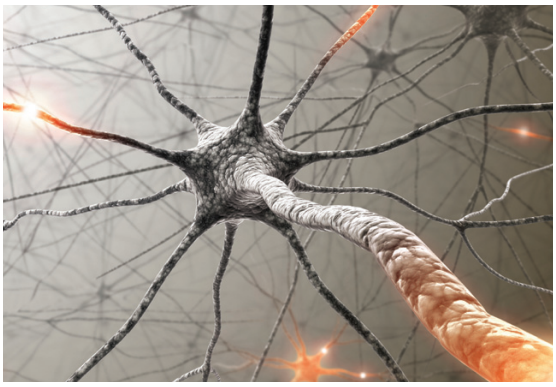
HIV TRANSMISSION RISK: A SUMMARY OF THE EVIDENCE



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LIST OF ACRONYMS

GUD	Genital ulcer disease
HAART	Highly active antiretroviral therapy
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
MSM	Men who have sex with men
OR	Odds ratio
PWID	People who inject drugs
RCT	Randomized controlled trial
STI	Sexually transmitted infection

EXECUTIVE SUMMARY

This report provides a synthesis of the current scientific evidence on the risk of transmission of human immunodeficiency virus (HIV) associated with sexual activities, injection and other drug use, and mother-to-child (vertical) transmission. This technical document is intended for use by health authorities and professional organizations to inform the development of policies, programs, and/or guidelines aimed at preventing HIV transmission.

METHODS

A search was conducted for literature published between January 2001 and May 2012. The search focused on systematic, meta-analytic, and narrative reviews, where they existed. For topics where no reviews existed, primary research studies were included.

MAJOR FINDINGS

SEXUAL TRANSMISSION OF HIV

Although there are challenges in quantifying risk by sex act, all studies consistently reported that anal intercourse is a higher risk act than vaginal intercourse, which in turn is a higher risk act than oral intercourse. There is also an increased risk associated with receptive intercourse (both vaginal and anal) compared with insertive intercourse.

The risk estimates for the sexual transmission of HIV, per sex act, range widely, from 0.5% to 3.38% (with mid-range estimates of 1.4% to 1.69%) for receptive anal intercourse; 0.06% to 0.16% for insertive anal intercourse; 0.08% to 0.19% for receptive vaginal intercourse (i.e., male-to-female); and approximately 0.05% to 0.1% for insertive vaginal intercourse (i.e., female-to-male). The risk of transmission from unprotected oral intercourse (whether penile-oral or vaginal-oral) is markedly lower than for anal or vaginal intercourse, and findings suggest a low but non-zero transmission probability. The risk of transmission to the receptive partner increases with ejaculation and the presence of oral ulcers and sexually transmitted infections (STIs) in the oropharynx.

The strongest predictor of HIV sexual transmission is plasma viral load. As plasma viral load increases, the risk of transmission also increases. However, much of what is known about viral load and HIV transmission is derived from studies of heterosexual populations. While the nature of the sex acts (i.e., vaginal versus anal intercourse) was not always specified, it is likely that the majority of the sex acts were penile-vaginal. As such, little is known about how viral load affects the risk of transmission through anal intercourse.

The presence of a concomitant STI has also been found to affect HIV transmission. STIs increase susceptibility to HIV by a factor of 2 to 4 and increase transmissibility 2 to 3 times.

Male circumcision decreases the risk of female-to-male sexual transmission of HIV by 50% to 60%. However, there is little epidemiological evidence to suggest that circumcision reduces the risk of transmission to female partners of circumcised men or is effective in the prevention of HIV among men who have sex with men (MSM).

HIV TRANSMISSION AMONG PEOPLE WHO USE DRUGS

For people who inject drugs, the risk of transmission per injection from a contaminated needle has been estimated to be between 0.7% and 0.8%. However, studies of contact with improperly discarded needles outside of the healthcare setting suggest that such exposures represent a low risk for HIV transmission, likely due to the low viability of the virus outside the body.

Sharing ancillary injecting equipment such as filters or cookers during injection drug use has been shown to increase the risk of transmission, even in the absence of sharing needles and syringes. Other factors that have been shown to increase the risk of HIV transmission for people who inject drugs include injecting in unsafe locations, type of drug used, and frequency of drug injection. While it is likely that viral load is associated with HIV transmission among injection drug users, the number of studies conducted on this topic has been limited.

People using non-injection drugs are also at risk of HIV infection. Drug use can alter sexual behaviours by increasing risk taking. In addition, several drugs have been reported to be independent risk factors for HIV transmission.

MOTHER-TO-CHILD TRANSMISSION OF HIV

In the absence of any preventive intervention, for example, highly active antiretroviral treatment (HAART), mother-to-child transmission (also known as "vertical" transmission) ranges from about 15% to 45% depending on whether breastfeeding alternatives are available. As with other modes of transmission, maternal plasma viral load has been consistently associated with the risk of vertical transmission. Since HAART, which is used to suppress viral replication, was introduced in 1997, the rate of mother-to-child transmission has dropped dramatically in Canada.

Beyond viral load, there are several factors associated with an increased risk of vertical transmission. Concurrent STIs and co-infection with either hepatitis C or active tuberculosis increase the risk of vertical transmission. While mode of delivery was once found to be associated with vertical transmission, since the introduction of HAART, studies indicate that there are probably no additional benefits to elective caesarean section for women with low viral loads.

Obstetric events, including prolonged rupture of membranes and intrapartum use of fetal scalp electrodes or fetal scalp pH sampling, have been found to increase the risk of perinatal transmission of HIV.

Mother-to-child HIV transmission can also occur through breastfeeding. The probability of transmission of HIV through breastfeeding is in the range of 9% to 16%. Co-factors that are associated with risk of transmission from breastfeeding include duration and pattern of breastfeeding, maternal breast health, and high plasma or breast milk viral load.

CONCLUSIONS

This review of the scientific literature on HIV transmission was based on over 250 references. Within each route of transmission, estimates of the risk of transmission varied widely, likely due to the role of behavioural and biological co-factors. Viral load (especially in plasma, but also in other relevant body fluids) appears to be an important predictor of transmission, regardless of the route of transmission. However, the evidence indicates that viral load is not the only determinant and that certain co-factors play a role in increasing (e.g., STIs) or decreasing (e.g., circumcision in female to male transmission) the risk of transmission.

This review of the evidence points to the growing and evolving nature of our knowledge of HIV transmission risk and the biological and behavioural co-factors that impact on risk.

1. INTRODUCTION

This technical report reviews the literature on the risk of human immunodeficiency virus (HIV) transmission. The intent is to assist health authorities and community-based organizations in developing policies, programs, and/or guidelines to reduce the transmission of HIV. This document makes no recommendations, but rather presents a summary of the evidence that can serve as a foundation to develop resources for public health professionals in risk analysis and counselling.

Understanding the biological determinants of HIV transmission is essential for:

- making predictions on the potential spread of HIV infection in a population,
- directing appropriate targeted prevention strategies, and
- assessing the risk of infection to an individual who has been exposed to the virus.

1.1 SCOPE

This technical report summarizes the evidence on the risk of HIV transmission, including the main co-factors that impact this risk.

This document covers sexual transmission, transmission via injection and other drug use, and mother-to-child transmission (also referred to as "vertical transmission") in Canada. The risk of transmission from sexual activities and drug use are responsible for the majority of new infections in Canada (1). While mother-to-child transmissions have declined substantially over the past decade, pediatric HIV infections continue to occur (2, 3). Vertical transmission is often the result of inadequate prenatal care, failure to diagnose maternal HIV in time, or non-adherence to therapy (2). It therefore remains an important means of transmission.

While psychological, economic, and social determinants play an important role in HIV transmission, a full description of these determinants is outside the scope of this report. For information on these determinants of health and how they impact the populations most at risk for HIV in Canada, consult the Public Health Agency of Canada's Population-Specific HIV/AIDS Status Reports.[1] Preventive measures and interventions that aim to prevent or reduce the risk of transmission are also not within the scope of this document. However, as a related and complementary initiative, The Agency is developing an HIV Screening and Testing Guide. The new guidelines recommend approaches to reduce the number of individuals who are living with HIV but unaware of their status, thereby (improving health outcomes and) contributing to reduced onward transmission.

This review focused on HIV-1, the predominant type in Canada and worldwide. HIV-2 is found mainly in West Africa. While HIV-2 has been detected in Canada, it is rare (4, 5).

1.2 METHODS

A literature search of Scopus, Embase and CINAHL was limited to articles in English and French published between January 2001 and May 2012. Systematic reviews, including meta-analyses and narrative reviews, were the focus of the literature search. Where reviews did not exist, primary research studies were included. Key primary research studies or commonly referenced publications outside of the 10-year time period were also included.

The following search terms were used: (HIV or "human immunodeficiency virus") and (transmission AND (probability OR rate OR risk)) OR (per AND contact) OR (per AND act) OR infectivity OR infectiousness OR transmissibility, along with key terms specific to each topic covered in this review.

1.3 ORGANIZATION OF THIS DOCUMENT

The document is divided into three sections based on three methods of HIV transmission: sexual transmission, transmission due to drug use, and mother-to-child transmission. Each section summarizes the risk of the type of transmission discussed and the co-factors that affect risk.

[1] www.phac-aspc.gc.ca/aids-sida/publication/ps-pd/index-eng.php

2.0 SEXUAL TRANSMISSION

2.1 BACKGROUND

Sexual transmission drives the HIV epidemic in most countries (6); in Canada, this is also the most common route of transmission. In 2008, an estimated 44% of new HIV infections were attributed to men who have sex with men (MSM) while about 36% were through heterosexual contact (which represents the two categories: heterosexual/endemic (16%) and heterosexual/non-endemic (20%)) (1). These estimates were roughly the same as those for 2005 (1).

This section provides estimates of risk by sex act. It also examines the main behavioural and biological co-factors that impact the risk of sexual transmission of HIV. It also examines whether the co-factors affect the infectiousness or the susceptibility of individuals, their relative effect on men and women, and the extent of their influence in different populations (i.e., heterosexual couples versus MSM).

2.2 RISK OF HIV TRANSMISSION BY SEX ACT

Estimates of the risk of HIV transmission by sex act vary widely. This variation may be due to differences in the prevalence of behavioural and biological co-factors in the populations studied (7, 8). There are also challenges in producing accurate measures of risk because study participants often practice a variety of sex acts (9) and the timing of an individual's seroconversion and subsequent transmission to a partner, the number of sex acts, and the potential HIV risk co-factors are rarely accurately known (7).

Despite the challenges in quantifying risk by sex act, all studies consistently report that anal intercourse is a higher risk act than vaginal intercourse, which in turn is a higher risk act than oral intercourse. Also consistently reported is that there is increased risk associated with receptive intercourse (both vaginal and anal) compared with insertive intercourse (9, 10).

Sexual transmission risk estimates are usually reported as per-act transmission probabilities (the risk per sexual contact) or per partner transmission probabilities (the risk over many sex acts in a partnership) (11). To maintain consistency in reporting, the sections below describe the transmission estimates per sex act, rather than per partner. In addition, estimates reflect the risk of acquiring HIV from an HIV-positive partner from unprotected sex acts, from sex acts where condom use was rare, or from studies that adjusted for condom use. Of note is that most transmission estimates are based on studies that were carried out before the advent of highly active antiretroviral therapy (HAART) (8, 9, 12). Thus, unless otherwise specified, the estimates presented reflect the risk associated with the average viral load of individuals with untreated chronic HIV-infection (13).

2.2.1 ANAL INTERCOURSE

Anal intercourse carries a higher risk of HIV transmission for both receptive and insertive partners when compared with vaginal intercourse. This is because rectal mucosa differs from vaginal mucosa. There is a higher density of lymphoid follicles (i.e., HIV target cells) in rectal mucosa and it is more susceptible to abrasions than vaginal mucosa (14, 15). The risk of transmission to the receptive partner resulting from receptive anal intercourse has been estimated to be between 5 and 18 times higher than the risk from receptive vaginal intercourse (9, 16).

Based on the results of cohort studies and meta-analyses, the per-act risk estimates of transmission from receptive anal intercourse range from 0.5% and 3.38% (see Table 1) (7, 10, 11, 13, 17, 18), with several estimates in the mid-range of 1.4% to 1.69% (10, 11, 17). Most of these estimates are based on studies of MSM. However, the risk associated with anal intercourse appears to be similar within heterosexual populations. In a meta-analysis of four observational studies (two of MSM couples and two of heterosexual couples), no difference was found between heterosexual and MSM couples in the risk of HIV transmission associated with anal intercourse (10).

Risk estimates for insertive anal intercourse range from 0.06% to 0.16%, lower than for those for receptive anal intercourse. Based on a systematic review of six studies, the insertive anal intercourse risk of transmission was estimated to be 0.07% per-act (13, 18). Two observational

studies also reported on insertive anal intercourse (18). One estimated the unprotected insertive anal intercourse per-act risk at 0.06%, which may be an underestimate because it was based on partners of men who were HIV positive or of unknown serostatus. (18). In the second study, the per-act probability of HIV transmission was estimated to be 0.16% (17).

Summary estimates of the risk of transmission from anal intercourse may be misleading as there is a considerable amount of heterogeneity in infectivity. This heterogeneity depends on the presence of co-factors. For some, the risk per act is much higher than suggested by a summary measure. A cohort of over 2,000 MSM found that of the 60 seroconversions observed, 9 occurred after only one or two episodes of unprotected receptive anal intercourse (18).

Most of the studies on transmissibility of HIV via anal intercourse were conducted in the pre-HAART era. As such, little is known about the impact of HAART on the risk of transmission from anal intercourse. A recent analysis of a cohort of MSM in Australia, among whom about 70% of HIV-diagnosed people were receiving HAART, found that the per-act risk from unprotected receptive anal intercourse was 1.43% with ejaculation and 0.65% with withdrawal. The per-act risk from unprotected insertive anal intercourse was 0.16% (17).

TABLE 1. Estimates of the per-act risk of transmission from anal intercourse

STUDY	TYPE OF STUDY	POPULATION	TYPE OF ANAL SEX ACT	TRANSMISSION PROBABILITY % (95% CI)
Powers et al., 2008 (7)	Meta-analysis (15 studies)	Heterosexual	Receptive	3.38 (1.85–4.91)
Boily et al., 2009 (11)	Meta-analysis (25 studies)	Heterosexual	Receptive	1.69 (0.32–8.91)
Baggaley et al., 2010 (10)	Meta-analysis (16 studies)	Heterosexual and MSM	Receptive	1.4 (0.2–2.5)
Jin et al., 2010 (17)	Cohort study (n=1,427)	MSM	Receptive (with ejaculation) Receptive (with withdrawal)	1.43 (0.48–2.85) 0.65 (0.15–1.53)
Vittinghoff et al., 1999 (18)	Cohort study (n=2,189)	MSM	Receptive	0.82 (0.24–2.76)
Fox et al., 2011 (13)	Meta-analysis (9 studies)	Heterosexual and MSM	Receptive	0.5[a]
Jin et al., 2010 (17)	Cohort study (n=1,427)	MSM	Insertive	0.16 (0.05–2.9)
Vittinghoff et al., 1999 (18)	Cohort study (n=2,189)	MSM	Insertive[b]	0.06 (0.02–0.19)
Fox et al., 2011 (13)	Systematic review (6 studies)	MSM	Insertive	0.07[a]

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MSM, men who have sex with men.

[a] 95% CI not reported.

[b] Unprotected insertive anal intercourse with an HIV-positive or unknown serostatus partner.

2.2.2 VAGINAL INTERCOURSE

The risk estimates of HIV transmission from receptive vaginal intercourse (i.e., risk to the female partner) range from 0.08% and 0.19% (11, 13, 19). The risk for insertive vaginal intercourse (i.e., risk to the male partner) has been estimated to be slightly lower, with estimates ranging from 0.05% to 0.1% (13, 19) (see Table 2).

Several studies have examined the risk of sexual transmission among heterosexual populations, without specifying the nature of the sex acts (i.e., vaginal versus anal intercourse). However, it is likely that the majority of the sex acts were penile-vaginal (19). In two meta-analyses and a recent analysis of a large cohort study, the risk of sexual transmission among heterosexuals was reported as 1 to 2 cases per 1,000 sex acts (or roughly 0.1%) (7, 11, 19). However, as in the case of risk estimates for anal intercourse, the summary risk estimates should be interpreted with caution due to the significant heterogeneity in (a) the infectiousness of HIV-positive individuals and (b) the susceptibility of their partners (7, 11, 19, 20).

TABLE 2. Estimates of the per-act risk of transmission from vaginal intercourse

STUDY	TYPE OF STUDY	DESCRIPTION OF EXPOSURE	TRANSMISSION PROBABILITY % (95% CI)
Hughes et al., 2012 (19)	Secondary analysis of RCT data (n=3,297 heterosexual couples)	Receptive vaginal	0.19 (0.10–0.37)
Fox et al., 2011 (13)	Systematic review (13 studies)	Receptive vaginal	0.1[a]
Boily et al., 2009 (11)	Meta-analysis (5 studies)	Receptive vaginal	0.08 (0.05–0.11)
Hughes et al., 2012 (19)	Secondary analysis of RCT data (n=3,297 heterosexual couples)	Insertive vaginal	0.1 (0.06–0.17)
Fox et al., 2011 (13)	Systematic review (12 studies)	Insertive vaginal	0.05[a]
Boily et al., 2009 (11)	Meta-analysis (43 studies)	Per coital act[b]	0.18 (0.11–0.30)
Gray et al., 2001 (21)	Secondary analysis of RCT data (n=174 heterosexual couples)	Per coital act[b]	0.11 (0.08–0.15)
Powers et al., 2008 (7)	Meta-analysis (5 studies)	Vaginal sex (overall risk)	0.08 (0.05–1.17)

Abbreviations: CI, confidence interval; RCT, randomized controlled trial.

[a] 95% CI not reported.

[b] Type of sex act not specified.

Higher rates have been reported for male-to-female sexual transmission compared with female-to-male sexual transmission. This may be due to biological mechanisms, such as a larger anatomical surface and/or higher numbers of vulnerable cell types in the vagina compared with the penis (8). However, at present it is not clear whether women are at higher risk than men in a discordant relationship (8). This association may vary by setting: in high-income countries, female-to-male transmission estimates were about half the male-to-female transmission estimates, while in low-income countries the estimates for female-to-male and male-to-female were similar (11). This finding was echoed in a recent analysis of a large prospective study of over 3,000 African serodiscordant couples, where no difference was found between male-to-female and female-to-male transmission rates per sex act, after adjustment for co-factors including viral load (19). Their findings suggested that differences in male-to-female and female-to-male infectivity may vary substantially in different settings according to differences in the prevalence of key co-factors such as viral load, concomitant sexually transmitted infection (STIs), and condom use (19).

2.2.3 ORAL INTERCOURSE

The risk of HIV transmission through oral intercourse has been difficult to quantify, in part because many individuals do not practice oral intercourse to the exclusion of other sex acts. However, it is clear that the risk of transmission by oral intercourse (whether penile-oral or vaginal-oral) is markedly lower than for anal or vaginal intercourse (see Table 3). The oral cavity has a thick epithelial layer, a low number of CD4 target cells, and antiviral antibodies, all of which make it relatively resistant to HIV transmission (22). In a meta-analysis of 10 studies, only four studies reported a non-zero estimate of risk from unprotected oral intercourse (23). While a pooled estimate of risk was not produced due to small sample sizes, their review suggested a low but not a zero probability of transmission (23).

While precise measures of risk have been difficult to develop, it is likely that ejaculation and the presence of oral ulcers or oropharyngeal inflammation or STIs increase the risk of HIV transmission to the receptive partner during oral intercourse (22–24). The findings of a case series of MSM believed to have acquired HIV through oral intercourse suggested that genital piercings increase the risk of HIV acquisition when practicing insertive oral sex (25).

There is a concern that while the risk of HIV transmission from oral intercourse is assumed to be low, this sex act may contribute to HIV transmission if there is a high frequency of unprotected oral intercourse in relation to higher risk practices, which are more likely to be protected (23, 24). Unprotected oral intercourse has been identified as a significant route of transmission in the recent resurgence in syphilis cases among MSM in developed countries (26–28).

TABLE 3. Estimates of the per-act risk of transmission from unprotected oral intercourse

STUDY	TYPE OF STUDY	DESCRIPTION OF EXPOSURE	TRANSMISSION PROBABILITY % (95% CI)
Baggaley et al., 2008 (23)	Meta-analysis (10 studies)	All oral intercourse (insertive and receptive penile-oral and vaginal-oral sex)	Unable to produce summary estimate due to lack of information
Del Romero et al., 2002 (29)	Cohort study of HIV-serodiscordant heterosexual couples (n=135 couples)	All oral intercourse	0.00 (0.00–0.02)a
Vittinghoff et al., 1999 (18)	Cohort study of MSM (n=2189)	Unprotected receptive oral intercourse with ejaculation	0.04 (0.01–0.17)
Raiteri et al., 1996 (30)	Cohort study of HIV-discordant female couples (n=28)	All oral intercourse	0.00 (0.00–0.45)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a] As calculated in Baggaley et al., 2008 (23)

2.3 OTHER BEHAVIOURAL CO-FACTORS

In addition to the nature of the sex act, several other behavioural co-factors, such as type of sexual partner (e.g., main or casual) and concurrency of sexual partners, have been suggested as likely playing a role in HIV transmission. The relative contribution of these co-factors is not known, however. For example, in the United States (U.S.), main partners were estimated to account for up to 68% of HIV transmissions among MSM, due to increased exposure and decreased use of condoms (12, 31, 32), whereas in Amsterdam, HIV transmission among MSM was predominantly driven by unprotected receptive anal intercourse with casual partners (33).

Concurrency of sexual partners (multiple, overlapping partnerships) has also been proposed to contribute substantially to HIV transmission, especially in the African context (12, 34). However, much of the evidence for concurrency as a contributor to HIV transmission is based on modelling studies, and the limited empirical evidence has suffered from flawed survey instruments and poor study designs. The lack of good quality evidence has led to questions about the importance of the role of concurrency in increasing HIV transmission (34).

Activities resulting in genital or anorectal mucosal injury lead to increased risk of HIV transmission (35, 36). For example, as previously mentioned, genital piercing has been associated with HIV transmission via oral intercourse (25). In a study of MSM, activities that could potentially cause anorectal mucosal injury (i.e., rectal douching, receipt of objects *in ano*, and receptive fisting) were strongly associated with HIV seropositivity (37).

Sexual assault is also associated with a higher risk of transmission because there is a higher likelihood of broken skin with a violent assault than with consensual sex (38). Mathematical modelling analysis of a conflict setting found that a rape survivor's risk of HIV may increase by a factor of 2.4 to 27.1 due to the potentially compounding effects of genital injury, penetration by multiple perpetrators, and the increased likelihood that the perpetrators are HIV infected (39).

2.4 BIOLOGICAL CO-FACTORS

As previously mentioned, estimates of the risk of HIV transmission following sexual exposure vary widely (7, 8, 11), likely due in part to differences in the prevalence of biological co-factors such as co-infection with other sexually transmitted infections, viral load and stage of disease, and circumcision in study populations (11). The impact of these biological co-factors is described below.

2.4.1 SEXUALLY TRANSMITTED INFECTIONS

There is a large body of evidence that suggests that STIs play a role in increasing the infectiousness of HIV-positive individuals and the susceptibility of HIV-negative individuals. However, the relationship between STIs and HIV is complex, and the evidence is at times contradictory or difficult to interpret due to the presence of confounders. The sections below discuss the impact of STIs on HIV transmission and some of the challenges in determining the relationship between the two.

2.4.1.1 IMPACT OF STIs ON THE SUSCEPTIBILITY TO HIV

STIs have consistently been associated with increased susceptibility to HIV in observational studies (40). However, there are serious limitations in the methods used in many of these. For example, the study design often does not allow causation to be determined (40). In addition, measurement of the exposure (e.g., the presence of an STI) may not have been accurate because of the use of retrospective methods, including self-report of STIs. Sexual behaviour itself is a confounder because both HIV and STIs are sexually transmitted and share the same risk behaviours: it is difficult to control for this in observational studies (41). Study designs that do not allow relative timing to be established and/or that measure broad, rather than specific, confounders have resulted in higher estimates of risk (42).

Several meta-analyses and systematic reviews have tried to address these issues by examining only those studies in which a temporal relationship could be determined, where objective methods of detecting STIs were used, and where possible confounders (e.g., sexual behaviour) were accounted for. Based on these reviews, the presence of STIs was found to increase susceptibility to HIV by a factor of 2 to 4. This effect has been found for both men and women, specifically for herpes simplex virus type 2 (HSV-2), syphilis, gonorrhoea, chlamydia, trichomonas, and exposure categorized as "any STI," "genital ulcer disease (GUD)" and "non-ulcerative STIs" (41–46). However, HSV-2 was not found to increase susceptibility in six studies of high risk women, and in a review of three studies, STIs did not increase susceptibility among MSM (43, 47).

More recent observational studies have also associated the presence of human papillomavirus with HIV acquisition among women, heterosexual men, and MSM (45, 46, 48, 49).

Several biological mechanisms have been suggested to explain how STIs increase susceptibility to HIV (50, 51). Both GUD and non-ulcerative STIs lead to increased presence and activity of HIV-susceptible cells in the genital tract (50). In addition, both GUD and non-ulcerative STIs lead to a breakdown of the mucosal barrier, which can expose HIV-susceptible sub-epithelial cells to infected fluids or blood (50, 52, 53).

2.4.1.2 IMPACT OF STIs ON THE INFECTIOUSNESS OF HIV

Few observational studies have examined the effect of STIs on the infectiousness of HIV (50). A systematic review identified only two studies that examined the impact of STIs on the infectiousness of HIV. These studies found that genital ulcers and syphilis significantly increased the risk of HIV transmission 2- to 3-fold (41).

Much of the evidence on STIs and increased infectiousness comes from indirect approaches, such as clinical studies that examine the possible biological mechanisms underlying the association between STIs and HIV. Such studies have found a range of syndromes/STIs associated with increased HIV shedding in the genital secretions of both men and women. A meta-analysis of 39 studies found that urethritis, cervicitis, GUD, gonorrhoea, and chlamydia all increased HIV shedding 2- to 3-fold (54). It has been suggested that infectiousness may be especially increased in the presence of GUD compared with non-ulcerative STIs due to the fact that genital ulcers frequently bleed during sexual intercourse (53). In addition, direct shedding can occur from genital ulcers. (HIV has been cultured from genital ulcers in both men and women (50, 53). A review of the role of HSV-2 on viral load found that chronic HSV-2 infection was associated with significantly increased HIV plasma viral load (55).

2.4.1.3 STI TREATMENT INTERVENTION TRIALS

As stated above, observational studies have consistently shown that STIs increase the risk of HIV transmission. However, the results of randomized controlled trials (RCTs) examining the impact of STI treatment on the risk of HIV transmission have been equivocal. Nine trials have been published to date: six assessed the effects of treating curable STIs, and three examined the impact of herpes suppressive therapy (56).

The only trial to find a significant impact of STI treatment on HIV incidence was the Mwanza trial, which found a 40% reduction in HIV incidence following improved STI services provided at government health units (57). Several papers have posited that this may be due to the type of epidemic within the community (52, 55, 56). The Mwanza trial was conducted in a concentrated epidemic, while other trials were implemented in generalized epidemics. In more mature, generalized epidemics, the probability of HIV transmission is relatively high, even outside of groups at high risk of STIs (56, 58). In such contexts, treatable STIs may be less important as a co-factor in HIV transmission. Suboptimal adherence to HSV-suppressive therapy and a lack of power to detect differences may have led to the inability of genital herpes treatment trials to demonstrate a significant effect on HIV incidence (40, 56).

2.4.2 VIRAL LOAD

The strongest predictor of sexual transmission of HIV is plasma viral load (59, 60). Studies have observed a dose-response relationship where each 10-fold increase in plasma viral load resulted in an increased relative risk of transmission of 2.5 to 2.9 per sexual contact (19, 61) (see Table 4 for the estimated risk of transmission by viral load). In a review of 11 cohorts of heterosexual couples, for individuals who were untreated but had a plasma viral load of less than 400 copies/ml, the transmission rate was 0.16 per 100 person years (62). There were no HIV transmission events in couples where individuals were treated with HAART and had a plasma viral load of less than 400 copies/ml (62). The difference in transmission risk between the treated and untreated groups may have been due to the positive impact of being in care (e.g., receiving counselling on risk-related behaviours) and/or lower viral load levels within the same range among those on treatment.

In the meta-analysis of 11 cohorts, the authors indicated that although no observed transmissions were found from people on HAART with an undetectable viral load on HAART, the data were compatible with one new infection for every 79 person-years of follow-up (62). Similarly, a mathematical model showed that the risk per act for an individual with a viral load of 10 copies per mL was minimal (e.g., cumulative probability of 0.004% for male-to-female sexual transmission per year) (63). However, over a 10-year span, among 10,000 serodiscordant heterosexual partnerships, about 425 seroconversions for male-to-female transmission were predicted. Among 10,000 male partnerships over a 10-year span, about 3,524 seroconversions were predicted due to the higher risk of transmission from anal intercourse (63).

TABLE 4. Estimated risk of transmission by sex act and viral load (regardless of treatment status)[a]

	RISK OF TRANSMISSION PER VIRAL LOAD IN COPIES/ML % RISK PER ACT					
TYPE OF SEX ACT	**10**	**40**	**400**	**1000**	**10,000**	**50,000**
Insertive vaginal	0.001	0.002	0.007	0.010	0.029	0.062
Receptive vaginal	0.002	0.005	0.013	0.020	0.059	0.124
Insertive anal	0.002	0.005	0.013	0.020	0.059	0.124
Receptive anal	0.036	0.069	0.199	0.304	0.881	1.854

Abbreviations: HIV, human immunodeficiency virus.

[a] Calculated with methods used by Wilson et al., 2008 (63). Assumes that each $\log_{10}$ increase in plasma HIV-1 RNA increases the per-act risk of transmission 2.9-fold (19) for all types of sex acts. Assumes risk of transmission per act in the absence of treatment of 0.05% for insertive vaginal intercourse; 0.1% for receptive vaginal intercourse, as used by Wilson et al (2008) (63); 1.5% for receptive anal intercourse (10, 11, 17); and 0.1% for insertive anal intercourse (13, 17, 18).

HAART reduces the risk of transmission by lowering an individual's viral load. However, in order to achieve viral suppression, high levels of adherence are needed (64, 65). While the minimum level of adherence needed to achieve viral suppression has not yet been clearly established, adherence is often defined as being >90% or ≥95% adherent. A meta-analysis of 25 North American studies found that only 59% of those on treatment were adherent (i.e., 59% reported an intake of ≥90% prescribed HAART) (66).

Very little is known about the relationship between HIV viral load and rate of transmission through anal intercourse (10, 16, 62, 67). Recent estimates of per contact risk of transmission through anal intercourse post-HAART were similar to those from the pre-HAART era (17). The similarity in results may be due to differences in sampling and mathematical methods. Alternatively, they may suggest that HIV transmission by anal intercourse is not as closely related to viral load as it is for transmission by vaginal intercourse (17).

Plasma viral load likely acts as a surrogate measure for HIV concentration in genital secretions (68, 69). The concentration of HIV in genital secretions plays a major role in sexual transmission (70, 71). While there is a strong correlation between HIV concentrations in plasma and in genital secretions, a number of factors affect that association. Some studies have found genital tract HIV shedding in 20% to 30% of men and women without detectable plasma viral load (8, 72, 73). Concurrent STIs have been found to increase the occurrence of genital tract HIV shedding, while HAART has been found to suppress HIV replication in the genital tract (70–72). Of note, different classes of HAART vary in their penetration of the genital tract compartments (70–72), and non-adherence to HAART has been associated with persistent genital shedding (71).

2.4.2.1 STAGE OF DISEASE

Primary (early) and late-stage HIV infection are marked by elevated viral load in plasma and in genital secretions (74, 75). Primary HIV infection is characterized by a high degree of viral replication because an immune response has not yet had time to develop. This results in an increased viral load in plasma and genital secretions (75). Primary HIV infection is also associated with a high prevalence of concomitant STIs, in particular GUD, and a lack of awareness of HIV serostatus (12). Thus, those in the primary stage of infection are at particularly high risk of transmitting HIV infection due to elevated viral load and other factors.

A meta-analysis of heterosexual transmission co-factors found that per coital act probabilities were 2.5/1,000 for early stage infection and 1.9/1,000 for late-stage infection compared with 1/1,000 for index partners with infections between those stages (7). A separate meta-analysis found that the risk of heterosexual transmission was 9 times higher when the index partner was in the primary stage and 7 times higher when the index partner was in the late stage of infection (11). These data were taken from studies of heterosexual populations, and it is not clear whether these summary results can be extrapolated to MSM populations because of potential differences in the risks associated with the sex acts these two populations likely practice (i.e., differences in the risks associated with vaginal and anal sex) (8).

Based on observational studies, phylogenetic studies, and mathematical models, the estimated proportion of HIV transmissions attributable to persons with primary or late HIV infection varies greatly, with estimates ranging from less than 1% to greater than 90% (75, 76). The variation probably stems from a differing contribution depending on the stage of the epidemic and characteristics of the population. Primary HIV infection plays a larger role early in the epidemic and in populations where there is a high prevalence of concurrent partnerships and frequent partner change (75, 76). Late-stage infection, despite the increased risk of transmission, is likely to have a limited contribution to an HIV epidemic since those with late-stage infection report less frequent sexual intercourse and fewer partners (77).

2.4.3 HIV-1 GENETIC SUBTYPE

HIV-1 is classified into three genetic groups, M (Major), O (Outlier), and N (non-M and non-O), with most infections globally being caused by group M viruses. Within group M, nine subtypes have been identified, A-D, F-H, J, and K (78). There are also recombinant forms, some of which play important roles in regional epidemics, such as subtype E in South-East Asia (79).

The distribution of the different subtypes varies globally. HIV-1 subtype C accounts for 50% of infections globally and predominates in India, Ethiopia, and southern Africa; HIV-1 subtype B is the dominant subtype in North America, Western Europe, and Oceania; subtype A predominates in Eastern Europe, Central Asia, and East and Central Africa (79).

Different subtypes may have different biological properties, which could have an impact on the efficiency of transmission. The limited number of studies of the relationship between HIV-1 subtype and sexual transmission have yielded inconsistent results. A study in southern Brazil comparing subtypes C and B showed an increased risk of heterosexual transmission associated with subtype C (80), and a study in Thailand found an association between subtype E (compared to subtype B) and increased risk for heterosexual transmission (81). Due to limitations with study design and difficulties in controlling for confounders, it is difficult to determine if there were other factors that may have biased this association between subtype and heterosexual transmission (82). In addition, a study from Uganda, where subtypes A and D predominate, found no significant difference in the distribution of subtypes among incident cases during a decade of follow-up, suggesting that one subtype did not have a selective advantage over the other (83).

2.4.4 CIRCUMCISION

There is substantial evidence that male circumcision decreases the risk of female-to-male sexual transmission. A number of biological explanations account for the increased susceptibility among uncircumcised men. During intercourse the foreskin is retracted, exposing the internal foreskin, which has a greater number of Langerhans cells and other HIV target cells (84, 85). The foreskin is also susceptible to tears and abrasions (85). In addition, circumcision may be protective by reducing the risk of GUD, which is associated with increased risk of HIV acquisition (86).

In addition to numerous observational studies pointing to the protective effect of circumcision (87, 88), the three RCTs that studied the effect of male circumcision all found a 50% to 60% reduced risk of HIV acquisition (89–91). A Cochrane systematic review of the three trials found a reduced risk of 54% at 21 and 24 months following circumcision (92). A separate meta-analysis of the three trials and ten good quality observational studies found a pooled reduced risk of 58% (93) (see Table 5).

Only one RCT has examined the impact of circumcision of HIV-infected men on transmission to women. This trial ended early due to futility (i.e., the likelihood of finding a treatment effect was deemed to be low): after 24 months, 18% of women in the intervention group and 12% of women in the control group acquired HIV, a statistically nonsignificant difference in transmission rates. This trial also pointed to a potential short-term increase in HIV transmission if sex is resumed before the surgical wound is completely healed (94). A meta-analysis of male circumcision and the risk of infection to female partners of HIV-positive circumcised men, which included the above RCT, found little epidemiological evidence to support the existence of a direct protective effect of male circumcision for women (95). Although women may not be directly protected by male circumcision, mathematical models have suggested that women would benefit indirectly from the expansion of male circumcision since the prevalence of HIV among potential male partners would decrease (96).

Numerous observational studies have explored the role of circumcision in the prevention of HIV among MSM with varying results. A meta-analysis of 18 studies found no significant protective effect of circumcision overall. Nor did they find a significant protective effect when the analysis was restricted to men who primarily engaged in insertive anal sex (97). A significant protective association was found when the analysis was restricted to studies conducted pre-HAART, but not when the analysis was restricted to studies conducted post-HAART. The authors suggested this may be due to increases in risky sexual behaviours post-HAART, which may have diminished the relative effectiveness of male circumcision (97).

A Cochrane systematic review of male circumcision and the prevention of HIV among MSM found no statistically significant effect overall. In a subgroup analysis of seven studies of men reporting primarily an insertive role, the pooled estimate was significant and circumcision was found to reduce HIV acquisition among these men (i.e., insertive partners) by 73% (98). However, the authors cautioned that the evidence was of low quality; they noted that all 21 studies included in the meta-analysis were observational rather than experimental in nature.

Also important to note is that the impact of circumcision in this population is likely to be small given that circumcision benefits the insertive partner and most MSM probably become infected through receptive, rather than insertive, anal sex. Further, only a minority of MSM predominantly practice insertive anal sex (98).

TABLE 5. Results of meta-analyses on the impact of circumcision on the risk of sexual transmission of HIV

STUDY	POPULATION	STUDIES INCLUDED IN META-ANALYSIS	RISK ESTIMATE (95% CI)
Siegfried et al., 2009 (92)	Heterosexual men	3 RCTs	IRR 0.46 (0.34–0.62)[a]
Byakika-Tusiime et al., 2008 (93)	Heterosexual men	13 studies (includes 3 RCTs)	aRR 0.42 (0.33–0.53)
Weiss et al., 2009 (95)	Heterosexual women	1 RCT and 6 observational studies	RR 0.80 (0.53–1.36)
Millett et al., 2008 (97)	MSM	15 observational studies	Risk overall OR 0.86 (0.65–1.13) Risk for those primarily engaging in insertive anal sex OR 0.71 (0.23–2.22) Pre-HAART OR 0.47 (0.32–0.69) Post-HAART OR 1.00 (0.77–1.30)
Wiysonge et al., 2011 (98)	MSM	21 observational studies	Risk overall OR 0.86 (0.70–1.06) Risk for those primarily engaging in insertive anal sex OR 0.27 (0.17–0.44)

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IRR, incidence rate ratio; MSM, men who have sex with men; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

[a] Over 24 months.

3.0 HIV TRANSMISSION AMONG PEOPLE WHO USE DRUGS

3.1 BACKGROUND

People who inject drugs (PWID) have high rates of infection with HIV and other blood-borne viruses, such as hepatitis C virus (HCV), mainly due to unsafe injecting behaviour (99). There are more than 13 million PWID worldwide, and most (about 80%) live in low- and middle-income countries (3.1 million in Eastern Europe and Central Asia; 3.3 million in South and South-East Asia; 2.3 million in East Asia and the Pacific) (100, 101). About 2.5 million PWID are HIV-positive (95). In Canada, an estimated 125,000 to 145,000 people inject drugs, and the prevalence of HIV among them varies by city, and has ranged from 1% to 48% (100, 101).

Canadian estimates suggest that the number of incident HIV infections attributed to PWID increased slightly between 2005 and 2008 (1); in 2005, 27% of new cases were related to PWID compared with 29% in 2008 (Figure 1). The national estimates have not dropped, primarily due to an increase in cases attributed to PWID in one province. In most other jurisdictions, newly diagnosed cases of HIV infections in PWID have been stable or declining (1). This trend echoes a pattern seen in other developed countries, including the U.S. and Western European countries (1, 102–104).

The reasons for these changes in epidemiological patterns are not entirely clear. The disproportionate risk of death experienced by PWID in some settings may help to explain why their role in national epidemics has declined dramatically. For example, while PWID accounted for 20.9% of people with diagnosed HIV infection in New York City in 2007, they also accounted for 38.1% of all deaths among HIV-diagnosed individuals (105). Studies suggest that the implementation of prevention programs, which have led to substantial reductions in sharing of injecting equipment, have also contributed to lowering the incidence of HIV infection among PWID (106–108). Finally, the drop in infections among PWID could be due partly to a change in the drugs that are used.

Although not the focus of this review, it is noteworthy that transmission of HCV among PWID is a significant public health problem. This virus is highly transmissible, and prevalence rates tend to be high within the population of PWID (109), often reported at 50% to 90% (110).

3.2 RISK OF TRANSMISSION FROM INJECTION DRUG USE

3.2.1 RISK PER INJECTION WITH A CONTAMINATED NEEDLE AND SYRINGE

Few studies have estimated the risk of HIV transmission per injection with a contaminated needle and syringe (111). Due to difficulties with accurately measuring the number of exposures (i.e., number of times a needle and syringe from an HIV-positive individual was shared) and other risk factors, for example, viral load, such transmission probabilities have been estimated indirectly using mathematical models. These models found the per injection probability of infection from a contaminated needle and syringe to be 0.67% and 0.84% (112, 113) (see Table 6). Much like estimates of the risk from sexual transmission, such summary measures may be misleading as they do not convey the heterogeneity that probably exists in the risk of transmission per injection, which depends on the infectiousness of the HIV-positive person who injects and the susceptibility of the uninfected person (113).

Reports of accidental percutaneous exposure by healthcare workers also provide information about the probability of HIV transmission from a contaminated needle and syringe. These estimates are more reliable, as the number of exposures (i.e., usually one per person) and the infection status of the index case are more likely to be known (111). Literature reviews have reported the risk of transmission from an accidental percutaneous exposure as 0.3% to 0.4% per exposure (114, 115). In a systematic review of 26 papers, the risk of transmission

TABLE 6. Estimates of HIV transmission probability through injection with a contaminated needle and syringe

STUDY	STUDY DESIGN	TYPE OF EXPOSURE	TRANSMISSION PROBABILITY %
Kaplan et al., 1992 (112)	Mathematical model	Use of contaminated needle and syringe	0.67
Hudgens et al., 2001 (113)	Mathematical model	Use of contaminated needle and syringe	0.84 95% CI, 0.7–1.0
Patz et al., 1995 (115)	Literature review	Accidental percutaneous injury	0.3–0.4
Lee et al., 2009 (114)	Literature review	Accidental percutaneous injury	0.3
Baggaley et al., 2006 (111)	Meta-analysis (26 articles)	Accidental percutaneous injury	0.00–2.4
Murray et al., 2003 (117)	Parameter estimation for use in mathematical model	Use of contaminated needle and syringe	2.0 Range: 0.3–3.3
Bayoumi et al., 2008 (116)	Parameter estimation for use in mathematical model	Use of contaminated needle and syringe	0.8 Range: 0.3–4.0

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

ranged from 0.00% (i.e., no risk) to 2.38% per needlestick exposure (111). However, these estimates are likely to be lower than the risk expected from sharing a contaminated needle and syringe for injection drug use since that probably represents a much greater volume of blood than the average needlestick injury (113).

Mathematical modellers have used point estimates of the risk of transmission from a contaminated needle and syringe to predict the costs or efficacy of some prevention programs for PWID. Table 6 presents the values used in two of these models (116, 117). The relatively wide range of values (i.e., bounds) that were used to give validity to the models reflects the heterogeneity of the probability of transmission (118, 119).

Although HIV has been found in injection material from PWID (120), there have been no confirmed reports of HIV transmission from improperly discarded needles outside of the healthcare setting in either the U.S. or U.K. (121). Similarly, a Montreal-based study found no seroconversions in 274 community-acquired needlestick injuries in the pediatric population indicating that the risk of transmission from these events is very low (122). In fact, a certain number of studies have reported that discarded syringes that had been used by an HIV-infected person represent a low risk for HIV transmission (121, 123–132). This is partly due to the low viability of the virus outside the body (133–135).

3.2.2 RISK OF TRANSMISSION FROM SHARING NEEDLES AND SYRINGES

As described above, few studies have focused on the absolute risk associated with using contaminated needles and syringes. However, there are a number of studies that have examined the risk to those sharing needles and syringes relative to those who do not share, and where the HIV status of the injecting partner was unknown. Despite inconsistencies in how sharing needles and syringes was measured, the epidemiological studies that investigated the risk of HIV transmission associated with needle and syringe sharing have all found a positive relationship. In cohort studies conducted across Canada, those who shared needles and syringes were 1.5 to 5.9 times more likely to seroconvert (136–138). In a cross-sectional study conducted in Winnipeg, PWID who ever used someone else's syringe had almost 9 times the risk of HIV infection compared with PWID who never shared (139) (see Table 7).

TABLE 7. Canadian studies reporting the risk of HIV transmission from sharing needles and syringes

STUDY	STUDY DESIGN	LOCATION	MEASURE OF SHARING	RISK (95% CI)
Bruneau et al., 2011 (136)	Cohort	Montreal	Sharing with person known to be HIV-positive Sharing	aHR 5.90 (4.17–8.34) aHR 2.94 (2.00–4.32)
Roy et al., 2011 (137)	Cohort	Eastern central Canada	Receptive sharing	aHR 2.36 (1.83–3.03)
Miller et al., 2006 (138)	Cohort	Vancouver	Receptive sharing	aHR 1.48 (1.00–2.21)
Wylie et al., 2006 (139)	Cross-sectional	Winnipeg	Receptive sharing (ever)	aOR 8.7 (2.0–38.5)

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus.

3.2.3 RISK OF TRANSMISSION FROM DRUG PREPARATION PRACTICES

Although the first studies on HIV transmissibility among PWID focused on needle and syringe sharing, it was soon evident that the situation was more complex than first thought. The steps involved in injecting drugs provide frequent opportunities to share equipment, potentially increasing the risk of HIV transmission even when needles and syringes are not shared or by adding to the risk associated with needle and syringe sharing (104). The following injection steps have been identified as potential risk factors for HIV transmission (140):

- Dividing the drug as a liquid
- Common use of mixing water
- Common use of a cooker
- Drawing up through a cooker
- Backloading/frontloading (dividing the drug using a syringe)
- Squirting back into the cooker
- Common use of a reservoir of rinse water
- Beating the cotton (sharing the cotton filter)

Studies suggest that sharing drug preparation equipment other than needles and syringes (e.g., sharing water, cooker or filter) increases the risk of HIV transmission. In a laboratory study, HIV DNA was detected in injection paraphernalia including cottons, cookers, and wash waters collected from shooting galleries in Miami (120). Further, a few observational studies have shown an epidemiological link between sharing drug preparation equipment and HIV transmission (see Table 8). In addition to the two studies described in Table 8, a Chicago cohort study reported that 10 of the 83 PWID who seroconverted reported sharing only cotton, cookers, or water, but not needles, during the risk period before conversion (141).

Stronger and more consistent evidence exists for the association between drug sharing practices, such as frontloading and backloading, and the risk of HIV transmission, with risk estimates ranging from 2.8 to 3.5 (see Table 8). Backloading is the practice of drawing up the drug into a syringe and then transferring a portion of the solution into a second syringe by removing the plunger of the second syringe. Frontloading involves removing the needle (rather than the plunger) from the second syringe and then drawing back the plunger to allow the first person to squirt in solution. Although these two terms, coined by social scientists, add descriptive precision, frontloading and backloading are functionally similar, and the terms used to describe these practices are varied (e.g. dividing, splitting).

While the prevalence of sharing drug preparation equipment and drug solution varies among PWID, reports consistently describe it as occurring more frequently than needle and syringe sharing (142), especially when people pool money to buy drugs (140). Due to the greater occurrence of these risky practices,

compared with sharing needles and syringes, these sharing behaviours may represent a sizable transmission route for infectious agents (143).

3.3 CO-FACTORS

3.3.1 VIRAL LOAD

There is very little information on viral load among PWID or its impact on the risk of HIV transmission. As previously mentioned, studies of the association between viral load and infectiousness have largely been conducted within the context of sexual transmission.

Of the few studies conducted among people who inject drugs, higher viral loads have been found during outbreaks of HIV among people who inject drugs (119, 150). In addition, community viral load has been shown to be associated with HIV incidence in Vancouver (151). The community viral load is the mean or total of viral load measurements from a population (152). This measure excludes those who are unaware of their HIV status, which could introduce bias into the estimate (152). Community viral load is an aggregate measure, thus any association with this group-level measure is subject to ecological fallacy (i.e., an association between aggregate measures does not necessarily reflect a causal relationship at the individual level) (152, 153). With these limited data, it is still unclear to what degree increases in viral load are related to increases in HIV transmission among PWID.

3.3.2 LOCATIONS

Several studies have demonstrated that risky injecting practices occur, in part, in response to the setting in which drug use takes place. Risky practices have been found to be more likely in visible areas without privacy, including alleys, cars, shooting galleries, parks, abandoned buildings, and public bathrooms (140). These physical environments are linked with less access to clean injecting equipment and difficulties with maintaining safer injecting routines due to worries about disruptions and getting caught by police (154–156). Shooting galleries are places where PWID gather to inject drugs, where injection material can be easily exchanged, and where sex workers are sometimes hired to provide clients with sex (157).

Studies show that people who inject drugs in the locations described above engage in significantly more HIV-related risk behaviours (158). Injecting in such locations is associated with 2 to 5 times the likelihood of sharing needles, syringes, and ancillary equipment (140, 159, 160). A cross-sectional study of PWID in Winnipeg found that those who reported injecting in shooting galleries were 2.9 times more likely to be HIV-positive (139). Similar increases in risk associated with location have been reported in other cities (159, 161).

TABLE 8. Studies reporting the risk of sharing drug preparation equipment and drug solutions

STUDY	STUDY DESIGN	LOCATION	EXPOSURE	RISK (95% CI)
Brogly et al., 2000 (144)	Cohort	Montreal, Canada	Shared injection equipment (other than needles and syringes)	aHR 2.3 (1.06–4.95)
Zhang et al., 2007 (145)	Cohort	Xinjiang, China	Sharing rinse water	aOR 1.47 (1.18–1.84)
Stark et al., 1996 (146)	Cross-sectional	Berlin, Germany	Frontloading	aPOR 3.5 (1.4–9.0)
Platt et al., 2008 (147)	Cross-sectional	Togliatti, Russia	Frontloading	aOR 3.1 (1.44–6.79)
Quan et al., 2008 (148)	Matched case-control	Bac Ninh, Vietnam	Frontloading	aOR 2.8 (1.17–6.48)
Kruse et al., 2009 (149)	Cross-sectional	St Petersburg, Russia	Frontloading, backloading, sharing cotton and cookers	Significant predictor of HIV status among heroin-only users[a]

Abbreviations: aPOR, adjusted prevalence odds ratio; aOR, adjusted odds ratio; aHR, adjusted hazard ratio; CI, confidence interval.

[a] No risk estimates provided.

3.3.3 TYPE OF DRUG

The type of drug most often injected also has an impact on risky injecting practices. Cocaine in particular has been associated with binge drug use (138), which *typically* involves erratic behaviours, in turn leading to increased likelihood of unsafe injecting practices (162).

Cross-sectional studies have found an association between injecting stimulants, cocaine or crack cocaine and increase in risky practices (149, 163–165) (see Table 9). In cohort studies, injecting crack cocaine or cocaine has been associated with 2.1 to 3.7 times the risk of HIV seroconversion (137, 166, 167) (see Table 9).

TABLE 9. Type of drug and association with injecting risk behaviours and HIV transmission

STUDY	STUDY DESIGN	LOCATION	TYPE OF DRUG INJECTED	OUTCOME	RISK (95% CI)
Buchanan et al., 2006 (164)	Cross-sectional	3 U.S. cities	Crack cocaine – ever injected	>120 injections in previous month Receptive sharing of needles and syringes	aOR 3.13 (1.45–6.74) aOR 1.91 (1.09–3.35)
Santibanez et al., 2005 (163)	Cross-sectional	6 U.S. cities	Crack cocaine	Injected in shooting gallery Injected with known HIV-positive person	OR 2.5 (1.9–3.2) OR 2.2 (1.6–3.0)
Kruse et al., 2009 (149)	Cross-sectional	St Petersburg, Russia	Stimulants-only	Receptive needle sharing	Significant associationa
Booth et al., 2008 (165)	Cross-sectional	3 cities in the Ukraine	Stimulants only	Sharing a used needle/syringe Always injecting with others Injecting drug solution from common container	Significant association[a]
Tyndall et al., 2003 (167)	Cohort	Vancouver, Canada	Cocaine	HIV seroconversion	aHR 3.72 (2.44–5.67)
Nelson et al., 2002 (166)	Cohort	Baltimore, U.S.	Cocaine only	HIV seroconversion	3.24 (2.12–4.93)
Roy et al., 2011 (137)	Cohort	Eastern central Canada	Cocaine most often	HIV seroconversion	aHR 2.05 (1.43–2.92)
Santibanez et al., 2005 (163)	Cross-sectional	6 U.S. cities	Crack cocaine	HIV-positive serostatus	OR 1.0 (0.5–2.0)
Buchanan et al., 2006 (164)	Cross-sectional	3 U.S. cities	Crack cocaine – ever injected	HIV-positive (self-reported)	1.00
Booth et al., 2008 (165)	Cross-sectional	3 cities in the Ukraine	Stimulants only	HIV serostatus	Not significant[a]

Abbreviations: aOR, adjusted odds ratio; aHR, adjusted hazard ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

[a] No risk estimates provided.

3.4 RISK OF SEXUAL TRANSMISSION AMONG PEOPLE WHO INJECT DRUGS

Although the HIV epidemic among PWID is driven primarily by the sharing of injecting equipment, over the past decade the prevalence of syringe sharing has decreased. Studies have shown that after accounting for injecting behaviours, sexual transmission is becoming an important route of transmission (168–170). HIV seroconversion among PWID has been independently associated with having an HIV-positive sexual partner and engaging in high risk sex behaviours (e.g. multiple sexual partners, sex trade work, and inconsistent use of condoms) (171, 172). From 2003–2009, among PWID recruited from prevention programs in eastern central Canada, sex work emerged as a new determinant of HIV incidence for participants (137).

Within the heterogeneous group of PWID, the reasons for engaging in risky sexual practices vary by gender, type of sexual interaction, and type of drug used (168). Sexual risks among PWID are often discussed within the context of intimate serodiscordant relationships, of sex trade work or transactional sex, and the synergistic effects of parenteral and sexual risk behaviours (168, 169).

Studies among PWID consistently report low levels of condom use and increased frequency of sharing injecting equipment with regular sex partners (173–175). In this context, risky injecting and sexual behaviours have been linked with valuing intimacy and the relationship above concerns about health risks, established gender roles, or stigma associated with disclosing HIV status (176).

There is some overlap between networks of PWID and that of sex trade workers. A sizeable proportion of commercial sex workers have been found to inject drugs, and PWID may sell or trade sex for drugs. Between 2003 and 2005, a Canadian HIV behavioural and biological surveillance system among PWID (I-Track) found that roughly one-third (32.1%) of women reported male client sex partners, 2.8% of men reported female client sex partners, and 6.2% of men reported male client sex partners within the previous 6 months (142). Financial pressures resulting from drug dependency means that sex trade workers who inject drugs may feel less able to insist on consistent condom use with their commercial sex partners. Compared with non-injecting sex workers, sex workers who injected were 40% less likely to have used a condom in the last episode of sex work (177). Sex workers have also been shown to be more likely to engage in risky injecting practices, when compared with their non-sex worker counterparts (178, 179). In studies in Montreal and Vancouver, PWID involved in the sex trade were 2 to 3 times more likely to engage in injecting risk behaviours than were PWID who were not in the sex trade (178).

PWID who engage in risky sexual behaviours are exposed to multiple potential transmission routes, resulting in higher rates of HIV seroconversion and/or prevalence. This is especially true for MSM (180). In San Francisco, MSM who injected drugs were almost 8 times more likely to be HIV-positive than MSM who did not (181). Studies in different settings have made similar observations (182–186). In Vancouver, MSM who injected drugs were twice as likely to report unprotected receptive anal intercourse with casual partners during the previous year compared with MSM who did not inject drugs (187). In the same cohort, MSM who practiced unprotected receptive anal intercourse with casual partners were 5 times more likely to seroconvert (188).

3.5 RISK OF TRANSMISSION AMONG PEOPLE WHO USE NON-INJECTION DRUGS

Use of some non-injection drugs has been reported as independent risk factors for HIV transmission. Crack smoking alone and amphetamines have been found to be independent risk factors for HIV seropositivity, increasing the risk 2- to 3-fold (182, 189, 190). Important limitations with these studies include their dependence on self-reported data and the difficulty of properly adjusting the analyses for confounding factors. Non-identified confounding factors outside of the knowledge of the investigating team could be at play, and answers to some questions have the potential to be biased.

Information on the mechanisms of HIV transmission solely through smoking or snorting is limited. Sharing drug paraphernalia like straws, banknotes and crack pipes or stems has been proposed as a transmission route. However, transmission of HIV through nasal secretion is low unless there is blood in the secretions (191). Blisters, sores, and cuts on the lips and in the mouths of crack smokers may facilitate oral transmission of HIV (192–194), with the evidence supporting this causal relationship building but still sparse (22, 192, 195, 196).

HIV transmission among people who use drugs through non-injecting routes may also be due to sexual contact. Studies have found that the exchange of sex for drugs and drugs for sex is pervasive in this group (197, 198).

It has also been suggested that high rates of HIV in people who use non-injection drugs may be the result, in part, of the effects of "bridging" or mixing with PWID, due to overlapping social and sexual networks (198). Women are especially vulnerable due to a greater likelihood of overlap between their drug and sexual networks (198).

Drug use can alter sexual behaviours by increasing risk taking. Research that has investigated this issue has focused mainly on crack cocaine and amphetamine use. Crack smoking has been associated with increased numbers of sex partners (199, 200), exchanging sex for drugs or money (201, 202), and unprotected sex (157, 203, 204). Amphetamines have also been associated with the risk of HIV transmission because they are often used to enhance and prolong sexual pleasure and to reduce sexual inhibitions (205, 206). Use of marijuana, ecstasy, poppers, cocaine, opiates, alcohol and erectile dysfunction medications has also been linked to risk-taking behaviours during sexual encounters (207–223).

These risky behaviours have the potential to be significant in some populations depending on the number of drug users. For example, a survey of HIV-seropositive MSM in 12 different U.S. states over 5 years found that 33% of the participants reported using alcohol, 51% marijuana, 31% non-injected cocaine, 16% crack cocaine, 13% injected cocaine, 8% injected heroine, and 8% injected stimulants (224).

These behaviours do not seem to change with aging. Although older drug users (50 years and older) are less likely to have sex than their younger counterparts, those who did reported risky sexual behaviours similar to those of younger drug users (225). Among the older drug users, those who smoked crack were at especially high risk of engaging in risky sexual behaviours (225).

Overall, the risk of HIV per sexual act in non-injection drug users is comparable to that of the rest of the population (this topic was covered earlier in the report). Drug users' higher risk of contracting HIV stems predominantly from an increased frequency of risk-taking behaviours during sexual encounters and prolonged intercourse before orgasm due to difficulties associated with ejaculation (193).

4.0 MOTHER-TO-CHILD TRANSMISSION

4.1 BACKGROUND

The number of Canadian women living with HIV is increasing (1), resulting in a growing number of infants who are perinatally exposed to HIV (2, 3). From 1990 to 1996 the average number of perinatally exposed infants was 53 per year, while from 1997 to 2010 the average number was 166 per year (2). However, the proportion of infants who were subsequently confirmed to be HIV-positive has declined dramatically since HAART was introduced in 1997. From 1990 to 1996 the rate of mother-to-child (vertical) transmission was 20.2% (n=73/362); since 1997 the rate has dropped to 2.9% (n=66/2297) (2). The Canadian rates of vertical transmission mirror those from other developed countries (see Table 10). Before HAART the rate of vertical transmission ranged from 14% to 33% in developed countries, and after HAART the rate ranged from 0.6% to 6% (2, 226–231).

Vertical transmission can occur through 3 routes: during gestation by microtransfusion of maternal blood across the placenta; during labour and delivery through exposure to maternal blood and genital tract secretions; and after the birth through breastfeeding (232).

This section starts with a review of the co-factors associated with the risk of vertical transmission during gestation and delivery. This is followed by a description of the risk of transmission and co-factors associated with breastfeeding.

4.2 RISK OF VERTICAL TRANSMISSION DURING GESTATION AND DELIVERY

For non-breastfeeding populations, about 4% of transmissions occur during the first 14 weeks of gestation, 16% between 14 and 36 weeks of gestation, half in the days before delivery, and another 30% during active labour and delivery (233). In the absence of any preventive intervention, it has been estimated that the probability of transmission during gestation and delivery ranges from 15%–30% (232).

TABLE 10. Rate of vertical HIV transmission before and after the introduction of HAART in developed countries

STUDY	SETTING	RATE OF TRANSMISSION PRE-HAART %	RATE OF TRANSMISSION POST-HAART %
Newell et al., 1996 (226)	7 European countries	16.4	
The Working Group on Mother-to-Child Transmission of HIV, 1995 (227)	European and North American countries	14–25	
Forbes et al., 2012(2)	Canada	20.2	2.9
Birkhead et al., 2010 (228)	New York State		4.2
Townsend et al., 2008 (229)	United Kingdom and Ireland		1.2
McDonald et al., 2009 (230)	Australia	32–33	6
Naver et al., 2006 (231)	Sweden	25	0.6

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

4.2.1 MATERNAL VIRAL LOAD

Maternal plasma viral load has been consistently associated with the risk of vertical transmission (234). Prospective cohort studies have shown that rates of transmission increase with corresponding increases in maternal plasma viral load (235–238). In a Zimbabwe study of HIV-positive women, for every 10-fold increase in maternal plasma viral load, a two-fold increase was seen in the rate of vertical transmission (235). There is no reported threshold below which transmission does not occur (237).

Viral load is high immediately following infection (i.e., during primary HIV infection) and in the advanced disease stage (as evidenced by low CD4 cell count). While vertical transmission during either of these stages of infection has not been well described, it is likely that the risk of infection increases with these stages of infection (232).

The amount of virus present in the genital tract has also been found to have an impact on the risk of mother-to-child transmission. An analysis of HIV-positive women who had vaginal deliveries found that the presence of HIV in the genital tract was associated with a 3-fold increase in the risk of vertical transmission, and each 10-fold increase in the mean titer of HIV DNA was associated with an almost 2-fold increase in the risk of vertical transmission (239). A nested case-control study found that cervical or vaginal shedding of HIV increased the risk of infant infection by more than 2 times, independent of maternal plasma viral load (240).

4.2.2 HIV-1 GENETIC SUBTYPE

There is some debate about whether maternal HIV-1 subtype can affect the risk of vertical transmission (82). The limited number of studies conducted have produced inconsistent results. Some have suggested that vertical transmission was more common in mothers infected with some subtypes (241–243), while others found no significant differences in the likelihood of vertical transmission between subtypes (244, 245). The inconsistent results may be due to differences in the study populations' virus or host, in environmental factors, or in study design and ability to control for confounders (79).

4.2.3 CO-INFECTIONS

Concurrent STIs have been found to increase the risk of vertical transmission. Specifically, observational studies suggest that GUD, including HSV-2 and syphilis, and non-GUD, including gonorrhea, increase the risk of HIV vertical transmission (240, 246–248). However, the role that STIs play in vertical transmission is unclear. They may contribute to the risk of transmission through increased genital shedding of HIV, local inflammation, or increased viral load (249).

Chorioamnionitis (bacterial infection of the fetal membranes and amniotic fluid), caused by ascending sexually transmitted or non-sexually transmitted bacterial infections, has been associated with a 4- to an almost 8-fold increase risk of vertical transmission (250, 251). However, an RCT found no difference in the rates of vertical transmission between women treated for chorioamnionitis with antibiotics and women given a placebo (252).

Co-infection with either HCV or active tuberculosis has also been associated with increased risk of vertical transmission of HIV (249, 253, 254). HCV may increase the risk of transmission through immunosuppression (253), while active tuberculosis is associated with high viral loads and placental inflammation, which may be the mechanisms for the increased risk of vertical transmission (254).

4.2.4 MODE OF DELIVERY

The results of an RCT and a meta-analysis indicated that elective caesarean section (caesarean delivery before labour and before ruptured membranes) lowers the risk of vertical transmission by 50% to 80% (255, 256). However, most of the studies took place before the widespread use of HAART, and participants in the RCT and in the observational studies used in the meta-analysis did not receive any antiretroviral drugs or received only one type during pregnancy.

Prenatal HAART substantially reduces the risk of transmission; studies indicate that there are likely no additional benefits to elective caesarean section for women with low viral loads, who are receiving HAART. In a 21-year review of vertical transmission in Canada, there was no significant difference in rates of transmission between vaginal deliveries and deliveries by caesarean

section when women received HAART. However, for those women who received sub-optimal or no therapy, the rate of HIV transmission with caesarean section deliveries was significantly lower (2). Given the higher risk of postpartum morbidity associated with caesarean section (257), most guidelines in developed countries, including Canada, no longer recommend routine elective caesarean sections for HIV-positive pregnant women (2, 258, 259)

4.2.5 OBSTETRIC EVENTS

Amniotic membrane rupture that occurs over a prolonged period of four hours or more before delivery increases the risk of transmission (260). A meta-analysis found that risk of transmission increases roughly 2% with each hour after membrane rupture . Intrapartum use of fetal scalp electrodes or fetal scalp pH sampling have been found to increase the risk of perinatal transmission of HIV by 5 (261).

4.2.6 MATERNAL BEHAVIOURS

Smoking and illicit drug use have been associated with increased risk of vertical transmission (262–264). A number of biological mechanisms have been suggested to explain how these behaviours influence transmission. Smoking, illicit drug use, and STIs are associated with obstetric complications, including premature rupture of membranes, that in turn, are associated with increased risk of HIV transmission (265). Cocaine use has been shown to increase HIV replication (263). Cocaine use and cigarette smoking have also been associated with placental damage, which might enhance *in utero* HIV transmission (264, 265).

4.3 RISK OF VERTICAL TRANSMISSION THROUGH BREASTFEEDING

Based on the results of two meta-analyses and an RCT, the probability of mother-to-child transmission of HIV through breastfeeding is in the range of 9% to 16% (266–268). A number of co-factors affect this risk of transmission. These co-factors, which include duration and pattern of breastfeeding, maternal breast health, and high plasma viral load, are described in greater detail below.

4.3.1 DURATION AND PATTERN OF BREASTFEEDING

A meta-analysis that used individual patient data found a risk of HIV transmission of 0.8% per month of breastfeeding (268). This risk was found to be both constant and cumulative throughout the breastfeeding period, resulting in a greater risk of transmission as the duration of breastfeeding increased (268). The pattern of breastfeeding may also have an impact on risk of transmission. In a comparison of mothers who breastfed exclusively, never breastfed, or who mixed breastfeeding and formula feeding, it was found that the cumulative probability of HIV transmission at six months was similarly low in those who breastfed exclusively and who never breastfed, but was higher in those who practiced mixed feeding (269). It was hypothesized that contaminated fluids and foods introduced in mixed feeding damage the lining of the stomach and intestines and facilitate the entry of HIV found in breast milk (269).

4.3.2 MATERNAL BREAST HEALTH

Breast problems, such as cracked or bleeding nipples, mastitis, or breast abscesses are associated with increased breast milk viral load and increased risk of postnatal transmission through breastfeeding (240, 270, 271). For example, a study conducted in Kenya reported that women with breast abscesses had 51.6 times the risk of late HIV transmission (occurring >2 months postpartum) and 21.8 times the risk of late transmission if the mother had mastitis (240). In another Kenyan study, maternal nipple lesions and mastitis were associated with 2 to 3 times the risk of postnatal transmission (272).

4.3.3 VIRAL LOAD

While data are limited, studies suggest that viral load in plasma and breast milk is an important determinant of transmission risk from breastfeeding (see Table 11). With each 10-fold increase in breast milk viral load, the risk of vertical transmission via breastfeeding increased 2-fold (273). The probability of breast-milk infectivity was found to be 4 times higher for mothers with more advanced disease with higher prenatal plasma viral loads (274). One study reported that maternal plasma viral load and detectable breast milk viral load were independently associated with 2 to 3 times the risk for mother-to-child

transmission of HIV up to 12 months of age (270). However, this study was limited in that it was not able to determine when transmission occurred in the HIV-infected infants (270). More recent research reported that mastitis was associated with postnatal transmission only when maternal plasma viral load was high (>5000 copies/mL) (275).

As mentioned earlier, plasma viral load is highest during primary and late-stage HIV infection, and these two stages of disease have been associated with an increased risk of transmission through breastfeeding (238,264,272).

TABLE 11. Summary of findings on the risk of maternal viral load and risk of transmission via breastfeeding

STUDY	TYPE OF STUDY	RELATIONSHIP BETWEEN VL AND TRANSMISSION VIA BREASTFEEDING
Rousseau et al., 2003 (273)	Secondary analysis of RCT data (275 women)	Each 10-fold increase in breast-milk VL associated with 2.0-fold increase in risk of transmission (95% CI, 1.3–3.0)
Richardson, et al., 2003 (274)	Secondary analysis of RCT data (358 liveborn singletons and twins)	Prenatal VL ≥43,000 copies/mL: risk per day of exposure=0.00044 (0.00019–0.00075) Prenatal VL <43,000 copies/mL: risk per day of exposure=0.00011 (0.00003–0.00025)
Semba et al., 1999 (270)	Secondary analysis of RCT data (134 women)	Detectable breast milk VL associated with vertical transmission of HIV to 12 months of age: OR, 2.97; (95% CI, 1.25–7.04)
Lunney et al., 2010 (275)	Secondary analysis of RCT data (559 mother-infant pairs)	Mastitis associated with postnatal transmission only when maternal plasma VL was >5000 copies/mL

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; RCT, randomized controlled trial; VL, viral load.

5.0 CONCLUSIONS

Over 250 papers were reviewed for this summary of the evidence on the risk of HIV transmission. Based on this large body of evidence, it is clear that certain acts confer greater risk of HIV transmission. In sexual transmission, unprotected receptive anal intercourse involves the greatest risk. For people who inject drugs, sharing used needles, syringes and other injecting equipment is risky. Vertical transmission is more likely to occur among women with high viral loads who are not receiving HAART.

The literature on this topic is clear that an individual's risk of HIV transmission is complex and depends on a number of behavioural and biological co-factors. It remains difficult, however, to accurately quantify the risk of transmission associated with specific acts. Across the routes of transmission, viral load appears to be an important predictor of transmission. However, while viral load (especially plasma viral load) is a key factor in whether HIV is transmitted, the evidence indicates that it is not the only determinant, and other co-factors play a role in increasing or decreasing the risk of transmission.

It is also clear from the literature that gaps in knowledge continue to exist. In sexual transmission, for example, much of what we know about viral load comes from studies of heterosexual couples. Very little is known about the effect of viral load on the risk of transmission for men who have sex with men and for injection drug users. This review of the evidence points to the growing and evolving nature of our knowledge of HIV transmission risk and the biological and behavioural co-factors that impact on risk.

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