

SCIENTIFIC RESEARCH ON THE RISK OF THE SEXUAL TRANSMISSION OF HIV INFECTION AND ON HIV AS A CHRONIC MANAGEABLE INFECTION

Update of section 3, “Scientific research on the risk of the sexual transmission of HIV infection on HIV and on HIV as a chronic and manageable infection,” in E. Mykhalovskiy, G. Betteridge and D. McLay, *HIV Non-Disclosure and the Criminal Law: Establishing Policy Options for Ontario*, August 2010. A report funded by the Ontario HIV Treatment Network.

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The context of this section

As set out in the previous section, Canadian courts have yet to clarify the legal meaning of the central element of assault-based HIV non-disclosure offences, namely “significant risk.” The inconsistency in the interpretation and application of the “significant risk” test is attributable in part to the complex and rapidly evolving nature of scientific research on HIV sexual transmission risks. Counsel and courts have struggled to adequately take into account this science. They have not firmly established the role that scientific knowledge regarding HIV transmission should play in the interpretation of the significant risk test or in the application of that test to the evidence in the particular circumstances of a case.

Principled development in areas of the criminal law that involve scientific controversy depends upon counsel and scientific expert witnesses providing context and clarity, and recognizing areas where consensus does and does not exist. This point was emphasized in the Goudge Report. In the context of HIV non-disclosure, such an approach will promote fairness in the criminal justice system. It will help clarify for people living with HIV the scope of their legal duties under the criminal law. It will encourage consistent exercise of discretion, based on current knowledge about HIV transmission risk, among police and Crown Counsel and help to alleviate concerns that their concerns are based on an inaccurate understanding of the risk of HIV transmission. Finally it will help respond to concerns that stigma and ignorance of HIV influence decision-making in HIV non-disclosure prosecutions.

This section of the report reviews scientific research on the risk of transmitting HIV through sexual activities. The goal of the review is to bring context and clarity to the literature, while highlighting areas where consensus exists and where knowledge is uncertain and still developing. This section also reviews the literature on HIV as a chronic manageable infection. As our discussion indicates, with the advent of HIV

antiretroviral therapy, HIV infection is no longer, in the words used by the Supreme Court in *Cuierrier*, “a devastating illness with fatal consequences.” (para 127, per Cory J).

Introduction

There have been considerable advances in our understanding of HIV since the beginning of the epidemic over 25 years ago. In the early 1980s, when little was known about the virus or how it was transmitted, this lack of knowledge led to a widespread fear of HIV and those living with it. However, we now know that HIV is difficult to transmit. Common forms of social contact, for example, swimming in the same pool, sharing a glass or mug, or everyday hugs and kisses carry no risk of transmission. Even those activities considered risky, such as unprotected sexual intercourse, carry a risk of transmission much lower than is often commonly believed. Indeed, most unprotected vaginal or anal intercourse^A involving an HIV-positive person and his or her HIV-negative partner does not result in transmission.^{1,2}

Furthermore, advances in the treatment of HIV mean that the disease is no longer considered an inevitable death sentence. With the advent of effective therapy in the mid-1990s, life expectancy for people living with HIV has steadily increased. The World Health Organization and other leading health authorities consider that, with proper medical care, HIV is a chronic manageable condition, similar in many ways to other chronic conditions such as diabetes or cardiovascular disease.³

In the context of sex, only four bodily fluids—blood, semen (including pre-ejaculate), and vaginal and anal fluids—contain enough HIV to potentially infect another person.^B Transmission can only occur when HIV contained in one of these bodily fluids enters the body of another person. This generally occurs when the virus comes in contact with the other person’s mucosal membranes, for example the membranes that line the vagina or rectum, though it can also occur through breaks in the skin. However, even then transmission is not guaranteed, as the virus must infect a sufficient number of target cells to establish an infection. If the amount of virus in the fluid from the HIV-positive person is low, the risk of infection is lower. Because HIV is a fragile virus and able to survive outside the body for only minutes, transmission usually requires intimate contact. During sex, this most often means unprotected anal or vaginal intercourse. HIV can also be transmitted through sharing equipment used to inject drugs and the transfusion of blood products infected with HIV, and vertical transmission between mother and child.

For sexual transmission of HIV, the risk of transmission is not constant for all sexual encounters. In understanding the risk of the sexual transmission of HIV, researchers often

^A By vaginal or anal intercourse we mean sexual activity involving the insertion of the penis into the vagina or anus. We use the term “unprotected” to refer to sexual activity without the use of a condom.

^B Other fluids considered infectious or potentially infectious are breast milk and several internal body fluids (including cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluids).⁹⁰

consider two broad categories: 1) the type of sex act, namely oral versus vaginal versus anal sex, and 2) biological and other factors, such as the level of virus in the HIV-positive partner or the presence of other sexually transmitted infections (STIs), that can decrease or increase risk.

The risk of sexual transmission of HIV depends, among other factors, on the type of sexual activity. Experts generally agree that our ability to precisely or accurately quantify the per-act risk of HIV transmission during any sexual activity is limited. Research has identified the potential for HIV transmission through oral sex (fellatio, cunnilingus, anilingus), vaginal sex and anal sex. Unprotected oral sex is considered to carry the lowest risk of transmission—the risk is so low that researchers have had difficulty quantifying it. The probability of HIV transmission during one act of unprotected vaginal intercourse is often stated to be approximately 0.1%, or 1 in 1,000.^{1,2,4} Unprotected anal intercourse is considered more risky, with an estimated per-act risk of 1 in 100 to 1 in 50, which a risk that is 10 to 20 times higher than for unprotected vaginal intercourse.^{1,5}

Reductions in the risk of transmission during unprotected vaginal or anal sex have been associated with three factors: condom use, male circumcision and lower amounts of HIV in the blood of the infected partner. Using condoms properly greatly reduces the risk of HIV transmission.²³ Studies have shown that circumcision provides some protection to an HIV-negative man who has unprotected vaginal intercourse with an HIV-positive woman.²⁷ Relatively lower amounts of virus in the blood of the HIV-positive partner (also known as blood viral load) have been associated with decreased HIV transmission during sex.²⁹⁻³¹ Anti-HIV therapy, called antiretroviral therapy, is effective at reducing blood viral load to levels undetectable by current assays, and there is a general consensus that antiretroviral therapy significantly reduces the risk of HIV transmission during sex.

There are a number of factors associated with increased risk of HIV transmission through sex. Transmission risk increases as the number of sex acts increases. Direct contact between ejaculate or other genital secretions and an open wound in or on the genitals or the mouth also increases the probability of transmission. Other factors known to increase the risk of transmission include being in the early phase of HIV infection and the presence of other sexually transmitted infections.

Viral load

Viral load testing measures the amount of HIV genetic material (viral RNA) in a bodily fluid. In the clinic, viral load is measured in the blood plasma; in research settings viral load can also be measured in fluids such as semen or cerebrospinal fluid. Viral load measurements are reported as copies of HIV per milliliter (copies/mL), and values can range from a few hundred to over a million copies/mL in people not receiving treatment. Assays currently used in Canada can measure blood plasma viral loads as low as 20 to 50 copies/mL. (Assays used to measure viral loads in other fluids are generally not as sensitive and measure down to 300 copies/mL.) Below this level, viral load is said to be undetectable. This does not mean that HIV has been eliminated from the body, but rather that it is below the level of detection of the test. The goal of antiretroviral therapy is to render viral load undetectable.

The Sexual Transmission of HIV

The sexual transmission of HIV from one person to another requires four conditions:

- a **fluid known to transmit HIV**—in the case of sex, the fluids are blood, semen (including pre-ejaculate) and vaginal and anal fluids;
- the **fluid makes contact with an area of the body**—a mucosal membrane lining the vagina, rectum or parts of the penis, a lesion or a break in the skin—**through which transmission can occur**;
- entry into the body of **sufficient virus** to establish infection; and
- an **initial infection** within immune cells of the mucosal membranes is established and a **subsequent spread of the infection** to other immune cells in the body.

While unprotected vaginal or anal intercourse may be the most risky sexual activity for HIV transmission, extensive research clearly confirms that not every unprotected act between an HIV-positive person and his or her HIV-negative partner leads to transmission of the virus. In fact, the per-act risk of transmission is low, commonly quoted as 0.1% (i.e., 1 transmission in 1000 sex acts) for unprotected heterosexual intercourse.^{1, 2, 4}

Many other sexual activities carry little to no risk of transmission. Sweat, saliva and tears do not contain enough HIV to transmit the virus. So, for example, kissing and even deep kissing (in the absence of oral sores or bleeding) pose virtually no risk of transmission.^{6, 8, 9} Masturbation and any other activity that does not expose the uninfected partner to an HIV-carrying fluid also carry no risk. HIV is fragile and able to persist outside the body only for minutes. Unbroken skin is an effective barrier to the virus and so contact between an HIV-containing fluid and healthy, intact skin is considered safe.⁷ Note, however, that lesions, even if microscopic, can provide an entry point for HIV. As well, HIV can pass through the mucosal membrane lining the rectum, vagina, urethra and in uncircumcised men, the inside of the foreskin, even if the membrane is intact. Thus, the sexual activities that carry the greatest risk of transmission are unprotected vaginal and anal intercourse.

Table 4 (see page 18) summarizes data on the per-act risk of HIV transmission associated with different types of sexual acts. This per-act risk is expressed as a percentage. The percentage reflects the probability of HIV transmission during one sexual act or the percentage of a population of HIV-negative people that could be expected to be infected by HIV during one sexual act with an HIV-positive sex partner. These are the best estimates to date (December 2011), though experts agree that there is room for improvement in the quality and quantity of data supporting them, and variation in the per-act risk estimates.

Heterosexual sex

Estimates of the risk of HIV transmission come from four types of studies.^{1,2} (See sidebar “Reading medical science” for more information on different types of medical studies and considerations for interpreting study results.)

- The first type involves “serodiscordant couples” cohorts (couples in which, at the outset of the study, one partner is infected with HIV and the other is not). Generally, the couples in these studies report that they were monogamous and engaged in vaginal sex as their only form of sexual intercourse. The couples were followed over time to find out if the HIV negative partner became infected with HIV during the study. Using data on frequency of intercourse, per-risk estimates can be calculated.

Serodiscordant cohort studies provide the advantage of controlling many variables, which permits a better estimation of the per-act risk. One criticism of these studies is that they likely miss transmissions that occur during the early phase of HIV infection during which HIV is more easily transmitted (because couples for which this happened would no longer be serodiscordant and thus not eligible for the study). Therefore, these studies may underestimate the overall per-act risk of transmission.

- The second type follows a cohort of HIV-negative individuals, for example, sex workers, who do not have steady HIV-positive partners but are presumed to be at risk of exposure to HIV, and tracks seroconversion over time.
- The third type, cross-sectional partner studies, tests the HIV status of the partners of a group of people who are known to be HIV positive.
- The fourth type of study is also cross-sectional, but assesses the HIV status of a group of people presumed to have been exposed to HIV.

All four study types are included in the following discussion.

The value of 0.1% per act is commonly cited as the risk of HIV transmission during unprotected vaginal intercourse. However, a 2009 analysis of existing published studies provided a slightly lower, and perhaps more precise, estimate of 0.08% per act. [Boily09] In other words, if 10,000 serodiscordant heterosexual couples had unprotected sex once, there would be 8 transmissions of HIV among them. This figure represents the average transmission risk per act of unprotected vaginal intercourse, and according to the Canadian researchers who published the estimate, indicates “a low risk of infection in the absence of antiretrovirals.”²

Taken together, the literature is equivocal about whether the probability of transmitting HIV from a man to a woman is higher than the probability of transmitting HIV from a woman to a man. Some studies have found no difference, while others suggest that the

probability of HIV passing from a man to a woman is about twice that of it passing from a woman to a man.^{1, 2, 8} A number of biological factors, such as increased surface area of the vaginal lining and greater degree of disruption of the lining during intercourse, could support a difference in the risk based on direction of transmission.⁹ Other factors known to influence transmission risk, such as being uncircumcised (which increases the risk for HIV-negative male partners), may have influenced results from studies that did not show a significant difference in risk of transmission.

Reading medical science

The findings from medical research involving people as subjects can often seem difficult to understand and interpret. There are a number of different study designs and research methods, all of which have particular intricacies and limitations. Let's review the salient points for this discussion.

Studies include at least one group of participants, who usually share certain characteristics, though they can also be a random group of people.

Types of studies

Observational studies do not try to influence the group in any way, but rather simply measure (or “observe”) a certain variable. **Comparative studies** compare a certain measure between two groups (or study arms) that differ in some pre-determined way.

*A study that collects data at only one time point is called a **cross-sectional study**. If data is collected over time, it is considered a **longitudinal study**. In this latter case, the group of people who are being studied is called a **cohort**. If the study is designed first and then the data are collected, the study is called a **prospective study**. If the study used data that was already collected for another reason, it is called a **retrospective study**. Prospective studies are less susceptible to various sources of possible bias.*

Interventional studies apply some sort of intervention (a drug treatment, for example) and look for a resulting change in some measure among participants. A study that contains two very similar groups, one that receives the intervention and one that does not, is commonly used to assess the effect of the intervention. By keeping as many variables (e.g. age, gender, HIV status) as possible the same between the groups, any difference between the groups can be ascribed to the intervention. Great care is taken to ensure all known variables are kept the same between the groups to minimize the potential that an unknown variable differs between the two groups and is the cause of the observed difference. The randomized, double-blind, placebo controlled trial is the gold standard for interventional studies.

Modelling studies attempt to develop a theoretical statistical model to explain observed data, often using data collected through epidemiological studies of large populations. Modelling studies are intended to generate hypotheses and do not provide experimental proof. These studies are difficult to interpret because they are based on many assumptions: often there are many variables that have not been identified or controlled for, which draws into question the validity of the explanations offered.

*A **systematic review** is a scientific method for synthesizing findings from a number of separately conducted scientific studies.¹⁰ A systematic review starts with an exhaustive search of published data using a well-defined search strategy. Appropriate studies are selected based on pre-determined criteria of study quality. When the studies included in a systematic review are similar enough to one another, it is possible to combine and analyze the studies' data or results using a process of statistical synthesis called **meta-analysis**.¹⁰ While meta-analyses provide a single best estimate based on several studies, they may conceal variability between results of different studies.*

Caveats when reading studies

*There are several **caveats** when considering the interpretation of studies and their broader application. First, in strict terms, the results of a study can only be applied to the study population in question. However, people may seek to apply results from one study cohort to another population. When doing so, it is important to know the characteristics of each study cohort, to take that information into account when relying on the results and conclusions from specific studies. For example, HIV transmission data from studies of people in high-income countries may be different from studies of people in low-income countries. In our review we have focused on studies of people in high-income countries, since Canada is a high-income country.*

Second, a scientific question is often repeatedly addressed in several similar studies. Obtaining a similar result over several studies confirms the finding and gives more confidence in its validity. In our review, when possible, we have used systematic reviews and meta-analyses, which take into account findings from multiple studies.

*Third, it is important to distinguish between what is being studied and the population that is being studied. Differences in findings may be due to true differences in what is being studied, **or** to differences attributable to the population studied. For example, compare estimates of risk of HIV transmission during anal sex with risk during vaginal sex. Ideally, it is best to compare anal and vaginal sex risk estimates from a study of one heterosexual population. If that was not possible, you could compare estimates for anal sex among men who have sex with men (MSM) with estimates for vaginal sex among heterosexuals, realizing that the difference in risk between anal and vaginal sex in the second study scenario may actually be due to differences in the populations (MSM and heterosexual) rather than the type of sex.*

Fourth, results are often expressed as a single quantified result accompanied by a range that indicates the range within which the true value likely falls. Think of poll results reported in the media: they are often reported as being accurate within X percentage points, 19 times out of 20. This means that the true answer is most likely somewhere in that range. These statistical ranges indicate how confident we are of the estimate. The smaller the range, the more confidence we can have in the result. We have not included ranges in our discussion, but it is important to remember that each estimate of per-act risk carries a degree of uncertainty.

Fifth, human behaviour is complex. Studies of human behaviour face the challenge of accounting for multiple, interacting variables. It is impossible to fully identify, capture and quantify all the relevant variables in a given study, including one that attempts to calculate the per-act risk of the sexual transmission of HIV. For example, condom use is often collected using subjective terms such as “always”, “occasionally” or “never.” To integrate this information into a calculation, these subjective terms must be given numerical values, and this “translation” introduces imprecision into the calculation and our confidence in the result. Recall bias (how well people remember their sexual activities over a period of time) and social desirability bias (the potential for people to answer questions about their sexual activities in a way that appears more socially acceptable) can also lead to imprecision in the collected data.

Finally, there remains the question of how to apply findings from a study involving a group of people to one person in one particular situation. When facing this issue, one question to ask is whether the study addressed a situation similar to the one in the individual case. For example, transmission estimates for studies of anal sex with a condom should not be applied to a situation of a person who engaged in unprotected oral sex. Another consideration is whether the study used a population similar to the one that applies to the person in question. The results should be from a population as similar as possible to the one to which the particular person belongs. Practically speaking, results from studies should be applied with an awareness of known differences (and the possibility of unknown ones) between the study population and the person in question.

Oral sex

Oral sex has been associated with a much lower HIV transmission risk than unprotected vaginal or anal intercourse.^{7, 11, 12} A lack of sufficient data has made it impossible to calculate a statistically sound estimate of the risk. However, a scientific consensus has developed that the risk of HIV transmission during oral sex is extremely low, albeit non-zero.⁸⁸

A systematic review of the literature identified three estimates of per-act risk based on results from three studies involving 2497 people. Two studies reported no new HIV infections resulting from oral sex. The 0.04% value quoted in the table is from a single study of almost 2200 men who have sex with men (MSM) and involved oral sex where a man who is HIV positive or of unknown status ejaculated in the mouth of the HIV-negative partner.¹³ However, the value of 0.04% per act may misrepresent the risk of transmission from oral sex. It is derived from applying complex data to a statistical model in order to estimate per-contact risk for each type of sex. This modelling may have resulted in an overestimation of the risk associated with oral sex alone since there were no seroconversions among study participants who reported only performing unprotected fellatio to ejaculation.¹³

Anal intercourse

Studies show that unprotected anal intercourse is associated with a higher HIV transmission risk than unprotected vaginal intercourse^{5, 14} and that the risk is higher when the HIV-positive person is the insertive rather than receptive partner.^{13, 15, 16}

While anal intercourse is part of both heterosexual and homosexual sexual activity, much of the data on HIV transmission risk during anal intercourse comes from studies of MSM. Estimates of per-act risk of HIV transmission for unprotected anal sex derive from individual studies and range widely, from 0.01% to over 3%.^{2, 13, 16-18} A 2010 systematic review and analysis that included four studies (two including MSM and two including heterosexual participants) reported a pooled estimate of 1.4% per act for unprotected receptive anal sex (that is, when the HIV-negative person is the receptive partner).⁹² There was no significant difference between the risk associated with heterosexual and homosexual activity. Because of the significant heterogeneity between estimates from the different studies, the authors urge caution when using the pooled estimate.

Two studies of MSM (one in Australia and one in the US) have reported risks of transmission to an HIV-negative receptive partner in the range of 0.65% to 1.43% per contact.^{13, 16} For an HIV-negative man who is the insertive partner, the range was 0.06% to 0.62%. The US study of MSM found that the risk of infection associated with being the receptive HIV-negative partner was about ten-fold higher than with being the insertive partner (0.82% versus 0.06%).¹³ The Australian study found that withdrawal before ejaculation reduced the risk to the receptive HIV-negative partner by over 50%, from 1.43% with ejaculation to 0.65% if withdrawal occurred before ejaculation.¹⁶

Factors modifying the risk of transmission

Researchers have identified several factors, such as condom use and concurrent STIs, that can affect the risk of HIV transmission during a sexual act. The transmission risk is dependent upon the interaction among these factors, some of which lower the risk of transmission and others of which increase the risk. While it is extremely difficult to quantify the HIV transmission risk for a single sex act between two people at one particular moment given the many contributing and interacting factors, it is important to recognize that certain factors are known to reduce HIV transmission risk.

Factors that reduce the risk of transmission

The factors associated with a reduction in the risk of transmission are condom use, circumcision and lower viral load in the HIV-positive partner.

Condoms

There is significant data supporting the role of condoms in reducing the risk of HIV transmission during sex, and health organizations world-wide promote condom use as a

primary means of reducing HIV transmission.¹⁹⁻²² When used consistently^C for vaginal intercourse, condoms reduce the transmission of HIV by an estimated 80%, on average.²³

A finding of an 80% reduction in HIV transmission does not mean that 80% of people using condoms are protected from HIV while 20% of people using condoms will become infected. Rather, it means that condoms prevent 80% of the transmissions that would have occurred if a condom had not been used. For example, assume a per-act risk of 0.08% for receptive vaginal sex and no other HIV risk factors, in a group of 10,000 women who had unprotected vaginal intercourse once with an HIV-positive man. If all 10,000 did not use a condom, about 8 women would become infected with HIV. If all 10,000 used a condom, 1 or 2 women would become infected with HIV.

Condoms are also generally considered effective in reducing transmission of HIV during anal intercourse, though there are considerably less data supporting this claim.²⁴ Unprotected receptive anal intercourse has been associated with increased risk of HIV transmission compared with intercourse with a condom.^{15, 25} As well, among a cohort of 2915 MSM in the US followed in the 1980s, consistent condom use was associated with decreased risk of HIV transmission.²⁶ In a separate study, the per-act risk of transmission to an HIV-negative receptive partner during protected anal sex was 0.2%, about one quarter the risk during unprotected anal sex (0.8%).¹³

Circumcision

Male circumcision is a well-studied factor that reduces HIV acquisition among men who have sex with women. Trials in Africa have validated the effectiveness of circumcision in reducing HIV acquisition by men from their HIV-positive female partners, with an approximately 60% reduction in risk for circumcised men compared to their uncircumcised counterparts.²⁷

The impact of circumcision on sexual transmission of HIV among MSM remains unclear, though a 2011 systematic review concluded that it might be protective for men who are primarily the insertive partner.⁹³ A 2010 observational study of 1136 MSM in Australia reported a more than 80% reduction in the per-contact risk of transmission to the HIV-negative insertive partner if the insertive partner was circumcised versus uncircumcised (0.11% versus 0.62%).¹⁶ However, other observational studies have produced conflicting results.²⁸

Antiretroviral therapy and undetectable viral load

Early studies showed an association between viral load and sexual HIV transmission risk. Among people who were not on therapy, lower levels of HIV in the blood were associated with lower rates of sexual HIV transmission.²⁹⁻³¹ Since antiretroviral drugs lower blood viral load, it was postulated that HIV positive people on therapy might also

^C Consistent use implies use of condom for all acts of penetrative vaginal intercourse. It does not imply correct use of the condom during all of those acts.

be less sexually infectious. Using antiretroviral treatment to inhibit transmission of HIV has been borne out by the use of antiretroviral therapy during pregnancy and delivery. Antiretroviral therapy has been shown to reduce the risk of HIV passing between mother and baby to less than 2%.³²⁻³⁴ In Canada from 1997 to 2004, only 15 infants (1.6%) were born HIV positive to 931 HIV-positive mothers who received antiretroviral therapy.³⁵

It is generally accepted that effective antiretroviral therapy, which reduces HIV viral load in the blood and slows disease progression, reduces the risk of sexual transmission of HIV. This is an area of intense study among researchers and 2011 saw a significant advance in our understanding of the extent of risk reduction: the first prospective, randomized, controlled trial of the impact of early antiretroviral treatment on sexual transmission of HIV provided the most reliable data so far on the impact of antiretroviral treatment on the sexual transmission of HIV.

The US study, called HPTN052, enrolled 1763 serodiscordant couples (97% of whom were heterosexual) from sites in both the developing and developed world.³⁸ The study evaluated the risk of sexual transmission of HIV in a group in which the HIV-positive partner started antiretroviral treatment right away and compared it to a group in which the HIV-positive person delayed treatment until it was medically necessary.

The clinical trial was slated to end in 2015 but the results were released ahead of schedule when analysis of early data showed that early initiation of treatment led to a 96% decrease in sexual transmission of HIV. These results are based on a clinical trial design that is considered “gold standard,” and so are regarded as the most solid data available on this issue.

To better understand this 96% reduction in risk, let us return to our group of 10,000 serodiscordant heterosexual couples who have no other risk factors and a per act transmission risk of 0.08% for unprotected vaginal intercourse. If all 10,000 HIV-positive partners were **not** on antiretroviral therapy, about 8 of the HIV-negative partners would become infected with HIV. If all HIV-positive partners were on antiretroviral therapy, less than one person would become infected with HIV. The group would have to be at least doubled before we would expect to see a transmission event. This reduction is associated with being on antiretroviral therapy, irrespective of whether the HIV-positive person had an undetectable viral load.

In late 2009, a European team published the first systematic review and meta-analysis of data on the relationship between antiretroviral therapy, blood viral load and the sexual transmission of HIV.³⁶ This analysis included 11 cohorts comprising 5021 serodiscordant heterosexual couples. The individual studies used different ways of defining their cohorts. Some studies only evaluated whether the participants were on antiretroviral therapy, while others evaluated whether participants on therapy had an undetectable viral load. Overall, the analysis found that antiretroviral therapy (without considering viral load) reduced heterosexual transmission by 92%. A second systematic review, published in 2011, and including seven observational trials with 9755 serodiscordant couples reported risk reductions ranging from 66% to 98%, depending on the analysis.⁹⁴

One would expect an undetectable viral load to be associated with at least an equal and, perhaps, a greater reduction in the risk of HIV transmission. However, the data regarding the effect of an undetectable viral load on HIV transmission are incomplete and, therefore, must be viewed with caution. (See sidebar “Viral load, antiretroviral therapy and transmission in context” for a more detailed discussion.) The European team notes that studies have found no transmission of HIV when blood viral load has been kept below 400 copies/mL by antiretroviral therapy. However, they also note that the two studies that did report transmission in the presence of antiretroviral therapy did not report viral load.³⁶ Also, information about other factors that can increase the risk of transmission, such as STIs, was not consistently reported across the studies examined in the systemic review and meta-analysis.

Due to the limited statistical power of the numerous studies involving a small number of participants, members of the European team stated they could not confidently conclude that sexual transmission is impossible when viral load is undetectable. They go on to state that the amount and statistical power of published data do not permit an accurate estimation of the per-act risk of transmission for people with an undetectable viral load.³⁶⁻³⁷ Based on current data and the studies’ statistical limitations, the HIV transmission risk estimate could be as high as 0.013% per act of sexual intercourse, or about 1.3 seroconversions among 10,000 acts.³⁶

There is a paucity of data on the association between viral load, antiretroviral therapy and the risk of sexual transmission of HIV among MSM populations. Designing transmission risk studies in this population has proven difficult (see section on oral sex).³⁹⁻⁴⁰ Two epidemiologic studies in MSM populations, in San Francisco and in Denmark, present indirect evidence that antiretroviral therapy may be effective in decreasing risk of transmission, at least when viewed from a broader population perspective.^{95,96} An Australian study found little impact, but its design contained flaws.¹⁶

While HTPN052 contained a small number of same-sex couples, it is not clear whether the study results apply equally to the MSM population.³⁸ However, the basic principle that, in a given encounter, being on antiretroviral therapy will translate into a reduced risk of transmission remains applicable. However, because anal sex seems to carry a higher absolute risk of transmission compared to vaginal sex, any benefit in relative risk reduction associated with antiretroviral therapy could still result in a higher absolute risk with anal sex.

Viral load, antiretroviral therapy and transmission in context

Evidence for the effect of antiretroviral therapy on sexual transmission of HIV comes from three sources: a randomized, controlled clinical trial, observational cohort studies and epidemiologic modeling studies. The evidence indicates that, despite known variations between blood and genital fluid viral loads, antiretroviral therapy reduces the risk of transmission.

The randomized, controlled clinical trial HPTN052 (described above) provides “gold-

standard” evidence that antiretroviral treatment significantly reduces the risk of transmitting HIV during sex.³⁸ Study results published to the end of 2011 provided little information on viral load levels in the HIV-positive participants. In the group that started treatment early, 89% had achieved a viral load below 400 copies/ml by three months, suggesting that treatment was effective. In the same group, 79% reported taking their drug regimen as prescribed at least 95% of the time, suggesting that adherence to drug therapy was high but not perfect.

There is no published data on viral load changes over time in study participants, but it can be assumed that blood and seminal viral loads varied as would be expected with antiretroviral therapy, including occasional detectable levels in both blood and seminal fluids. Regardless, HTPN052 showed a decrease in transmission in people who started treatment early.

Early observational cohort studies found either that blood viral load was on average lower among couples who did not transmit HIV or that the number of transmissions decreased with decreasing blood viral load.²⁹⁻³¹ This was extended to seminal viral load in a 2011 study that reported genital viral load is an independent predictor of the risk of transmission.⁹⁷ These studies were conducted without antiretroviral therapy, and what remains unclear is whether a naturally low viral load has the same characteristics as a low viral load achieved through antiretroviral therapy.

More recent cohort studies have compared the HIV transmission rates in heterosexual couples where the HIV-positive person was receiving antiretroviral therapy with transmission rates among couples where the HIV-positive partner was not receiving therapy, and have found lower transmission rates in the presence of therapy. Three cohort studies involving 762 couples found no heterosexual transmission from people on antiretroviral therapy—two of the studies evaluated viral load and found it undetectable in the majority of participants.⁵¹⁻⁵³ Two other studies reported 79% and 92% reductions in the estimated risk of transmission where the HIV-positive person in the couple was receiving antiretroviral therapy.^{54, 55} Another study of nearly 3400 couples observed a 92% reduction in new infections in couples who started antiretroviral therapy and a final study noted an approximately 80% reduction in transmission after the introduction of antiretroviral therapy in a Spanish population.^{56, 57}

These studies have two principal limitations. First, they did not control for, and thus their results may not exclude, the influence of other factors known to have an impact on HIV transmission. For example, in the Spanish study, 50% of the participants reported always using condoms during intercourse.⁵⁷ It is therefore difficult to determine whether the reduction in transmission was due to condom use or antiretroviral therapy. Second, the studies were of a short duration.

Epidemiologic modeling studies are studies in which researchers try to explain changes in the incidence of HIV within a population with models based on social or biological change. Two studies, one in San Francisco⁵⁸ and another in Taiwan,⁵⁹ observed drops in new HIV cases after the introduction of antiretroviral therapy in the late 1990s.

However, both of these studies have been criticized for serious flaws in their design. A separate San Francisco study found no change in HIV incidence,⁶⁰ while a fourth study, in Amsterdam, found that a decrease in HIV incidence preceded rather than followed the introduction of antiretroviral therapy.⁶¹ More recent results from British Columbia, San Francisco and Denmark have found that HIV transmission has decreased as the proportion of the community receiving antiretroviral treatment increases.^{95,96,98,99} While these results are conflicting and are based on studies with known design flaws, they provide a second line of evidence supporting the role of antiretroviral therapy in reducing transmission.

However, scientists have found that antiretroviral therapy may lead to undetectable blood viral loads but incomplete suppression of HIV in genital fluids. Several studies have found that in a proportion of people with no detectable virus in their blood, detectable levels of HIV can be found in semen,^{41-43, 100} cervicovaginal fluids^{44-46, 101} and in the lining of the anal cavity.⁴⁷ While semen viral load is generally lower than blood viral load, studies estimate between 5 to 15% of men who have an undetectable blood viral load as a result of antiretroviral therapy still have detectable virus in semen samples.^{42, 48-50, 102} This raises questions about whether a person with undetectable viral load in the blood may still possess sufficient levels of virus in the genital fluids to transmit HIV infection to another person during sex.

To reconcile the seemingly contradictory evidence of the effects of antiretroviral therapy on HIV transmission with the occasional presence of virus in genital fluids, some researchers are hypothesizing that antiretroviral therapy may reduce the risk of transmission at a population level while leaving the possibility for transmission, at least occasionally, on an individual level.^{100,101}

Factors increasing the risk of transmission

Any factor that increases one of the required conditions of HIV transmission potentially increases the risk of transmission. For example, ejaculation by an HIV-positive partner who is the insertive partner during penetrative intercourse likely increases the risk of transmission because of the introduction of a larger volume of HIV-containing fluid than would otherwise be the case. Having lesions or abrasions at the site of exposure would also increase risk. Two other factors known to increase the risk of transmission are stage of HIV infection and the presence of other sexually transmitted infections.

Stage of infection

It is generally agreed that the risk of sexual HIV transmission is higher during “primary infection,” defined as the first two to three months of infection. Estimates range from an eight- to 43-fold increase in per-act risk of HIV transmission during primary infection when compared with the chronic phase of infection.^{2, 14, 62-64} Advanced HIV disease has also been associated with a seven- to 20-fold increase in risk of HIV transmission.^{2, 14, 63} These periods of high blood viral load may partly explain the increased infectivity,

though the level of infectivity is higher than would be expected for a given viral load versus other factors that increase the risk of HIV infection, such as STIs.⁶³

Sexually transmitted infections (STIs)

There is considerable evidence that having a STI or another infection of the genitourinary tract increases the risk of transmission of HIV, regardless of whether the STI is in the HIV-positive or HIV-negative partner.^{1, 65, 103, 104} Several infections have been implicated, including herpes simplex virus (HSV), bacterial vaginosis, gonorrhea, Chlamydia and vaginal candidiasis.^{39, 65-68} The risk is generally in the range of one and one-half to five times higher than that seen in the absence of STIs.^{2, 39, 66-69}

Rates of STIs vary with time, over geographic areas and among populations. In groups with increasing rates of STIs, such as rates of syphilis among MSM in some urban centres in Ontario and southern Quebec during the early to mid 2000s,⁹¹ STIs may play an important role in increasing the risk of sexual transmission of HIV.

To investigate how STIs may be increasing the risk of transmission, researchers are evaluating changes in viral load in genital fluids in the presence of STIs. So far, results have been mixed, with some studies reporting a correlation between the two¹⁰⁵⁻¹⁰⁸ and others not.^{109,110}

Living with HIV, a chronic manageable infection

Thanks to advances in therapy, HIV infection has changed from a terminal disease to a chronic, manageable condition in the eyes of many experts and people living with the virus.^{3, 70} Antiretroviral therapy blocks the virus's ability to reproduce, which lessens the deleterious effect on the immune system. While the virus is not eliminated, it is controlled. When HIV is under control, the progression to the more serious stages of HIV disease, including AIDS, is slowed if not halted. Combination antiretroviral therapy has been available only since 1996. There is no reason to suspect that it will not continue to suppress the virus in the decades to come.

HIV, HIV therapy and AIDS

People with HIV have a chronic infection that is incurable but manageable. Without treatment, HIV infection generally leads to the slow dismantling of the immune system. This process of immune decline takes many years during which people remain relatively healthy. AIDS, the most advanced stage of HIV disease, is characterized by the presence of certain infections and cancers that only appear in people with weakened immune systems.

AIDS was once considered the inevitable and irreversible outcome of living with HIV. However, thanks to effective antiretroviral therapy, people with AIDS can be treated, their immune systems allowed to rebuild and their health to return.

This shift to an understanding of HIV as a chronic, manageable infection is supported by scientific research focused on changes in the rate of death, the cause of death and the life expectancy of people living with HIV. The introduction of effective combination antiretroviral therapies in 1996 was associated with a dramatic decrease in death due to HIV/AIDS.⁷¹⁻⁷⁵ Data collected by the Public Health Agency of Canada show that the reported deaths due to AIDS dropped from 1063 in 1996 to 473 in 1997. In 2008, 45 people died of AIDS in Canada, representing 3% of the 1501 deaths in 1995, the peak of AIDS deaths in the Canadian epidemic.⁷⁶ Two large US studies have reported a rate of 7 to 10 deaths per 100 person-years in the pre-1996 era. By the mid-2000s, that rate had dropped to less than 2 deaths per 100 person-years.^{74, 75} Recent studies suggest that the death rate among some groups of people with HIV may be approaching that of the general population.⁷⁷

In addition to fewer deaths among people with HIV, there has also been a shift in the causes of death away from the traditional AIDS-defining illnesses—infections such as pneumocystis pneumonia (PCP), or cancers, such as Kaposi’s sarcoma—towards non-HIV related causes. In one US study, deaths at least partially attributable AIDS-related causes decreased ten-fold, from 3.79 per 100 person-years in 1996 to 0.32 per 100 person-years in 2004. At the same time, the proportion of people with HIV dying from non-HIV related causes rose from 13% in 1996 to over 40% in 2004.⁷⁴ Similar figures have been obtained in another US study.⁷⁵ These non-HIV related causes of death are very similar to those affecting the general population and include heart, liver and lung disease and non-AIDS-related cancers, although the incidence of these conditions is greater among people with HIV than among the general population. Both HIV infection and the long-term toxicities associated with antiretroviral therapy may be involved in this increased incidence.^{74, 78}

Life expectancy for people living with HIV has greatly increased with the introduction of effective antiretroviral therapy. A 2007 Canadian study found that average life expectancy for someone who became infected with HIV at age 20 increased from 9 years in 1993-1995 to 23.6 years in 2002-2004. This means that in 2004, a person who was 20 years old and newly infected with HIV could have expected to live another 23.6 years on average, or to the age of about 44.⁷⁹ A 2008 study estimated the average life expectancy for someone infected with HIV at age 20 to be almost 50 years, while preliminary results from a 2010 modeling study suggest that life expectancy for people with HIV in Holland who receive proper care could match that of the general population.^{70, 80}

With increased life expectancy, people with HIV are facing opportunities and challenges associated with long life. The medical community has increasingly recognized the importance of managing both HIV and health issues associated with aging, from menopause to cardiovascular disease.^{74, 75, 81-83} As well, with the prospect of a long life and the knowledge that it is possible to prevent mother-to-child transmission, HIV positive people are having children.^{84, 85} Some are also accessing fertility services if they have trouble conceiving.⁸⁶ A 2009 study of HIV-positive women of reproductive age in Ontario reported that 69% desired to give birth and 57% intended to give birth in the future.⁸⁷

Weighing the data on sexual transmission risk

The data provided in Table 4 are drawn from published peer-reviewed sources providing the most comprehensive and up-to-date analyses available in early 2010. Risk estimates use a variety of different terms to describe HIV transmission associated with the same sexual activity in a similar cohort of people—for example, studies use the terms heterosexual intercourse, penile-vaginal intercourse and male to female transmission. This variation is based on the fact that, when designing individual studies, researchers may have used different definitions of sexual intercourse or designed their study to capture only particular data. We use the most precise term possible when describing the data. The risk estimates presented in the table are derived from studies undertaken in high-income countries, which parallels the reality of HIV in Canada.

*The data concerning **heterosexual transmission** are drawn from two recent systematic reviews and meta-analyses^{1,2} and one older review published in 1996.⁴*

- The two systematic reviews with meta-analyses, completed by a Canadian group (Boily et al.)² and an American group (Power et al.)¹ were included in this table because they provide a current, comprehensive overview of published literature. The estimates quoted from the Canadian group, while based on fewer studies, were shown statistically not to be heterogeneous, that is to say that the meta-analysis did not conceal variability among the studies used to derive the estimates.*
- The 1996 review included here was chosen because it represents the first published attempt to seriously evaluate literature on sexual transmission of HIV, providing a historical perspective on the evolution of the data. It is also the review that gave rise to the commonly quoted value of 0.1% per-act risk of transmission for unprotected vaginal intercourse.*

*Data for the HIV transmission risk associated with **unprotected anal sex** are reported from one systematic review and analysis and several individual studies. These studies represent the best published attempts to quantify per-act transmission risks. Given the paucity of data, these estimates must be viewed with caution.*

*Data for the HIV transmission risk associated with **oral sex** are reported from the single systematic review published on the topic (Baggaley et al.)⁸⁸ This review could not provide a statistical analysis of the data and so the estimate is reported as a range.*

Table 4: Summary of per-act risk estimates for transmission of HIV during different types of sexual intercourse		
Type of intercourse	Risk per act	Comments
Heterosexual (no distinction made in direction of transmission)	0.077%	<i>Author/date:</i> Boily et al., 2009 <i>Study type:</i> systematic review and meta-analysis of 43 publications from 25 heterosexual cohorts <i>Estimate derivation:</i> 4 estimates from studies involving 116 couples in high-income countries
	0.056%	<i>Author/date:</i> Powers et al., 2008 <i>Study type:</i> systematic review and meta-analysis of 27 publications from 15 heterosexual cohorts <i>Estimate derivation:</i> 8 estimates from studies involving 1402 couples in high-income countries
	0.05 – 0.1%	<i>Author/date:</i> Mastro and de Vincenzi, 1996 <i>Study type:</i> review including 11 studies reporting per-act risks for sexual transmission of HIV <i>Estimate derivation:</i> range from 3 reports involving over 550 couples from high-income countries <i>Comments:</i> one of the first reviews on the topic and the source of the oft quoted per-risk estimate of 0.1%
Male to female (predominantly penile-vaginal sex, but may include other acts (anal and oral))	0.08%	<i>Author/date:</i> Boily et al., 2009 <i>Study type:</i> systematic review and meta-analysis of 43 publications from 25 heterosexual cohorts <i>Estimate derivation:</i> 10 estimates from studies involving 1744 couples in high-income countries
	0.064%	<i>Author/date:</i> Powers et al., 2008 <i>Study type:</i> systematic review and meta-analysis of 27 publications from 15 heterosexual cohorts <i>Estimate derivation:</i> 10 estimates from studies involving 4088 susceptible participants in high- and low-income countries
	0.08-0.14%	<i>Author/date:</i> Mastro and de Vincenzi, 1996

		<p><i>Study type:</i> review including 11 studies reporting per-act risks for sexual transmission of HIV</p> <p><i>Estimate derivation:</i> 3 reports involving over 226 couples from high-income countries</p> <p><i>Comments:</i> one of the first reviews on the topic</p>
Male to female, vaginal intercourse only	0.076%	<p><i>Author/date:</i> Boily et al., 2009</p> <p><i>Study type:</i> systematic review and meta-analysis of 43 publications from 25 heterosexual cohorts</p> <p><i>Estimate derivation:</i> 5 estimates from studies involving 755 couples and 499 individuals in high-income countries</p>
Female to male (predominantly penile-vaginal sex, but may include other forms (anal and oral))	0.04%	<p><i>Author/date:</i> Boily et al., 2009</p> <p><i>Study type:</i> systematic review and meta-analysis of 43 publications from 25 heterosexual cohorts</p> <p><i>Estimate derivation:</i> 3 estimates from studies involving 221 couples in high-income countries</p>
	0.064%	<p><i>Author/date:</i> Powers et al., 2008</p> <p><i>Study type:</i> systematic review and meta-analysis of 27 publications from 15 heterosexual cohorts</p> <p><i>Estimate derivation:</i> 6 estimates from studies involving 1037 susceptible participants, including commercial sex workers, in both high- and low-income countries</p> <p><i>Comments:</i> sex work is associated with a higher risk of HIV transmission</p>
Anal (combined)	0.8 – 3.2%	<p><i>Author/date:</i> DeGruttola et al., 1989</p> <p><i>Study type:</i> prospective, cross-sectional cohort study</p> <p><i>Participants:</i> 287 MSM in the US</p> <p><i>Comments:</i> a range is given because this study fits different models of behaviour and infectivity to the observed prevalence of HIV among the partners of a group of men already known to be HIV positive</p>
	0.01 – 0.1%	<p><i>Author/date:</i> Jacquez et al., 1994</p> <p><i>Study type:</i> retrospective modelling study</p> <p><i>Participants:</i> 2 MSM cohorts in the US</p> <p><i>Comments:</i> estimates derived as part of a model explaining epidemiological trends in HIV prevalence early in the epidemic</p>

Receptive (when the HIV-negative person is the receptive partner)	1.4% (heterosexual and MSM)	<i>Author/date:</i> Baggaley et al., 2010 <i>Study type:</i> systematic review and meta-analysis of 4 publications <i>Estimate derivation:</i> 4 estimates from 4 studies involving 3367 heterosexual and MSM participants in high-income countries <i>Comments:</i> The authors found no difference between estimates from MSM and heterosexuals
	0.65%, 1.43% (MSM)	<i>Author/date:</i> Jin et al., 2010 <i>Study type:</i> prospective, cohort study <i>Participants:</i> 1136 MSM in Australia <i>Comments:</i> The lower figure for withdrawal before ejaculation and the higher figure is for ejaculation in the rectum
	0.82% (MSM)	<i>Author/date:</i> Vittinghoff et al., 1999 <i>Study type:</i> prospective, cohort study <i>Participants:</i> 2189 MSM in the US
Insertive (when the HIV-negative person is the insertive partner)	0.11%, 0.62% (MSM)	<i>Author/date:</i> Jin et al., 2010 <i>Study type:</i> prospective, cohort study <i>Participants:</i> 1136 MSM in Australia <i>Comments:</i> The lower figure is for circumcised men, the higher figure is for uncircumcised men
	0.06% (MSM)	<i>Author/date:</i> Vittinghoff et al., 1999 <i>Study type:</i> prospective, cohort study <i>Participants:</i> 2189 MSM in the US <i>Comments:</i> the insertive partner is HIV negative, the receptive partner is HIV positive or of unknown status, meaning this estimate may under-represent the true risk of infection
Oral (receptive)	0 – 0.04%	<i>Author/date:</i> Baggaley et al., 2008 <i>Study type:</i> systematic review (no meta-analysis due to the small number of studies) of 10 studies and 14 estimates, including both per-act estimates and per-partner estimates (not shown here); studies included penile-oral sex and vaginal-oral sex (but not anal-oral sex) involving heterosexual, gay and lesbian participants <i>Estimate derivation:</i> range based on three studies and three estimates; two studies (one involving 135 heterosexual couples and one, 38 lesbian participants) from Europe reported

		<p>no seroconversions (of all 10 studies, 6 reported no seroconversions); the third study included 1583 MSM from the US.</p> <p><i>Comments:</i> the 0.04% estimate is from MSM and involves oral sex with ejaculation by a person who is HIV-positive or of unknown status into the mouth of the HIV-negative partner</p>
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