Risk of HIV acquisition among men who have sex with men infected with other sexually transmitted infections: A systematic review and meta-analysis

**Supplementary Material**

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# Appendix A: Database search strategies and de-duplication process

Appendix A Contents:

1. Search methods
2. Yield of databases
3. PubMed search strategy
4. Embase (OVID) search strategy
5. Web of Science search strategy
6. De-duplication process in EndNote
7. **Search methods**

We searched PubMed and Web of Science in December 2017 and Embase (OVID) in January 2018 using keywords and index terms for HIV, STI pathogens, and study design. We included all languages and geographic locations. We used EndNote X7 software**1** to remove duplicate database records and to filter titles with irrelevant keywords (e.g., pregnancy, non-human animals), which were manually reviewed by one rater. We conducted dual screening of all remaining database records and of systematic reviews found in the database search and during preliminary scoping searches. Two raters independently reviewed the full articles for abstracts promoted by either rater. Raters resolved disagreements via discussion or a supervisor. As quality assurance, other authors reviewed 5% of database-derived studies excluded at the title/abstract and full-text review levels.

Full-text articles were screened in two phases. First, we excluded manuscripts that failed our criteria regarding population, study design, document type, or quantitative data. Second, we verified that the STI diagnosis occurred prior to HIV sero-conversation, contacting study authors if ambiguous [See Appendix C]. We also decided to exclude HSV-2 data due to redundancy with a high-quality review published in 2017. [See Appendix D]

1. **Yield of databases**

|  |  |
| --- | --- |
| PubMed | 6,081 |
| Embase (OVID) | 8,919 |
| Web of Science | 6,165 |
| Gross total | 21,154 |
| Subtract duplicates | 6,950 |
| NET TOTAL | 14,199 |

1. **PubMed search strategy**

|  |  |  |
| --- | --- | --- |
| **Search** | **PubMed Query (5 January 2018)** | **Records** |
| #6 | #5 AND AND ("1996/01/01"[Date - Completion] : "2017/12/31"[Date - Completion]) | 6,081 |
| #5 | #1 AND #2 AND #3 AND #4 | 7,390 |
| #4 | “HIV Seropositivity”[mh] OR "Sexually Transmitted Diseases/transmission"[majr] OR “HIV Infections/transmission”[majr] OR “HIV Infections/epidemiology”[mh] OR “Acquired Immunodeficiency Syndrome/transmission”[mh] OR “Probability”[mh] OR acquisition[tiab] OR transmission[tiab] OR acquiring[tiab] OR transmitting[tiab] OR “per act”[tiab] OR “per sex act”[tiab] OR “per sexual act”[tiab] OR “per coital act”[tiab] OR “per coitus”[tiab] OR “per partner”[tiab] OR “per couple”[tiab] OR “person years”[tiab] OR incidence[tiab] OR incident[tiab] OR infectivity[tiab] OR infectiousness[tiab] OR probability[tiab] OR susceptible[tiab] OR susceptibility[tiab] OR seroconversion[tiab] OR sero-conversion[tiab] OR seroconvert\*[tiab] OR sero-convert\*[tiab] OR sero-incidence[tiab] OR seroincidence[tiab] OR shedding [tiab] OR (sexually transmitted disease\*[tiab] AND clinics[tiab]) | 2,647,758 |
| #3 | “HIV Infections”[mh] OR “HIV”[mh] OR hiv[tiab] OR hiv-1\*[tiab] OR hiv-2\*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect\*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun\*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun\*[tiab]) AND (deficiency syndrome[tiab])) | 367,763 |
| #2 | "Mycoplasma infections"[mh] OR “Mycoplasma genitalium”[mh] OR "Chlamydia"[mh] OR "Herpesvirus 2, Human"[mh] OR "Lymphogranuloma Venereum"[mh] OR "Neisseria gonorrhoeae"[mh] OR "Pelvic Inflammatory Disease"[mh] OR "Syphilis"[mh] OR "Trichomonas"[mh] OR "Urethritis"[mh] OR "Uterine Cervicitis"[mh] OR "Vaginosis, Bacterial"[mh] OR cervicitis[tiab] OR mycoplasma[tiab] OR genitalium[tiab] OR chlamydia[tiab] OR “genital ulcer disease”[tiab] OR GUD[tiab] OR (genital\*[tiab] AND ulcer\*[tiab]) OR herpes[tiab] OR herpesvirus[tiab] OR HSV[tiab] OR hsv2[tiab] OR hsv-2[tiab] OR gonorrhoea[tiab] OR gonorrhea[tiab] OR gonnorhea[tiab] OR “pelvic inflammatory”[tiab] OR PID[tiab] OR syphilis[tiab] OR “treponema pallidum”[tiab] OR trichomonas[tiab] OR trichomoniasis[tiab] OR urethritis[tiab] OR vaginosis[tiab] OR “sexually transmitted”[tiab] OR “sexually transmissible”[tiab] OR STD[tiab] OR STDs[tiab] OR STI[tiab] OR STIs[tiab] OR genital infect\*[tiab] | 223,603 |
| #1 | “Randomized controlled trial”[pt] OR “Clinical trial”[pt] OR "Cohort Studies"[mh] OR “Longitudinal studies”[mh] OR “Prospective studies”[mh] OR “Observational study”[pt] OR “Meta-analysis”[pt] OR “Review”[pt] OR “clinical trial”[tiab] OR “controlled trial” OR cohort\*[tiab] OR observational[tw] OR prospective\*[tiab] OR retrospective\*[tiab] OR nested[tiab] OR longitudinal[tiab] OR “systematic review”[tiab] OR meta-analysis[tiab] OR metaanalysis[tiab] OR evaluat\*[tiab] OR follow-up[tiab] | 7,304,882 |

1. **Embase search strategy (note: Embase search conducted via Ovid)**

|  |  |  |
| --- | --- | --- |
| **No.** | **Query (29 December 2017)** | **Results** |
| #5 | #1 AND #2 AND #3 AND #4 | 9,306 (8,919 unique) |
| #4 | Sexually transmitted disease/di, ep OR Human immunodeficiency virus infection/di, ep OR Acquired immune deficiency syndrome/ep, di OR Probability/ OR acquisition[tiab] OR transmission[tiab] OR acquiring[tiab] OR transmitting[tiab] OR “per act”[tiab] OR “per sex act”[tiab] OR “per sexual act”[tiab] OR “per coital act”[tiab] OR “per coitus”[tiab] OR “per partner”[tiab] OR “per couple”[tiab] OR “person years”[tiab] OR incidence[tiab] OR incident[tiab] OR infectivity[tiab] OR infectiousness[tiab] OR probability[tiab] OR susceptible[tiab] OR susceptibility[tiab] OR seroconversion[tiab] OR sero-conversion[tiab] OR seroconvert\*[tiab] OR sero-convert\*[tiab] OR sero-incidence[tiab] OR seroincidence[tiab] OR shedding[tiab] OR (sexually transmitted disease\*[tiab] AND clinics[tiab]) | 2,119,384 |
| #3 | Human immunodeficiency virus infection/ OR Human immunodeficiency virus/ OR hiv[tiab] OR hiv-1\*[tiab] OR hiv-2\*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect\*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun\*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun\*[tiab]) AND (deficiency syndrome[tiab])) | 440,220 |
| #2 | Mycoplasma infections/ OR Mycoplasma genitalium/ OR Chlamydia/ OR Herpes simplex virus 2/ OR Lymphogranuloma venereum/ OR Neisseria gonorrhoeae/ OR Pelvic inflammatory disease/ OR Syphilis/ OR Trichomonas/ OR Trichomonas vaginalis/ OR Urethritis/ OR Uterine cervicitis/ OR Vaginitis/ OR cervicitis[tiab] OR mycoplasma[tiab] OR genitalium[tiab] OR chlamydia[tiab] OR “genital ulcer disease”[tiab] OR GUD[tiab] OR (genital\*[tiab] ulcer\*[tiab]) OR herpes[tiab] OR herpes virus[tiab] OR HSV[tiab] OR hsv2[tiab] OR hsv-2[tiab] OR gonorrhoea[tiab] OR gonorrhea[tiab] OR gonnorhea[tiab] OR “pelvic inflammatory”[tiab] OR PID[tiab] OR syphilis[tiab] OR “treponema pallidum”[tiab] OR trichomonas[tiab] OR trichomoniasis[tiab] OR urethritis[tiab] OR vaginosis[tiab] OR “sexually transmitted”[tiab] OR “sexually transmissible”[tiab] OR STD[tiab] OR STDs[tiab] OR STI[tiab] OR STIs[tiab] OR genital infect\*[tiab] | 225,940 |
| #1 | Major clinical study/ OR Review/ OR ((controlled OR clinical OR randomized) AND trial)[tiab] OR (prospective or cohort or observational or retrospective or nested or longitudinal)[tiab] OR systematic review\*[tiab] OR meta-analy\*[tiab] OR metaanaly\*[tiab] | 6,437,460 |

1. **Web of Science search strategy**Note: Boxes ticked only for SCI-EXPANDED and CPCI-S.

|  |  |  |
| --- | --- | --- |
| **No.** | **Query (4 January 2018)** | **Results** |
| #5 | #1 AND #2 AND #3 AND #4 | 6,165 |
| #4 | TS=("Randomized controlled trial\*" OR "Clinical trial\*" OR "Cohort Stud\*" OR "Longitudinal stud\*" OR Prospective\* OR Observational\*OR "Meta-analysis" OR Review OR "controlled trial\*" OR cohort\* OR retrospective\* OR nested\* OR longitudinal\* OR "systematic review" OR "meta-analysis" OR metaanalysis OR evaluat\* OR follow-up\*) Indexes=SCI-EXPANDED, SSCI Timespan=1982-2017 | 7,101,363 |
| #3 | TS=((“human immunodeficiency\*” OR hiv OR “acquired immun\*”) and (seropositivity OR transmission OR epidemiology OR probability OR acqu\* OR transmit\* incidence OR incident OR infectivity OR infectiousness OR probability OR susceptible OR susceptibility OR seroconversion OR “sero-conversion” OR seroconvert\* OR sero-convert\* OR “sero-incidence” OR seroincidence OR shedding) OR ("sexually transmitted diseases” and transmission)) Indexes=SCI-EXPANDED, SSCI Timespan=1982-2017 | 99,106 |
| #2 | TS=("Mycoplasma infections" OR “Mycoplasma genitalium” OR "Chlamydia" OR "Herpesvirus 2\*" OR "Lymphogranuloma Venereum" OR "Neisseria gonorrhoeae" OR "Pelvic Inflammatory Disease" OR "Syphilis" OR "Trichomonas" OR "Urethritis" OR "Uterine Cervicitis" OR "Vaginosis, Bacterial" OR cervicitis OR mycoplasma OR genitalium OR chlamydia OR “genital ulcer disease” OR GUD OR (genital\* AND ulcer\*) OR herpes OR herpesvirus OR HSV OR hsv2 OR "hsv-2" OR gonorrhoea OR gonorrhea OR gonnorhea OR “pelvic inflammatory” OR syphilis OR “treponema pallidum” OR trichomonas OR trichomoniasis OR urethritis OR vaginosis OR “sexually transmitted\*” OR “sexually transmissible\*” OR STD OR STDs OR STI OR STIs OR "genital infect\*") Indexes=SCI-EXPANDED, SSCI Timespan=1982-2017 | 179,213 |
| #1 | TS=("HUMAN IMMUNODEFICIENCY\*" OR HIV\* OR "ACQUIRED IMMUN\*") | [336,920](http://apps.webofknowledge.com.ucsf.idm.oclc.org/summary.do?product=WOS&doc=1&qid=9&SID=6B2VWq46uhUU5lbSlQP&search_mode=AdvancedSearch&update_back2search_link_param=yes) |

1. **De-duplication process in EndNote**

Each database has different regimens for articulating author names, article titles, journal names and volumes & pagination. For example, they may capitalize all letters, or all first letters of words, or use sentence case. This can make it tricky to identify redundant records in EndNote.

After importing all records into EndNote, we set preferences for duplicates. In the first instance, we tick only the box for “titles.” This captures the majority of redundant records. We put these into a new “duplicates” folder. We then recalibrate our preferences for duplicates, un-ticking the box for titles and ticking those for “year,” “author” and “pages.” We may adjust the search as needed to narrow the duplicate result list. We then review results manually to exclude true duplicates while preserving unique records.

# Appendix B: Filtering and partitioning of likely-irrelevant titles

**Approach**

Following de-duplication of records in EndNote, we apply the search function in EndNote to identify and partition studies with likely-irrelevant keywords in their titles. Matching citations are subsequently reviewed by one rater, who promotes relevant records to full-text review by both raters.

The table below reports keywords used and the number of records separated based on each search. Note that because titles of some records may include terms used in multiple categories, the number of records identified for each search depends upon the sequence of the searches. For example, a record with “behavior” and “cocaine” in its title would go to the category for which the first search was done first – in this example “drugs” – it would not go to both categories. If one search is recreated out of sequence, EndNote may return a different number of results.

Of the 4,636 partitioned records, we promoted 133 (2.9%) to full-text review. We observed that promoted records frequently reflected keywords related to behavior or interventions such as vaccines. Although it had been our expectation that behaviorally-focused and interventional studies would be likely irrelevant to our search, abstracts suggested that the promoted studies may have measured exposure (STI) and HIV outcome, in addition to behavioral measures, and may have controlled for intervention exposure or reported control-arm outcomes, which made them elegible for our review. Of the 133 title/abstract records promoted to full-text review, four were included in our analyses.

**Searches within EndNote and results:**

| Search sequence | Category (subfolder) | Records partitioned | Terms used in EndNote, searching only titles (asterisk denotes that plural forms & forms with additional subsequent letters were also searched) |
| --- | --- | --- | --- |
| 1 | Animal | 109 | animal\* or baboon\* or canine or cats or chimp\* or dogs or feline or guinea pig\* or hamster\* or lapine or macacque\* or macaque\* or mice or mouse or murine or rabbit\* or rat model or rats or rhesus or simian or swine or zoonos\* |
| 2 | In vitro etc. | 102 | deoxy\* or in vitro or in vivo or molecule or nano\* or polymorph\* or ribosom\* |
| 3 | Drugs | 609 | alcohol or amphetamine\* or cocaine or crack or drug user\* or drug using or harm reduction or heroin or IDU or injecting drug or injection drug\* or intravenous drug\* or methamphetamine\* or narcotic\* or needle\* or opioid\* or PWID or stimulant\* or syringe\* or tobacco |
| 4 | Other conditions | 1,139 | cancer\* or carcinogen\* or carcinoma\* or chickenpox or digestive or Epstein-Barr or Epstein Barr or hematopoie\* or imaging or immune reconstitution or Kaposi\* or Karposi\* or lymphoma or malaria\* or malignan\* or necrosis or neurolog\* or neoplasia or nervous or oncology or radiolog\* or transfus\* or transplant\* or tuberculosis or zoster or arthritis or zika or ebola |
| 5 | Mother-to-child transmission and obstetrics | 887 | babies or baby or breast milk or breastmilk or caesarean or cesarean or children or infant\* or mother to child or mother-to-child or MTCT or PMTCT or mothers or neonatal or neonate\* or nevirapine or perinatal or postnatal or prenatal or antenatal or pregnan\* or vertical or foetal or fetal or fertility or infertility or intrauterine or uterine or birth or miscarriage or postpartum or post-partum or preterm or pre-term |
| 6 | Other specific interests | 345 | budget\* or condom availability or condom distribution or economic\* or financial or guidelines or mathematical or outbreak\* or vaccin\* or knowledge transfer or knowledge translation or mass media or school-based or social market\* |
| 7 | Qualitative | 173 | attitudes or beliefs or perception or preferences or qualitative |
| 8 | Acquired immune | 82 | acquired immun\* |
| 9 | Behavior | 1,190 | abstinen\* or behav\* or condom use or disclos\* or educat\* or intention\* or outreach or self-report\* |
| Total records partitioned: | | 4, 636 |  |

# Appendix C. Citation screening process flowchart2-4



# 

# Appendix D: Studies excluded after full-text review, by reason

## Studies excluded: Temporality inapplicable or unclear

1. Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. Journal of acquired immune deficiency syndromes (1999). 2010;53(4):537-43.

2. Bhattar S, Bhalla P, Chadha S, Tripathi R, Kaur R, Sardana K. Chlamydia trachomatis infection in HIV-infected women: need for screening by a sensitive and specific test. Infectious diseases in obstetrics and gynecology. 2013;2013:960769.

3. Bollinger RC, Brookmeyer RS, Mehendale SM, Paranjape RS, Shepherd ME, Gadkari DA, et al. Risk factors and clinical presentation of acute primary HIV infection in India. Jama. 1997;278(23):2085-9.

4. Burn S, Horner PJ. Rectal gonorrhoea as an independent risk factor for HIV infection in homosexual males. Genitourinary medicine. 1995;71(5):335-6.

5. Butler DM, Smith DM, Cachay ER, Hightower GK, Nugent CT, Richman DD, et al. Herpes simplex virus 2 serostatus and viral loads of HIV-1 in blood and semen as risk factors for HIV transmission among men who have sex with men. AIDS (London, England). 2008;22(13):1667-71.

6. Castillo R, Konda KA, Leon SR, Silva-Santisteban A, Salazar X, Klausner JD, et al. HIV and Sexually Transmitted Infection Incidence and Associated Risk Factors Among High-Risk MSM and Male-to-Female Transgender Women in Lima, Peru. Journal of acquired immune deficiency syndromes (1999). 2015;69(5):567-75.

7. Coll J, Videla S, Leon A, Ornelas A, Garcia F, Fernandez E, et al. Early detection of HIV infection and of asymptomatic sexually transmitted infections among men who have sex with men. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2018;24(5):540-5.

8. Dong Z, Xu J, Zhang H, Dou Z, Mi G, Ruan Y, et al. HIV incidence and risk factors in Chinese young men who have sex with men--a prospective cohort study. PloS one. 2014;9(5):e97527.

9. Fisher M, Pao D, Brown AE, Sudarshi D, Gill ON, Cane P, et al. Determinants of HIV-1 transmission in men who have sex with men: a combined clinical, epidemiological and phylogenetic approach. AIDS (London, England). 2010;24(11):1739-47.

10. Gallagher KE, Baisley K, Grosskurth H, Vallely A, Kapiga S, Vandepitte J, et al. The Association Between Cervical Human Papillomavirus Infection and Subsequent HIV Acquisition in Tanzanian and Ugandan Women: A Nested Case-Control Study. The Journal of infectious diseases. 2016;214(1):87-95.

11. Gray JA, Dore GJ, Li Y, Supawitkul S, Effler P, Kaldor JM. HIV-1 infection among female commercial sex workers in rural Thailand. AIDS (London, England). 1997;11(1):89-94.

12. Guy RJ, Spelman T, Stoove M, El-Hayek C, Goller J, Fairley CK, et al. Risk factors for HIV seroconversion in men who have sex with men in Victoria, Australia: results from a sentinel surveillance system. Sexual health. 2011;8(3):319-29.

13. Hightow LB, Miller WC, Leone PA, Wohl DA, Smurzynski M, Kaplan AH. Predictors of repeat testing and HIV seroconversion in a sexually transmitted disease clinic population. Sexually transmitted diseases. 2004;31(8):455-9.

14. Kilmarx PH, Limpakarnjanarat K, Mastro TD, Saisorn S, Kaewkungwal J, Korattana S, et al. HIV-1 seroconversion in a prospective study of female sex workers in northern Thailand: continued high incidence among brothel-based women. AIDS (London, England). 1998;12(14):1889-98.

15. Kunawararak P, Beyrer C, Natpratan C, Feng W, Celentano DD, de Boer M, et al. The epidemiology of HIV and syphilis among male commercial sex workers in northern Thailand. AIDS (London, England). 1995;9(5):517-21.

16. Laga M, Alary M, Nzila N, Manoka AT, Tuliza M, Behets F, et al. Condom promotion, sexually transmitted diseases treatment, and declining incidence of HIV-1 infection in female Zairian sex workers. Lancet (London, England). 1994;344(8917):246-8.

17. Leal L, Torres B, Leon A, Lucero C, Inciarte A, Diaz-Brito V, et al. Predictive Factors for HIV Seroconversion Among Individuals Attending a Specialized Center After an HIV Risk Exposure: A Case-Control Study. AIDS research and human retroviruses. 2016;32(10-11):1016-21.

18. Li D, Jia Y, Ruan Y, Liu Y, Li Q, Liang H, et al. Correlates of incident infections for HIV, syphilis, and hepatitis B virus in a cohort of men who have sex with men in Beijing. AIDS patient care and STDs. 2010;24(9):595-602.

19. Li D, Li S, Liu Y, Gao Y, Yu M, Yang X, et al. HIV incidence among men who have sex with men in Beijing: a prospective cohort study. BMJ open. 2012;2(6).

20. Reynolds SJ, Risbud AR, Shepherd ME, Rompalo AM, Ghate MV, Godbole SV, et al. High rates of syphilis among STI patients are contributing to the spread of HIV-1 in India. Sexually transmitted infections. 2006;82(2):121-6.

21. Wang QQ, Chen XS, Yin YP, Liang GJ, Zhang RL, Jiang N, et al. HIV prevalence, incidence and risk behaviours among men who have sex with men in Yangzhou and Guangzhou, China: a cohort study. Journal of the International AIDS Society. 2014;17:18849.

22. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. The Journal of infectious diseases. 2005;191(9):1403-9.

23. Weinstock H, Sweeney S, Satten GA, Gwinn M. HIV seroincidence and risk factors among patients repeatedly tested for HIV attending sexually transmitted disease clinics in the United States, 1991 to 1996. STD Clinic HIV Seroincidence Study Group. Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association. 1998;19(5):506-12.

24. Yu M, Jiang G, Dou Z, Li Z, Guo Y, Xu P, et al. [HIV infection incidence among men who have sex with men in common bathing pool in Tianjin: a cohort study]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2016;37(3):362-6.

## Studies excluded: Systematic reviews (handsearched)

1. Arora P, Nagelkerke NJ, Jha P. A systematic review and meta-analysis of risk factors for sexual transmission of HIV in India. PloS one. 2012;7(8):e44094.

2. Barnabas RV, Webb EL, Weiss HA, Wasserheit JN. The role of coinfections in HIV epidemic trajectory and positive prevention: a systematic review and meta-analysis. AIDS (London, England). 2011;25(13):1559-73.

3. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. The Lancet Infectious diseases. 2009;9(2):118-29.

4. Bonell C, Hickson F, Beaumont M, Weatherburn P. Sexually transmitted infections as risk factors for HIV infection among MSMs: systematic review. Sexually transmitted diseases. 2008;35(2):209.

5. Bonell C, Weatherburn P, Hickson F. Sexually transmitted infection as a risk factor for homosexual HIV transmission: a systematic review of epidemiological studies. International journal of STD & AIDS. 2000;11(11):697-700.

6. Champredon D, Bellan SE, Delva W, Hunt S, Shi CF, Smieja M, et al. The effect of sexually transmitted co-infections on HIV viral load amongst individuals on antiretroviral therapy: a systematic review and meta-analysis. BMC infectious diseases. 2015;15:249.

7. Chen L, Jha P, Stirling B, Sgaier SK, Daid T, Kaul R, et al. Sexual risk factors for HIV infection in early and advanced HIV epidemics in sub-Saharan Africa: systematic overview of 68 epidemiological studies. PloS one. 2007;2(10):e1001.

8. Feng Y, Bu K, Li M, Zhang X, Jin S, Wang L. [Meta-analysis of HIV infection incidence and risk factors among men who have sex with men in China]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2015;36(7):752-8.

9. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sexually transmitted infections. 1999;75(1):3-17.

10. Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. AIDS (London, England). 2006;20(1):73-83.

11. Hilber AM, Francis SC, Chersich M, Scott P, Redmond S, Bender N, et al. Intravaginal practices, vaginal infections and HIV acquisition: systematic review and meta-analysis. PloS one. 2010;5(2):e9119.

12. Kissinger P, Adamski A. Trichomoniasis and HIV interactions: a review. Sexually transmitted infections. 2013;89(6):426-33.

13. Li HM, Peng RR, Li J, Yin YP, Wang B, Cohen MS, et al. HIV incidence among men who have sex with men in China: a meta-analysis of published studies. PloS one. 2011;6(8):e23431.

14. Looker KJ, Elmes JAR, Gottlieb SL, Schiffer JT, Vickerman P, Turner KME, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. The Lancet Infectious diseases. 2017;17(12):1303-16.

15. Napierala Mavedzenge S, Weiss HA. Association of Mycoplasma genitalium and HIV infection: a systematic review and meta-analysis. AIDS (London, England). 2009;23(5):611-20.

16. Poon AN, Li Z, Wang N, Hong Y. Review of HIV and other sexually transmitted infections among female sex workers in China. AIDS care. 2011;23 Suppl 1:5-25.

17. Powers KA, Poole C, Pettifor AE, Cohen MS. Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. The Lancet Infectious diseases. 2008;8(9):553-63.

18. R K, P A, N D. HIV-1 trends, risk factors and growth in India. New Delhi, India: Ministry of Health and Family Welfare; 2005.

19. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sexually transmitted diseases. 2001;28(10):579-97.

20. Sexton J, Garnett G, Rottingen JA. Metaanalysis and metaregression in interpreting study variability in the impact of sexually transmitted diseases on susceptibility to HIV infection. Sexually transmitted diseases. 2005;32(6):351-7.

21. Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. The Journal of infectious diseases. 2002;185(1):45-52.

22. Yah CS, Tambo E, Adeagbo O, Magida A. HIV and sexually transmitted co-infections among sex workers in the Southern African economic region. Annals of Tropical Medicine and Public Health. 2017;10(5):1128-36.

23. Zhang X, Chow EP, Wilson DP, Sun X, Zhao R, Zhang J, et al. Prevalence of HIV and syphilis infections among long-distance truck drivers in China: a data synthesis and meta-analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2013;17(1):e2-7.

## Studies excluded: HSV-2

Analysis for the following studies was deferred as the only pathogen of interest was HSV-2 or pooled analysis of multiple STIs including HSV-2.

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## Studies excluded: Proxy HIV outcome reported

The following studies reported changes in viral load or HIV RNA but not HIV transmission or acquisition outcomes.

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## Studies excluded: Self-report

The following studies relied on self-reported HIV status and/or self-reported STI exposure with no reference to formal diagnosis or testing.

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## Studies excluded: Interventional

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## Studies excluded: Insufficient quantitative data

The following studies did not report necessary data points for incorporation in quantitate synthesis.

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## Studies excluded: Population

The following studies did not report data specifically for men who have sex with men, sex workers, or other high-risk heterosexual populations as defined in our protocol.

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## Studies excluded: Outcome not HIV

The following studies did not report HIV acquisition and/or transmission.

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## Studies Excluded: Study Design

The following studies used an ineligible study design (e.g., cross sectional) in any analysis of the relationship between STI infection and HIV acquisition or transmission.

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# Appendix E. Risk of bias indicator definitions used for data extraction

Raters applied the following guidance when evaluating risk of bias. Because each indicator is described in question form, raters used responses phrased as “definitely yes,” “probably yes,” “probably no,” and “definitely no,” which corresponded to very low risk of bias, low risk of bias, medium risk of bias, and high risk of bias, respectively.

| Risk of Bias Indicator | Modified Domain | Definition | Instructions |
| --- | --- | --- | --- |
| Assessment of exposure | D1 - STI Assessment | Rater is confident in the assessment of STI exposure? | Consider diagnostic technology/practice: are diagnostics adequate for the pathogen assessed?   * Very low risk of bais (“definitely yes”): Lab-confirmed (NAAT) OR Serology for Syphilis (treponemal and non-treponemal tests) * Low risk of bias (“probably yes”): Lab-confirmed (Non-NAAT) OR language indicates a diagnosis was made for a bacterial infection (except for syphilis – see below) * Medium risk of bias (“probably no”): Medical exam only OR if pathogen is HSV-2 or syphilis and test type is unknown or are as follow:   + HSV-2: a non-type-specific test   + Syphilis: a treponemal test only   + High risk of bias (“definitely no”): self-report (Exclude)   Note: If a study reports using diagnostics that fall into multiple categories, code with the greater risk of bias category |
| Assessment of outcome | D2 - Outcome assessment | Rater is confident in the assessment of outcome? | Considering the HIV diagnostics, is the risk of false positive very low?   * Very low risk of bais (“definitely yes”): RNA test OR 4th-generation ELISA OR  ELISA + Western Blot / PCR OR ELISA +P24 to confirm HIV infection * Low risk of bias (“probably yes”): 1st - 3rd-generation ELISA * Medium risk of bias (“probably no”): Medical record (unspecified test) * High risk of bias (“definitely no”): Self-report (Exclude) |
| Adequate matching and/or adjustment for confounders | D3 - Confounding | Study matched on or adjusted for all potential confounders? | When extracting a PECO from paper's sub-analysis, consider whether sub-analysis outcome is adjusted with the same rigor as the primary analysis (e.g., in a study primarily evaluating the impact of HPV on HIV infection, if authors adjust data for HPV exposure but not HSV-2 exposure, code with greater risk of bias for an HSV-2 PECO. Because STI & HIV are similar outcomes, they will share causal factors (condom use, religion, age, etc.).   * Very low risk of bais (“definitely yes”): properly matched or controlled for (by using multivariate model) on all key confounders and 2 other potentially important factors (e.g., Renzi 20035) * Low risk of bias (“probably yes”): matched or controlled for at least three key confounders (e.g., condom use, sexual partnership, HIV partner) (e.g., Kingsley 19906) * Medium risk of bias (“probably no”): only matched on one factor such as time of testing (e.g., Keet 19907) * High risk of bias (“definitely no”): no attempt on matching or adjustment   Key confounders: number of sex partners, drug injection, other STDs, condom breakage, condom use / unprotected sex, any HIV-positive partner or partner of unknown HIV status, sexual partnership type, unprotected receptive anal intercourse  Other potential confounders: age, race/ethnicity; health insurance, place/site of recruitment; and year of HIV seroconversion |
| Cohort: Both cohorts from same population? | D4 - Groups comparability | Exposed & unexposed groups drawn from the same population? | Consider variation across study sites, control group, etc.   * Very low risk of bais (“definitely yes”): properly selected STI diagnosed and undiagnosed groups from the same source population. * Low risk of bias (“probably yes”): * Medium risk of bias (“probably no”): * High risk of bias (“definitely no”): STI diagnosed and undiagnosed groups are selected in a way that can seriously influence risk of outcomes.   Consider studies that compared pre-baseline STI diagnosis to predict HIV sero-conversation among HIV negative people after baseline. This analysis may differentially exclude those who sero-converted to HIV positive due to STI before the baseline. See Table 3 in Desai 20178 as an example. |
| Cohort: Could preclude existence of outcome at baseline? | D5 - Preclude baseline HIV | Rater is confident that HIV infection not present at baseline? | Consider HIV testing method used to ascertain HIV – before STI diagnosis, is the risk of false negative very low?   * Very low risk of bais (“definitely yes”): RNA test OR 4th-generation ELISA with venous blood OR at least two sequential negative tests (any type) 6-8 weeks apart * Low risk of bias (“probably yes”): Single 4th-generation ELISA/P24 using fingerstick or unspecified blood sample * Medium risk of bias (“probably no”): Single 1st - 3rd-generation ELISA OR medical record (test unspecified) * High risk of bias (“definitely no”): Self-report |
| Cohort: Assessment of prognostic factors | D6 - Temporality | Raters is confident that STI occurred prior to HIV sero-conversion? | Can raters be sure that STI was present prior to HIV infection? Study must conform to one set of criteria specified at the selected level (i.e., option a) or b)). Note that interval times apply to both prospective and retrospective study designs.  Very low risk of bais (“definitely yes”):   * 1. For bacterial STI diagnosis at baseline only:      + single HIV assessment in <= 3 months OR      + multiple HIV assessments in intervals of 3 months & duration of exposure accounted for   2. For incident bacterial STI: can establish that STI preceded HIV AND STI-HIV assessment intervals < =3 months AND STI diagnoses as time dependent variable   Low risk of bias (“probably yes”):   1. For bacterial STI diagnosis at baseline only:    * + single HIV assessment in >3 month <=6 OR      + multiple HIV assessment in intervals of >3 month <=6 AND duration of exposure accounted for 2. For incident bacterial STI: can establish STI preceded HIV AND STI-HIV assessment intervals of >3 months <=6 AND STI diagnosis as time dependent variable   Medium risk of bias (“probably no”):   1. For bacterial STI diagnosis at baseline only: 2. single HIV assessment in >6 months <=12 OR 3. multiple HIV assessment intervals of >6 months <=12 AND duration of exposure accounted for 4. For incident bacterial STI: can establish STI preceded HIV AND STI-HIV assessment intervals >6 <=12 months AND STI diagnosis as time dependent variable  * High risk of bias (“definitely no”):   1. Assessment intervals > 12 mon OR   2. For incident STI, STI not treated as time-dependent   Note:   1. Exclude when unclear that STI was present before HIV 2. For HSV-2, the assessment time interval issue is not applied. 3. For baseline STI, if multiple HIV measures without taking the duration into account, downgrade one level, for example from “probably yes” to “probably no.” |
| Cohort: Co-intervention similarity? | D7 - Co-intervention similarity | Co-interventions similar between groups? | Consider secondary interventions that intercepted study arms. E.g., if enhanced counseling was offered to STI-infected participants. |
| Case-Control: Case Selection | D8 - Case selection | Cases properly selected? | Consider variation in selection across sites, variation in risk level, etc., as well as criteria for HIV diagnostic (e.g., self-report, presumed positive).  Consider interventions for cases, such as adherence follow-up which could result in an HIV+ population with such a low VL that transmission is especially unlikely. |
| Case-Control: Control Selection | D9 - Control selection | Controls properly selected? | Consider potential for HIV- to be in window period (i.e., no RNA test), whether population/cohort is the same, whether selection is randomized, whether matching accounts for hard-to-measure factors (such as time of visit)  Consider comparability of population, e.g. do cases reside in a community with different risk behaviors and/or interventions than controls? |
| Cohort: Adequate Follow-up | Not Applied | Will not be assessed | Contextually duplicative with indicator D5 |

Context: The following indicators are extracted to document the handling of STI data and inform risk-of-bias coding.

| STI Timing Indicator | Definition | Values |
| --- | --- | --- |
| PECO-Level STI assessment timing | When did the STI test linked to HIV outcome occur? | * Baseline only * Baseline or follow-up * Follow-up only |
| STI Treated as Time-Dependent Variable? | Do authors report treating STI diagnosis as a time-dependent (as opposed to fixed) variable, or does variable function as time-dependent (i.e. using STI diagnosis at beginning of time interval to predict HIV diagnosis during that time interval)? | * Yes * No * Not reported |
| Was STI assessed before HIV seroconversion? | Are you certain that STI associated with HIV infection was assessed prior to HIV diagnosis (or prior to estimated time of HIV seroconversion – typically mid-point of interval between an HIV-negative test & the following HIV-positive test)? | * Yes * No * Unsure/Mixed |
| Do authors discuss duration of STI exposure? | Do authors discuss or control for duration of exposure (i.e., whether STI likely still present at time of HIV acquisition)? | * Yes * No |
| STI Assessment Interval (months) | The number of months between STI and HIV assessments | (numeric value) |
| HIV baseline diagnostic procedures |  | * RNA * PCR * 4th-generation ELISA (venous blood) * 4th generation (fingerstick/ unknown) * 3rd generation ELISA * 2nd generation ELISA * 1st generation ELISA * Unspecified ELISA * Sequential testing (any type) * WB or p24 to all * Not reported |
| HIV outcome diagnostic procedures |  | * RNA * PCR * 4th-generation ELISA (venous blood) * 4th generation (fingerstick/ unknown) * 3rd generation ELISA * 2nd generation ELISA * 1st generation ELISA * Unspecified ELISA * WB or p24 to all * Not reported |

# Appendix F. Risk of Bias Results (n = 26 studies)

| **Author, year** | **Cohort Studies** | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **D1 –  STI assessment** | | **D2 –  Outcome assessment** | **D3 – Confounding** | | | **D4 –  Group comparability** | **D5 –  Preclude baseline HIV** | **D6 – Temporality** | | **D7 –  Co-intervention similarity** |
| Beymer 20169 | Low\*†‡ | Very Low§ | Low | High | | | Low | Medium | Medium | | Low |
| Cheung 201610 | Low†‡ | Very Low\*§ | Low | High | | | Low | Medium | Medium | | Low |
| Desai 20178 | Medium | | Medium | Medium†‡§ | | High\* | Very Low | Medium | Medium | | Low |
| Garofalo 201611 | Very Low | | Medium | High | | | Very Low | Medium | High | | Very Low |
| Giuliani 201412 | Low† | Very Low§ | Low | High | | | Very Low | Medium | High | | Low |
| Harrison 199913 | Medium | | Low | Medium | | | Very Low | Medium | Medium | | Very Low |
| Jia 201514 | Very Low | | Very Low | High | | | Very Low | Very Low | High | | Very Low |
| Jin 201015 | Very Low | | Very Low | Low† | High\*§ | | Very Low | Low | Medium\*† | High§ | Low |
| Kelley 201516 | Very Low | | Very Low | Medium‖ | | High¶ | Very Low | Medium | High | | Low |
| Koblin 201317 | Low | | Very Low | Low | | | Very Low | Very Low | Low | | Low |
| Lam 201718 | Very Low | | Low | Low\*\* | | High†† | Very Low | Medium | Medium | | Low |
| Li 201219 | Very Low | | Low | Medium | | | Very Low | Medium | High | | Very Low |
| Meireles 2015a20 | Medium | | Low | Medium§ | | High† | Very Low | Medium | High | | Low |
| Mitchell 201721 | Low | | Medium | Medium | | | Very Low | Medium | Medium | | Low |
| Pathela 201322 | Medium | | Very Low | High | | | Very Low | Very Low | High | | Low |
| Sanders 201323 | Low | | Very Low | Low | | | Very Low | Low | Low | | Low |
| Solomon 201424 | Very Low | | Low | High | | | Very Low | Medium | Very Low | | Low |
| Thienkrua 201625 | Very Low | | Low | Medium | | | Very Low | Medium | Medium | | Low |
| van Griensven 201326 | Very Low | | Low | Medium | | | Very Low | Medium | High | | Low |
| Wang 201427 | Very Low | | Very Low | High | | | Very Low | Medium | Medium | | Low |
| Xu 201028 | Very Low | | Very Low | Medium | | | Very Low | Medium | Medium | | Low |
| Xu 201329 | Very Low | | Very Low | Medium | | | Very Low | Very Low | High | | Low |
| Yang 201030 | Very Low | | Very Low | High | | | Very Low | Medium | Low | | Low |
| Zhao 201331 | Medium | | Very Low | High | | | Very Low | Medium | High | | Low |
| **Author, year** | **Case Control Studies** | | | | | | | | | | |
| **D1 –  STI assessment** | | **D2 –  Outcome assessment** | **D3 – Confounding** | | | **D8 –  Case selection** | | **D9 –  Control selection** | | |
| Page-Shafer 199732 | Low† | Medium§ | Very Low | Medium | | | Very Low | | Very Low | | |
| Zetola 200933 | Medium | | Very Low | Medium | | | Very Low | | Very Low | | |

Key: NA = Not applicable; STI = Sexually transmitted infection

\*Chlamydia

†Gonorrhea

‡Any bacterial STI, anatomical site unspecified

§Syphilis

‖Any bacterial STI, rectal

¶ Any bacterial STI, ureteral

\*\* Syphilis and HIV strain CRF01\_AE

†† Chlymadia or Gonorrhea and HIV strains other than CRF01\_AE

# Appendix G. Summary of results on the effect of multiple bacterial pathogen STIs estimates on risk of HIV acquisition among MSM by multivariate adjustment, geography, temporality, testing, high quality data, and combined

|  |  |  |
| --- | --- | --- |
|  | **Multiple Bacterial Pathogens** | |
| **Multivariate Adjustment** | **Unadjusted RR** | **Adjusted RR** |
| **Pooled RR (95%)** | 2·19 (1·64, 2·91) | 2·36 (1·44 3·87) |
| **I2, p value** | 19·5%, p=0·293 | 86·2%, p=0·000 |
| **K** | 4 | 5 |
| **Geography** | **OECD**\* | **Non-OECD** |
| **Pooled RR (95%)** | 2·28 (1·65, 3·13) | -- |
| **I2, p value** | 77·9%, p=0·000 | -- |
| **K** | 9 | -- |
| **Risk of Bias: Temporality**† | **Less Risk** | **More Risk** |
| **Pooled RR (95%)** | 2·25 (1·41, 3·58) | 2·42 (1·81, 3·25) |
| **I2, p value** | 87·9%, p=0·000 | 0·0%, p=0·408 |
| **K** | 5 | 4 |
| **Risk of Bias: Testing**‡ | **Less Risk** | **More Risk** |
| **Pooled RR (95%)** | 2·20 (1·75, 2·77) | 2·22 (1·29, 3·81) |
| **I2, p value** | 0·0%, p=0·642 | 87·2%, p=0·000 |
| **K** | 4 | 5 |
| **High Quality Data§** | **Model 1** | **Model 2** |
| **Pooled RR (95%)** | -- | 2·19 (0·94, 5·11) |
| **I2, p value** | -- | 92·9%, p=0·000 |
| **K** | -- | 3 |
| **Combined** | **Combined** | |
| **Pooled RR (95%)** | 2·28 (1·65, 3·13)¶ | |
| **I2, p value** | 77·9%, p=0·000 | |
| **K** | 9 | |
| **SA RR Range||** | 2·10-2·53 | |

\*OECD countries are members of the Organisation for Economic Co-operation and Development (OECD). Study data is drawn from the following OECD countries: Australia, Italy, Portugal, United Kingdom, United States, and a multi-country study. Study data is drawn from the following non-OECD countries: Brazil, China, Kenya, Thailand.

†Risk of bias in temporality is defined as more risk where there was an interval of >12 months between STI exposure and HIV outcome assessments and less risk where the interval <=12 months. Incident STI exposure treated as a fixed variable is classified as higher risk of bias.

‡Risk of bias in testing is defined as more risk if STI exposure and/or HIV outcome were drawn from medical records and less risk if investigators reported using laboratory test for both STI and HIV.

§Model 1: Data excluded if: HIV and STI assessment was based on medical records (vs. if directly confirmed by lab test), if there was no attempt to match or adjust for confounders, a case-control study design was used, and/or assessment intervals were > 12 months.

Model 2: Data excluded if: There was no attempt to match or adjust for confounders and/or assessment intervals were >12 months. ¶Reflects estimate using an adjusted estimate from Kelly 201516 based on rectal STI exposure. That study also reports an unadjusted estimate based on urethral exposure. When the adjusted estimate from Kelley 2015 is replaced by the unadjusted estimate from the same study, the combined estimated RR would be 2·23 (1·58, 3·15).

||Sensitivity analysis RR range when one study removed from analysis.

K = Number of effect size estimates included; RR = Risk ratio; SA = Sensitivity analysis

# Appendix H. Funnel plot for the effect sizes of bacterial STIs on risk of HIV acquisition among MSM

1. Effect sizes included in the crude meta-analysis for the effect of syphilis



1. Effect sizes included in the crude meta-analysis for the effect of gonorrhea



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