

## 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.

Update completed in December 2011 by: David McLay, Ph. D.

Update completed in February 2013 by: David McLay, Ph. D.

Reviewed by: Rupert Kaul, Ph. D., M.D., Canada Research Chair in HIV, Assistant Professor, Department of Medicine and Immunology, University of Toronto

### 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 (WHO) 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

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<sup>A</sup> 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.

<sup>B</sup> 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>

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 certain, 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 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.<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 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 a general consensus that effective 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.<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 1 (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 (February 2013), 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 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, and this value was reported as recently as February 2012 from a large, prospective cohort study of serodiscordant couples undertaken in Africa.<sup>111</sup> However, a 2009 analysis of existing published studies provided a slightly lower, and perhaps more precise, estimate of 0.08% per act from studies in high-income countries.<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, 111</sup> One study found that this difference could be explained by higher viral loads in men and other confounding factors in the study.<sup>111</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 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 were 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.<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, 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.<sup>7, 11, 12</sup> 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.<sup>88</sup>

A systematic review of the literature identified three estimates of per-act risk based on results from three studies involving a total of 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.<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 per-act risk of HIV transmission for unprotected anal sex derive from individual studies and range widely, from 0.01% to over 3%.<sup>2, 13, 16-18</sup> 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).<sup>92</sup> 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.<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 associated with being the receptive HIV-negative partner was about ten-fold higher than with being 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%.<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 are 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> A 2002 systematic review and meta-analysis found that when used consistently<sup>C</sup> for vaginal intercourse, condoms reduce the transmission of HIV by an estimated 80%, on average.<sup>23</sup> The report noted that this estimate may not accurately estimate the effectiveness of condoms if condom use is associated with any other risk factor for HIV transmission in the individual studies used in the analysis.

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, 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

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<sup>C</sup> 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.

approximately 60% reduction in risk for circumcised men compared to their uncircumcised counterparts.<sup>27</sup> Since 2007 the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) has recommended male circumcision as an additional strategy for the prevention of HIV transmission in higher prevalence countries where circumcision rates are low and the foreskin is assumed to be the predominant route for men to become infected, particularly in Africa.<sup>112</sup>

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.<sup>93</sup> 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%).<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 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 in 2011 a prospective, randomized, controlled trial provided what is to date the most reliable data on the impact of early antiretroviral treatment on risk of 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.<sup>38</sup> 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.

Of note in HPTN052, only two transmissions occurred while an HIV-positive partner was on antiretroviral therapy. In both cases, antiretroviral therapy had been initiated just prior (about 1 to 3 months) to the transmission event, leaving the possibility that in these cases the virus had not yet been fully suppressed when transmission occurred.<sup>121</sup> 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 slightly, as would be expected with antiretroviral therapy, including occasional detectable levels in both blood and seminal fluids. (See the sidebar “Viral load, antiretroviral therapy and transmission” for further discussion.) Regardless, the trial showed a dramatic decrease in transmission in people who started treatment early.

Since 2009, four systematic reviews and meta-analyses have evaluated the data on the relationship between antiretroviral therapy, blood viral load and the sexual transmission of HIV.<sup>36, 94, 113, 114</sup> The two studies published in early 2013 include results from HPTN052.<sup>113, 114</sup> Table 2 (see page 22) summarizes data from these studies. Three of the four analyses estimate the reduction in relative risk at over 90%, with the best estimate from the fourth being a reduction of 84%.

In addition, some of these reports have noted conditions under which **no** transmissions occurred, including when the blood viral load was kept under 400 copies/mL by antiretroviral therapy<sup>94</sup>, or when the HIV-positive person’s CD4 count (a marker of immune system strength and overall health) was relatively high (over 350 cells/microL).<sup>36</sup> One of the 2013 systematic review and meta-analysis, by Canadian researchers, found no transmissions occurred in these couples in which the HIV-positive partner was on effective therapy and had an undetectable viral load. The researchers focused on cohort studies that confirmed undetectable viral load in the HIV-positive partner of serodiscordant couples. The review identified three studies involving 991 heterosexual couples from Brazil, Spain and Uganda.<sup>113</sup> The researchers note that their “data only apply to heterosexual couples with some degree of variable condom use and does not incorporate the impact of STIs.”

The findings from these systematic reviews and meta-analyses carry caveats. First, results may be based on incomplete data. For example, the analysis reporting no transmissions when viral load was under 400 copies/mL notes that two studies that did report transmission in the presence of antiretroviral therapy did not report viral load.<sup>36</sup> Second, other factors that can impact transmission, such as presence of STIs or condom use, are not consistently reported across studies and so their impact on the results (and the applicability of the results to real-world settings) is impossible to know.

The role of condom use, which is common in these studies, in the observed reductions in risk remains a significant question. To address this, the PARTNER study, a European-based collaboration, is looking to assess the risk of HIV transmission among serodiscordant couples who do not consistently use condoms and in which the HIV-positive partner is on antiretroviral therapy. The study, due to end in mid-2014, is designed to provide information on the absolute risk of HIV transmission for both vaginal and anal sex when the HIV-positive partner is on antiretroviral therapy.<sup>115</sup>

There is less known about the association between viral load, antiretroviral therapy and the risk of sexual transmission of HIV among MSM populations. Following the release of findings from HPTN052, which contained a small number of same-sex couples, the WHO and US National Institutes of Health convened a working group on treatment for HIV prevention among MSM. The group reviewed available evidence and concluded, “there is reason to believe that early initiation of ART for HIV prevention will benefit MSM, transgender women, and others who have anal intercourse, although the magnitude of the effect may be different from that observed in serodiscordant heterosexual couples.”<sup>116</sup>

Despite these limitations, there is strong agreement that effective antiretroviral therapy significantly reduces the risk of HIV transmission during sex and thus has an important role to play in the prevention of HIV transmission. Several national and international health authorities, including the WHO, the Swiss National AIDS Commission, the US Centers for Disease Control and the British HIV Association, have released statements or guidelines on the use of antiretroviral therapy for the prevention of sexual transmission of HIV.<sup>117, 118, 119, 120</sup>

### **Viral load, antiretroviral therapy and transmission**

*Extensive evidence supports the notion that, in general, decreases in HIV blood viral load are associated with decreases in the risk of sexual transmission of the virus. Several observational cohort studies have 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>29-31,111</sup> This was extended to genital viral load in a 2011 study that reported genital viral load is an independent predictor of the risk of transmission, that is in general, the lower the genital viral load, the lower the risk of transmission.<sup>97</sup>*

*Scientists have found that antiretroviral therapy that leads to undetectable blood viral loads also generally leads to a suppression of HIV in genital fluids. However, some degree of discordance between blood and genital fluid viral loads is a consistent finding. Several studies have shown detectable levels of HIV in semen,<sup>41-43, 100</sup> cervicovaginal fluids<sup>44-46, 101, 124</sup> and in the lining of the anal cavity<sup>47</sup> in people on effective therapy. For example, between 5 to 48% of men who have an undetectable blood viral load as a result of antiretroviral therapy still have intermittent detectable virus in semen samples.<sup>42, 48-50, 102, 125-129</sup> More recent studies report that the levels of this intermittent viral shedding are low, ranging up to about 2500 copies/mL<sup>125-128</sup>, and it is not clear whether HIV shedding*

*at these levels is infectious. Furthermore, this intermittent HIV shedding in semen is most common during the first few months after a person starts antiretroviral therapy, and it becomes much less common after a year or more of effective therapy.*<sup>129</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 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.<sup>1, 65, 103, 104</sup> Several infections have been implicated, including herpes simplex virus (HSV), bacterial vaginosis, gonorrhea, Chlamydia and vaginal candidiasis and trichomoniasis.<sup>39, 65-68, 124, 130, 131, 132</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.

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 two<sup>105-108</sup> and others not.<sup>109,110</sup> Emerging evidence suggests that antiretroviral therapy may attenuate the increases in genital viral load seen with STIs.<sup>107, 127, 128, 133</sup> On the other hand, two separate studies of people on effective antiretroviral therapy found that having a genital

tract infection was associated with detectable virus in the seminal or cervicovaginal fluid, suggesting that therapy did not counter the impact of STIs on genital viral load levels.<sup>107, 127</sup> As before, it is not clear whether these levels are infectious.

## 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.

### **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.<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 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 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 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.<sup>79</sup> A 2008 study estimated the average life expectancy for someone infected with HIV at age 20 to be almost 50 years, while results from modeling studies suggest that life expectancy for people with HIV in developed countries who receive proper care could approach that of the general population.<sup>70, 80, 134</sup>

With increased life expectancy, people with HIV are facing similar opportunities and challenges as the HIV-negative population. A 2013 Danish study on the impact of smoking among people with HIV concluded that “in a setting where HIV care is well organized and antiretroviral therapy is free of charge, HIV-infected smokers lose more life-years to smoking than to HIV.”<sup>135</sup> The medical community has 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>

### **Weighing the data on sexual transmission risk**

*The data provided in Table 1 are drawn from published peer-reviewed sources providing the most comprehensive and up-to-date analyses available in early 2013. 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 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.).<sup>88</sup> This review could not provide a statistical analysis of the data and so the estimate is reported as a range.*

<b>Table 1: Summary of per-act risk estimates for transmission of HIV during different types of sexual intercourse</b>		
<b>Type of intercourse</b>	<b>Risk per act</b>	<b>Comments</b>
<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 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>
<b>Anal</b> (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
<b>Oral</b> (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

		no seroconversions (of all 10 studies, 6 reported no seroconversions); the third study included 1583 MSM from the US. <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
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**Table 2: Summary of estimates of relative reductions in risk of sexual transmission of HIV associated with antiretroviral therapy**

	<b>Relative reduction in risk</b>	<b>Comments</b>
<b>Systematic reviews and meta-analyses</b>	92%	<i>Author/date:</i> Attia et al., 2009 <i>Study type:</i> systematic review and analysis of 11 cohorts comprising 5021 serodiscordant heterosexual couples
	66 %*, 84%**	<i>Author/date:</i> Anglemyer et al., 2011 <i>Study type:</i> systematic review and meta-analysis of 7 observational trials with 9755 serodiscordant couples <i>Comments:</i> * Includes two trials with incomplete data; estimate contains considerable heterogeneity ** Excludes two trials with incomplete data; estimate contains no noted heterogeneity
	91%	<i>Author/date:</i> Baggaley et al., 2013 <i>Study type:</i> systematic review and meta-analysis of 8 prospective studies comprising 7681 serodiscordant heterosexual couples

	0.05 (odds ratio <sup>***</sup> )	<p><i>Author/date:</i> Loutfy et al., 2013</p> <p><i>Study type:</i> systematic review and meta-analysis of 6 studies comprising 7061 serodiscordant heterosexual couples; three cohort studies confirmed undetectable virus, two had unconfirmed viral loads at time of transmission, and the sixth study was HPTN052</p> <p><i>Comments:</i> <sup>***</sup>This odds ratio (OR) means that in the presence of ART, the odds of transmitting HIV were 5% of the odds of it passing when no ART was used; an odds ratio can approximate relative risk when risk rate in the control group (in this case, the people not receiving antiretroviral therapy) is low, however not enough information is provided to make this calculation</p>
<b>Prospective, randomized, controlled trial</b>	96%	<p><i>Author/date:</i> Cohen et al., 2011</p> <p><i>Study type:</i> prospective, randomized, controlled trial comparing health outcomes and risk of transmission between immediate and delayed start of antiretroviral therapy among 1763 couples (97% heterosexual)</p> <p><i>Comments:</i> To date, the most reliable data on the relative risk reduction associated with starting antiretroviral therapy early; only two transmissions occurred when people were on antiretroviral therapy and these transmissions occurred soon after treatment was started, meaning the virus may not have been fully suppressed</p>

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NB. Citations struck through have been removed during updating.

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