

# **Scientific research on the risk of the sexual transmission of HIV infection and on HIV as a chronic manageable infection**

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## **Background to this document**

This document is an excerpt from a policy options report on the criminal law and HIV non-disclosure in Ontario Canada.

This document provides a review of current scientific research on two topics: (1) the risks of transmission of HIV during sexual relations; and (2) HIV as a chronic manageable infection. The section:

- outlines the conditions required for transmission of HIV from one person to another;
- reviews research on the risks of unprotected sexual activities including heterosexual sex, oral sex and anal intercourse;
- reviews research on factors that increase or decrease the risk of sexual transmission of HIV, emphasizing the results of the most current research on antiretroviral therapy and viral load; and;
- closes with a brief discussion of research on HIV as a chronic manageable infection, emphasizing current research on changes in the rate and cause of death and in life expectancy that have followed the introduction of effective antiretroviral therapy.

This section has been externally reviewed by Dr. Rupert Kaul, Canada Research Chair in HIV, Assistant Professor, Department of Medicine, University of Toronto and Dr. Paul MacPherson, Ottawa Hospital Research Institute, Specialist, Division of Infectious Disease, Assistant Professor, Department of Medicine, University of Ottawa.

The criminal law regarding HIV disclosure to sexual partners in Canada lacks clarity. The legal test for disclosure was established by the Supreme Court in 1998 and is based on the phrase “significant risk of serious bodily harm.” The Supreme Court did not establish a legal test assessing risk of HIV transmission. This document contributes to evidence-based policy by providing a review and analysis of risk estimates and other key developments in scientific knowledge about HIV and its sexual transmission that can help

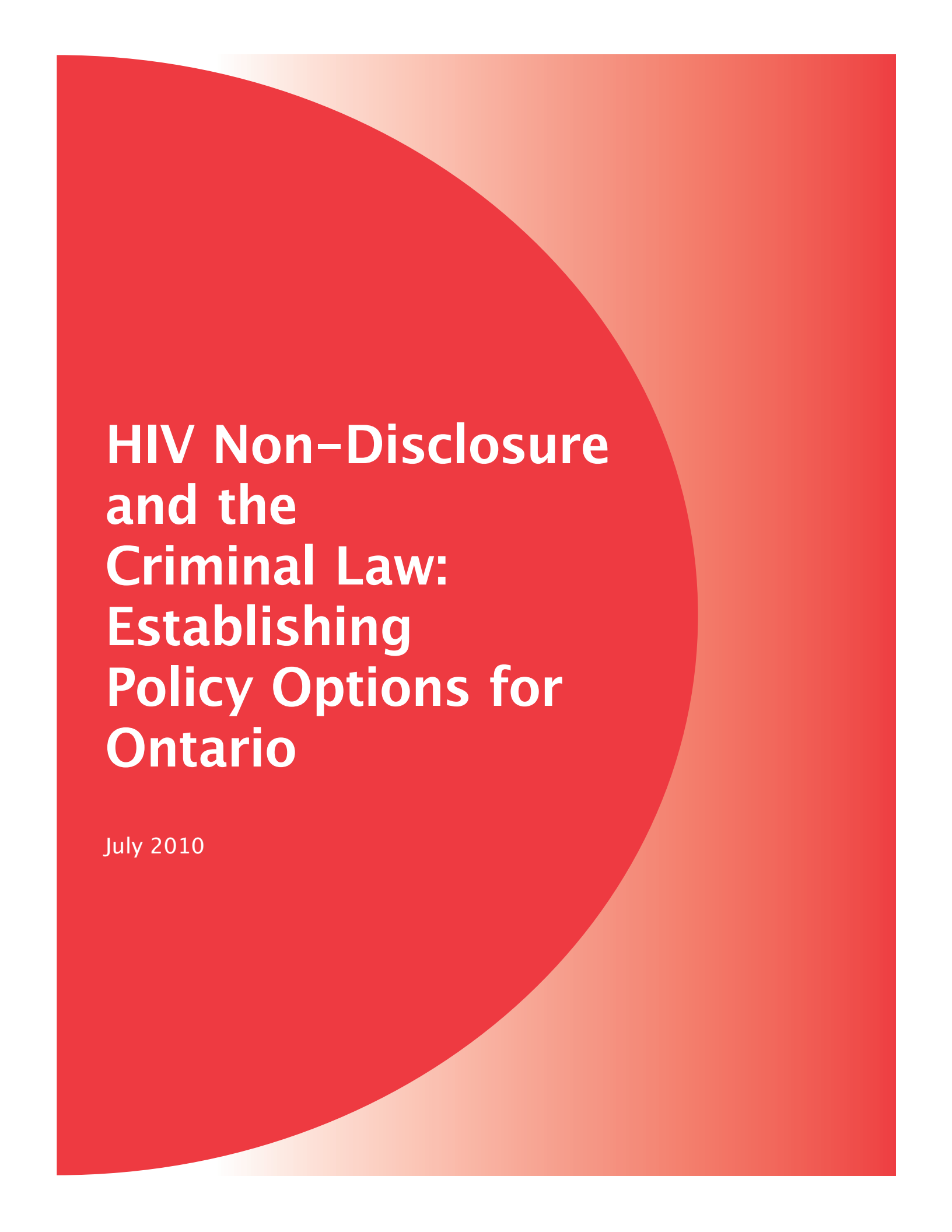
clarify the legal test for when the criminal law imposes a duty of HIV disclosure on people living with HIV.

This document has been provided to the Canadian HIV/AIDS Legal Network for inclusion in its *Responding to the criminalization of HIV transmission or exposure: resources for lawyers and advocates*.

Our full report also includes:

- an analysis of the demographic characteristics of people facing charges, temporal trends and geographic patterns in criminal cases, and an aggregate analysis of the disposition of criminal cases in Ontario;
- an analysis of how the concept of significant risk of serious bodily harm has been presented to, understood by and applied by Ontario courts;
- an original empirical analysis of the effect of criminalization of HIV non-disclosure on people living with HIV/AIDS in Ontario and those working in HIV prevention, treatment, care and support, and;
- a discussion of prosecutorial guidance as a policy option.

For further information or to receive a copy of the full report please direct inquiries to Dr. Eric Mykhalovskiy at [ericm@yorku.ca](mailto:ericm@yorku.ca)



# **HIV Non-Disclosure and the Criminal Law: Establishing Policy Options for Ontario**

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## SECTION 3

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

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 about inaccurate understandings 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 *Cuerrier*, “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<sup>a</sup> involving an HIV-positive person and his or her HIV-negative partner does not result in transmission.<sup>1,2</sup>

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.<sup>3</sup>

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.<sup>b</sup> 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 by sharing equipment used to inject drugs, by transfusing blood products infected with HIV, and through 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 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, analingus), 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.<sup>1,2,4</sup> Unprotected anal intercourse is considered more risky, with an estimated per-act risk of 1 in 100 to 1 in 50, which is a risk that is 10 to 20 times higher than for unprotected vaginal intercourse.<sup>1,5</sup>

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.<sup>23</sup> Studies have shown that circumcision provides some protection to an HIV-negative man who has unprotected vaginal intercourse with an HIV-positive woman.<sup>27</sup> 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.<sup>29-31</sup> Anti-HIV therapy, called antiretroviral therapy, is effective at reducing blood viral load to levels undetectable by current assays, and there is considerable scientific and public health interest in the extent to which antiretroviral therapy 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 or rectum, 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.<sup>1, 2, 4</sup>

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.<sup>6, 8, 9</sup> 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.<sup>7</sup> 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 37) 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 (July of 2010), 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.<sup>1, 2</sup> (See “Reading medical science” page 29) 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 recent analysis of existing published studies provided a slightly lower, and perhaps more precise, estimate of 0.08% per act.<sup>2</sup> 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.”<sup>2</sup>

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.<sup>1,2,8</sup> 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.<sup>9</sup> Other factors known to influence transmission risk, such as being uncircumcised (which increases the risk for HIV-negative male partners), may have influenced results in studies that did not show a significant difference in risk of transmission.

### Oral sex

Oral sex has been associated with a much lower HIV transmission risk than unprotected vaginal or anal intercourse.<sup>7,11,12</sup> A lack of sufficient data has made it impossible to calculate a statistically sound estimate

### 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 calls 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.<sup>10</sup> 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**.<sup>10</sup> 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, how does one compare estimates of the 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 is not possible, one 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 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.

of the risk. However, a scientific consensus has developed that the risk of HIV transmission during oral sex is extremely low, albeit non-zero.<sup>88</sup>

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 Table 4 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.<sup>13</sup> 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.<sup>13</sup>

### Anal intercourse

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

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 the per-act risk of HIV transmission for unprotected anal sex among MSM derive from individual studies and range widely, from 0.01% to over 3%.<sup>13, 16-18</sup> For heterosexual couples, a recent study by Canadian researchers included an estimate of 1.69% per act.<sup>2</sup>

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.<sup>13, 16</sup> 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 for the receptive HIV-negative partner was about ten-fold higher than for the insertive partner (0.82% versus 0.06%).<sup>13</sup> 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.<sup>16</sup>

### 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.<sup>19-22</sup> When used consistently<sup>c</sup> for vaginal intercourse, condoms reduce the transmission of HIV by an estimated 80%, on average.<sup>23</sup>

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.<sup>24</sup> Unprotected receptive anal intercourse has been associated with increased risk of HIV transmission compared with intercourse with a condom.<sup>15,</sup><sup>25</sup> 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.<sup>26</sup> 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%).<sup>13</sup>

### 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.<sup>27</sup>

The impact of circumcision on sexual transmission of HIV among MSM remains unclear. A recent 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%).<sup>16</sup> However, other observational studies have produced conflicting results.<sup>28</sup>

### 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.<sup>29-31</sup> Since antiretroviral drugs lower blood viral load, it was postulated that HIV positive people on therapy might also 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%.<sup>32-34</sup> In Canada from 1997 to 2004, only 15 infants (1.6%) were born HIV positive to 931 HIV-positive mothers who received antiretroviral therapy.<sup>35</sup>

It is now 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. The exact magnitude of the reduction in the risk of sexual transmission of HIV during unprotected sex with people on antiretroviral therapy including those with an undetectable viral load remains unknown. This is an area of intense study among researchers and, at this time, there is insufficient data to make definitive statements about the full extent of risk reduction. (See “The evidence behind viral load, antiretroviral therapy and transmission” page 33 for a more detailed discussion.)

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.<sup>36</sup> 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%.

To better understand this 92% 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, 1 or 2 people would become infected with HIV. This reduction is associated with being on antiretroviral therapy, irrespective of whether the HIV-positive person had an undetectable viral load.

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. 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.<sup>36</sup> 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.<sup>36-37</sup> 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.<sup>36</sup>

A group in the USA is undertaking a large-scale, prospective, randomized, controlled study of the role of antiretroviral therapy in heterosexual HIV transmission.<sup>38</sup> It is expected that the results of this study will provide the most solid information to date on the extent to which taking antiretroviral therapy reduces

### The evidence behind viral load, antiretroviral therapy and transmission

Evidence of the effect of antiretroviral therapy on sexual transmission of HIV comes from two principal sources: cohort studies involving serodiscordant couples (early and more recent studies), and epidemiologic modeling studies. (Please see explanation of study types in section on risk estimates for heterosexual sex.)

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.<sup>29-31</sup> These studies were completed before the introduction of antiretroviral therapy, and it is not clear whether a naturally low viral load has the same characteristics as a low viral load achieved through antiretroviral therapy.

Scientists have found that antiretroviral therapy may lead to undetectable blood viral loads but incomplete suppression of HIV in genital fluids, which arguably play a greater role than blood in the sexual transmission of the virus. Several studies have found that in a significant proportion of people with no detectable virus in their blood, detectable levels of HIV can be found in semen,<sup>41-43</sup> cervicovaginal fluids<sup>44-46</sup> and in the lining of the anal cavity.<sup>47</sup> 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.<sup>42, 48-50</sup> 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. As yet there have been no studies assessing the relationship of this residual seminal virus to the risk of HIV transmission.

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.<sup>51-53</sup> 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.<sup>54, 55</sup> 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.<sup>56, 57</sup>

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.<sup>57</sup> 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. These studies were initially used as a second line of evidence used to support the role of antiretroviral therapy in reducing the risk of HIV transmission. Two studies, one in San Francisco<sup>58</sup> and another in Taiwan,<sup>59</sup> 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,<sup>60</sup> while a fourth study, in Amsterdam, found that a decrease in HIV incidence preceded rather than followed the introduction of antiretroviral therapy.<sup>61</sup> These results are conflicting and are based on modeling studies with known design flaws. The cohort studies discussed above provide more reliable data to support the role of antiretroviral therapy in reducing sexual transmission of HIV.

the risk of passing HIV during sex. As of early 2010, the trial was still enrolling its target of 1750 couples, and final results are not expected for several years.

The association between viral load and the risk of sexual transmission of HIV among MSM populations has been difficult to determine. Designing transmission risk studies in this population has proven difficult (see section on oral sex, page 29).<sup>39-40</sup>

### 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.<sup>2, 14, 62-64</sup> Advanced HIV disease has also been associated with a seven- to 20-fold increase in risk of HIV transmission.<sup>2, 14, 63</sup> 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.<sup>63</sup>

### Sexually transmitted infections (STIs)

There is considerable evidence that having an 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.<sup>1, 65</sup> Several infections have been implicated, including herpes simplex virus (HSV), bacterial vaginosis, gonorrhea, Chlamydia and vaginal candidiasis.<sup>39, 65-68</sup> The risk is generally in the range of one and one-half to five times higher than that seen in the absence of STIs.<sup>2, 39, 66-69</sup>

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,<sup>91</sup> STIs may play an important role in increasing the risk of sexual transmission of HIV.

### 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.<sup>3, 70</sup> 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.

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.<sup>71-75</sup> 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.<sup>76</sup> 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

### 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 can be rebuilt and their health returned.

person-years.<sup>74, 75</sup> Recent studies suggest that the death rate among some groups of people with HIV may be approaching that of the general population.<sup>77</sup>

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 to 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.<sup>74</sup> Similar figures have been obtained in another US study.<sup>75</sup> 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.<sup>74, 78</sup>

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

## 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<sup>1,2</sup> and one older review published in 1996.<sup>4</sup>

- ◆ The two systematic reviews with meta-analyses, completed by a Canadian group (Boily et al.)<sup>2</sup> and an American group (Power et al.)<sup>1</sup> 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 individual studies and one combined analysis of two 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.)<sup>88</sup> This review could not provide a statistical analysis of the data and so the estimate is reported as a range.

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.<sup>70, 80</sup>

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.<sup>74, 75, 81-83</sup> 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.<sup>84, 85</sup> Some are also accessing fertility services if they have trouble conceiving.<sup>86</sup> 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.<sup>87</sup>

**Table 4:**

*Summary of per-act risk estimates for transmission of HIV during different types of sexual intercourse*

<i>Type of intercourse</i>	<i>Risk per act</i>	<i>Comments</i>
<b>Heterosexual</b> (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 33 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 33 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 <i>Study type:</i> review including 11 studies reporting per-act risks for sexual transmission of HIV <i>Estimate derivation:</i> 3 reports involving over 226 couples from high-income countries <i>Comments:</i> one of the first reviews on the topic
Male to female, vaginal intercourse only	0.076%	<i>Author/date:</i> Boily et al., 2009 <i>Study type:</i> systematic review and meta-analysis of 33 publications from 25 heterosexual cohort <i>Estimate derivation:</i> 5 estimates from studies involving 755 couples and 499 individuals in high-income countries

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<i>Type of intercourse</i>	<i>Risk per act</i>	<i>Comments</i>
Female to male (pre-dominantly penile-vaginal sex, but may include other forms (anal and oral))	0.04%	<i>Author/date:</i> Boily et al., 2009 <i>Study type:</i> systematic review and meta-analysis of 33 publications from 25 heterosexual cohorts <i>Estimate derivation:</i> 3 estimates from studies involving 221 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> 6 estimates from studies involving 1037 susceptible participants, including commercial sex workers, in both high- and low-income countries <i>Comments:</i> sex work is associated with a higher risk of HIV transmission
<b>Anal</b> (combined)	0.8 – 3.2%	<i>Author/date:</i> DeGruttola et al., 1989 <i>Study type:</i> prospective, cross-sectional cohort study <i>Participants:</i> 287 MSM in the US <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
	0.01 – 0.1%	<i>Author/date:</i> Jacquez et al., 1994 <i>Study type:</i> retrospective modelling study <i>Participants:</i> 2 MSM cohorts in the US <i>Comments:</i> estimates derived as part of a model explaining epidemiological trends in HIV prevalence early in the epidemic
Receptive (when the HIV-negative person is the receptive partner)	1.69% (heterosexual)	<i>Author/date:</i> Boily et al., 2009 <i>Study type:</i> systematic review and meta-analysis of 33 publications from 25 heterosexual cohorts <i>Estimate derivation:</i> 2 estimates from studies with over 500 participants in high-income countries
	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

Type of intercourse	Risk per act	Comments
	0.06% (MSM)	<p><i>Author/date:</i> Vittinghoff et al., 1999</p> <p><i>Study type:</i> prospective, cohort study</p> <p><i>Participants:</i> 2189 MSM in the US</p> <p><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</p>
<b>Oral</b> (receptive)	0 – 0.04%	<p><i>Author/date:</i> Baggaley et al., 2008</p> <p><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</p> <p><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 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>

## Endnotes

- 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.
- Other fluids considered infectious or potentially infectious are breast milk and several internal body fluids (including cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluids).<sup>90</sup>
- Consistent use implies use of a condom for all acts of penetrative vaginal intercourse. It does not imply correct use of a condom during all of those acts.

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