Appendix 2 (as submitted by the authors):
Protocol:
Part II – An overview and update of systematic reviews and meta-analyses on the risks of HIV transmission in the context of antiretroviral therapy, viral load suppression, and condom use

Version: May 2017
Amended: June 7, 2017; June 27, 2017; September 27, 2017
This protocol is not registered.

Centre for Communicable Diseases and Infection Control
Infectious Disease and Prevention Control Branch
Public Health Agency of Canada
Government of Canada

Summary of amendments:

- On June 7, 2017, following consultation with a content expert, we decided to change the risk of bias (ROB) assessment tools chosen for the update (i.e., the Cochrane ROB tool and Newcastle-Ottawa Scale). The Quality In Prognosis Studies (QUIPS) tool, was selected as more appropriate for the types of key questions our study seeks to answer. In addition, we added additional details about how we will be assessing the quality of evidence across studies using the GRADE system (see '3.9 Amendment to update protocol [June 7, 2017]').
- On June 27, following consultation with an expert in statistical analysis, the 'Data analysis' section of the protocol was updated to include the use of pooled incidence estimates. Specifically, where more than one cohort study is available, we will pool the data to calculate an overall absolute risk estimate (i.e. pooled incidence rate). Sum total transmissions and sum total person-years of follow-up will be used to calculate point estimates, and exact Poisson 95% confidence intervals will be calculated in SAS Enterprise Guide 5.1. Forest plots will be developed in Excel to display the pooled incidence rates (see '3.10 Amendment to update protocol [June 27, 2017]').
- On September 27, 2017, more information was added to the protocol about the name and role of the funder/sponsor of the protocol and project. The Public Health Agency of Canada funded and approved the protocol and final evidence synthesis.

Source of funding and role of the funder

- The Public Health Agency of Canada funded the development of this protocol and the resulting evidence synthesis, and approved the final products.

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1 BACKGROUND

In Canada, an estimated 65,040 people[1] were living with HIV (PLHIV) at the end of 2014 (1), with approximately 82.2% having acquired their infection through sexual transmission (2). Men are estimated to account for the majority of PLHIV, (77.6%), while women account for 22.8% of those living with infection (2). Approximately 49.3% of all PLHIV in 2014 were men who have sex with other men.

Under current law in Canada as set out in the 1998 Supreme Court of Canada (SCC) decision in *R v Cuerrier* and updated in the 2012 decisions of *R v Mabior* and *R v D.C.,* PLHIV who are aware of their status can be convicted under criminal law for not disclosing their HIV status to sexual partners (3). The most recent SCC ruling requires disclosure of one's HIV-positive status before sex acts that 'pose a realistic possibility of HIV transmission' (3). The current application of the criminal law, however, has been described by some Canadian HIV and legal experts as overly broad and not reflective of the most recent scientific evidence on HIV transmission (3,4) .

The Public Health Agency of Canada (PHAC) (5) and the US Centers for Disease Control and Prevention (CDC) (6) have published summaries of scientific evidence related to HIV transmission risk; however, new evidence on the effect of anti-retroviral therapy (ART) and viral load suppression on preventing HIV transmission has emerged since the publication of these summaries (7). This new evidence has impacted stakeholder messaging around the risks of HIV transmission, for example, through the Prevention Access Campaign, which states that the risk of HIV transmission from a PLHIV who is on ART and has an undetectable viral load for six months is "negligible to non-existent" (7). This new evidence on risk of HIV transmission may also have implications for the criminal justice system review of the application of criminal law to HIV non-disclosure in Canada (8). A synthesis of evidence on HIV transmission risks, specifically in the context of preventive measures, is warranted.

Throughout this protocol, we have applied the UNAIDS terminology guidelines; we use the terms 'HIV-positive' or 'people living with HIV' (PLHIV) to refer to individuals diagnosed with HIV (9).

2 OBJECTIVE

The objective of this synthesis of evidence is to rigorously identify and synthesize scientific evidence related to the transmission risk of HIV under various scenarios that protect against HIV transmission, further defined below. This document outlines the proposed protocol for conducting a systematic review update (hereinafter 'update') based on the results of the overview described in Part I of the protocol.

[1] The estimated plausible range of individuals living with HIV in Canada is 53,980 to 76,100

3 METHODS

The second stage of the evidence synthesis will consist of updating systematic reviews to retrieve relevant new primary studies published since the systematic reviews included in our overview. Pre-existing search strategies extracted from high quality systematic review(s) identified in the overview will be adapted to retrieve these relevant primary studies. Condom use alone is not included as part of our update, as we identified one high quality systematic review by Weller et al. (10) on the effectiveness of condom use in reducing heterosexual transmission of HIV that was deemed as conclusive evidence in 2012[2], and no systematic review eligible to update on condom use effectiveness for penile-anal sex.

This update will adhere to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions (11) and the methods described by Garner et al. for updating systematic reviews (12). The study protocol has been developed to align with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (13).

3.1 Key questions

What are the absolute risks of HIV transmission associated with sex[3], when the following preventive measures are taken to reduce the risk of transmission between an HIV-positive and an HIV-negative sex partner:

1. The HIV-positive sex partner takes antiretroviral therapy (ART)[4]?
2. The HIV-positive sex partner takes ART and has a suppressed viral load[5]?
3. The HIV-positive sex partner takes ART[4] and either partner uses condoms (or other barrier methods)?
4. The HIV-positive sex partner takes ART and has a suppressed viral load, and either partner uses condoms (or other barrier methods)?

3.2 Analytic framework

The following framework illustrates the scenarios that protect against HIV transmission between HIV-serodiscordant sex partners outlined in our key questions (1-4).

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[2] In consultation with the Cochrane Review Group, reviews can be declared as stable if their conclusions are of high certainty and new information is unlikely to change the findings. No further updates are undertaken for conclusive reviews.

[3] We will define sex to include unspecified sex acts (any type of sex act, frequencies, and combinations), insertive penile-anal sex, insertive penile-vaginal sex, receptive penile-anal sex, receptive penile-vaginal sex, receiving anal-oral sex, receiving vaginal-oral sex, receiving penile-oral sex, performing anal-oral sex, performing vaginal-oral sex, and performing penile-oral sex. If other sex acts are identified in the primary studies (e.g. vaginal-vaginal sex, penile-penile sex) we will also include them.

[4] ART use in the first and third questions reflects a study population of PLHIV with varying levels of viral load; some individuals in these studies may have undetectable viral loads.

[5] 'Suppressed viral load' refers to a reduction in HIV-1 RNA in the blood. In this synthesis, it will be defined according to data derived from the included studies, and vary according to study definition. We will use the terms 'suppressed viral load/viral load suppression' as terms that encompass 'undetectable viral load.' We will specify the HIV-1 RNA level in copies/mL for each of these terms when used.

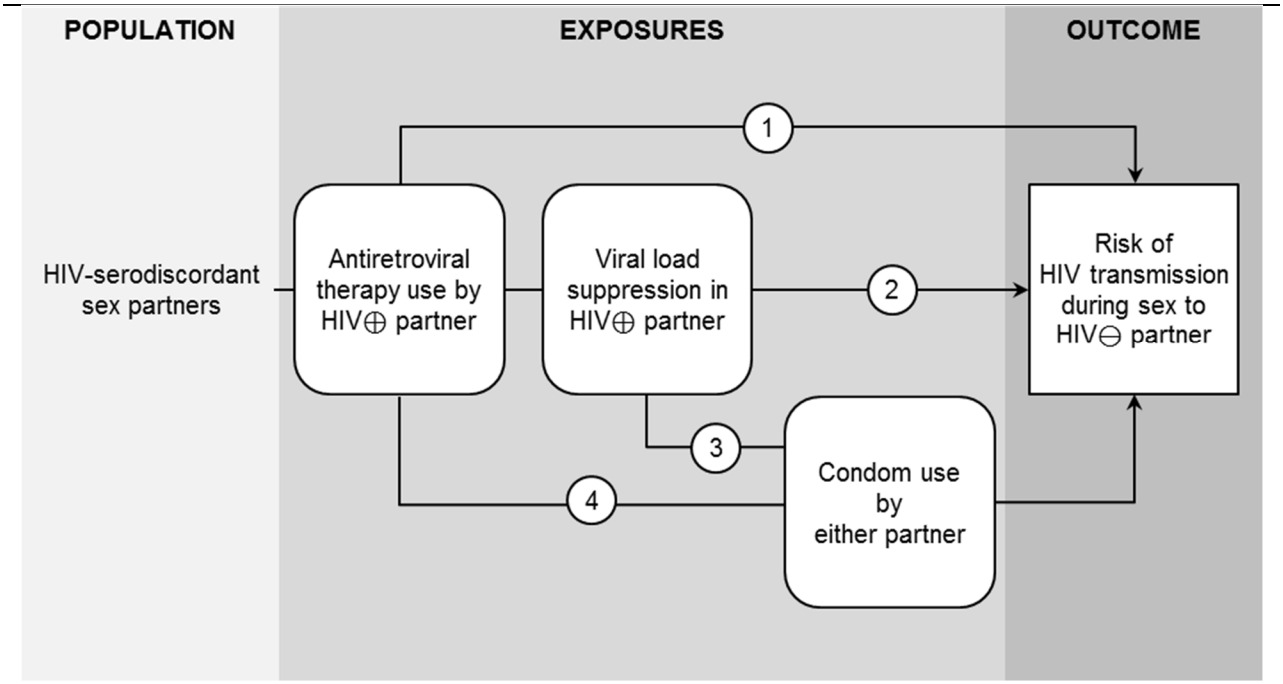

Figure 1. Analytic framework illustrating scenarios where preventive measures are taken to reduce the risk of transmission between HIV-serodiscordant sex partners. The numbers in the corresponding pathways illustrate the risk of HIV transmission to the HIV-negative (HIV⊖) partner during sex when ① the HIV-positive (HIV⊕) partner takes antiretroviral therapy (ART); ② the HIV⊕ partner takes ART and has a suppressed viral load; ③ the HIV⊕ partner takes ART and either partner uses condoms or other barrier methods; ④ the HIV⊕ partner takes ART and has a suppressed viral load, and either partner uses condoms or other barrier methods.

3.3 Selecting systematic reviews to update

Based on the results of our overview, we chose to update two systematic reviews to identify new primary studies since the selected reviews were published: (1) Supervie et al. (14), which addressed the absolute risk of HIV transmission among heterosexual serodiscordant couples under combination ART for greater than six months and with unspecified viral suppression and (2) Loutfy et al. (15), which addressed the absolute risk of HIV transmission among heterosexual and same-sex serodiscordant couples when the HIV-positive partner had a suppressed viral load on combination ART. We selected these two reviews to update key questions 1-4.

Supervie et al. (14) and Loutfy et al. (15) conducted different but complementary analyses on the same six primary studies identified in their reviews. Supervie et al. (14) used Bayesian statistics to infer the risk of HIV transmission per unprotected sex act with an HIV-positive individual on cART in clinical care for greater than six months, whereas Loutfy et al. (15) conducted a meta-analysis to assess the summary HIV transmission rate among the included studies.

We selected the search strategy by Supervie et al. (14) to update, as they had conducted the most recent systematic search of the literature across all countries, had reviewed the reference

lists of earlier systematic reviews included in our overview, and ultimately identified the same primary studies as the earlier review by Loutfy et al. (15). While Supervie et al. (14) limited their study population to heterosexual HIV-serodiscordant couples, we will seek to update their search strategy to include studies on sex partners regardless of the type of relationship (e.g. same-sex partners), in keeping with the inclusion criteria of Loutfy et al. (15). Loutfy et al. (15) sought to report on both heterosexual and same-sex couples, but did not find any published studies on same-sex couples that met their inclusion criteria. As we seek to include any type of couple or relationship, and to avoid missing studies on same-sex partners that may have been published between the dates of the two reviews, we will conduct our literature search according to the earlier search date used by Loutfy et al. (15). We constructed our updated search terms using the work of Supervie et al. as a base (14) given the full search strategy by Loutfy et al. (15) was not published and the available search strategy was overly broad, yet led to inclusion of the same studies as Supervie et al. (14).

3.4 Criteria for selecting primary studies for this update

Primary studies included in the review by Supervie et al. (14) had to "(1) examine HIV transmission among heterosexual couples where the HIV-infected partner was on cART, and provide information on (2) incident HIV infections among seronegative partners, (3) viral load of the treated index partner, (4) condom use, and (5) sexual activity." Studies included in the review by Loutfy et al. (15) were on "heterosexual or same-sex couples that provided data regarding all of the following: (1) sexual contact, (2) HIV-positive partner taking cART, (3) confirmed undetectable viral load at the time of HIV transmission, and (4) reported HIV infection rates in HIV-negative partner…[s]tudies that did not confirm index case viral loads at the time of transmission were considered for a secondary meta-analysis." The authors included the same five cohort studies and single randomized controlled trial in their reviews. A summary of criteria for selecting studies in our update is included in **Table 1**.

Table 1. Summary of criteria for selecting studies

Key questions	What are the absolute risks of HIV transmission associated with sex, when the following preventive measures are taken to reduce the risk of transmission between an HIV-positive and HIV-negative sex partner: KQ1. the HIV-positive sex partner takes ART; KQ2. the HIV-positive sex partner takes ART and has a suppressed viral load; KQ3. the HIV-positive sex partner takes ART and either partner uses condoms (or other barrier methods); and KQ4. the HIV-positive sex partner takes ART and has a suppressed viral load, and either partner uses condoms (or other barrier methods) alone?	
Study criteria	***Inclusion:***	***Exclusion:***
Participants	HIV-serodiscordant sex partners practicing: • Unspecified sex acts (any type of sex act(s)) • Insertive: penile-anal sex, penile-vaginal sex • Receptive: penile-anal sex, penile-vaginal sex • Receiving: anal-oral sex, vaginal-oral sex, penile-oral sex • Performing: anal-oral sex, vaginal-oral sex, penile-oral sex • Other specified acts (e.g., genital-genital)	Individuals or dyads not exposed to HIV exclusively through sex: • Infants exposed through vertical transmission • People who use injection drugs • People receiving blood transfusions • Workers exposed to occupational hazards (e.g. needle-stick)
Exposures	• Use of ART in the HIV-positive sex partner • Use of ART and having a suppressed viral load in the HIV-positive sex partner • Use of ART in the HIV-positive sex partner and use of condoms (or other barrier methods) by either partner • Use of ART and having a suppressed viral load in the HIV positive sex partner; and use of condoms (or other barrier methods) by either partner	• Use of single-agent ART (monotherapy) • Use of antiretroviral medication as pre-exposure or post-exposure prophylaxis (PrEP or PEP) • Use of ART without virological monitoring • Use of ART without reporting on condom use • Use of microbicides without ART or condoms • Use of male circumcision without ART or condoms • Use of semen washing without ART or condoms
Comparators	• Any or none	• No exclusions
Outcome measures	• Absolute risks of HIV transmission associated with sex	• Relative risks of HIV transmission during sex • Risk of vertical HIV transmission • Risk of HIV transmission from blood transfusion • Risk of HIV transmission from occupational exposure
Settings	• All	• No exclusions
Study designs	• Randomised controlled trials • Non-randomised controlled trials • Cohort studies	• Other types of observational studies • Ecological studies • Modelling studies • Reviews • Editorials • Commentaries
Language	• All	• No exclusions
Publication dates	• 01 November 2012 to April 2017	

3.4.1 Types of studies

We will consider studies eligible for inclusion if they were randomised or non-randomised controlled trials or cohort studies based on the inclusion criteria from the selected reviews (14,15). Following the lead of Loutfy et al. (15), we excluded other study designs (including

observational studies, ecological studies, modelling studies, reviews, editorials, and commentaries).

3.4.2 Types of participants

We will expand on the search strategy of Supervie et al. (14) to seek out studies that describe HIV-serodiscordant sex partners regardless of the type of partnership (e.g. same-sex) or type of relationship (e.g. casual, short-term, not exclusively monogamous). We will exclude studies exclusively on populations where HIV is not primarily transmitted through sex, such as during the vertical transmission of HIV between serodiscordant mothers and their infants or fetuses, as well as the horizontal transmission of HIV during blood transfusion, occupational exposures, and injection drug use.

3.4.3 Types of exposures

Based on Supervie et al.'s study selection criteria (14), we will include studies where the HIV-positive sex partner was on ART with virological monitoring, and in which the extent of condom use (or other barrier method) is reported. The exposures of interest are the use of ART in an HIV-positive sex partner, alone or in combination with having a suppressed viral load and/or condom use (or other barrier method) by either partner. Supervie et al. (14) excluded studies without virological monitoring as it is a "key component of successful treatment programs aiming to reduce HIV transmission." For ART use, we will describe the level of treatment adherence and timing of ART initiation based on the definitions in the systematic reviews. We will define having an "undetectable viral load" according to the detection limit of the assay used in the studies. We will define condom use (e.g. frequency) and type of barrier method (e.g. female condoms, dental dams) based on how it was reported in the study. We will describe the modifying effect of stage of disease and co-infection with other sexually transmitted infections. We will exclude studies that are exclusively on non-oral ART, monotherapy ART, or other preventive measures that reduce the risk of HIV transmission (e.g. pre-exposure and post-exposure prophylaxis use by an HIV-negative individual, male circumcision, use of microbicides, and semen washing).

3.4.4 Types of comparators and outcomes

Similar to Supervie et al. (14) and Loutfy et al. (15), we will include studies with any or no comparator. Our primary outcome will be the absolute risk of horizontal HIV transmission during sex expressed in terms of incidence [e.g. number of incident linked and/or unlinked HIV infections per person-years or sex act], where confirmatory HIV-testing was performed in the HIV-negative partner. We will define sex to include unspecified sex acts (all types of sex acts, frequencies, and combinations), insertive penile-anal sex, insertive penile-vaginal sex, receptive penile-anal sex, receptive penile-vaginal sex, receiving anal-oral sex, receiving vaginal-oral sex, receiving penile-oral sex, performing anal-oral sex, performing vaginal-oral sex, and performing penile-oral sex. If other sex acts are identified in the studies (e.g. vaginal-vaginal sex, penile-penile sex) we will also include them. We exclude systematic reviews and meta-analyses exclusively on relative risks of HIV transmission during sex, risk of vertical HIV transmission, risk

of HIV transmission from blood transfusion, risk of HIV transmission from occupational exposure.

3.5 Search methods for identification of studies

Our draft search strategy was developed by adapting the search strategy published by Supervie et al. (14) and updating from the date of the search conducted by Loutfy et al. (15) with the assistance of a Health Canada reference librarian. The search was peer-reviewed by two additional Health Canada librarians and will be peer-reviewed by an external librarian using the PRESS checklist (16). Our search strategy was designed to increase the sensitivity of the original search and account for slight changes in our review question and inclusion criteria, as outlined in previous sections. In order to increase the inclusiveness of our search, we will include a wider variety of terms to capture sexual minorities. The search strategy used in PubMed described by Supervie et al. (14) is included in **Appendix 1**. We highlight the added search terms in our updated search strategy for Ovid MEDLINE included in **Appendix 2.**

3.5.1 Electronic search

We will conduct an updated search on the following electronic databases, from 01 November 2012 to April 2017:

- MEDLINE
- EMBASE
- Cochrane Register of Controlled Trials (CENTRAL)
- Web of Science

Where Supervie et al. (14) searched the Cochrane Library, we will limit our search to CENTRAL as we are seeking to retrieve primary studies and completed a search of the Cochrane Library in our overview.

3.5.2 Trial registries

We will search ClinicalTrials.gov (https://clinicaltrials.gov/) and the Health Canada Clinical Trials Database (https://health-products.canada.ca/ctdb-bdec/index-eng.jsp) to identify in-progress and completed studies.

3.5.3 Other searches

We will search the reference lists of included primary studies to identify additional relevant studies. We will also contact subject matter experts in Canada and the United States to assess whether any relevant studies are in-progress ahead of publication.

3.6 Data collection

3.6.1 Data management

We will use the DistillerSR (Evidence Partners) secure web-based platform for managing citations during screening, data extraction, and quality assessment.

3.6.2 Selection of studies

Title and abstract as well as full-text screening forms will be developed and piloted using a subset of primary studies. Four reviewers will independently screen the titles and abstracts of every record retrieved (two reviewers per record), to determine which records should be assessed in a full-text review. Disagreements will be resolved through a third reviewer. Citations which meet the above inclusion/exclusion criteria (or those for which it is unclear) at title/abstract will be selected for full-text review. Four reviewers will then independently review full-text records for inclusion (two reviewers per record), with disagreements resolved by a third reviewer. Multiple reports (duplicate, overlapping, or companion reports) of the same study will be linked during full-text review. Results of the study selection will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

3.6.3 Data extraction

A data extraction form will be developed and piloted using a subset of primary studies. Two reviewers working independently will extract data from the primary studies. When consensus on data extraction is not reached through discussion between two reviewers, disagreements will be resolved through a third reviewer. We will follow-up with study authors for clarification as necessary. The extracted data will be presented in tables (e.g. a 'Characteristics of included studies' table). We will follow-up with study authors for clarification as necessary. Studies excluded at the full-text screening phase and the reasons for exclusion will be listed in a table. See Appendix 3 for a list of extracted data items.

Data on study characteristics
We will extract data on the study characteristics including: study design, exposures, study years, number of enrolled participants, number of participants included in analyses, duration of follow-up, and loss to follow-up.

Data on participants
We will extract data on participants including: age, sex, gender, sexual orientation, sex of sex partners, and type/frequency of sex acts.

Data on exposures and effect modifiers
We will extract data on the exposures and effect modifiers including: type of ART, timing of ART initiation, ART adherence, duration of ART, frequency of viral load testing, frequency of CD4 testing, limit of detection of viral load assay, type of assay used, viral load of HIV-positive sex partner at time of transmission, frequency of HIV testing in HIV-negative sex partner, presence of STIs, frequency of STI testing, stage of HIV infection, and level of condom use.

Data on outcomes

We will extract data on the outcomes including: incidence of HIV transmission per person-years, incidence of HIV transmission per sex act, incidence of HIV transmission by type of sex, number of incident HIV transmissions, number of HIV-positive partners on ART, person-years of follow-up on ART, time from ART initiation to HIV transmission, whether HIV transmission was genetically linked to index partner, and direction of transmission.

Data on settings

We will extract data on the study settings including: local setting(s) of the study and country(s).

3.7 Assessment of methodological quality of included studies

3.7.1 Risk of bias assessment (See '3.9 Amendment to update protocol (June 7, 2017)')

Two reviewers will independently assess the quality of included studies with the standard tools used by Supervie et al. (14) and Loutfy et al. (15): Cochrane Risk of Bias (ROB) tool for randomized studies (17) and the Newcastle-Ottawa Scale (NOS) (18).The ROB tool assesses six domains of bias in randomized studies: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias (17). The NOS tool employs a 'star system' to assess nonrandomized studies across three domains: the selection of the study groups, the comparability of the study groups, and the ascertainment of the outcome of interest (18). Disagreements on independently completed quality assessments will be resolved through discussion or through a third reviewer when consensus is not reached through discussion between two reviewers.

3.7.2 Assessment of reporting biases

As we were interested in collecting data on absolute HIV transmission risk, as opposed to relative risk, we are unable to assess publication bias using graphical methods, such as a funnel plot. We sought to minimize the potential for publication bias by increasing the sensitivity of the published search terms by Supervie et al. (14), searching trial registries, and contacting experts for unpublished trials and studies. Also, we will assess and report on the potential for publication bias in our body of evidence based on factors such as the comprehensiveness of the search (for published, in progress, and unpublished reports) and the inclusion of studies of varying sizes, as part of our quality assessment (see amendment to update protocol (June 7, 2017)).

3.8 Data analysis (See '3.10 Amendment to update protocol (June 27, 2017)')

We will present a narrative synthesis of the results obtained from the included primary studies, which will be incorporated into the synthesis of relevant past systematic reviews identified in the overview of reviews. Data will be presented in tables and figures (e.g. a 'Summary of study findings' table). We will also summarize the quality of these included studies in tables. Where possible, we will report on the absolute risks of HIV transmission between serodiscordant sex partners associated with the sex acts outlined in previous sections, including direction of

transmission. We will describe the strength of the body of evidence on each outcome, considering the methodological quality of the included studies.

3.9 Amendment to update protocol (June 7, 2017)

The Cochrane ROB tool for randomized studies and the Newcastle-Ottawa Scale (NOS) were initially selected to assess included study quality, based on their previous use in Supervie et al. and Loutfy et al. (14,15). However, upon consultation with subject matter experts we concluded that although the use of these same tools would allow us to adopt the methodologies of previous reviews, they are not the ideal risk of bias assessment tools for our specific key questions. Given that our key questions are, in essence, prognostic questions (e.g. how often do transmissions happen while on ART?) as opposed to comparative questions (e.g. how many fewer transmissions occur while on ART versus while not on ART?), these aforementioned assessment tools are not appropriate. We will assess risk of bias in all of our included studies using the Quality in Prognosis Studies (QUIPS) tool (19).

The QUIPS tool assesses bias based on six key domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each of these domains is rated as low, moderate, or high risk of bias based on a number of criteria (19). Based on the six domains, each study is also given an overall risk of bias assessment (low, moderate, or high) (19). Two reviewers will independently assess the quality of included studies using the QUIPS tool, and disagreements on independently completed quality assessments will be resolved through discussion or through a third reviewer when consensus is not reached through discussion between two reviewers.

3.9.1 Assessment of quality of evidence across studies

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence for our outcome (absolute HIV transmission risk) across the body of evidence (20). We selected absolute HIV transmission risk as the outcome in consultation with the Canadian Federal Department of Justice, as it was viewed as essential for making sound public health and prosecutorial recommendations. We will follow GRADE for prognostic studies (21) because our review estimates the risk of future HIV transmission events in a broadly defined population.

GRADE is a system for assessing the certainty or confidence in the evidence regarding, in this case, absolute HIV transmission. Certainty is rated as high, moderate, low or very low and is synonymous with quality of the evidence arising from the body of eligible studies. In making inferences regarding prognosis, observational studies, including single arms of randomized controlled trials, start as high quality evidence (21). Using the GRADE approach, five domains were considered for rating down confidence in the estimates of transmission risk: risk of bias, inconsistency, imprecision, indirectness, and publication bias. We will consider the GRADE criteria for rating up confidence in prognostic estimates (e.g., whether a dose-response gradient exists). The balance of these ratings will allow us to assess the quality of the evidence and

whether our certainty in the reported HIV transmission risks should be high, moderate, low or very low (20). We will use GRADEpro GDT software (https://gradepro.org/) to assign a quality level of evidence around the data extracted and generate evidence profiles and summary of findings tables in Microsoft Word 2010.

GRADE assessments will be completed independently by two reviewers. Assessments will be reviewed for consistency by the two reviewers. Conflicts will be resolved through discussion with a third reviewer when consensus is not reached through discussion between the two reviewers.

3.10 Amendment to update protocol (June 27, 2017)

A narrative synthesis was initially planned, but upon reviewing the initial evidence obtained in the review, and consulting with experts in statistical analysis, we will instead produce pooled estimates and present the data using forest plots.

3.10.1 Data analysis

We will calculate incidence of HIV transmission per 100 person-years in situations where included studies do not explicitly report a desired outcome but provided sufficient information to calculate point estimates (e.g. number of transmissions, person-years of follow-up). We will calculate 95% confidence intervals (CI) using the exact Poisson method (22). We will denote values calculated by the research team in our results. We performed all analyses using SAS Enterprise Guide 5.1 (SAS Institute). For each key question, where more than one cohort study is available, we will pool the data to calculate an overall absolute risk estimate (i.e. pooled incidence rate). Since we are interested in only the absolute risk of transmission we use the sum total of events divided by the sum total number of person years to calculate the overall pooled absolute risk estimate (23). We will use the exact Poisson method (22) to calculate the confidence interval for the pooled incidence estimate. All pooled analyses will be presented with exact 95% CIs in forest plots created in Microsoft Excel (24). Given that we are assessing absolute risk, as opposed to comparisons between groups, we will assess statistical heterogeneity visually with the forest plots and as part of the ‘inconsistency’ criterion of the GRADE assessment of the evidence. In addition, we will explore potential reasons for small variations in estimates between studies due to factors such as study design and participant characteristics in the discussion.

APPENDIX 1. Description of the original systematic review search strategy

The following description of the search strategy is published in the supplementary material accompanying the systematic review by Supervie et al. (14):

“A comprehensive and systematic literature search was conducted in PubMed Medline, Embase, Cochrane Library and Web of Science databases using MeSH terms and relevant keywords. We adopted a search strategy similar to that reported by Anglemyer et al. (2013), a recent Cochrane review regarding the effectiveness of antiretroviral therapy in preventing HIV transmission among HIV-discordant couples. The code that we used for our Pubmed Medline search contained three key items #1-3, each of them having a precise focus.

Item #1 focused on finding papers about antiretroviral therapy, item #2 on finding papers about sexual partnership, and item #3 on finding papers about HIV. We created an item #4 which combines the previous three and yields the search results. The search code is as follows.

#1 Search (HAART[title/abstract] OR ART[title/abstract] OR ARV[title/abstract] OR ARVs[title/abstract] ORantiretroviral[title/abstract] OR anti-retroviral[title/abstract] OR anti-viral[title/abstract] OR antiviral[title/abstract] OR \Antiretroviral Therapy, Highly Active"[Mesh] OR \Anti-Retroviral Agents"[Mesh])

#2 Search (Couples[title/abstract] OR (sex*[title/abstract] AND partner*[title/abstract]) OR husband[title/abstract] OR wife[title/abstract] OR boyfriend*[title/abstract] OR girlfriend*[title/abstract] OR spouse*[title/abstract] OR dyad*[title/abstract] OR married[title/abstract] OR marital[title/abstract] OR \Marriage"[Mesh] OR \Spouses"[Mesh] OR serodiscord*[title/abstract] OR sero-discord*[title/abstract] OR discord*[title/abstract])

#3 Search (HIV Infections[MeSH] OR HIV[MeSH] OR hiv[title/abstract] OR hiv-1[title/abstract] OR hiv-2*[title/abstract] OR hiv1[title/abstract] OR hiv2[title/abstract] OR hiv infect*[title/abstract] OR human immunodeficiency virus[title/abstract] OR human immune deficiency virus[title/abstract] OR human immuno-deficiency virus[title/abstract] OR human immune-deficiency virus[title/abstract] OR ((human immun*) AND (deficiency virus[title/abstract])) OR acquired immunodeficiency syndromes[title/abstract] OR acquired immune deficiency syndrome[title/abstract] OR acquired immuno-deficiency syndrome[title/abstract] OR acquired immune-deficiency syndrome[title/abstract] OR ((acquired immun*[title/abstract]) AND (deficiency syndrome[title/abstract])) OR \sexually transmitted diseases, viral"[mh] OR HIV[title/abstract] OR HIV/AIDS[title/abstract] OR HIV-infected[title/abstract])

#4 Search (#1 AND #2 AND #3)

The above search strategy was adapted accordingly for the Embase, Cochrane Library and Web of Science databases. There were no restrictions on study design, publication date, type, status or language. Reference lists of articles retrieved as well as previously published systematic reviews (Attia et al. (2009); Baggaley et al. (2013); Loutfy et al. (2013); Anglemyer et al. (2013); Wang et al. (2012)) were scanned for additional relevant articles. Abstracts from

conferences (IAS Conference on HIV Pathogenesis, Treatment and Prevention 2001-2013, Conference on Retroviruses and Opportunistic Infections 1993-2013, International AIDS Conference 1985-2012, were also searched."

APPENDIX 2. Search strategy for update

Update search strategy used in MEDLINE (modified for use in EMBASE, Web of Science, and Cochrane Library as necessary) executed April 19th and 27th, 2017. Additions to Supervie et al.'s search strategy are highlighted in yellow:

#	Searches
1	antiretroviral therapy, highly active/ or exp anti-retroviral agents/
2	(haart or art or arv or arvs or antiretroviral or anti-retroviral or antiviral or anti-viral).ti,ab.
3	1 or 2
4	marriage/ or spouses/ or sexual partners/ or exp sexual minorities/ or exp sexual behavior/ or exp sexuality/
5	(couple* or (sex* and partner*) or husband* or wife or wives or boyfriend* or girlfriend* or spouse* or dyad* or married or marital or serodiscord* or sero-discord* or discord* or "men who have sex with men" or ?msm or msom or mswm or "women who have sex with women" or ?wsw or wswm or intercourse or coitus or homosexual* or heterosexual* or bisexual* or transsexual* or "gay men" or lesbian* or intersex* or transgender* or LGBT* or "casual partner*").ti,ab.
6	(sex* adj3 (behavio?r* or activit* or oral* or anal* or vaginal* or minorit*)).ti,ab.
7	4 or 5 or 6
8	exp hiv infections/ or exp hiv/ or sexually transmitted diseases, viral/
9	(hiv or hiv-1* or hiv-2* or hiv1 or hiv2 or hiv infect* or "human immunodeficiency virus*" or "human immune deficiency virus*" or "human immuno-deficiency virus*" or "human immune-deficiency virus*" or ("human immun*" and "deficiency virus*") or "acquired immunodeficiency syndrome*" or "acquired immune deficiency syndrome*" or "acquired immuno-deficiency syndrome*" or "acquired immune-deficiency syndrome*" or ("acquired immun*" and "deficiency syndrome*") or hiv?aids or hiv-infected).ti,ab.
10	8 or 9
11	3 and 7 and 10
12	(201308* or 201309* or 20131* or 2014* or 2015* or 2016* or 2017*).dc.
13	11 and 12
14	remove duplicates from 13
15	(201211* or 201212* or 201301* or 201302* or 201303* or 201304* or 201305* or 201306* or 201307*).dc.
16	11 and 15
17	Remove duplicates from 16

Update search strategy used in MEDLINE (modified for use in EMBASE, Web of Science, and Cochrane Library as necessary) executed April 27th, 2017 to include additional terms highlighted in yellow:

#	Searches
1	antiretroviral therapy, highly active/ or exp anti-retroviral agents/
2	(haart or art or arv or arvs or antiretroviral or anti-retroviral or antiviral or anti-viral).ti,ab.
3	1 or 2
4	marriage/ or spouses/ or sexual partners/ or exp sexual minorities/ or exp sexual behavior/ or exp sexuality/
5	(couple* or (sex* and partner*) or husband* or wife or wives or boyfriend* or girlfriend* or spouse* or dyad* or married or marital or serodiscord* or sero-discord* or discord* or "men who have sex with men" or ?msm or msom or mswm or "women who have sex with women" or ?wsw or wswm or intercourse or coitus or homosexual* or heterosexual* or bisexual* or transsexual* or "gay men" or lesbian* or intersex* or transgender* or LGBT* or "casual partner*").ti,ab.
6	(sex* adj3 (behavio?r* or activit* or oral* or anal* or vaginal* or minorit*)).ti,ab.
7	4 or 5 or 6
8	exp hiv infections/ or exp hiv/ or sexually transmitted diseases, viral/
9	(hiv or hiv-1* or hiv-2* or hiv1 or hiv2 or hiv infect* or "human immunodeficiency virus*" or "human immune deficiency virus*" or "human immuno-deficiency virus*" or "human immune-deficiency virus*" or ("human immun*" and "deficiency virus*") or "acquired immunodeficiency syndrome*" or "acquired immune deficiency syndrome*" or "acquired immuno-deficiency syndrome*" or "acquired immune-deficiency syndrome*" or ("acquired immun*" and "deficiency syndrome*") or hiv?aids or hiv-infected).ti,ab.
10	8 or 9
11	3 and 7 and 10
12	(201211* or 201212* or 2013* or 2014* or 2015* or 2016* or 2017*).dc.
13	11 and 12
14	antiretroviral therapy, highly active/ or exp anti-retroviral agents/
15	(haart or art or arv or arvs or antiretroviral or anti-retroviral or antiviral or anti-viral).ti,ab.
16	(antiretroviral* or cart).ti,ab.
17	14 or 15 or 16
18	marriage/ or spouses/ or sexual partners/ or exp sexual minorities/ or exp sexual behavior/ or exp sexuality/
19	(couple* or (sex* and partner*) or husband* or wife or wives or boyfriend* or girlfriend* or spouse* or dyad* or married or marital or serodiscord* or sero-discord* or discord* or "men who have sex with men" or ?msm or msom or mswm or "women who have sex with women" or ?wsw or wswm or intercourse or coitus or homosexual* or heterosexual* or bisexual* or transsexual* or "gay men" or lesbian* or intersex* or transgender* or LGBT* or "casual partner*").ti,ab.
20	(sex* adj3 (behavio?r* or activit* or oral* or anal* or vaginal* or minorit*)).ti,ab.
21	((sex* adj3 casual*) or (monogam* or "gay m#n")).ti,ab.
22	18 or 19 or 20 or 21
23	exp hiv infections/ or exp hiv/ or sexually transmitted diseases, viral/
24	(hiv or hiv-1* or hiv-2* or hiv1 or hiv2 or hiv infect* or "human immunodeficiency virus*" or "human immune deficiency virus*" or "human immuno-deficiency virus*" or "human immune-deficiency virus*" or ("human immun*" and "deficiency virus*") or "acquired immunodeficiency syndrome*" or "acquired immune deficiency syndrome*" or "acquired immuno-deficiency syndrome*" or "acquired immune-deficiency syndrome*" or ("acquired immun*" and "deficiency syndrome*") or hiv?aids or hiv-infected).ti,ab.
25	23 or 24
26	17 and 22 and 25
27	(201211* or 201212* or 2013* or 2014* or 2015* or 2016* or 2017*).dc.
28	26 and 27
29	28 not 13

Appendix 3. List of extracted data items for update

Criteria	Extracted items	
Study characteristics	• Study design • Interventions • Study years • Number of enrolled participants	• Number of participants included in analyses • Duration of follow-up • Loss to follow-up
Participants	• Age • Sex • Gender	• Sexual orientation • Sex of sex partners • Type/frequency of sex acts
Exposures and effect modifiers	• Type of ART • Timing of ART initiation • ART adherence • Duration of ART • Frequency of viral load testing • Frequency of CD4 testing • Limit of detection of viral load assay • Type of assay used	• Viral load of HIV-positive sex partner at time of transmission • Frequency of HIV testing in HIV-negative sex partner • Presence of STIs • Frequency of STI testing • Stage of HIV infection • Level of condom use
Outcomes	• Incidence of HIV transmission per person-years • Incidence of HIV transmission per sex act • Incidence of HIV transmission by type of sex • Number of incident HIV transmissions	• Number of couples on ART • Person-years of follow-up on ART • Time from ART initiation to HIV transmission • Whether HIV transmission was genetically linked to index partner • Direction of transmission
Settings	• Local setting(s) of the study and country(s)	

APPENDIX 4. Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist for update of systematic reviews

Section and topic	Item No.	Checklist item	Line number
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Not registered, line 8
Authors			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Government of Canada, line 10-13
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	N/A
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	17-35, 344-413
Support			
Sources	5a	Indicate sources of financial or other support for the review	39-41
Sponsor	5b	Provide name for the review funder and/or sponsor	39-41
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	39-41
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	81-105
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	111-117, 133-142
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study	180-236, Table 1

		design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	237-266
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	237-247, 457-466
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	268-270
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	271-281
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	282-290
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	291-311, Appendix 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	304-309, Table 1
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	344-363
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	391-394
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any	396-413

		planned exploration of consistency (such as I2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	325-333
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	364-389

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