | Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis | 2741 | Technical 4th, Standard care 4th |
| Cramer, 2006 | The Effect of Dosing Frequency on Compliance and Persistence with Bisphosphonate Therapy in Postmenopausal Women: A Comparison of Studies in the United States, the United Kingdom, and France | 15640 | Technical 4th, Standard care 4th |
| Delmas, 2007 | Effect of Monitoring Bone Turnover Markers on Persistence with Risedronate Treatment of Postmenopausal Osteoporosis | 2302 | Technical 4th, Standard care 4th |
| Homer, 2009 | Providing patients with information about disease-modifying antirheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction | 62 | Educational 4th, Educational + Technical 4th |
| Nielson, 2010 | Patient education in groups increases knowledge of osteoporosis and adherence to treatment: A two-year randomized controlled trial | 300 | Educational 4th, Standard care 4th |
| Rabenda, 2008a | Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women | 29157 | Technical 4th, Standard care 4th |
| Rabenda, 2008b | Low Incidence of Anti-Osteoporosis Treatment After Hip Fracture | 306 | Technical 4th, Standard care 4th |
| Soloman, 2012 | Osteoporosis Telephonic Intervention to Improve Medication Adherence (OPTIMA): A Large Pragmatic Randomized Controlled Trial | 2087 | Attitudinal 4th, Educational 4th |
| Zwikker, 2014 | Effectiveness of a group-based intervention to change medication beliefs and improve medication adherence in patients with rheumatoid arthritis: A randomized controlled trial | 123 | Attitudinal 4th, Educational 4th |

1. Psychological diseases

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| **Study ID** | **Title** | **Study size** | **Interventions** |
| Ball, 2006 | A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-Term Change | 52 | Attitudinal 4th, Standard care 4th |
| Capoccia, 2004 | Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care | 74 | Educational + Technical 4th, Standard care 4th |
| Lam, 2003 | A Randomized Controlled Study of Cognitive Therapy for Relapse Prevention for Bipolar Affective Disorder | 103 | Attitudinal 4th, Standard care 4th |
| Pyne, 2011 | Effectiveness of Collaborative Care for Depression in Human Immunodeficiency Virus Clinics | 178 | Educational + Technical 4th, Standard care 4th |
| Reinares, 2008 | Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial | 113 | Educational + Attitudinal 4th, Standard care 4th |
| Silveira, 2014 | Randomized Controlled Trial to Evaluate the Impact of Pharmaceutical Care on Therapeutic Success in HIV-Infected Patients in Southern Brazil | 332 | Educational 4th, Standard care 4th |
| Valencia, 2008 | A psychosocial skills training approach in Mexican out-patients with schizophrenia | 82 | Educational 4th, Standard care 4th |
| Velligan, 2008 | The Use of Individually Tailored Environmental Supports to Improve Medication Adherence and Outcomes in Schizophrenia | 61 | Attitudinal 4th, Standard care 4th |
| Williams, 2014 | Efficacy of an Evidence-Based ARV Adherence Intervention in China | 110 | Educational + Attitudinal 4th, Standard care 4th |
| Zillich, 2012 | Evaluation of Specialized Medication Packaging Combined With Medication Therapy Management: Adherence, Outcomes, and Costs Among Medicaid Patients | 14621 | Educational 4th, Standard care 4th |

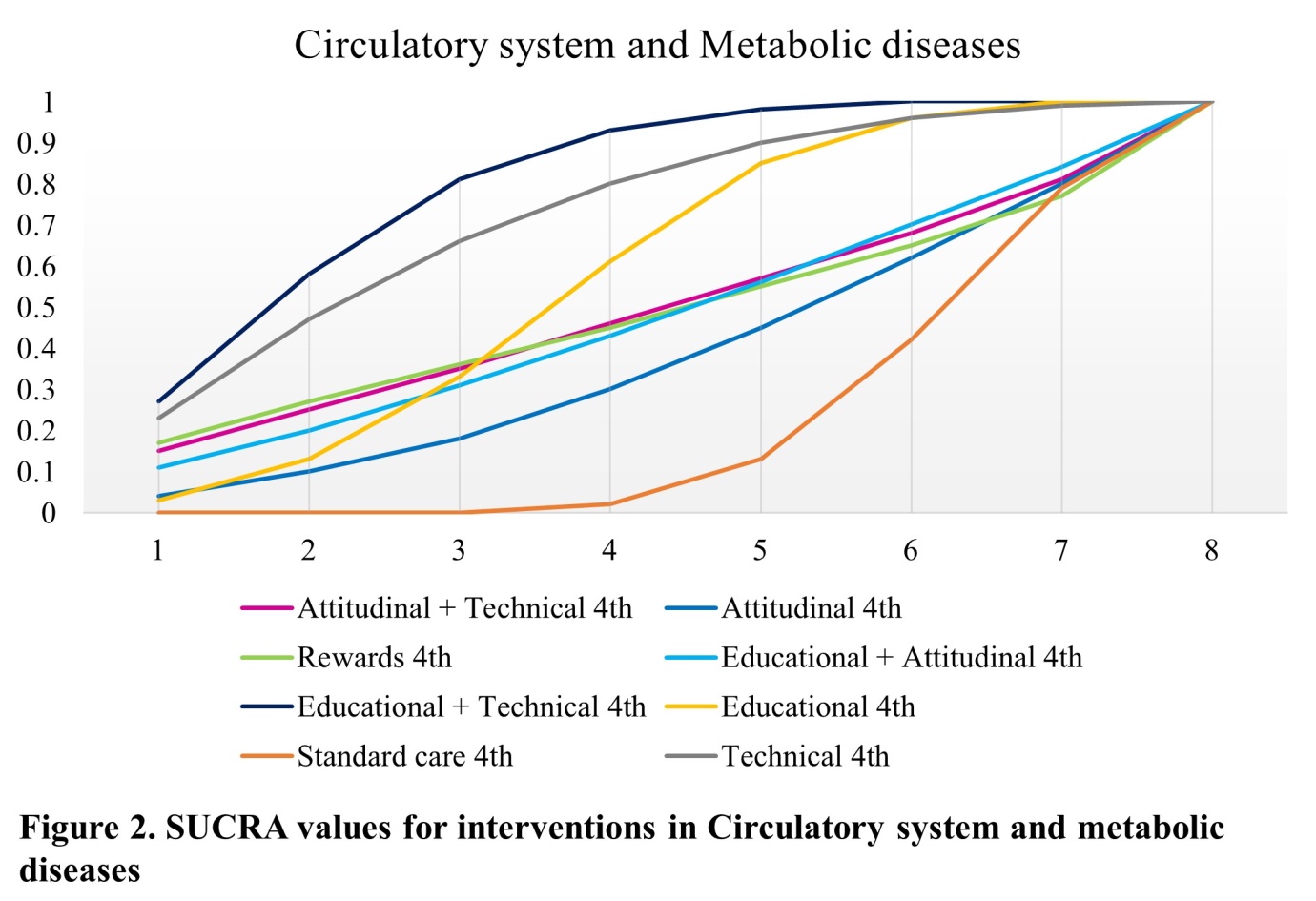
1. **Node-splitting analyses per disease group (Musculoskeletal and Psychological conditions do not have node-splitting analysis as this is only possible when there are close-loops in the networks)**
2. Cardiovascular and metabolic diseases

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| **Name** | **Direct Effect** | **Indirect Effect** | **Overall** | **P-Value** |
| Attitudinal, Educational | -0.61  (-2.22, 1.01) | 0.87  (-0.40, 2.19) | 0.29  (-0.77, 1.34) | 0.19 |
| Attitudinal, Standard care | 0.30  (-0.91, 1.49) | -1.15  (-2.87, 0.60) | -0.17  (-1.19, 0.87) | 0.19 |
| Educational, Educational + Attitudinal | 0.25  (-1.51, 1.93) | -0.60  (-2.44, 1.18) | -0.16  (-1.40, 1.06) | 0.6 |
| Educational, Standard care | -0.61  (-1.14, -0.08) | 0.68  (-0.86, 2.17) | -0.46  (-0.98, 0.06) | 0.9 |
| Educational + Attitudinal, Standard care | 0.10  (-1.64, 1.87) | -0.74  (-2.61, 1.02) | -0.31  (-1.56, 0.95) | 0.5 |
| Educational + Technical, Technical | -0.01  (-1.68, 1.60) | 0.57  (-1.21, 2.29) | 0.03  (-1.12, 1.16) | 0.6 |

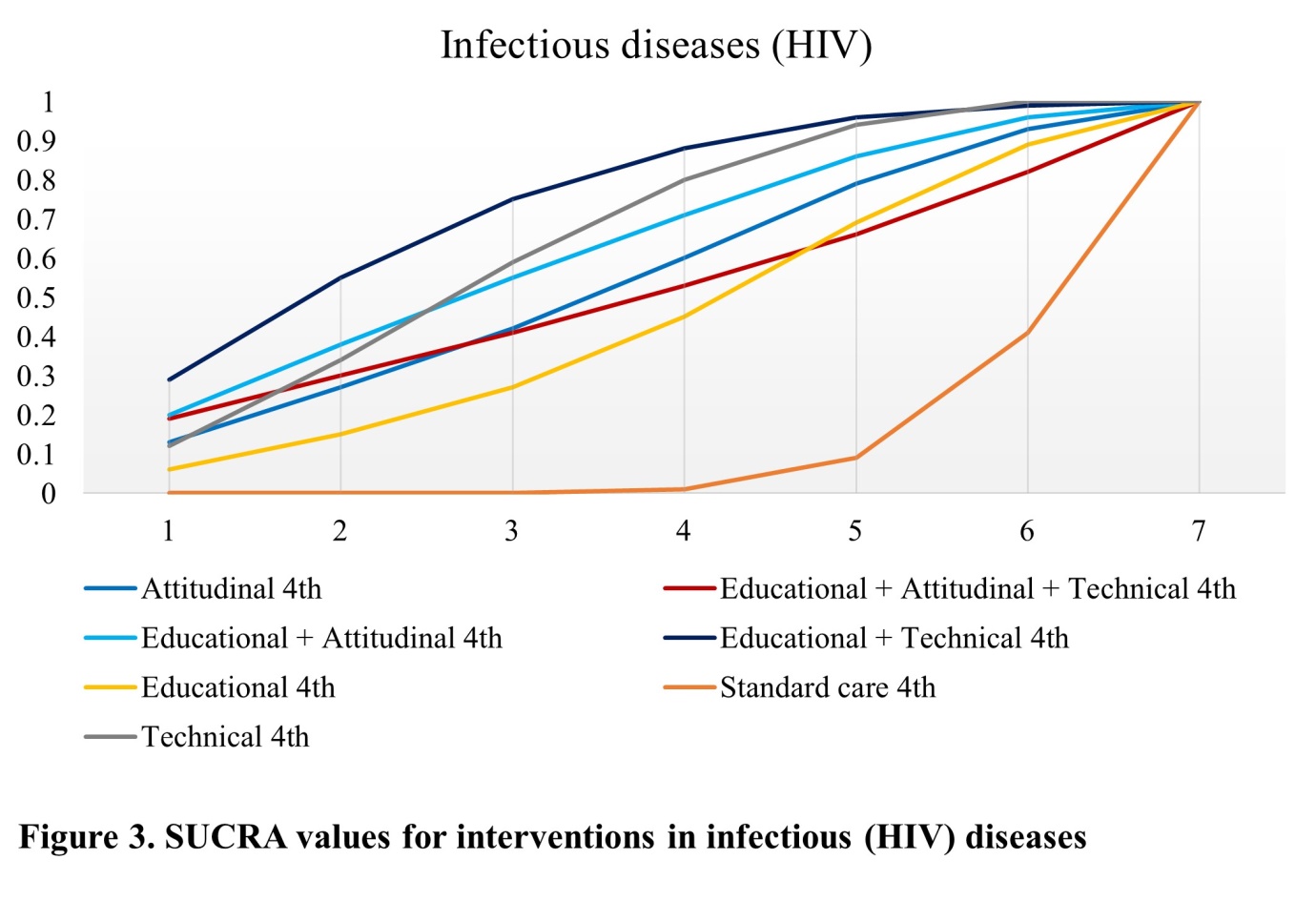
1. HIV

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| **Name** | **Direct Effect** | **Indirect Effect** | **Overall** | **P-Value** |
| Attitudinal, Educational | -0.28  (-1.44, 0.89) | 0.04  (-0.97, 0.97) | -0.09  (-0.84, 0.60) | 0.66 |
| Attitudinal, Standard care | -0.32  (-1.07, 0.38) | -0.62  (-1.93, 0.71) | -0.40  (-1.00, 0.22) | 0.67 |
| Educational, Educational + Attitudinal | 0.53  (-1.71, 2.89) | 0.16  (-0.66, 1.02) | 0.17  (-0.56, 1.00) | 0.75 |
| Educational, Standard care | -0.37  (-1.00, 0.32) | -0.05  (-1.18, 1.12) | -0.31  (-0.84, 0.28) | 0.63 |
| Educational + Attitudinal, Standard care | -0.47  (-1.11, 0.15) | -0.77  (-3.30, 1.50) | -0.48  (-1.10, 0.11) | 0.8 |
| Educational + Technical, Technical | 0.76  (-0.96, 2.88) | -0.15  (-0.72, 0.42) | -0.10  (-0.64, 0.45) | 0.32 |

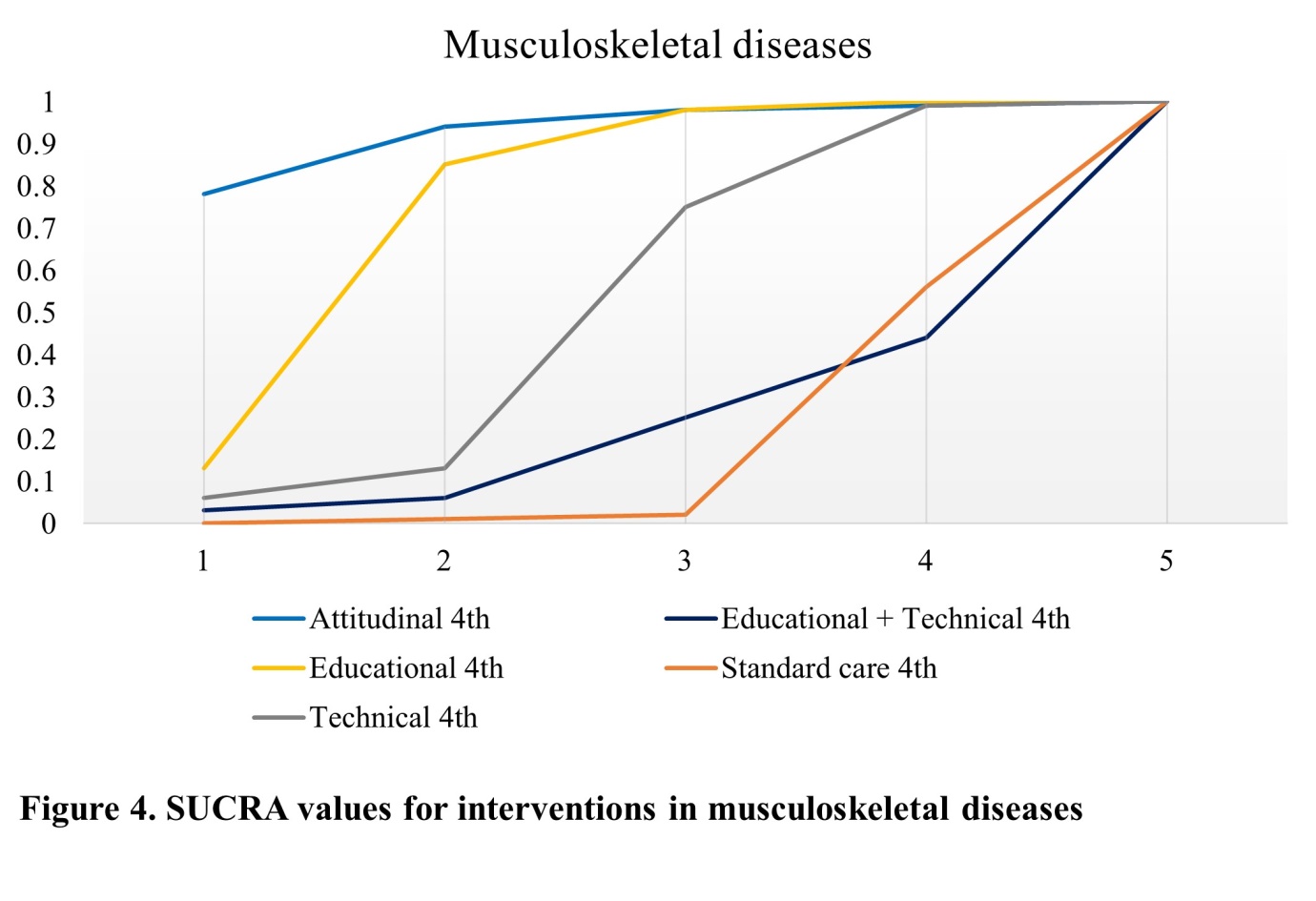
1. **SUCRA analyses per disease group**
2. Circulatory system and metabolic diseases



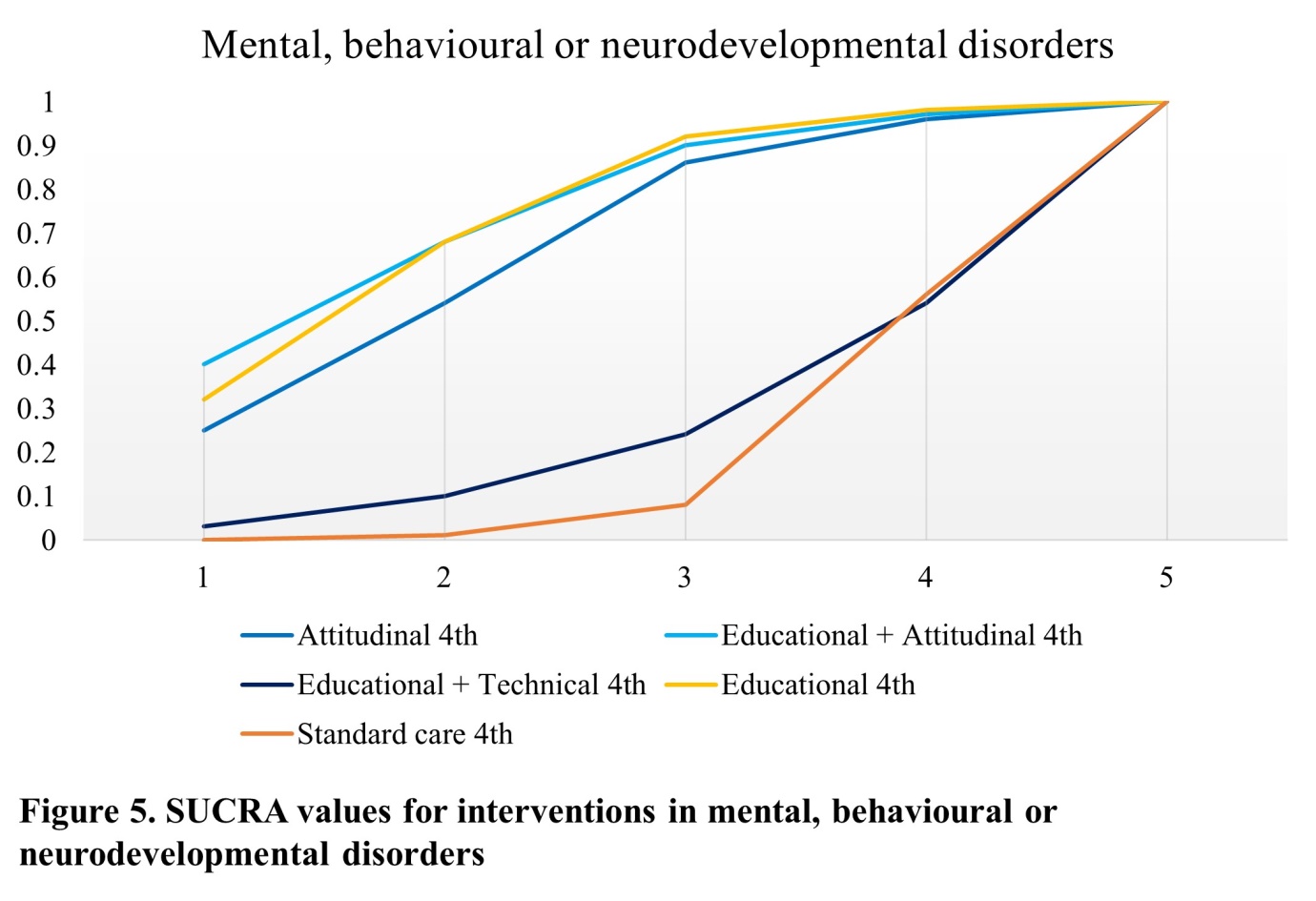
1. Infectious diseases (HIV)



1. Musculoskeletal diseases



1. Mental, behavioural or neurodevelopmental disorders

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