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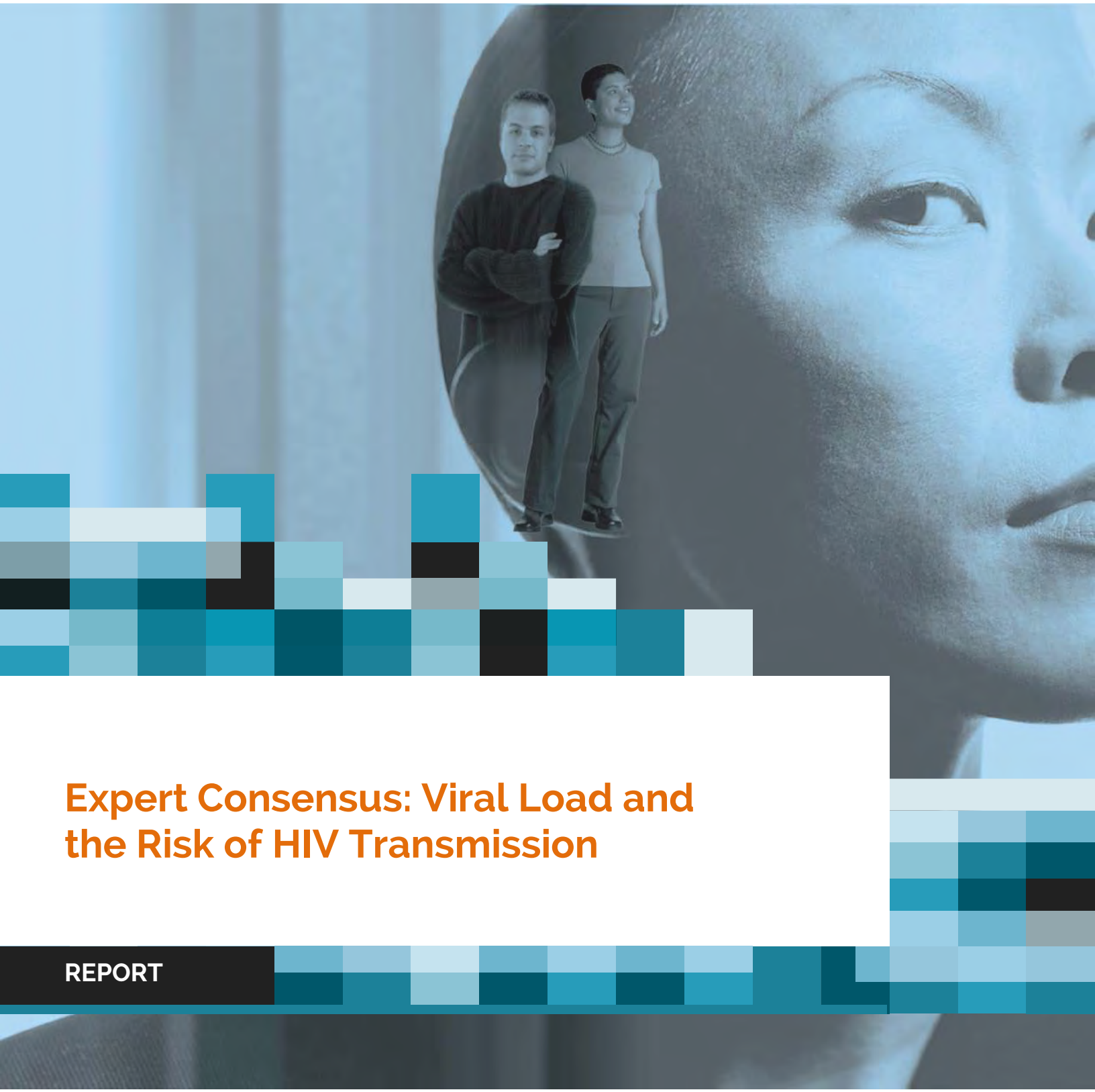

Expert Consensus: Viral Load and the Risk of HIV Transmission

REPORT

Québec

Expert Consensus: Viral Load and the Risk of HIV Transmission

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Direction des risques biologiques et de la santé au travail

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A more recent publication based on new studies has just been issued by the Ministère de la Santé et des Services sociaux. This update is titled «L'effet du traitement des personnes vivant avec le VIH sur le risque de transmission sexuelle de l'infection» (The impact of treating people living with HIV on the risk of sexual transmission of the infection) can be found here: http://publications.msss.gouv.qc.ca/msss/document-002173/ (french only)

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1 Background

In January 2013, the Service de lutte contre les ITSS (SLITSS) [Department of the battle against STBBIs] of the Ministère de la Santé et des Services sociaux (MSSS) [Ministry of health and social services] of Québec asked the Comité sur les infections transmissibles sexuellement et par le sang (CITSS) [Committee on sexually transmitted and blood-borne infections – STBBIs Committee] of the Institut national de santé publique du Québec (INSPQ) [Québec's national institute for public health] to assess the effect of an undetectable viral load on the risk for HIV transmission. The purpose of the request was to support updating the tool *Estimation du risque associé aux activités sexuelles* [Estimated risk associated with sexual practices],[1] a resource designed to guide risk-reduction counselling [1]. An additional aim of this request was to support the assessment of STBBI reports according to section 95 of Québec's *Public Health Act*.

The CITSS was asked the following questions:

- Can you more clearly define the expression "undetectable viral load" (e.g., clinical value; undetectable period; in blood, semen, and other bodily fluids)?
- Which factors could make the viral load detectable again (e.g., presence of an STBBI, treatment adherence)?
- What is the effect of undetectable viral load on the transmission risks associated with condomless oral, vaginal, and anal sex?
- Is the transmission risk similar, greater, or lower for the above-mentioned sexual practices when protected with a condom?

These questions were asked as part of a risk-reduction approach in light of recent major scientific advances concerning the influence of antiretroviral therapy (ART) on HIV transmission risk.

[1] http://publications.msss.gouv.qc.ca/acrobat/f/documentation/2013/13-308-14W.pdf.

2 Methodology

A review of the literature in PubMed on the risk of HIV transmission during oral, vaginal, and anal intercourse and the effect of undetectable viral load on transmission risk was conducted using the following keywords: (HIV) AND (viral load OR undetectable viral load*)* AND (risk of transmission OR transmission) AND (oral sex OR vaginal sex OR anal sex OR sex OR heterosexual OR homosexual OR MSM). Various searches were performed using this sequence. To complete the literature review, the bibliographic references of the selected articles were also searched and the partners were consulted. For each article, information that was relevant to the project was identified and data quality was assessed.

The extracted data were discussed and analyzed by an expert subcommittee. This initial analysis enhanced the information and culminated in a written report submitted to the CITSS of the INSPQ. The present expert consensus was then reached and adopted. The CITSS adopted the report on November 11, 2013.[2] Appendix 1 presents a list of the CITSS members for year 2013–2014 who contributed to the work and adopted the report.

2.1 Assessment of the evidence

The criteria for **assessing the evidence** were inspired by those used by the US Preventive Service Task Force (USPSTF) [2] and by the *Comité consultatif sur la prise en charge clinique des personnes vivant avec le VIH* [Advisory committee on the clinical management of people living with HIV-AIDS] [3]. They are applied here to indicate the scientific value of the advocated position.

- **I (High)**: The research methodology is robust, as with, for example, randomized trials. The samples are representative of the population. There is low probability that the results will be contradicted by future studies.
- **II (Moderate/Low)**: The data allow estimating effects on health, but their validity and reliability are affected by methodological limitations, as found in population, observational, and case studies. The conclusions could be affected by further advances in knowledge.
- **III (Expert opinion)**: In the absence of conclusive evidence, or in the presence of conflicting data, recommendations are based on the opinions of experts in the field.

2.2 Risk assessment categories

In order to provide a framework for **assessing the HIV transmission risk** for oral, vaginal, and anal sex, we have used the categories proposed by the Canadian AIDS Society (CAS) [4] and used in the MSSS table *Estimation du risque associé aux activités sexuelles*[3] [1].

- **No Risk**: To our knowledge, there is no conclusive evidence that any practice in this category has led to HIV transmission. There is no risk of transmission because the following basic conditions are not met: a source of infection, means of transmission, a host susceptible to infection, a route for HIV to reach cells targeted by HIV, and sufficient quantity of virus for transmission to occur.

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[2] N.B.: Although Public Health Agency of Canada (PHAC) contributed to the efforts of the expert subcommittee, it preferred to abstain from adopting the report. PHAC intends to await the results of further studies before taking a position on the report's conclusions.

[3] Please note that this table is currently under review. Some categories are subject to change in future revisions.

- **Negligible or Very Low Risk**: This category does not indicate a complete absence of risk. All activities in this category carry some potential for HIV transmission. Transmission risk is associated with the exchange of bodily fluids (semen, pre-ejaculate, vaginal secretions, blood, or breast milk). However, the small quantities of bodily fluid or virus as well as the medium of exchange act to greatly reduce transmission risk.
- In their review, the CITSS found only one reported case where HIV was transmitted when the viral load was determined to be undetectable. However, the validity of this case was subsequently called into question in the literature.
- **Low Risk**: All activities in this category carry some risk for HIV transmission. Transmission risk is associated with the exchange of bodily fluids (semen, pre-ejaculate, vaginal secretions, blood, or breast milk). Cases of infection attributed to these practices have generally been reported in case studies or anecdotal reports, and they occurred in very specific conditions.
- **High Risk**: All the practices in this category carry a high risk of HIV transmission. Transmission risk is associated with the exchange of bodily fluids (semen, pre-ejaculate, vaginal secretions, blood, or breast milk). Numerous studies have repeatedly established a link between these practices and HIV infection. Even in cases where the specific transmission mechanism remains unclear, the results lead us to conclude that these are high-risk practices.

These categories include certain limitations:

- The risk categorization depends on the quality of the studies on the topic and the statistical power of the results.
- The use of categories does not allow assessing the risk on a continuous scale. Consequently, within a single category, certain practices may be more risky than others.
- The terms used to categorize the risks may be interpreted and understood differently by different people. It is therefore essential to apply these definitions judiciously so as to fully grasp the risks for the sexual behaviors assessed in this document. For example, a negligible or low risk does not mean zero risk.

3 Viral load

The viral load refers to the number of viral copies of the HIV RNA strands per millilitre (mL), and is usually measured in the plasma. There is a strong correlation, albeit imperfect, between the plasma viral load and the viral load measured in vaginal and rectal secretions. Generally, the quantity of RNA virus copies present in the plasma is related to the quantity found in genital and rectal secretions. However, the quantity of viral copies found in genital and rectal secretions may be higher than that measured in the plasma, even if undetectable [5-10], particularly in the presence of cytomegalovirus or Epstein-Barr virus in the anogenital area [11].

3.1 Undetectable viral load

The definition of an undetectable viral load depends on the capacity of the testing kit used to detect and measure the virus, usually in the plasma [12].

The results of the diverse tests used must be interpreted with caution due to the different detection thresholds, which are determined by the manufacturers. Although the various tests are calibrated according to international standards set by the World Health Organization (WHO), they may differ significantly in terms of detection threshold. The detection threshold may also vary according to the HIV-1 genotype. Nevertheless, the differences in detection threshold between the various kits used in Québec are minor and nonsignificant [13].

In Québec, the test currently used to measure viral load is the Abbott RealTime HIV-1 Assay. According to the protocol used in Québec, the detection threshold, as specified by the manufacturer, is 40 copies/mL of HIV-1 RNA in the plasma. This assay kit could be improved in future to lower the viral load detection threshold.

3.2 Variations in viral load

In addition to normal slight fluctuations in the viral load, called “blips,”[4] certain factors are known to substantially influence the viral load so that it becomes detectable in the plasma or in genital and rectal secretions or tracts, even in persons living with HIV (PLHIV) who are on treatment. Among others, these factors include:

- The presence of another sexually transmitted or blood-borne infection (STBBI) [5, 7, 14]
- The type of ART [5, 7] and the extend to wich it penetrates the genital area [5]
- Suboptimal treatment adherence [3, 7]
- Viral resistance to treatment [7]
- Stage of the HIV infection [7].

No published studies to date have established the short- or long-term effects of a systemic infection such as cold, flu, or pneumonia on the viral load of a PLHIV and having undetectable viral load due to effective ART.

[4] During treatment, minor and transient viral increases called “blips” may be observed. Unlike a low-level persistent virus in the blood, these intermittent episodes are not associated with the viral mutations that enable viral resistance, and may simply reflect variations in test procedures. [Translated from the *Guide sur la thérapie antirétrovirale pour les professionnels du Québec.* A condensed version is available in the article, “Antiretroviral therapy for adults infected with HIV: Guidelines for health care professionals from the Québec HIV care committee”] [3].

3.3 Viral load and risk of HIV transmisison

The precise viral load threshold, measured in the plasma or in genital or rectal secretions or tracts, below which there is no transmission risk remains unknown. However, studies that assessed HIV transmission in terms of plasma viral load have demonstrated that a threshold of 1500 copies/mL in the plasma considerably is linked to a considerably reduced transmission risk [15]. The Rakai Health Sciences Program found no HIV transmission in couples that included a seropositive partner, even without treatment, when the viral load was below the two thresholds selected for the study: 400 copies/mL and 1500 copies/mL [15]. Two other studies found no cases of transmission for plasma viral load below 400 copies/mL in participants on ART [16, 17]. However, one case of transmission was reported in another study when the viral load was below 400 copies/mL, although the PLHIV was not on ART [18]. Other studies have shown no transmission from the seropositive partner to the other partner when the plasma viral load was undetectable, at below the 50 copies/mL threshold [18-22]. These findings are presented in detail in Appendix 2.

In Québec, the target for ART is to achieve a viral load of 50 copies/mL [3]. The criterion for optimally effective ART is to achieve an undetectable viral load. However, this threshold varies according to the sensitivity of the test kits used. ART has been demonstrated beneficial for both health [3] and prevention [16]. It is easier to maintain a low viral load when the initial viral load is below the 50 copies/mL threshold. Temporary fluctuations in viral load are also smaller because the infection is generally better controlled.

Other expert groups have retained a threshold of 50 copies/mL [6] or a similar threshold (40 copies/mL [14]) in position statements on viral load and the HIV transmission risk.

Textbox 1. Undetectable viral load

In this expert consensus, an undetectable viral load is defined as a threshold below 40 copies/mL or below the minimum quantification threshold in force in Québec.

In clinical terms, the viral load normally becomes undetectable after 16 to 24 months of treatment [3]. This should be maintained for at least 6 months, and on 2 consecutive measures, before concluding that the transmission risk is reduced [6]. These are the *sine qua non* conditions for all positions taken in this expert consensus.

4 Main findings of the literature review

The studies on the effect of ART and undetectable viral load on HIV transmission risk were conducted exclusively in heterosexual couples. These couples practised mainly vaginal intercourse. However, couples who had oral and/or anal sex were not excluded, although the proportions of couples who engaged in these practices were not specified in the participants' descriptions. The findings on HIV transmission risk are presented for heterosexual couples first, followed by the findings for men who have sex with men (MSM).

4.1 Heterosexual couples

All the reviewed studies underscored that ART can prevent HIV transmission. Appendix 3 presents the reviewed studies and their results on the effect of undetectable viral load or effective ART on transmission risk **mainly for vaginal intercourse**.

The Rakai study in Uganda [15], which followed 415 heterosexual couples for 30 months, and in which one partner is seropositive for HIV-1 and not necessarily on treatment, found no transmission between 51 couples when the viral load of the seropositive partner was below the threshold of 400 copies/mL or 1500 copies/mL. The authors concluded that viral load was the strongest predictive factor for heterosexual transmission, and that transmission risk was lower for viral load below 1500 copies/mL.

Ten years later, the randomized trial HPTN-052 [16] in 1763 serodiscordant couples (only one of the partners was HIV-1 seropositive) showed that ART was beneficial both clinically and for preventing HIV transmission. Their main research objective was to determine whether the treatment prevented HIV transmission. In all, 39 cases of HIV transmission were observed. Of these, 28 were confirmed as being transmitted within the couple. Of these 28 cases of transmission, only one occurred in the couples in which the infected partner was on precocious therapy (since the beginning of the study), which reduced the viral load. The other cases of transmission occurred in the control group, where the seropositive partner had not been treated to achieve the specified CD4 threshold (350-500 cells/mm). Moreover, a more detailed analysis revealed that the case of transmission in the group that was being treated since the beginning of the study occurred a short time (3 months) after the participant began ART, and before the first viral load measurement, suggesting that the treatment effect had not yet rendered the viral load undetectable. Finally, it is noteworthy that all participants received regular counselling on risk reduction, condom use, and treatment adherence, as well as regular medical follow-ups for STBBI screening and treatment.

A systematic literature review using Cochrane's approach [23] and a meta-analysis [24] also highlighted that effective antiretroviral treatment can prevent HIV transmission in serodiscordant couples. Transmission rates were considerably lower in groups that were on treatment. However, some transmission risk remains, underscoring the need to provide counselling on risk-reduction strategies.

The findings of another systematic literature review [22] suggest, based on six studies, that the minimum HIV transmission risk in serodiscordant heterosexual couples in which the seropositive partner has undetectable viral load due to ART is 0/100 person-years (95% CI = 0–0.01). This means that the lifetime risk of transmission from the seropositive to the seronegative partner varies from 1/200 to 1/500 person-years (0.2–0.5% lifetime risk, or 0.1% risk per 10 years of active sexual relations). Nevertheless, the researchers were unable to draw conclusions about specific sexual

practices, the presence of other STBBIs, or condom use. In fact, their literature review identified several limitations in estimating the transmission risk in terms of viral load (see section 4.4).

It is worth mentioning that in the reviewed studies, counselling on procuring and using condoms was included in the research protocol. Condom use rates varied from 35% to 96% for couples who reported using them *"regularly"* or *"always"* [16, 17, 19-21, 25]. The effectiveness assessment of condom use in reducing the HIV transmission risk is discussed in section 5.

The studies that found no transmissions have a number of points in common [15, 17, 18, 20-22, 26]. They were conducted in stable and exclusive heterosexual couples in which the seropositive partner was on effective ART with a confirmed undetectable viral load. This absence of transmission was found in studies where the following three conditions were met:

- Treatment adherence[5]
- Absence of STBBIs
- Regular medical follow-up and counselling, including guidelines for risk reduction and condom use.

With respect to **oral and anal intercourse**, the reviewed studies did not discriminate the results in terms of these sexual practices. Nor did they specify the proportion of respondents who reported practising them. Instead, estimates and expert opinions were proposed (Appendices 4 and 5). However, given that the risk associated with oral sex is lower than that for vaginal intercourse, which is lower in turn than that for anal intercourse [5], the risks would probably be in the same order for undetectable viral load.

The Public Health Agency of Canada (PHAC) has estimated the HIV transmission risk during unprotected vaginal intercourse or oral sex according to viral load (regardless of treatment) using Wilson et al.'s calculation method. Their estimates show that when the viral load is below 40 copies/mL, the HIV transmission risk would be 0.002% for insertive vaginal intercourse,[6] 0.005% for receptive vaginal intercourse[7] or insertive anal intercourse, and 0.069% for receptive anal intercourse [5].

Using data taken from the literature, risk modelling was performed for HIV transmission by sexual act and by partner during anal intercourse with and without ART in heterosexual couples and MSM [27]. Two transmission risk estimates were obtained for unprotected anal intercourse when the seropositive partner was on treatment. The first estimate is based on data from the Rakai Health Sciences Program, indicating an estimated 96% reduction in risk per coital act (i.e., per sexual act). The second estimate is based on data from the Zambian cohort, indicating a 99.9% reduction in risk per sexual act.

Without treatment, the transmission risk per sexual act during unprotected receptive anal intercourse was estimated at 1.4%. With treatment, the transmission risk per sexual act, according to the Rakai study, would be 0.013% for insertive vaginal or anal intercourse and 0.061% for receptive anal intercourse. According to the estimate for the Zambian cohort, the transmission risk per sexual act would be 0.0002% for insertive vaginal or anal intercourse and 0.0011% for receptive anal intercourse [27].

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5 The *Guide sur la thérapie antirétrovirale pour les professionnels du Québec* specifies that at least 95% adherence to ART is required to maintain viral suppression [3]. This is also the threshold retained in the HPTN-052 trial [16].

6 "Insertive" refers to the person who penetrates a partner.

7 "Receptive" refers to the partner who is penetrated.

However, the authors caution against overgeneralizing the results. The estimates are heterogeneous, with large confidence intervals. The variances between the raw and adjusted data hinder the interpretation of results. The authors also underscore the lack of empirical evidence for the transmission risk and the lack of information on the sexual practices of the study respondents, all of which complicate the interpretation of results [27].

Although an ongoing European study, the Partner study [28], is expected to advance current knowledge, the final results will not be available until 2017. The first phase (2014) tests the hypothesis that the transmission risk is extremely low for unprotected penetrative intercourse when the viral load is undetectable. This phase will assess the average transmission risk in followed couples, of which 40% practice condomless anal intercourse. The second phase (2017) will test the same hypothesis irrespective of sexual practices. The aim is to establish the risk for couples that practice anal intercourse and for couples that practice vaginal intercourse exclusively.

4.1.1 What the experts say

In 2008, the Swiss National Aids Commission announced that persons living with HIV who are on effective ART and have suppressed their blood viral load will not transmit the HIV virus as long as they follow regular treatment, are monitored by a physician, and are free of any other STBBIs [14].

In 2013, the British HIV Association and the Expert Advisory Group on AIDS (BHIVA–EAGA) issued a position statement on the use of ART by PLHIV to reduce the risk of HIV transmission. Based on the available evidence and expert opinion, they estimate that the risk of a PLHIV who is on effective ART for transmitting HIV to his or her partners through vaginal intercourse is extremely low as long as the following conditions are met:

- There are no other sexually transmitted infections (STBBIs) in either partner.
- The person who is HIV positive has had a sustained plasma viral load below 50 HIV RNA copies/mL for more than 6 months, and the viral load is below 50 copies/mL on the most recent test.
- Viral load testing to support the strategic use of ART as prevention should be undertaken regularly (3–4-monthly testing).

They emphasize that in their opinion, these guidelines should apply only to heterosexual couples practising vaginal intercourse, because the published data were generated largely from this population, and the evidence does not allow generalizing the conclusions to other sexual practices. However, according to their expert opinion, the transmission risk for other sexual practices could also be extremely low under the same conditions [6].

Textbox 2. Assessment of transmission risk in heterosexual couples

The transmission risk for **unprotected vaginal intercourse** drops from ***high to negligible or very low*** for stable and exclusive heterosexual couples[8] when the seropositive partner has maintained an undetectable viral load for at least 6 months and on 2 consecutive measures due to effective ART, and under the following conditions: absence of any STBBIs, adherence to treatment, medical follow-up, and regular and appropriate counselling, as defined at the end of this textbox (III).

The risk associated with **unprotected oral sex**[9] may also be reduced to ***negligible or very low*** when undetectable viral load has been maintained for at least 6 months and on 2 consecutive measures due to effective ART, as long as the following conditions are met: the partners are in a stable and exclusive couple, absence of any STBBIs, treatment adherence, and regular and appropriate medical follow-up and counselling (III).

According to theoretical and mathematical estimates [5], the risk associated with **unprotected insertive anal intercourse** with undetectable viral load maintained for at least 6 months and on 2 consecutive measures due to effective ART is similar to that for unprotected vaginal intercourse, at ***negligible or very low***,* as long as the following conditions are met: partners are in a stable and exclusive couple, absence of any STBBIs, treatment adherence, and regular and appropriate medical follow-up and counselling (III).

Although the risk is higher for **unprotected receptive anal intercourse**, it remains in the ***negligible or very low*** risk category* when the viral load is undetectable for at least 6 months and on 2 consecutive measures due to effective ART, as long as the following conditions are met: partners are in a stable and exclusive couple, absence of any STBBIs, treatment adherence, and regular and appropriate medical follow-up and counselling (III).

* One case of transmission by presumed anal intercourse in an MSM couple has been reported in the literature [29]. However, the validity of this finding has been critized [30]. It cannot be excluded that the risk is greater than *negligible or very low*.

Treatment adherence must be at least 95%, as recommended in the *Guide sur la thérapie antirétrovirale pour les professionnels du Québec* [3].

Because the current recommendations in Québec for medical HIV follow-up include an examination every 3 to 6 months, it should be clarified that if a PLHIV is on ART with an undetectable viral load, committed to a stable and exclusive heterosexual couple, and practising unprotected sex, the follow-up should be more intensive, at 3- or 4-month intervals.

- Regular and appropriate medical follow-up includes:
- Measurement of HIV viral load for the PLHIV
- STBBI screening for the PLHIV
- STBBI screening (including HIV) for the seronegative partner.

[8] Meaning the partners are mutually committed. For example, in the HPTN-052 study, the couples had to be together for at least 3 months.

[9] In the current version (2011), the table Estimation du risque selon l'activité sexuelle assesses the HIV transmission risk for unprotected oral sex as low, and for unprotected receptive oral sex as negligible. The presence of ulcers in the oral mucous or on the penis increases the transmission risk [1].

Regular and appropriate counselling includes information on the above-mentioned conditions as well as risk reduction, including correct condom use. For any person living with HIV, the counselling should also address other issues, including an awareness of legal aspects, conception, and immunization.[10]

4.2 Men who have sex with men (MSM)

The studies that assessed transmission risk according to viral load were conducted in heterosexual individuals only, and their results on HIV transmission risk estimates when the viral load was undetectable due to effective ART are therefore not directly transferable to MSM [22]. For purposes of the present document, the risk assessment for oral and anal intercourse in MSM is limited to mathematical and theoretical estimates [5] and expert opinions [6].

Estimates of the HIV transmission risk for anal intercourse in MSM were also calculated based on data from the literature. These estimates carry the same limitations and cautions as those reported in the previous section. The researchers used two mathematical calculations taken from two studies to develop their models. No conclusive evidence was found as to whether the HIV transmission risk per sexual act for anal intercourse between MSM would differ from that found for heterosexual couples [27]. It should be recalled that, with treatment, the transmission risk per sexual act, according to the Rakai estimates, would be 0.013% for insertive vaginal or anal intercourse and 0.061% for receptive anal intercourse. According to the estimates for the Zambian cohort, the transmission risk per sexual act would be 0.0002% for insertive vaginal or anal intercourse and 0.0011% for receptive anal intercourse [27]. The transmission risk was estimated at 1.4% for receptive anal intercourse when the seropositive partner was not on treatment.

In Germany, one case of HIV-1 transmission was reported, despite undetectable viral load (below 50 copies/mL), in a serodiscordant MSM couple that was practicing anal intercourse. The index case was on treatment and had undetectable blood viral load. Moreover, his viral load was already undetectable at the time when the partner's test results confirmed the seroconversion. The index case and the treating physician confirmed the absence of STBBIs as well as good treatment adherence. The index case and his partner had not had other sexual partners since the beginning of their relationship, and the phylogenetic analysis showed that the two cases were related [29].

Nevertheless, this case study was criticized, and has rarely been cited in the literature. The main criticisms are the lack of documented evidence that the viral load had been undetectable for at least 6 months from the time that the partner would have been exposed, as well as the lack of previously documented negative tests for the partner. The hypothesis that a third person was involved in the HIV transmission besides the index case and his partner cannot be excluded, because the phylogenetic analysis revealed a prevalent HIV strain. Furthermore, it is possible that the partners had had sexual relations at the beginning of the index case's treatment program, when his viral load was not yet undetectable [30].

Two ongoing studies include MSM couples in their population: the Partner study [28] in Europe and the Opposites Attract study [31] in Australia. Both studies address HIV transmission risk reduction in serodiscordant MSM couples when the PLHIV is on treatment with undetectable viral load.

[10] The *Guide québécois de dépistage des ITSS*, the *Guide pour les professionnels de la santé du Québec – L'examen médical périodique de l'adulte vivant avec le VIH*, and the *Supplément-Dépistage du VIH dans les points de service à l'aide de trousses de dépistage rapide* specify the issues to address when providing appropriate counselling to PLHIV and their partners (available in French at http://www.msss.gouv.qc.ca/sujets/prob_sante/itss/index.php?guides).

4.2.1 WHAT THE EXPERTS SAY

Let us recall that the BHIVA–EAGA issued an expert opinion on the lack of conclusive evidence, indicating that the transmission risk for sexual acts other than vaginal intercourse, and particularly anal intercourse, could be extremely low under the same conditions (both partners are free of STBBIs, plasma viral load below the threshold of 50 copies/mL for more than 6 months and on the most recent test, and regular viral load measurements) [6].

However, other experts doubt, or at least question, the effect of ART on the transmission risk for anal intercourse. Certain biological and epidemiological data suggest that ART may be less effective in reducing the transmission risk for anal intercourse, particularly receptive anal intercourse, because it is a more risky transmission route from the outset [9, 32, 33].

Textbox 3. Assessment of transmission risk in MSM couples

When the viral load has been undetectable for at least 6 months and on 2 consecutive measures due to effective ART and under certain conditions (partners in a stable[11] and exclusive couple, absence of STBBIs, treatment adherence, regular and appropriate medical follow-up and counselling), the risk associated with **unprotected oral sex** may be reduced to *negligible or very low* (III).

As is the case for heterosexual couples, when the viral load is undetectable for at least 6 months and on 2 consecutive measures due to effective ART and under certain conditions (partners in a stable and exclusive couple, absence of STBBIs, treatment adherence, regular and appropriate medical follow-up and counselling), the risk associated with **unprotected insertive anal intercourse,** according to theoretical and mathematical estimates [5], could be similar to that for unprotected vaginal intercourse, at *negligible or very low** (III).

The risk for **unprotected receptive anal intercourse** would be higher, although remaining in the *negligible or very low risk* category* when the viral load is undetectable for at least 6 months and on 2 consecutive measures due to effective ART, as long as the following conditions are met: partners in a stable and exclusive couple, absence of STBBIs, treatment adherence, and regular and appropriate medical follow-up and counselling (III).

* One case of HIV transmission by presumed anal intercourse in an MSM couple has been reported in the literature [29], but the validity of this finding has been criticized [30]. It cannot be excluded that the risk would be greater than the *negligible or very low* risk category.

Treatment adherence must be 95% or better, as recommended in the article “Antiretroviral therapy for adults infected with HIV: Guidelines for health care professionals from the Quebec HIV care committee” [3], which considers this percentage sufficient for sustainable viral suppression.

Because the current recommendations in Québec for medical HIV follow-up include an examination every 3 to 6 months, it should be clarified that if a patient is living with HIV, on ART with an undetectable viral load, committed to a stable and exclusive heterosexual couple, and practising unprotected sex, the follow-up should be more intensive, at 3- or 4-month intervals.

[11] Meaning the partners are mutually committed. For example, in the HPTN-052 study, the couples had been together for at least 3 months.

Regular and appropriate medical follow-up includes:

- Measurement of HIV viral load for the PLHIV
- STBBI screening for the PLHIV
- STBBI screening (including HIV) for the seronegative partner.

Regular and appropriate counselling includes information on the above-mentioned conditions as well as risk reduction, including correct condom use. For any PLHIV, the counselling should also address other issues, including an awareness of legal aspects, conception, and immunization.[12]

4.3 Factors influencing transmission risk when viral load is undetectable

In addition to the sexual practices that influence transmission risk [5, 22], the presence of another STBBI increases the likelihood of contracting HIV and could also increase the (previously undetectable) viral load in the genital and rectal tracts of a PLHIV [5, 6, 14]. Although it is practically impossible to exclude the presence of any STBBIs in both partners, it would be inadvisable to rely on treatment as the sole preventive strategy, even though ART may have a protective effect. Correct condom use remains the recommended practice [6, 14].

The literature shows that the herpes simplex type 2 virus (HSV-2) is associated with increased plasma HIV viral load (estimated at 0.22 $\log_{10}$ copies/mL [34]) as well as a risk of transmitting and acquiring HIV, even in the absence of ulcers [34-36]. This risk persists beyond HSV activation or reactivation This is explained in part by the persistent presence of HIV in bodily cells after HSV-2 activation or reactivation in PLHIV [37], or by the persistence of genital inflammation, which increases the risk of acquiring HIV even if HSV reactivation is controlled in persons who are HIV seronegative [34]. Suppressive treatment for herpes (acyclovir or valacyclovir) would have only a weak impact on the risk of acquiring HIV in seronegative HIV persons with HSV-2 [38]. However, when taken consistently, this herpes treatment may reduce the HIV viral load in PLHIV after HSV reactivation (although this is yet to be confirmed) to a sufficiently low level to prevent transmission, even without ART [36]. The results of a study in the United Kingdom suggest that in patients on ART, HIV replication is well controlled, and that even though an HVS-2 infection activates the CD4 lymphocytes and facilitates HIV entry, there appears to be no increase in the HIV plasma viral load over patients who are not on ART [39]. However, this finding has been corroborated by only one study in 10 recruited patients: a retrospective review of medical records published as a letter to the editor.

Generally, the available data suggest that the antiretrovirals used to treat HIV may help prevent rises in the HIV plasma viral load that are linked to the presence of an HSV-2 coinfection. Although the presence of HVS-2 increases the HIV transmission and acquisition risks, the HSV-2 virus plays only a marginal role in HIV transmission between MSM having undetectable viral load due to effective ART.

[12] *Le Guide québécois de dépistage des ITSS*, *le Guide pour les professionnels de la santé du Québec – L'examen médical périodique de l'adulte vivant avec le VIH*, and the *Supplément-Dépistage du VIH dans les points de service à l'aide de trousses de dépistage rapide* specify the aspects to address when providing counselling to PLHIV and their partners.

4.4 Limitations of the reviewed studies

In their systematic literature review, Loutfy and collegues [22] summarize the limitations of the knowledge on risk reduction associated with sexual acts when the viral load is undetectable due to effective ART. These authors emphasize the lack of data on:

- Homosexual couples
- Specific sexual practices (vaginal, anal, oral)
- The transmission risk per sexual act
- Number of sexual acts within a given period
- Transmission direction (male-to-female, female-to-male)
- A precise measure of the viral load at the time of transmission
- Genital viral load
- STBBI rates
- Frequency of condom use
- Use of hormonal contraceptives.

Our work has been subjected to the same data limitations. Consequently, our analysis is equally limited. It is also noteworthy that few studies on this topic have generated high-quality, conclusive data (I).

5 Undetectable viral load versus the condom

The effectiveness of the condom cannot be simply compared to that of undetectable viral load in reducing the HIV transmission risk during sex. The two strategies operate differently, and studies have assessed them distinctly [6]. In addition, the undetectable viral load strategy allows for combining, controlling, and measuring the optimal conditions for effectiveness,[13] which is not the case for condom use. At the time of writing this report, the numerous factors involved remain complicated or impossible to fully document.

The authors of the HPTN-052 study concluded that, in order to be effective, a preventive treatment strategy must combine a set of interventions, and that appropriate condom use should continue to be recommended and encouraged. It is noteworthy that in their study, the participants received intensive couples counselling, including risk reduction and treatment adherence. They also received free condoms. In the two study groups, only 4% to 6% of participants reported that they did not use condoms. However, this measure was self-reported. It is therefore possible that the participants who reported regular condom use did not actually use condoms every time they had sex (100% of the time), as suggested by the fact that some participants became pregnant during the study. The authors also demonstrated that condom use combined with undetectable viral load was more effective than condom use alone. Nevertheless, the results do not allow concluding that condom use combined with undetectable viral load was more effective than undetectable viral load alone, because this parameter was not assessed [16]. Thus, as mentioned in the textbox at the end of this section, neither strategy appears to work better than the other.

Based on the 2011 version of the table *Estimation du risque associé aux activités sexuelles* [1], condom-protected oral sex carries a *negligible* risk. However, condom-protected vaginal and anal intercourse carry a *low* risk due to the possibility of condom breakage. The accurate measure of this risk would be consistent and correct condom use. Inadequate use results in less effective protection, among others because it raises the risk of condom breakage, which in turn raises the transmission risk [1].

Nevertheless, it is highly challenging to assess the effectiveness of condom use in lowering the HIV transmission risk. Among others, we may note inconsistent condom use, incorrect condom use,[14] and social desirability and measurement errors in self-reports of condom use by study participants. A review of the literature shows that incorrect condom use is frequently reported in studies around the world, and by diverse clientele [40]. According to the findings of different studies, the estimated effectiveness of condom use to reduce the HIV transmission risk varies from 67% to 95% [41-44].

For example, a recent analysis of the data from two American studies in MSM[15] determined the condom effectiveness rate at 72.2% for receptive anal intercourse when participants reported 100% use (compared to 61.7% for insertive intercourse). No statistically significant difference in condom effectiveness was found between inconsistent condom use (“*sometimes”*) and no condom use (“*never”*). Furthermore, few respondents stated that they consistently used a condom over a lengthy period of time (65.0% over a 6-month period). However, these analyses addressed seropositive partners with unknown viral load [42].

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[13] This means undetectable viral load for at least 6 months and on 2 consecutive measures due to effective ART, and under the following conditions: absence of STBBIs, treatment adherence, medical follow-up, and regular and appropriate counselling.

[14] Among others, incorrect condom use includes issues of storage, application, and condom size.

[15] Data were combined from the EXPLORE study (1999–2001) and the VAX004 trial (1998–1999) [42].

Nevertheless, unlike the undetectable viral load strategy, condom use can reduce the risk of unwanted pregnancy and the transmission of other STBBIs, which we should be reminded is one of the conditions for reducing the risk transmission with undetectable viral load.

Both undetectable viral load due to ART and consistent and correct condom use are effective preventive strategies. However, there is no expert consensus on whether either strategy is more effective than the other.

6 Expert consensus of the STBBIs Comittee

The CITSS working group was mandated to assess the effect of undetectable viral load on HIV transmission risk in order to support updating the *Estimation du risque associé aux activités sexuelles*, a resource designed to help guide risk-reduction counselling [1] and to support the assessment of STBBI reports according to section 95 of Québec's *Public Health Act*.

The CITSS has established that an undetectable viral load (fewer than 40 copies/mL, or below the minimal quantification threshold in force for testing kits in Québec), typically achieved after 16 to 24 weeks of treatment and maintained for at least 6 months and on 2 consecutive measures due to effective ART, reduces the HIV transmission risk for vaginal intercourse between heterosexual couples. The risk for condomless vaginal intercourse is therefore reduced from ***high to negligible or very low*** (II), as defined in section 2.2. With respect to the methodologies of the reviewed studies and their results, this finding applies **only as long as the following conditions** are consistently met:

- Undetectable viral load maintained for at least 6 months and on 2 consecutive measures, due to effective ART
- At least 95% treatment adherence
- Partners in a stable and exclusive couple
- Confirmed absence of STBBIs in both partners
- Intensive medical follow-up for 3 to 4 months, including measurement of the viral load and STBBI screening for the PLHIV, and STBBI screening, including HIV screening, for the seronegative partner
- Regular and appropriate counselling for both partners covering the above-mentioned conditions as well as risk reduction, including correct condom use.

If any of these conditions is not met, the risk may still be reduced. However, the available evidence does not allow estimating that risk. For PLHIV, the counselling should also address other issues, including awareness of legal aspects, conception, and immunization.[16]

With respect to the risk associated with **condomless oral sex** between stable and exclusive couples, either heterosexual or homosexual, mathematical and theoretical estimates suggest that the risk would be reduced to ***negligible or very low***[17] when the viral load is undetectable for at least 6 months and on 2 consecutive measures due to effective ART. This finding applies **only as long as the following conditions** are consistently met (III):

- Undetectable viral load maintained for at least 6 months and on 2 consecutive measures due to effective ART
- At least 95% treatment adherence
- Partners in a stable and exclusive couple
- Confirmed absence of STBBIs in both partners

[16] The *Guide québécois de dépistage des ITSS*, the *Guide pour les professionnels de la santé du Québec – L'examen médical périodique de l'adulte vivant avec le VIH*, and the *Supplément-Dépistage du VIH dans les points de service à l'aide de trousses de dépistage rapide* specify the issues to address when providing appropriate counselling for PLHIV and their partners.

[17] The table *Estimation du risque selon l'activité sexuelle* assesses the HIV transmission risk for unprotected oral sex as *low* and for unprotected receptive oral sex as *negligible*. The presence of ulcers in the oral mucous or on the penis increases the transmission risk [1].

- Intensive medical follow-up for 3 to 4 months, including measurement of the viral load and STBBI screening for the PLHIV and STBBI screening, including HIV screening, for the seronegative partner
- Regular and appropriate counselling for both partners covering the above-mentioned conditions as well as risk reduction, including correct condom use.

According to mathematical and theoretical estimates, the risk associated with **condomless insertive anal intercourse** in stable and exclusive couples, either heterosexual or homosexual, when the viral load is undetectable for at least 6 months and on 2 consecutive measures due to effective ART may be the same as that for receptive vaginal intercourse, at ***negligible or very low***. This finding applies **only as long as the following conditions** are consistently met (III):

- Undetectable viral load maintained for at least 6 months and on 2 consecutive measures due to effective ART
- At least 95% treatment adherence
- Partners in a stable and exclusive couple
- Confirmed absence of STBBIs in both partners
- Intensive medical follow-up for 3 to 4 months, including measurement of the viral load and STBBI screening for the PLHIV and STBBI screening, including HIV screening, for the seronegative partner
- Regular and appropriate counselling for both partners covering the above-mentioned conditions as well as risk reduction, including correct condom use.

Condomless receptive anal intercourse when the viral load has been undetectable for at least 6 months and on 2 consecutive measures due to effective ART carries a higher risk, but still within the ***negligible or very low*** category according to the established criteria (section 2.2). However, one case of transmission by presumed anal intercourse between a MSM couple has been reported in the literature [29], although the evidence of the transmission has been called into question [30]. It cannot be excluded that the risk could be greater than ***negligible or very low***. In the absence of compelling evidence, this conclusion is based on expert opinion alone (III). Therefore, this finding applies **only as long as the following conditions** are consistently met (III):

- Undetectable viral load maintained for at least 6 months and on 2 consecutive measures due to effective ART
- At least 95% treatment adherence
- Partners in a stable and exclusive couple
- Confirmed absence of STBBIs in both partners
- Intensive medical follow-up for 3 to 4 months, including measurement of the viral load and STBBI screening for the PLHIV and STBBI screening, including HIV screening, for the seronegative partner
- Regular and appropriate counselling for both partners covering the above-mentioned conditions as well as risk reduction, including correct condom use.

Finally, the consensus has established that even when the viral load is undetectable and all the above-mentioned conditions are met, there is no guarantee of zero risk. Some transmission risk may remain, albeit much lower.

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Appendix 1

List of members of the STBBIs Committe for year 2013-2014 who adopted the report and participated in the work

List of members of the STBBIs Committe for year 2013-2014 who adopted the report and participated in the work

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[18] N.B.: Although PHAC contributed to the efforts of the expert subcommittee, it preferred to abstain from adopting the report. PHAC intends to await the results of further studies before taking a position on the report's conclusions.

Appendix 2

Undetectable viral load threshold according to the testing kits used and transmission rates in the reviewed studies

Undetectable viral load threshold according to the testing kits used and transmission rates in the reviewed studies

References	Detectability threshold	Testing kit	HIV transmission rate	No. of cases of transmission on ART
Quinn et al. 2000 [15]	400 copies/mL	Amplicor HIV-1 Monitor, version 1.5, Roche	• Total: 0	0 transmissions in 51 couples in which the seropositive partner had undetectable viral load (400 copies/mL) or below 1500 copies/mL.
Cohen 2011 [16]	400 copies/mL	CD4 kit, quantification not specified	• Total: 0.9 P-Y (0.6–1.3) • On ART: 0.1 P-Y (0.0–0.04) • No ART: 2.1 P-Y (1.5–3.1)	1 transmission linked to the seropositive partner was observed in the group that received precocious treatment (at recruitment vs. after 2 consecutive measures of 50 cells/mL^3). This transmission was identified at the beginning of the study before the viral load was measured and confirmed as undetectable.
Reynolds 2011 [17]	400 copies/mL	Amplicor HIV-1 Monitor, version 1.5, Roche	• Total: 8.2 P-Y (6.1–10.9) • On ART: 0 P-Y (0–6.7) • No ART: 9.2 P-Y (6.59–12.36)	0 cases
Donnell 2010 [25]	240 copies/mL	Cytometry by two local laboratories for CD4 + plasma RNA quantification at the end with COBAS TaqMan real-time HIV-1 RNA assay, version 1.0	• Total: 2.13 P-Y (1.76–2.58) • On ART: 0.37 P-Y (0.09–2.04) • No ART: 2.44 P-Y (1.84–2.72)	1 case
Attia et al. 2009 [18] (results based on 2 studies [21, 45])	50 copies/mL on ART	Branched-DNA assay according to local standards [21] and with the Bayer Diagnostics Kit [45]	• On ART: 0.0 P-Y (IC 97.5% = 0–1.27)	0 cases
Melo 2008 [21]	50 copies/mL	Branched-DNA assay according to local standards	• Total: 3.1 P-Y (1.4–6.5) • On ART: 0 P-Y (0.0–4.1) • No ART: 5.7 P-Y (2.6–11.8)	0 cases

References	Detectability threshold	Testing kit	HIV transmission rate	No. of cases of transmission on ART
Del Romero 2010 [20]	500 copies/mL up to 1999; 50 copies/mL 1999 and after	Cytometry and Branched-DNA assay	• Total: 0.4 P-Y (0.1–0.9) total • On ART: 0 P-Y (0.0–1.1) • No ART: 9.2 P-Y (6.59–12.36) • Per 1000 sexual acts: 0.02 P-Y (0.1–0.6)	0 case
Apondi 2011 [19]	50 copies/mL	Cobas Amplicor HIV-1 Monitor, version 1.5 Roche	• On ART: 0.05 P-Y (0.01–3.0) • (longitudinal study; all participants on therapy)	1 case

Note: P-Y = person-years.

Appendix 3

Studies and main findings on viral load (or ART) and transmission risk for vaginal intercourse (or heterosexual intercourse)

Studies and main findings on viral load (or ART) and transmission risk for vaginal intercourse (or heterosexual intercourse)

	Description	Main findings	Transmission risk	Assessment
[16]	**Cohen et al. 2011** HPTN-052: • Randomized trial • 1763 serodiscordant couples in 9 countries • Inclusion criteria: o Stable couple for at least 3 months o At least 3 episodes of vaginal or anal intercourse/3 months o Voluntary disclosure of HIV status to partner o CD4 = 350–500 cells/mm^3 o Never received ART • Protocol: o Random allocation at 1:1 ratio o ART given at recruitment o ART begins when CD4 count drops or HIV-associated condition appears o 3-month follow-ups after recruitment: 4 visits/year o Participants on ART had a supplementary visit 2 weeks after beginning treatment • Negative partner tested at 3 months and encouraged to accompany the partner to all follow-ups for counselling on condom use, STBBI screening and treatment, and follow-up for other medical conditions. • Free condoms provided.	• Sample: o 54% of subjects living in Africa o 50% of partners living with HIV were men o 97% were heterosexual o Less than 5% had an STBBI at recruitment; equal between the 2 groups o No. of diagnosed STBBIs during the study was similar for the 2 groups o 95% and 96% of the PLHIV in each group reported using a condom 100% of the time o Less than 5% had had more than 1 partner in the last 3 months o 79% and 74% of respondents on treatment were adherent at least 95% of the time o 39 seroconversions, for an incidence of 1.2 per 100 P-Y o 4 seroconversions in the precocious treatment group (0.3 per 100 P-Y) o 35 seroconversions in the delayed treatment group (2.2 per 100 P-Y) • 28 transmissions were linked to the sexual partner (1 for the group on treatment), 7 transmissions were not linked, and 3 were unclassifiable. • Kaplan–Meier estimator shows reduced transmission risk after ART was begun, for cases that were linked or not to the partner in the couple. • Consistent self-reported condom use (100%) was also associated with a significant reduction in transmission	• Precocious ART reduced the sexual transmission risk and clinical events. • Although a large proportion of respondents reported using condoms, several pregnancies occurred during the study. • Intensive counselling on risk reduction was provided.	I

	Description	Main findings	Transmission risk	Assessment
		risk. • The majority of transmissions were reported in Africa (82%). • Median blood viral load in the seropositive partner in the 27 couples where transmission occurred was measured at 4.9 $\log_{10}$ on the nearest test to detected seroconversion of the seronegative partner.		
[15]	**Quinn et al. 2000** Rakai Health Sciences Program study (formerly the Rakai Project): • Study in a region of Uganda • Followed for 30 months; viral load measured every 10 months.	• Male-to-female transmission rate: 12.0/100 P-Y • Female-to-male transmission rate: 11.6/100 P-Y • Viral load was significantly higher in seropositive partners in couples where transmission occurred.	• Viral load was the strongest predictive factor for heterosexual transmission of HIV-1, and no transmission appeared to occur below 1500 copies of RNA/mL.	I
[22, 26]	**Loutfy et al. 2013 Letchumanan et al. 2013** Systematic literature review and meta-analysis • Inclusion criteria: o Studies published up to November 2012 in serodiscordant heterosexual or homosexual couples. o Data on: - sexual contacts - seropositive partner on ART - confirmed undetectable viral load at time of transmission - HIV transmission rate between the seropositive and seronegative partner.	• Only 3 studies met all the criteria. 3 others (6 articles) were added for a 2nd analysis. • For the 3 cohort studies with confirmed undetectable viral load, the transmission rate was 0/100 P-Y (CI 95% = 0–0.5%). • When the 3 other studies were added (including the 4 cases of transmission when the viral load was unconfirmed or suspected to be detectable), the transmission rate rose to 0.14/100 P-Y (CI 95% = 0.04–0.31). • Excluding the data from studies with participants not on ART, the rate was 0.05/100 P-Y (CI (95% = 0.01–0.17). • Sensitivity analysis: the transmission rate for all studies, except for the 4 cases of transmission, was 0/100 P-Y (CI 95% = 0–0.01)	• Transmission rate estimated from 6 studies of heterosexual couples where the seropositive partner was on ART with confirmed undetectable viral load: 0/100 P-Y (CI 95% = 0–0.01). o According to the estimates, this rate means that the lifetime transmission risk from a seropositive to a seronegative partner varies from 1/200 to 1/500 (0.2–0.5% lifetime risk, or 0.1% risk for 10 years of sexual relations within the couple). • Lack of data on homosexual couples, types of sexual practices (vaginal, oral), number of sexual acts within a given period, transmission direction (male-to-female or female-to-male), accurate viral load measure at the time of transmission, STBBI rates, and condom use. • Minimal HIV transmission risk in serodiscordant couples when the seropositive partner on ART has undetectable viral load, but with reservations with respect to sexual practices, presence of STBBIs, and condom use. • Results not applicable to homosexual relations.	I

	Description	Main findings	Transmission risk	Assessment
[18]	**Attia et al. 2009** Systematic literature review and meta-analysis • Search for articles and abstracts from January 1996 to May 2008, updated February 2009: o 26 articles and abstracts retained o All studies addressed heterosexual couples o 11 cohorts comprising 5,021 couples and 461 episodes of HIV transmission.	• In general, the HIV transmission risk from a treated patient to a heterosexual partner is 0.46 [0.19–1.09] per 100 P-Y, independently of viral load and the presence of another STBBI (result based on 5 seroconversion episodes). • 2 studies that stratified the data according to viral load showed no transmission/291 P-Y. • In individuals with viral load below 400 copies/mL, irrespective of STBBI, the transmission rate was 0.16 [0.02–1.13]/100 P-Y based on 1 transmission episode in 6 studies. • 1 transmission episode was documented when the seropositive partner had plasma viral load below 400 copies/mL, although this individual was not on ART. • The transmission rate increased to 9.03 [3.87–21.09]/100 P-Y in individuals with viral load of at least 50,000 copies/mL.	• This systematic review did not allow identifying studies where the HIV transmission risk was directly quantified for each unprotected sexual act in individuals with undetectable viral load and on ART. • Due to lack of data, the authors could not validate the 'Swiss Statement' that the HIV transmission risk is less than 1/100,000 sexual acts when the viral load is below 40 copies/mL due to ART and when there are no concomitant STBBIs. • Insufficient data.	II
[23]	**Anglemyer et al. 2012** Systematic literature review according to Cochrane's method • 8 studies (1 randomized trial and 7 observational studies): o 464 transmission episodes o 72 couples on ART o 392 couples not on ART.	• The sole randomized study: ART was associated with a significantly lower risk (RR = 0.04; CI 95%: 0.000–0.27). • 6 cohort studies: significantly lower risk (RR: 0.08–0.88). • 1 study found no significant reduction with RR = 1.44 (CI 95%: 0.85–2.44) when comparing couples on and not on therapy. • Meta-analysis of 7 cohort studies: RR = 0.34; CI 95% = 0.13–0.92, but large heterogeneity. • Meta-analysis of 5 studies retained after sensitivity analysis: RR = 0.16; CI 95% = 0.07–0.35), with no heterogeneity.	• ART can potentially prevent HIV transmission in discordant couples, but almost no studies stratified their results in terms of CD4 count. • The results of this meta-analysis cannot be generalized to MSM populations because the study population was heterosexual. • The results were obtained from studies in stable couples, and are therefore unrepresentative of overall transmission rates.	II

	Description	Main findings	Transmission risk	Assessment
[5]	**PHAC 2013** Synthesis of data published from January 2001 to May 2012 • Randomized clinical trials • Systematic review • Meta-analysis.	• HIV transmission risk (average viral load of individuals with chronic, untreated infection) • Receptive vaginal intercourse (male-to-female): 0.08% to 0.19% • Insertive vaginal intercourse (female-to-male): 0.05% to 0.1%.	• Descending order of risk: anal > vaginal > oral sex. • Increasing order of risk: receptive < insertive intercourse • The strongest predictive factor for sexual transmission is plasma viral load: high viral load increases the risk. However, the risk was assessed in heterosexual couples only. • Presence of STBBIs increases the transmission risk 2-fold to 4-fold. • Male circumcision reduces the female-to-male transmission risk by 50–60%.	II
[14]	**The Swiss National AIDS Commission: The 'Swiss Statement' 2008** Based on epidemiological and biological evidence.	• When ART is effective, no free viruses are detectable in either the blood or genital secretions. • In cases of full viral load suppression, the residual risk for HIV transmission for unprotected intercourse is far below 1:100,000.	• A seropositive individual without any other STBBIs, on ART, and with fully suppressed viral load does not transmit HIV via a sexual route. That is, the virus is not transmitted through sexual contact. • This statement remains valid only as long as the following conditions are met: o The seropositive individual follows ART to the letter and is followed appropriately by a treating physician. o The viral load remains below the detection threshold for at least 6 months. o The seropositive individual does not contract another STBBI.	III
[6]	**BHIVA–EAGA 2013** UK expert position statement based on a literature review.	• HPTN-052: 96% lower transmission risk, but randomized trials include limitations: the real risk remains unknown for the population that does not participate in the controlled study. A meta-analysis and cohort studies demonstrated condom use effectiveness at 79–93% for lowering the transmission risk in respondents who reported using condoms 100% of the time.	• HIV transmission by vaginal intercourse is significantly lower (extremely low) in heterosexual couples when the seropositive partner is on effective ART. ART is considered as effective as condom use. • The transmission risk is extremely low as long as: o The PLHIV is on effective ART and neither the PLHIV nor the partner has another STBBI. o The PLHIV is on effective ART and has maintained undetectable viral load at 50 copies or less for at least 6 months and on the most recent test; • Viral load is regularly tested (every 3 to 4 months). • HIV status and absence of STBBI must be confirmed in both partners.	III

Note: P-Y = person-years; RR = relative risk.

Appendix 4

Studies and main findings on viral load (or ART) and transmission risk for oral sex

Studies and main findings on viral load (or ART) and transmission route for oral sex

Ref.	Methodology	Main findings	Transmission risk	Assessment
[5]	**PHAC 2013** Synthesis of scientific evidence published from January 2001 to May 2012 • Meta-analysis • Cohort study • Systematic review.	• The risk for unprotected oral sex is lower than that for unprotected vaginal or anal intercourse. The data indicate a low risk, but not zero (0.00–0.04). • Ejaculation and the presence of ulcers in the oral mucous or an STBBI in the oropharynx increase the risk of transmission to the receptive partner. • The presence of piercing can increase the risk.	• Descending order of risk: anal > vaginal > oral sex • Increasing order of risk: Receptive > insertive • The strongest predictive factor for sexual transmission is plasma viral load: high viral load increases the risk. However, the risk was assessed in heterosexual couples only. • Presence of STBBIs increases the transmission risk 2-fold to 4-fold.	II

Appendix 5

Studies and main findings on viral load (or ART) and transmission risk for anal intercourse

Studies and main findings on viral load (or ART) and transmission risk for anal intercourse

Ref.	Methodology	Main findings	Transmission risk	Ass.
[5]	**PHAC 2013** Synthesis of scientific evidence published from January 2001 to May 2012 • Meta-analysis • Cohort study • Systematic review	• HIV transmission risk (average viral load of individuals with chronic untreated infection) o Receptive anal intercourse: 0.5%–3.38% (average: 1.4–1.69%) o Insertive anal intercourse: 0.06–0.16%	• Descending order of risk: anal intercourse > vaginal intercourse > oral sex • Descending order of risk: Receptive > insertive • The strongest predictive factor for sexual transmission is plasma viral load: high viral load increases the risk. However, the risk was assessed in heterosexual couples only. • Presence of STBBIs increases the transmission risk 2-fold to 4-fold.	II
[27]	**Baggaley et al. 2010** Systematic literature review according to MOOSE guidelines and meta-analysis, including mathematical estimates. • 12 studies in MSM • 3 studies in heterosexuals • 1 study in a mixed population	Without treatment effect: • The estimated HIV transmission risk for unprotected receptive anal intercourse is 1.4% per sexual act and 40.4% per partner. • The estimated transmission risk per partner is 39.9% if anal intercourse is 50% receptive and 50% insertive. • The risk is 21.7% for unprotected insertive anal intercourse. With treatment (according to the Rakai data) • The estimated transmission risk per sexual act for: o Unprotected vaginal intercourse or unprotected insertive anal intercourse: 0.013% o Receptive anal intercourse: 0.061% • I.e., 96% risk reduction • 1000 sexual acts carry a male-to-female transmission risk per partner of 12.2% with no anal intercourse, and 12.6%, 14.3%, 16.3%, and 20.2% if anal intercourse makes up 1%, 5%, 10%, and 20% of all sexual acts. • In MSM, 1000 sexual acts carry a transmission risk per partner of 30.9% if the partners alternate between insertive and receptive anal intercourse, and 45.6% if the initially seronegative partner is consistently receptive. With treatment (according to data from the Zambian cohort).	• The estimated transmission risk per sexual act for unprotected receptive anal intercourse is 1.4%. • The estimated transmission risk per partner is 39.9% for insertive and receptive anal intercourse, 40.4% for exclusively receptive anal intercourse, and 21.7% for exclusively insertive anal intercourse. • The researchers obtained two transmission risk estimates for unprotected anal intercourse when the seropositive partner was on treatment. o First, based on data from the Rakai cohort, the risk per sexual act was reduced by 96%. o Second, based on data from the Zambian cohort, the risk per sexual act was reduced by 99.9%. • However, the researchers cautioned against overgeneralizing these estimates. o The estimates are heterogeneous, with large confidence intervals. o The variances between raw and adjusted data hinder the interpretation of results. o It is difficult to produce distinct transmission risk estimates per sexual act and per partner. The transmission potential is heterogeneous, and other factors must be considered (e.g., exposure duration, condom use, frequency of unprotected sexual acts).	II

Ref.	Methodology	Main findings	Transmission risk	Ass.
		• The estimated transmission risk per sexual act for: o Unprotected vaginal intercourse or insertive anal intercourse: 0.0002% o Receptive anal intercourse: 0.0011% • I.e., 99.9% risk reduction • 1000 sexual acts carry a male-to-female transmission risk per partner of < 0.5% even when anal intercourse makes up 20% of all sexual acts. • In MSM, 1000 sexual acts carry a < 1% transmission risk per partner if the partners alternate between insertive and receptive anal intercourse, and 1.1% if the initially seronegative partner is consistently receptive.		
[6]	**BHIVA–EAGA 2013** UK expert position based on a literature review.	• For each plasma viral load increase of $\log_{10}$, the risk per sexual act increases by 2.9 times (CI 95%, 2.2–3.8) [46, 47]. • The transmission risk is 10 times higher for receptive than insertive anal intercourse [27, 46, 47]. • The risk for insertive anal intercourse is similar to that for either receptive or insertive vaginal intercourse (5–6/10,000 exposures) [27, 46, 47, 48]. • The estimated risk for receptive anal intercourse is 10 times higher (50/10,000 exposures) [27, 46, 47, 48]. • 1 study found a correlation between transmission by anal intercourse and viral load, recent HIV infection, and recent STBBI (RR 5:32; CI 95%: 2.51–11.29) [48].	• Despite the lack of evidence to conclusively determine the transmission risk for sexual practices other than vaginal intercourse, the expert group posits an extremely low risk for anal intercourse (male–male or male–female) when the viral load is undetectable.	III
Ongoing studies: **Opposites Attract study:** An Australian study on reduced HIV transmission risk in serodiscordant MSM couples with the PLHIV on treatment and having undetectable viral load: http://www.oppositesattract.net.au/. **Partner study:** European study. Final results expected in 2017 [28]. 2014: The tested hypothesis is that the transmission risk is very low for unprotected intercourse with penetration when the viral load is undetectable. The objective is to assess the average transmission risk in followed couples who practice about 40% condomless anal intercourse. 2017: The same hypothesis is tested, but irrespective of sexual practice. The objective is to determine transmission risk for couples that practice anal intercourse and for couples that practice vaginal intercourse exclusively.			

Note: P-Y = person-years; RR = relative risk.

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