Appendix 1 (as submitted by the authors):
Protocol:
Part I – 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: April 2017
Amended: 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 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 sexual transmission risk of HIV under various scenarios that protect against HIV transmission, further defined below.

This document outlines the protocol for the first stage of our evidence synthesis, which will consist of conducting an overview of systematic reviews and meta-analyses (hereinafter 'overview').

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

3 METHODS

This overview is being conducted to identify existing synthesized evidence on HIV transmission risks and identify candidate systematic reviews that may be eligible to update in order to capture more recent primary studies on HIV transmission risks.

3.1 Key questions

What are the absolute risks of HIV transmission associated with sex[2], when the following preventive measures are taken to reduce the risk of transmission between an HIV-positive and HIV-negative sex partner:

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

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 (1-5).

[2] We will define sex to include unspecified sex acts (any type of sex act(s)), 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 reviews (e.g. vaginal-vaginal sex, penile-penile sex) we will also include them.

[3] 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.

[4] '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.

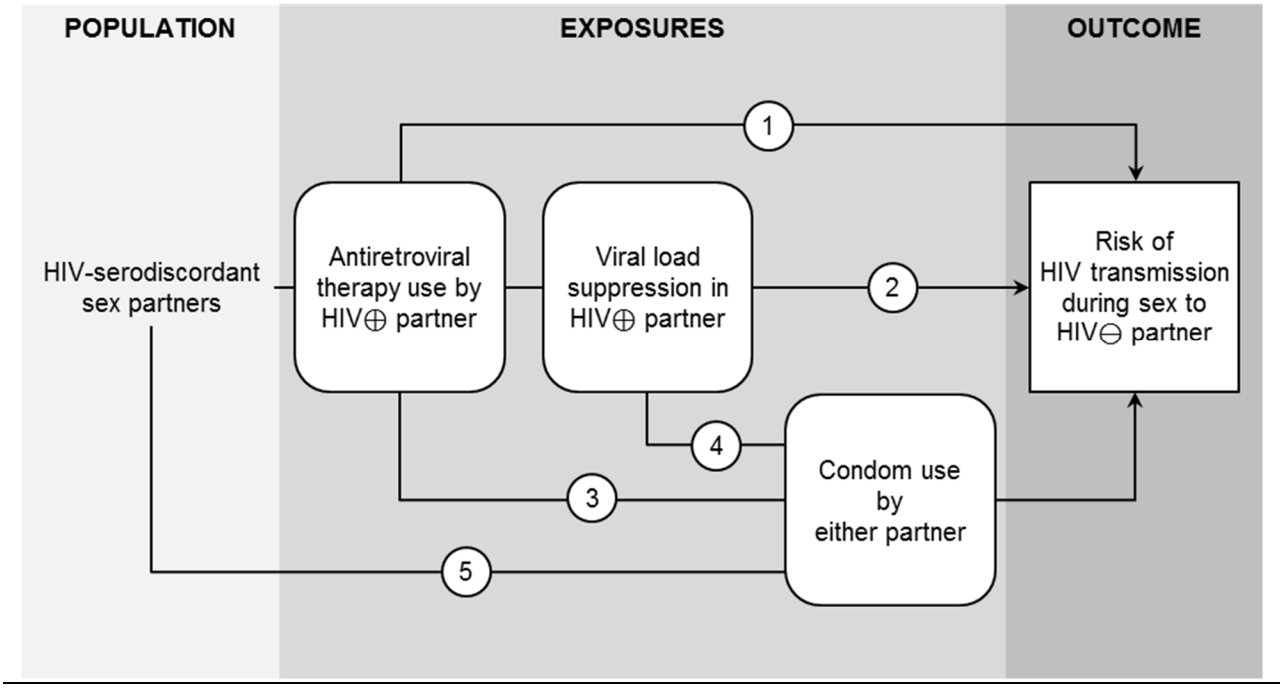

Figure 1. Analytic framework illustrating scenarios where preventive measures are taken to reduce the risk of transmission between HIV-serodiscordant sex partners. The numbers in the corresponding pathways illustrate the risk of HIV transmission to the HIV-negative (HIV⊖) partner during sex when ① the 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; ⑤ either partner uses condoms or other barrier methods alone.

3.3 Criteria for selecting systematic reviews and meta-analyses for this overview

This overview will adhere to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions (10). The study protocol has been developed to align with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (11). A summary of criteria for selecting systematic reviews and meta-analyses is outlined in **Table 1.**

3.3.1 Types of reviews

We will include systematic reviews and meta-analyses that were based on a comprehensive review of the literature, as determined per the third 'A Measurement Tool to Assess Systematic Reviews' (AMSTAR) criterion "Was a comprehensive literature search performed?" (12). Systematic reviews and meta-analyses that do not meet the aforementioned AMSTAR criterion will be excluded. We will exclude editorials and commentaries.

3.3.2 Types of participants

We will include systematic reviews and meta-analyses that include HIV-serodiscordant sex partners, where one individual is seropositive for HIV while the other is seronegative for HIV regardless of the type of partnership (e.g. same-sex) or relationship (e.g. casual, short-term, not exclusively monogamous). We will exclude systematic reviews and meta-analyses 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.

3.3.4 Types of exposures

We will include systematic reviews and meta-analyses that include 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. We will also include condom use alone (or other barrier method) by either partner. 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 “viral suppression” according to the detection limit of the assays used in the systematic reviews. 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 systematic review. We will describe the modifying effect of stage of disease and co-infection with other sexually transmitted infections (STIs). We will exclude systematic reviews and meta-analyses on 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).

3.3.5 Types of comparators and outcomes

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]. 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 reviews (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, and risk of HIV transmission from occupational exposure.

Table 1. Summary of criteria for selecting reviews

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); KQ4. the HIV-positive sex partner takes ART and has a suppressed viral load, and either partner uses condoms (or other barrier methods); and KQ5. 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 sex 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 condoms (or other barrier methods) by either 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 antiretroviral medication as pre-exposure or post-exposure prophylaxis (PrEP or PEP) • 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	• Systematic reviews and meta-analyses	• Reviews and meta-analyses not based on comprehensive literature review • Editorials • Commentaries
Language	• English or French	• Other languages
Publication dates	• 2007 to 2017 • Where a review published between 2007 and 2017 reports a meta-analysis outcome from a systematic review published prior to 2007 without updating the analysis, the original review will be included.	

3.4 Search methods for identification of reviews

Our search strategy was designed with the assistance of a Health Canada research librarian and peer-reviewed by two additional Health Canada research librarians. We will use the search terms included in Appendix 1.

3.4.1 Electronic search

We will search the following electronic databases, from 01 January 2007 to 13 March 2017:

- MEDLINE
- EMBASE
- Global Health
- Cochrane Library

3.4.2 Systematic review registries

We will search PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) and the Cochrane Library to identify potentially relevant unpublished or in-progress reviews.

3.4.3 Other searches

We will search the reference lists of included systematic reviews and meta-analyses to identify additional relevant reviews. Where a review published between 2007 and 2017 reports a meta-analysis outcome from a systematic review published prior to 2007 without updating the analysis, the original systematic review will be included if it meets our inclusion criteria. We will contact subject matter experts in Canada and the United States to assess whether any relevant studies are in-progress ahead of publication.

3.5 Data collection

3.5.1 Data management

We will upload our records into the DistillerSR (Evidence Partners) internet-based systematic review software. This software platform will be used during the screening of eligible systematic reviews and meta-analyses (hereinafter ‘reviews’), data extraction, and quality assessment.

3.5.2 Selection of reviews

Title and abstract as well as full-text screening forms will be developed and piloted using a subset of reviews. Four reviewers will independently screen the titles and abstracts of every record retrieved (two reviewers per record) to determine which reviews should be assessed in a full-text review. We will retrieve all potentially relevant records for full-text review. Disagreements will be resolved through a third reviewer. Four reviewers will then independently review full-text records for inclusion (two reviewers per record), with disagreements resolved by a third reviewer. Results of the review selection will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

3.5.3 Data extraction

A data extraction form will be developed and piloted using a subset of reviews. Two reviewers working independently will extract data from the reviews. 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 reviews' table). Systematic reviews and meta-analyses excluded at the full-text screening phase and the reasons for exclusion will be listed in a table. See Appendix 2 for a list of extracted data items.

Data on study characteristics

We will extract data on the review characteristics including: type of review, included study designs, settings, exposures, study years, number of participants, and duration of 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 (monotherapy or combination), 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, 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).

3.6 Assessment of methodological quality of included reviews

3.6.1 AMSTAR assessment

Two reviewers will independently assess the quality of included systematic reviews and meta-analyses using the AMSTAR assessment tool (12). Disagreements will be resolved through a third reviewer when consensus is not reached through discussion between two reviewers.

Ideally, the assessment of meta-biases (e.g. publication bias) will have been performed by the authors of the reviews included in this overview. Whether or not an analysis of publication bias was performed in the included systematic reviews is an element of the AMSTAR assessment, and will be taken into account as part of our assessment of included study quality. The AMSTAR assessment tool also takes into account other criteria related to study quality and reporting, including whether there was an 'a priori' design, duplicate study selection and data extraction, comprehensive search strategy, description of included studies, assessment and

consideration of scientific quality of included studies, appropriate methodology for combining study results, and statement on conflicts of interest. We will describe the methodological quality of the included systematic reviews and meta-analyses.

In order to select reviews that are eligible for a systematic review update, we will consider whether the reviews had a published recent comprehensive search strategy that can be replicated, had defined inclusion criteria for study selection, and was of high methodological quality.

3.7 Data analysis

We will present a narrative synthesis of the results obtained from the included systematic reviews and meta-analyses. We will summarize the quality of the included reviews and the manner and extent to which they provide data to inform each of the key questions. Data will be presented in tables and figures (e.g. an ‘Overview of reviews’ table).

APPENDIX 1. Search strategy for overview

Overview search strategy used in MEDLINE (modified for use in EMBASE, Global Health, and Cochrane Library as necessary) executed on March 13th, 2017:

#	Searches
1	exp *HIV/
2	exp *HIV Infections/
3	*HIV Seropositivity/ or HIV Infections/tm [Transmission]
4	(hiv or hiv+ or hiv-1 or hiv-2 or hiv1 or hiv2 or hiv?aids or (human immun* adj2 virus)).ti.
5	1 or 2 or 3 or 4
6	disease transmission, infectious/ or seroconversion/
7	risk factors/ or risk assessment/ or Risk-Taking/
8	((risk* or probabilit* or likel* or incidence*) adj3 (transmi* or infect* or spread* or contract* or acquir* or factor* or assess* or analy* or per-act? or contact* or sero*)).tw,kf.
9	6 or 7 or 8
10	exp meta-analysis as topic/ or Review Literature as Topic/
11	meta-analysis/
12	(meta analy* or metaanaly* or (systematic* adj2 (review* or overview*))).tw,kf.
13	10 or 11 or 12
14	5 and 9 and 13
15	14 not (animals/ not humans.sh.)
16	limit 15 to (english or french)
17	16 and 2007:2017.(sa_year).
18	remove duplicates from 17

APPENDIX 2. List of extracted data items for overview

Criteria	Extracted items	
Study characteristics	• Type of review • Included study designs • Interventions	• Study years • Number of participants • Duration of follow-up
Participants	• Age • Sex • Gender	• Sexual orientation • Sex of sex partners • Type/frequency of sex acts
Exposures and effect modifiers	• Type of antiretroviral therapy (ART; monotherapy or combination) • 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 • Viral load of HIV-positive sex partner at time of transmission	• Frequency of HIV testing in HIV-negative sex partner • Presence of sexually transmitted infections (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 3. Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist for overview

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	15-18, 22-25
Support			
Sources	5a	Indicate sources of financial or other support for the review	24-25
Sponsor	5b	Provide name for the review funder and/or sponsor	24-25
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	24-25
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	54-80
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	85-92, 98-108

Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	118-158, Table 1
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	160-179
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	248-251
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	181-184
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)	185-193
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	194-201
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	202-222, Appendix 2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	215-220, 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	224-227
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe	N/A

		planned summary measures, methods of handling data and methods of combining data from studies, including any 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	243-247
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	228-237
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A (see update protocol)

REFERENCES

(1) Public Health Agency of Canada. Summary: Measuring Canada's progress on the 90-90-90 HIV targets. 2016.

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(8) Government of Canada - Department of Justice Canada. Minister Wilson-Raybould issues statement on World AIDS Day. 2016; Available at: http://news.gc.ca/web/article-en.do?nid=1163979. Accessed 03/09, 2017.

(9) UNAIDS. UNAIDS terminology guidelines 2015. 2015; Available at: http://www.unaids.org/en/resources/documents/2015/2015_terminology_guidelines.

(10) Higgins JPT, Green S editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. : The Cochrane Collaboration; 2011.

(11) Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;349:g7647.

(12) Shea BJ, Grimshaw JM, Wells GA, Boers MA, Hamel C, Porter AC, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7(1):10.