BRIEF — SYNOPSIS OF THE CURRENT EVIDENCE ON THE RISK OF HIV TRANSMISSION

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KEY WORDS: HIV/AIDS, TRANSMISSION

Structured abstract

BACKGROUND:
Knowledge of the risk of HIV transmission has evolved over the past decade as evidence on the impact of biological and behavioural co-factors, such as viral load, has come to light. We undertook a comprehensive review of the evidence on the risk of 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. For topics where no reviews existed, primary research studies were included.

RESULTS:
The risk estimates for the sexual transmission of HIV, per sex act, ranged 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; and approximately 0.05% to 0.1% for insertive vaginal intercourse. For people who inject drugs, the risk of transmission from a contaminated needle, per injection, was estimated to be between 0.7% and 0.8%. A number of factors impact the risk, including viral load, the presence of other sexually transmitted infections (STIs), and male circumcision.

CONCLUSIONS:
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 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., male circumcision) the risk of transmission.

Introduction
Knowledge of the risk of HIV transmission and the co-factors that impact on risk, particularly viral load and its role in the transmission of HIV, is evolving. This information is valuable to health care professionals conducting risk assessments and counselling. It also provides a foundation for a better understanding of emerging HIV prevention approaches. In 2011, an estimated 84% of new infections were attributed to sexual transmission (47% among men who have sex with men (MSM); 17% heterosexual/endemic exposure; and 20% heterosexual/non-endemic exposure), and 14% of new infections were among people who inject drugs (PWID) (1).
Understanding the biological determinants of HIV transmission is essential for making predictions on the potential spread of HIV infection in a population, directing appropriate prevention strategies, and assessing the risk of infection to an individual who has been exposed to the virus. Our current knowledge of HIV transmission comes from various types of evidence, including animal studies, observational studies, randomized clinical trials (RCTs) and systematic reviews.

This is a summary of the current evidence on sexual transmission and transmission via injection and other drug use, the two most common routes of transmission in Canada. A review of the evidence on the risk of vertical transmission, in addition to a more detailed description of the risk associated with sexual transmission and transmission via drug use, can be found in the full document. (2).

Methods
We searched Scopus, Embase and CINAHL, and limited the search to articles published between 2001 and 2012 in English and French. Systematic reviews were the focus of the search. Where reviews did not exist, we included primary research studies. Key studies or commonly referenced publications outside of the 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.

Results
SEXUAL TRANSMISSION
Although there are challenges in quantifying risk by sex act, anal intercourse has consistently been shown to be a higher risk act than vaginal intercourse, which in turn is a higher risk act than oral intercourse. There is also a higher risk associated with receptive intercourse (both vaginal and anal) compared with insertive intercourse (Table 1).

The risk estimates for the transmission of HIV via anal intercourse, per sex act, ranges from 0.5% to 3.38% for receptive anal intercourse (3-6) and 0.06% to 0.16% for insertive anal intercourse (6-8). While most of these estimates are based on studies of MSM, the risk associated with anal intercourse appears to be similar within heterosexual populations (4).

The risk estimates of HIV transmission from receptive vaginal intercourse (male-to-female) range from 0.08% to 0.19% (5, 6, 9); and 0.05% to 0.1% for insertive vaginal intercourse (female-to-male) (6, 9).

A meta-analysis suggested a low but non-zero transmission probability from unprotected oral intercourse (whether penile-oral or vaginal-oral) (10). The risk of transmission to the receptive partner during oral intercourse increases with ejaculation and in the presence of oral ulcers and oropharyngeal sexually transmitted infections (STIs) (10, 11).

VIRAL LOAD
Plasma viral load is the strongest predictor of sexual transmission of HIV (12). For each 10-fold increase in plasma viral load, the relative risk of transmission increases by 2.9 per sexual contact (9). The use of highly active antiretroviral therapy (HAART), which lowers viral load, was associated with a 96% reduction in the number of linked transmissions in an RCT of serodiscordant couples (most of which were heterosexual) (13). It is currently unclear whether there is a viral load threshold under which transmission no longer occurs. Also, little is known about the impact of viral load on the risk of transmission via anal intercourse. It is possible that the degree of risk reduction associated with HAART is not as great for this higher risk route of transmission. The results of ongoing studies (the PARTNER and Opposites Attract studies) will be useful in answering this question.
Plasma viral load likely acts as a surrogate measure for HIV viral load in genital secretions (14), which plays a major role in sexual transmission (15-17). Concurrent STIs have been found to increase genital tract HIV shedding (15-17). Although HAART has been found to suppress HIV replication in the genital tract, non-adherence has been associated with persistent genital shedding of the virus (16). Further, shedding of the virus in the genital tract has been found even among those with undetectable plasma viral load (18, 19). The implications of this finding on the risk of transmission are currently unclear.

Primary (early) and late-stage HIV infections are marked by elevated viral load in plasma and in genital secretions (20, 21). In primary infections, this is due to the high degree of viral replication prior to the development of an immune response (20). Those in the primary stage of infection may also have other risk factors that led to the HIV infection (22). Late-stage infection, despite the elevated viral load, 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 (21).

**SEXUALLY TRANSMITTED INFECTIONS (STIs)**

STIs have consistently been associated with increased susceptibility to HIV in observational studies (23). Several systematic reviews of high quality observational studies found that the presence of STIs increased 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 also exposure categorized as “any STI,” "genital ulcer disease (GUD),” and “non-ulcerative STIs” (24-26). More recent observational studies have also associated the presence of human papillomavirus (HPV) with HIV acquisition among women, heterosexual men, and MSM (27, 28).

Studies indicate that STIs are also associated with increased infectiousness. Much of the evidence for this relationship comes from indirect approaches such as clinical studies that examine the possible biological mechanisms underlying the association. Few observational studies have examined this association (29); however, a systematic review of two studies found that genital ulcers and syphilis significantly increased the risk of HIV transmission 2- to 3-fold (24).

In contrast to the results of observational studies, the results of RCTs examining the impact of STI treatment on the risk of HIV transmission have been equivocal. The results of nine trials have been published to date: six assessed the effects of treating curable STIs, and three examined the impact of herpes suppressive therapy (30). The only trial to find a significant impact was the Mwanza (Tanzania) trial, which found a 40% reduction in HIV incidence following improved STI treatment services (31). The equivocal results may have been due to the type of epidemic within the community (30). In concentrated HIV epidemics, such as in Mwanza, treatable STIs may be an important co-factor in HIV transmission, which might not be the case in generalized epidemics found in the other trials (30, 32). Suboptimal adherence to HSV-suppressive therapy and a lack of power may have led to the inability of HSV treatment trials to demonstrate a significant effect (23, 30).

**INTACT FORESKIN IN MEN**

The three RCTs that studied the effect of male circumcision all found a 50% to 60% reduced risk of HIV acquisition (33). However, there is little epidemiological evidence to suggest that circumcision reduces the risk of transmission to female partners of circumcised men (34) or is effective in the prevention of HIV among MSM, except perhaps for men who report primarily an insertive role (35).

**TRANSMISSION VIA DRUG USE**

**USE OF INJECTION DRUGS**

The probability of HIV transmission per injection with a contaminated needle and syringe has been estimated indirectly using mathematical models, 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 (e.g., viral load). Based on these models, the per injection probability of infection from a contaminated needle and syringe was found to be between 0.67% and 0.84% (36, 37). Much like estimates of the risk from sexual transmission, such
summary measures may be misleading as they do not convey the heterogeneity that exists in the risk of transmission per injection (37).

A number of observational studies have examined the risk of sharing, relative to not sharing, needles and syringes, where the HIV status of the injecting partner was unknown. Despite inconsistencies in how sharing needles and syringes was measured, studies have consistently found a positive relationship between the risk of HIV transmission, and needle and syringe sharing. In cohort studies conducted across Canada, those who shared needles and syringes were 1.5 to 5.9 times more likely to seroconvert (38, 39).

Studies suggest that sharing ancillary injecting equipment (e.g., water, cookers or filters) also increases the risk of HIV transmission. In a laboratory study, HIV DNA was detected in injection paraphernalia collected from shooting galleries in Miami (40) and observational studies have shown an epidemiological link between sharing drug preparation equipment and HIV transmission (41, 42).

**VIRAL LOAD**

There are few good quality studies on the association between viral load and the risk of transmission among PWID. For PWID on HAART, the degree of reduction in infectiousness is not known. Higher plasma viral loads have been found during outbreaks of HIV among PWID (43, 44). In addition, the community viral load of PWID was associated with HIV incidence in Vancouver (45). The community viral load is the mean or total of viral load measurements from a population (46). 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) (46).

**SEXUAL TRANSMISSION AMONG PWID**

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 in this group (47). HIV seroconversion among PWID has been independently associated with having an HIV-positive sexual partner and engaging in risky sex behaviours (e.g., multiple sexual partners, sex trade work, and inconsistent use of condoms) (48, 49).

**USE OF NON-INJECTION DRUGS**

Use of some non-injection drugs has been reported as an independent risk factor for HIV transmission. Crack smoking (in isolation) and amphetamine use have been identified as independent risk factors for HIV seropositivity, increasing the risk 2- to 3-fold (50, 51). Important limitations with these studies include their dependence on self-reported data and the difficulty of adjusting for confounding factors.

There is limited information on the mechanisms of HIV transmission solely through smoking or snorting. Sharing drug paraphernalia, like straws, banknotes, and crack pipes or stems, has been proposed as a transmission route. Blisters, sores, and cuts on the lips and in the mouths of crack smokers may facilitate oral transmission of HIV (52-54), with the evidence supporting this causal relationship building but still sparse (11).

**Conclusion**

An individual’s risk of HIV transmission is complex and depends on a number of behavioural and biological co-factors. It remains difficult to accurately quantify the risk of transmission associated with specific acts, however, in sexual transmission, unprotected receptive anal intercourse involves the greatest risk. Across the routes of transmission, plasma viral load appears to be an important predictor of transmission. However, while 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. This review of the evidence points to the
The growing and evolving nature of our knowledge of HIV transmission risk and the biological and behavioural co-factors that impact on that risk.

Acknowledgements

Many thanks to Chris Archibald, Christopher Boodram, Katherine Dinner, Katie Freer, Brian Gottheil, Ping Yan, and Ameeta Singh for their review and comments on the full document.

Conflict of interest statement

There are no conflicts of interest to declare.

Funding

This work was supported by the Public Health Agency of Canada.

<p>| TABLE 1. ESTIMATES OF THE PER-SEX-ACT AND PER-INJECTION RISK OF TRANSMISSION |
|-------------------------------------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Route of transmission</th>
<th>Transmission probability</th>
<th>References</th>
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<tbody>
<tr>
<td>Receptive anal intercourse</td>
<td>0.5% to 3.38%</td>
<td>(2-5)</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>0.06% to 0.16%</td>
<td>(5-7)</td>
</tr>
<tr>
<td>Receptive vaginal intercourse</td>
<td>0.08% to 0.19%</td>
<td>(4,5,8)</td>
</tr>
<tr>
<td>Insertive vaginal intercourse</td>
<td>0.05% to 0.1%</td>
<td>(5,8)</td>
</tr>
<tr>
<td>Oral intercourse</td>
<td>low but non-zero</td>
<td>(9)</td>
</tr>
<tr>
<td>Sharing contaminated needle and syringe</td>
<td>0.67-0.84</td>
<td>(35,36)</td>
</tr>
</tbody>
</table>

References


