Risk of HIV acquisition among high-risk heterosexuals 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**

Two librarians with extensive systematic review experience created and performed searches inPubMed 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. There will invariably still be some redundant records, whether many or few. We then recalibrate our preferences for duplicates, un-ticking the box for titles and ticking those for “year,” “author” and “pages.” Naturally, an author may publish many articles over the course of one year, but it is unlikely that different articles would have the same pagination. The only exception is that with many online-only journals and citations that entered databases as e-pubs ahead of print, where pagination is omitted. In such cases, the absence of page numbers appears to be a “match.” However, by sorting the much smaller yield of resulting records “by title” and scanning them visually, we can quickly discern when, for example “Article 1” is incorrectly presented as a match for “Article 2.”

If after this we still notice duplicates among the records, we set preferences again, ticking only “year,” “journal” and “pages,” Since it is possible that EndNote is having trouble with author names. In a hypothetical example, records from different databases for the same article there list the same author as “Des Jarlais,” “des Jarlais” or “DesJarlais.” While only the first of the three is correct, each database has used different methods in indexing the literature and it is possible that error has slipped into their respective process.

All redundant records should by now have been detected. In the event that screening teams identify surviving duplicates, we record the newly-identified duplicates and update search records to reflect them.

# 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. 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 20036) * 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 19907) * Medium risk of bias (“probably no”): only matched on one factor such as time of testing (e.g., Keet 19908) * 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 20179 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? 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. Baseline STI:      + single HIV assessment in <= 3 months OR      + multiple HIV assessments in intervals of 3 months & duration of exposure accounted for   2. Incident 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. Baseline STI:    * + single HIV assessment in >3 month <=6 OR      + multiple HIV assessment in intervals of >3 month <=6 AND duration of exposure accounted for 2. Incident 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. Baseline STI: 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. Incident 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 E: Studies excluded after full-text review

## 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.

1. Aguayo N, Laguna-Torres VA, Villafane M, Barboza A, Sosa L, Chauca G, et al. Epidemiological and molecular characteristics of HIV-1 infection among female commercial sex workers, men who have sex with men and people living with AIDS in Paraguay. Revista da Sociedade Brasileira de Medicina Tropical. 2008;41(3):225-31.

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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: 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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### HSV-2

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### Population men who have sex with men for separate analysis

The following studies were included in analysis published separately.

Beymer MR, Weiss RE, Halkitis PN, et al. Disparities Within the Disparity-Determining HIV Risk Factors Among Latino Gay and Bisexual Men Attending a Community-Based Clinic in Los Angeles, CA. *Journal of acquired immune deficiency syndromes (1999)* 2016; **73**(2): 237-44.

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# Appendix F. Risk of Bias Results for Meta-Analyzed Effect Sizes (k=97)

| **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** |
| Auvert 2011 | Low | | | | | | V. Low | Low | | | | V. Low | | Med. | | High | | | | Low |
| Braunstein 2011b | TV: Low | CT, NG, TP: V. Low | | | | | Low | CT, TV: High | | NG, TP: Med. | | V. Low | | V. Low | | CT, NG: High | TP, TV: Med. | | | Low |
| Deschamps 1996 | V. Low | | | | | | V. Low | High | | | | V. Low | | Med. | | High | | | | Low |
| Ghys 2001 | NG, TV: Low | | | | TP: V. Low | | Low | NG, TP: Med. | | TP: High | | V. Low | | Med. | | High | | | | Low |
| Hanson 2005 | NG: Low | | | | TP: V. Low | | V. Low | Med. | | | | V. Low | | Med. | | NG-Female, TP: High | | NG-Male: Med. | | Low |
| Heffron 2011 | V. Low | | | | | | Low | Low | | | | V. Low | | Med. | | High | | | | Low |
| Hughes 2012 | V. Low | | | | | | V. Low | CT, TP: High | | TV: Med. | | V. Low | | V. Low | | High | | | | Low |
| Kapiga 2007 | CT, TV: Low | | | | TP: V. Low | | Low | High | | | | V. Low | | Med. | | Low | | | | Low |
| Kaul 2004 | TV: Low | | | | CT, NG: V. Low | | Low | High | | | | V. Low | | V. Low | | V. Low | | | | High |
| Martin 1998 | CT, NG, TV: Low | | | | | TP: V. Low | Low | Low | | | | V. Low | | Med. | | V. Low | | | | Low |
| Masese 2015 | Low | | | | | | Low | Low | | | | V. Low | | Med. | | V. Low | | | | Low |
| McClelland 2007 | Low | | | | | | Low | Low | | | | V. Low | | Med. | | V. Low | | | | Low |
| Metha 2006 | NG: Low | | | TP: V. Low | | | Low | Med. | | | | V. Low | | Med. | | High | | | | Low |
| Mlisana 2012 | V. Low | | | | | | V. Low | Low | | | | V. Low | | V. Low | | High | | | | Low |
| Nagot 2005 | Low | | | | | | Low | High | | | | V. Low | | Med. | | Low | | | | Low |
| Otten 1994 | Low | | | | | | Low | High | | | | V. Low | | Med. | | High | | | | Low |
| Plourde 1994 | CT, NG, TV: Low | | | | | TP: V. Low | V. Low | High | | | | V. Low | | Med. | | Low | | | | Low |
| Plummer 1991 | Low | | | | | | V. Low | Low | | | | V. Low | | Low | | CT: Med. | TP: Low | | | Low |
| Priddy 2011 | TV: Low | | CT, NG, TP: V. Low | | | | Low | Med. | | | | V. Low | | Med. | | CT, NG: Low | TP, TV: V. Low | | | Low |
| Rakwar 1999 | CT: Low | | TP: V. Low | | | | V. Low | High | | | | V. Low | | Med. | | High | | | | Low |
| Ramjee 2005 | Low | | | | | | Low | Med. | | | | V. Low | | Med. | | V. Low | | | | Low |
| Riedner 2006 | V. Low | | | | | | Low | Low | | | | V. Low | | Med. | | V. Low | | | | Low |
| Ruzagira 2011 | V. Low | | | | | | V. Low | Med. | | | | V. Low | | V. Low | | High | | | | Low |
| Su 2016 | V. Low | | | | | | V. Low | High | | | | V. Low | | Med. | | Low | | | | Low |
| Telzak 1993 | V. Low | | | | | | V. Low | High | | | | High | | Med. | | Med. | | | | Low |
| Vandepitte 2013 | TP, TV: Low | | | CT, NG: V. Low | | | Low | Low | | | | V. Low | | Med. | | Low | | | | Low |
| Wall 2017 | V. Low | | | | | | Low | High | | | | V. Low | | Med. | | High | | | | Low |
| Wang 2012 | TP, TV: Low | | | CT, NG: V. Low | | | V. Low | High | | | | V. Low | | Med. | | Med. | | | | Low |
| Watson-Jones 2009 | TP, TV: Low | | | CT, NG: V. Low | | | V. Low | Med. | | | | V. Low | | V. Low | | CT, NG, TV: Med. | | | TP: V. Low | Low |
| **Author, year** | **Case Control Studies** | | | | | | | | | | | | | | | | | | | |
| **D1 – STI assessment** | | | | | | **D2 – Outcome assessment** | | **D3 - Confounding** | | | | **D8 – Case selection** | | **D9 – Control selection** | | | | | |
| Kassler 1994 | Low | | | | | | V. Low | | TP, TV: High | | NG: Low | | Low | | Low | | | | | |
| Laga 1993 | CT, NG, TV: Low | | | TP: V. Low | | | V. Low | | TP: High | | CT, NG, TV: Low | | Low | | Low | | | | | |
| Vandepitte 2014 | V. Low | | | | | | Low | | Med. | | | | Low | | Low | | | | | |

CT = Chlamydia; Med = Medium; NA = Not applicable; NG = Gonorrhea; STI = Sexually transmitted infection; TP = Syphilis; V. Low = Very low

# Appendix G. Comparison of Organization for Economic Co-Operation and Development (OECD)- and non-OECD study settings on the effect of nonviral STI diagnosis on risk of HIV acquisition among high-risk heterosexuals

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Females** | | | | **Males** | |
| **Syphilis** | | **Gonorrhea** | | **Syphilis** | |
| Pooled RR (95% CI) | 1.67 (1.23, 2.27) | | 2.81 (2.25, 3.50) | | 1.77 (1.22, 2.58) | |
| I2, p value | 43.7%, 0.028 | | 10.9%, 0.329 | | 8.5%, 0.358 | |
| SA RR Range | 1.56-1.821 | | 2.58, 3.053 | | 1.51-2.53 | |
| k | 17 | | 16 | | 5 | |
| All Female Populations by Geography | *OECD* | *Non-OECD* | *OECD* | *Non-OECD* | *OECD* | *Non-OECD* |
| Pooled RR (95% CI) | 3.86  (1.59, 9.38) | 1.48  (1.11, 1.98) | 1.60  (0.38, 6.77) | 2.86  (2.29, 3.57) | 2.51  (1.05, 6.00) | 1.74 (1.02, 2.97) |
| I2, p value | 13.7%, 0.282 | 32.5%, 0.109 | 56.8%, 0.128 | 7.3%, 0.372 | 0.0%, 0.599 | 8.5%, 0.358 |
| k | 2 | 15 | 2 | 14 | 2 | 3 |

**All studies of females in high-risk occupations were conducted in non-OECD countries. All studies of trichomoniasis, chlamydia, and *mycoplasma genitalium* were conducted in non-OECD countries.**

# Appendix H. Forest plot for risk ratios of diagnosis of syphilis and risk of HIV acquisition among male high-risk heterosexuals (k=5)



***High-risk occupation***

**Study Author and Year**

***Mixed risk groups***

***STI clinic patients***

***Having an HIV-serodiscordant partner***

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