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.
Update completed in July 2016 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 30 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 penetrative sexual intercourse without a condom, carry a risk of transmission much lower than is often commonly believed. Indeed, most vaginal or anal intercourse involving a person with HIV does not result in transmission.[1,2] And that's not factoring in the dramatic impact of effective antiretroviral treatment, or of other forms of protection such as pre-exposure prophylaxis (PrEP) for the HIV-negative partner, in reducing HIV risks of sexual transmission.

Notes about language
*This text uses medical terms to describe body parts, specifically vagina, penis and anus, while acknowledging that some people may use other terms. By **vaginal intercourse** we mean sexual activity involving the insertion of the penis into the vagina. By **anal intercourse** we mean sexual activity involving the insertion of the penis into the anus.*

*The term **unprotected sex** has traditionally denoted sex without a condom, while protected sex denoted sex using a condom. However, condoms are no longer the only proven way to protect against HIV; effective HIV treatment (see page 10) and PrEP (see page 9) also reduce the chance of HIV transmission. Our language evolves to acknowledge this; when we refer to "intercourse" or "sex" in this text, we assume no form of protection is used. We use more specific terms, such as condomless sex or sex without a condom, when clarification is needed.*

*Finally, we use the terms **female**, **woman**, **male** and **man**. In this text, female and woman refer to cisgender women who have a vagina, and male and man refer to cisgender men who have a penis. (Cisgender refers to a person whose gender identity aligns with the sex they were assigned at birth.) We acknowledge that women and men, including transgender women and transgender men, may have genitals different from this classification. Little research into the risk of HIV transmission during sex has involved transgender people and so results should applied with caution to transgender people.*

Furthermore, advances in the treatment of HIV mean that the disease is no longer 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.[3]

In the context of sex, only four bodily fluids—blood, semen (including pre-ejaculate), and vaginal and anal fluids—contain enough HIV to potentially infect another person.[A] **Transmission can only occur when HIV contained in one of these four 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 certain, as the virus must infect a sufficient number of target cells to establish an infection. The lower the amount of virus in the fluid from the person with HIV, the lower is the risk of infection.

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 anal or vaginal intercourse without protection, such as condoms. HIV can also be transmitted through sharing equipment used to inject drugs, the transfusion of blood products infected with HIV, and vertical transmission between mother and child, that is during pregnancy, childbirth or breastfeeding.

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 partner with HIV or the presence of other sexually transmitted infections (STIs), that can decrease or increase risk.

Experts generally agree that our ability to precisely or accurately quantify the per-act risk of HIV transmission during any sexual activity is limited. Oral sex (fellatio, cunnilingus, analingus) is considered to carry the lowest risk of transmission—the risk is so low that researchers have had difficulty quantifying it. Cunnilingus performed on an HIV-positive

---

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

woman, in particular, has never been definitely associated with transmission of HIV.[141] Based on current research, the probability of HIV transmission during one act of vaginal intercourse is about 0.08% or 8 in 10,000.[1, 2, 4, 136] Anal intercourse is considered more risky, with an estimated per-act risk of 1.4% (or 1 in 70) when the person with HIV is the insertive partner and 0.1% (or 1 in 1,000) when the person with HIV is the receptive partner.[136] However, certain factors in either partner can substantially decrease or increase this "average" risk during a specific episode of sex.

Reductions in the risk of transmission during vaginal or anal sex have been associated with three main factors: condom use, male circumcision and lower amounts of HIV in the blood of the infected partner.[23, 27, 29-31] Increases in the risk of transmission have been linked to the early phase of HIV infection and the presence of other sexually transmitted infections.

Viral load and antiretroviral therapy
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. (Measuring viral loads in other fluids is generally not as sensitive and measured 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 levels in blood are below the level of detection of the test.

*Anti-HIV therapy, called **antiretroviral therapy**, is a combination of drugs that are taken daily with the goal of suppressing viral replication. Antiretroviral therapy can reduce blood viral load to levels undetectable by current assays (hereinafter "effective antiretroviral therapy"). The goal of antiretroviral therapy is to render viral load undetectable. Effective antiretroviral therapy dramatically reduces the probability of HIV transmission during sex.*

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 vaginal or anal intercourse without protection is the most risky sexual activity for HIV transmission, extensive research clearly confirms that only a minority of unprotected acts between an HIV-positive person and his or her HIV-negative partner leads to transmission of the virus.

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 no risk of transmission.[6, 8, 9] Masturbation and any other activity that does not expose the uninfected partner to an HIV-carrying fluid also carry no risk. HIV is fragile and able to persist outside the body only for minutes. Unbroken skin is an effective barrier to the virus and so contact between an HIV-containing fluid and healthy, intact skin is safe.[7] Note, however, that lesions, even if microscopic, can provide an entry point for HIV. As well, HIV can pass through the mucosal membrane lining the rectum, vagina and urethra. Thus, the main modes of HIV transmission through sex are vaginal and anal intercourse.

Table 1 (see page 18) summarizes data from individual studies or analyses 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 as a result of one sexual act with a sex partner who has HIV.

Table 2 (see page 20) presents data published in 2014 by the US-based Centers for Disease Control and Prevention (US CDC). The centre published a systematic review summarizing current knowledge of per-act risk estimates for different sex acts, as well as other modes of HIV transmission.[136] The report reviewed, evaluated and presented the most scientifically solid information produced to date (some of which is also included in Table 1). The CDC report also included relative risks for factors that increase or decrease per-act HIV transmission risk during sex, as well as modeled estimates of the impact of condom use and antiretroviral therapy use on per-act risk for vaginal and anal intercourse.

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

- The first type involves "serodiscordant couples" cohorts (couples in which, at the outset of the study, one partner has HIV and the other does 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, a time when a significant number of forward transmissions occur. These transmissions are missed because couples in which early transmission occurred would no longer be serodiscordant and thus not included in the study. Therefore, these studies may underestimate the overall per-act risk of transmission.

- The second type follows a cohort of HIV-negative individuals, who do not have steady partners with HIV 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 have contributed to our current understanding of the sexual transmission of HIV.

Heterosexual sex

A 2009 analysis of existing published studies in high-income countries estimated the risk of HIV transmission at 0.08% per act of vaginal intercourse.[2] In other words, if 10,000 serodiscordant heterosexual couples had sex once without protection, there would be 8 transmissions of HIV among them. This figure represents the average transmission risk per act of vaginal intercourse, and according to the Canadian researchers who published the estimate, indicates "a low risk of infection in the absence of antiretrovirals."[2] This study and its resulting estimate is cited in the 2014 updates of per-act HIV transmission risk published by the US CDC (Table 2).

It is not completely clear whether the probability of transmitting HIV from a man to a woman is higher than the probability of transmitting HIV from a woman to a man. Some studies have found no difference, while others suggest that the probability of HIV passing from a man to a woman is about twice that of it passing from a woman to a man.[1, 2, 8, 111] Though untested, a number of biological factors, such as increased surface area of the vaginal lining and the possibility of greater degree of its disruption during intercourse, could support a difference in the risk based on direction of transmission.[9]

Reading medical science
The findings from medical research involving people as participants 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.

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

<u>*Types of studies*</u>
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 are collected over time, the study is considered a **longitudinal study**. In this latter case, the group of people who are participating in the study is called a **cohort**. If the study is designed first and then 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 many variables have not been identified or controlled for, which draws into question the validity of the explanations offered.*

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

Caveats when reading studies

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

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

*Third, it is important to distinguish between what is being studied and the population that is being studied. Differences in findings may be due to true differences in what is being studied, **or** to differences attributable to the population studied. For example, compare estimates of risk of HIV transmission during anal sex with risk during vaginal sex. Ideally, it is best to compare anal and vaginal sex risk estimates from a study of one heterosexual population. If that was not possible, 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 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 condomless 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 vaginal or anal intercourse.[7, 11, 12] A lack of sufficient data has made it impossible to calculate a statistically sound estimate of the risk. However, a scientific consensus has developed that the risk of HIV transmission during oral sex is extremely low, albeit non-zero.[88, 136]

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.[13] It is derived from applying complex data to a statistical model in order to estimate per-contact risk for each type of sex. Actual results from the study showed no seroconversions among participants who reported performing only fellatio (to ejaculation), so the modelling may have overestimated the risk associated with oral sex.[13]

Anal intercourse

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

While anal intercourse is part of both heterosexual and homosexual sexual activity, much of the data on HIV transmission risk during anal intercourse comes from studies of MSM. The US CDC report (Table 2) lists the per-act risk of HIV transmission at 1.38% for receptive anal sex (that is, when the HIV-negative person is the receptive partner), and 0.11% for insertive anal sex (that is, when the HIV-negative person is the insertive partner).[136] A 2010 systematic review and analysis reported a similar pooled estimate of 1.4% per act for receptive anal sex (that is, when then HIV-negative person is the receptive partner).[92] There was no significant difference between the risk associated with heterosexual and homosexual activity in this analysis. Individual studies have produced

estimates of per-act risk of HIV transmission for anal sex from 0.01% to over 3%.[2, 13, 16-18, 137]

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 significantly reduce HIV transmission risk independently of other factors.

Factors that reduce the risk of transmission

The main factors associated with a reduction in the risk of transmission are condom use, circumcision of an HIV-negative male partner and lower viral load in the partner with HIV. Pre-exposure prophylaxis (PrEP)—the use of antiretrovirals by HIV-negative people—also reduces the risk of transmission. However, it is not included in this discussion. For more information on PrEP, see www.catie.ca/en/prep.

Condoms

In a 2014 Canadian consensus statement on HIV transmission, experts wrote, "When used correctly and no breakage occurs, condoms are 100% effective at stopping the transmission of HIV because they prevent the contact between HIV-containing bodily fluid and the target cells of an HIV-negative individual."[141]

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.[19-22] A 2002 systematic review and meta-analysis found that when used consistently[B] for vaginal intercourse, condoms reduce the transmission of HIV by an estimated 80%, on average.[23] Condoms are also considered effective in reducing transmission of HIV during anal intercourse; studies have reported effectiveness rates between 70% and 89%.[13, 15, 25, 137, 138] The reason studies do not report 100% effectiveness is the possibility of incorrect use or breakage.

A finding of an 80% reduction in HIV transmission with consistent use of condoms (with possible instances of incorrect use or breakage) does not mean that 80% of people using condoms are protected from HIV while 20% of people using condoms will become HIV positive. 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

[B] 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.

women who had unprotected vaginal intercourse once with a man with HIV. 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.

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 female partners with HIV, with an approximately 50% to 60% reduction in risk for circumcised men compared to their uncircumcised counterparts.[27, 136] 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 exposure of the penis to HIV is assumed to be the predominant route for men to be become infected, particularly in Africa.[112]

Circumcision may also decrease sexual transmission of HIV among MSM for HIV-negative men who are exclusively the insertive partner. A 2011 systematic review reported a 73% reduction in the per-contact risk for circumcised HIV-negative men who were the insertive partner.[93] A 2010 observational study reported a more than 80% reduction in the per-contact risk of transmission to the HIV-negative insertive partner if the insertive partner was circumcised versus uncircumcised (0.11% versus 0.62%).[16] However, other observational studies have produced conflicting results.[28] It is clear that penile circumcision is unlikely to provide significant protection if both the rectal mucosa and penis are exposed to HIV (that is, if a person practices both receptive and insertive anal sex), because the rectal mucosa is much more susceptible to HIV.

Antiretroviral therapy and undetectable viral load

Early studies had showed an association between viral load and sexual HIV transmission risk. Among people who were not on therapy, lower levels of HIV in the blood were associated with lower rates of sexual HIV transmission.[29-31] Since antiretroviral drugs lower blood viral load, it was postulated that people living with HIV 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.[35]

It is now well established and uncontested that effective antiretroviral therapy, which reduces HIV viral load in the blood and slows disease progression, dramatically reduces the risk of sexual transmission of HIV. This has been an area of intense study among researchers over the past several years. Current studies are seeking to quantify the actual (or absolute) risk of transmission among people on therapy. These studies build on earlier investigations into the relative reduction in risk provided by antiretroviral therapy, that is, studies that quantified the reduction in transmission among people on therapy compared to people not on therapy. This distinction is important because a relative reduction is not the actual risk.

Studies estimating the actual per-act risk
Current studies are attempting to estimate the actual (or absolute) per-act risk of transmission during sex, in both heterosexual and homosexual people, in the presence of antiretroviral therapy. The PARTNER study, a European-based collaboration, assessed the risk of HIV transmission among serodiscordant couples who do not consistently use condoms and in which the partner with HIV is on antiretroviral therapy and has a viral load below 200 copies/mL.[115] The final results from the study, presented in 2016, included results from 888 couples, 38% of whom where gay male couples, and reported **zero transmissions** over an estimated 58,213 sex acts without condoms.[149] This lack of transmission occurred even in the presence of diagnosed STIs during the study (See *Sexually Transmitted Infections*, page 14).

While it is not possible to say that the absolute risk of transmission is zero, the study authors commented during a presentation of the results that "on the basis of this data, we can fairly say that the chance of transmission from a virally-supressed HIV-positive individual during heterosexual sex is negligible."[150]

Data from gay couples in PARTNER are fewer than from heterosexual couples, because gay couples comprised a smaller proportion of the study cohort, and so the authors note that additional data is needed before making a similar statement with the same degree of certainty for homosexual sex. An extension of the study is expected to continue until 2017, with results available in 2018.

The Opposites Attract study, being conducted in Australia, Thailand and Brazil, is tracking HIV transmission among serodiscordant gay male couples in which the partner with HIV is on antiretroviral therapy and couples are having condomless anal sex at least some of the time. An interim analysis, presented in 2015, reported zero transmissions over an estimated 5905 acts of anal sex without condoms among 234 couples.[148]

In 2014, a French group completed a modeling study to investigate the per-act risk of HIV transmission through condomless sex with a person with HIV who is on antiretroviral therapy.[139] The researchers identified results from 1672 couples in which the partner with HIV had been taking antiretrovirals for at least 6 months. Six months is generally considered the time needed to ensure viral load is effectively controlled. Among an estimated 113,480 sex acts, of which 17% were condomless, at most 1 transmission occurred. However, researchers were not able to determine whether the transmission occurred before or after the partner being on therapy for 6 months. Thus, they reported two per-act estimates: 0.0087% and 0.013%, depending on when the transmission occurred.

In their 2014 report, the US CDC also calculated the potential impact of antiretroviral therapy on the per-act risk of transmission. Table 2 summarizes their estimated per-act risks for vaginal and anal sex adjusted for the impact of antiretroviral therapy and/or condom use. For example, the per-act risk estimate for vaginal sex with a male partner with HIV who is taking effective antiretroviral therapy is 0.0032% or 3.2 in 100,000.

That estimate falls to 0.0006% per-act when both effective therapy and condoms are used. The authors estimate that "when the two are used together, antiretroviral treatment and condom use could reduce HIV transmission by up to 99.2%."[136]

Studies estimating relative reduction in risk

Prior to studies estimating the absolute risk of transmission when someone is on effective antiretroviral therapy, researchers studied the relative reduction in risk provided by antiretroviral therapy. The prospective, randomized controlled trial called HPTN052 enrolled 1763 serodiscordant couples (97% of whom were heterosexual) from sites in both the developing and developed world.[38] The study evaluated the risk of sexual transmission of HIV in a group in which the partner with HIV started antiretroviral treatment right away and compared it to a group in which the person with HIV 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 interim analysis of data showed that early initiation of treatment led to a 96% decrease in sexual transmission of HIV. Final study results, released in 2016, reported a sustained 93% reduction in HIV transmission. Experts are debating the meaning of the final findings due to the fact that researchers changed the study design after the interim results were collected. Most importantly, researchers observed that **no infections** occurred when HIV viral load was stably undetectable in people on antiretroviral therapy, and that all infections that occurred from people on therapy occurred either early in treatment, before viral load was stably undetectable, or at a time when treatment had stopped working.[38, 151]

From 2009 to 2013, four systematic reviews evaluated the data, including data from HPTN052, on the relationship between antiretroviral therapy, blood viral load and the sexual transmission of HIV.[36, 94, 113, 114] 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 88%.

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[94], 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).[36]

One of the 2013 systematic review and meta-analysis was conducted by Canadian researchers and found **no** transmissions occurred in these couples in which the partner with HIV was on effective therapy and had an undetectable viral load. The researchers focused on cohort studies that confirmed undetectable viral load in the partner with HIV of serodiscordant couples.[113]

In 2016 a group of world-leading HIV experts, including prominent investigators from HPTN052 and PARTNER studies, endorsed a statement that people with HIV on

antiretroviral treatment with an undetectable viral load have a negligible risk of sexual transmission of HIV.[152] A strong international consensus has emerged 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. This is true in Canada as well as internationally; several world-leading 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.[117, 118, 119, 120, 140-143]

The links between 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.[29-31,111] 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.[97]

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,[41-43, 100] cervicovaginal fluids [44-46, 101, 124] and in the lining of the anal cavity[47] 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.[42, 48-50, 102, 125-129] More recent studies report that the levels of this intermittent viral shedding are low, ranging up to about 2500 copies/mL[125-128], 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.[129]

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, lesions or abrasions at the site of exposure would 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 when viral load can be as high as several million copies/mL or more and people may not know their HIV status. A systematic review and meta-analysis of studies reported a range from a 0.8-fold to over

43-fold increase in risk.[144] The authors noted that studies consistently found that higher viral loads during the period led to higher transmission rates.

Advanced HIV disease has also been associated with a seven- to 20-fold increase in risk of HIV transmission.[2, 14, 63] These periods of high blood viral load may partly explain the increased infectivity, though the level of infectivity is higher than would be expected for a given viral load versus other factors that increase the risk of HIV infection.[63]

Sexually transmitted infections (STIs)

There is considerable evidence that having a STI or another infection of the genitourinary tract in the absence of antiretroviral therapy increases the risk of transmission of HIV, regardless of whether the STI is in the HIV-positive or HIV-negative partner.[1, 65, 103, 104] Several infections and conditions have been implicated, including herpes simplex virus (HSV), bacterial vaginosis, gonorrhea, Chlamydia and vaginal candidiasis and trichomoniasis.[39, 65-68, 124, 130, 131, 132] The risk is generally in the range of one and one-half to five times higher than that seen in the absence of STIs.[2, 39, 66-69]

Rates of STIs vary with time, over geographic areas and among populations. In groups with high and increasing rates of STIs, such as rates of syphilis among MSM in some urban centres in Ontario and southern Quebec since the early 2000s,[91, 145] 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. Results have been mixed, with some studies reporting a correlation between the two[105-108] and others not.[109,110] Emerging evidence suggests that antiretroviral therapy likely attenuates the increases in genital viral load seen with STIs, though in at least three studies detectable virus in genital fluids has been associated with a genital tract infection in people on effective antiretroviral therapy.[107, 127, 128, 133, 146] But it is not clear whether these levels are high enough to transmit HIV.

A 2015 systematic review and meta-analysis completed by a team including Canadian researchers, looked at viral load measurements in blood and/or genital fluids and found that being infected with another STI did not significantly increase viral load among people on antiretroviral therapy.[147]

While acknowledging that certain STIs may have larger effects, the Canadian researchers "cautiously posit that ART manages—on average—to sustain its effectiveness at keeping HIV viral loads low during STI co-infection episodes, at the anatomical sites considered in this review (blood plasma, semen and cervicovaginal), and thus would be expected to maintain its effectiveness at preventing transmission." This position is supported by the results of the PARTNER study and Opposites Attract study, which show no transmission from a person with HIV on effective therapy even in the presence of diagnosed STIs.[148, 149]

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 experts and people living with the virus.[3, 70] Antiretroviral therapy blocks the virus's ability to reproduce itself, 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 HIV may never develop AIDS. For people who develop AIDS, their infection can be treated, often allowing their immune systems to rebuild and their health to return to normal.

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

In addition to fewer deaths among people with HIV, there has also been a shift in the causes of death away from the traditional AIDS-defining illnesses—infections such as *Pneumocystis* pneumonia (PCP), or cancers such as Kaposi's sarcoma—towards non-HIV related causes. In one US study, deaths at least partially attributable 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.[74] Similar figures have been obtained in another US study.[75] These non-HIV related causes of death are very similar to those affecting the general population and include heart, liver and lung

disease and non-AIDS-related cancers, although the incidence of these conditions is greater among people with HIV than among the general population. Both HIV infection and the long-term toxicities associated with antiretroviral therapy may be involved in this increased incidence.[74, 78]

Life expectancy for people living with HIV has greatly increased with the introduction of effective antiretroviral therapy. A 2007 Canadian study found that average life expectancy for someone who became infected with HIV at age 20 increased from 9 years in 1993-1995 to 23.6 years in 2002-2004. This means that in 2004, a person who was 20 years old and newly infected with HIV could have expected to live another 23.6 years on average, or to the age of about 44.[79] A 2008 study estimated the average life expectancy for someone infected with HIV at age 20 to be almost 50 years, while 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.[70, 80, 134]

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

Weighing the data on sexual transmission risk

The data provided in Table 1 are drawn from published peer-reviewed sources providing the most comprehensive and up-to-date analyses available in early 2016. 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 systematic reviews and meta-analyses.[1,2] The two systematic reviews with meta-analyses, completed by a Canadian group (Boily et al.)[2] and an American group (Power et al.)[1] were included in this table because they provide a 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.*

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

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

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

17

Table 1: Summary of per-act risk estimates for transmission of HIV during different types of sexual intercourse		
Type of intercourse	**Risk per act**	**Comments**
Heterosexual (no distinction made in direction of transmission)	0.077%	*Author/date:* Boily et al., 2009[2] *Study type:* systematic review and meta-analysis of 43 reports from 25 heterosexual cohorts *Estimate derivation:* 4 estimates from studies with 116 couples in high-income countries
	0.056%	*Author/date:* Powers et al., 2008[1] *Study type:* systematic review and meta-analysis of 27 reports from 15 heterosexual cohorts *Estimate derivation:* 8 estimates from studies with 1402 couples in high-income countries
Male to female (predominantly penile-vaginal sex, but may include other acts (anal and oral))	0.08%	*Author/date:* Boily et al., 2009 *Study type:* systematic review and meta-analysis of 43 reports from 25 heterosexual cohorts *Estimate derivation:* 10 estimates from studies with 1744 couples in high-income countries
	0.064%	*Author/date:* Powers et al., 2008 *Study type:* systematic review and meta-analysis of 27 reports from 15 heterosexual cohorts *Estimate derivation:* 10 estimates from studies with 4088 susceptible participants in high- and low-income countries
Male to female, vaginal intercourse only	0.076%	*Author/date:* Boily et al., 2009 *Study type:* systematic review and meta-analysis of 43 reports from 25 heterosexual cohorts *Estimate derivation:* 5 estimates from studies with 755 couples and 499 individuals in high-income countries
Female to male (predominantly penile-vaginal sex, but may include other forms (anal and oral))	0.04%	*Author/date:* Boily et al., 2009 *Study type:* systematic review and meta-analysis of 43 reports from 25 heterosexual cohorts *Estimate derivation:* 3 estimates from studies with 221 couples in high-income countries
	0.064%	*Author/date:* Powers et al., 2008 *Study type:* systematic review and meta-analysis of 27 reports from 15 heterosexual cohorts *Estimate derivation:* 6 estimates from studies with 1037 susceptible participants, including commercial sex workers, in both high- and low-income countries *Comments:* sex work is associated with a higher risk of HIV transmission
Anal Receptive (when the	1.4% (heterosexual	*Author/date:* Baggaley et al., 2010[92] *Study type:* systematic review and meta-analysis of 4 publications

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

18

HIV-negative person is the receptive partner)	and MSM)	*Estimate derivation:* 4 estimates from 4 studies with 3367 heterosexual and MSM participants in high-income countries *Comments*: Authors found no difference between estimates from MSM and heterosexuals
	0.65%, 1.43% (MSM)	*Author/date:* Jin et al., 2010[16] *Study type:* prospective, cohort study of 1136 MSM in Australia *Comments:* The lower figure is for withdrawal before ejaculation; the higher figure, for ejaculation in the rectum
	0.82% (MSM)	*Author/date:* Vittinghoff et al., 1999[13] *Study type:* prospective, cohort study of 2189 MSM in the US
Insertive (when the HIV-negative person is the insertive partner)	0.11%, 0.62% (MSM)	*Author/date:* Jin et al., 2010 *Study type:* prospective, cohort study of 1136 MSM in Australia *Comments:* Lower figure is for circumcised men; higher figure, for uncircumcised men
	0.06% (MSM)	*Author/date:* Vittinghoff et al., 1999 *Study type:* prospective, cohort study of 2189 MSM in the US *Comments:* the insertive partner is HIV negative, the receptive partner is HIV positive or of unknown status, meaning this estimate may under-represent the true risk of infection
Oral (receptive)	0 – 0.04%	*Author/date:* Baggaley et al., 2008[88] *Study type:* 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 *Estimate derivation:* 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. *Comments:* the 0.04% estimate is derived 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

Table 2: Summary of per-act risk estimates for transmission of HIV during different types of sexual intercourse with a person living with HIV, as published by the US CDC in Patel et al., 2014.[136]				
Type of intercourse	Risk per act	Risk per act with consistent[*] condom use	Risk per act in the presence of antiretroviral therapy[**]	Risk per act when consistent condom use and antiretroviral therapy[**]
Receptive penile-vaginal	0.08%	0.016%	0.0032%	0.0006%
Insertive penile-vaginal	0.04%	0.008%	0.0016%	0.0003%
Receptive anal	1.38%	0.28%	0.06%	0.011%
Insertive anal	0.11%	0.02%	0.004%	0.0009%
Oral sex	Low, that is "risk is considered to be low relative to the other sexual exposures, but it is not zero."			
[*] Consistent means using a condom for all acts of penetrative intercourse. It does not mean correct use for all acts. [**] Antiretroviral therapy in the partner with HIV				

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

20

References
NB. Citations struck through have been removed during updating.

1. Powers KA, Poole C, Pettifor AE and Cohen MS. (2008). Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. *Lancet Infect Dis*. Sep;8(9):553-63.
2. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ and Alary M. (2009). Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *Lancet Infect Dis*. Feb;9(2):118-29.
3. Dieffenbach CW and Fauci AS. (2009). Universal voluntary testing and treatment for prevention of HIV transmission. *JAMA*. Jun 10;301(22):2380-2.
4. Mastro TD and de Vincenzi I. (1996). Probabilities of sexual HIV-1 transmission. *AIDS*.10 Suppl A:S75-82.
5. Halperin DT, Shiboski SC, Palefsky JM and Padian NS. (2002). High level of HIV-1 infection from anal intercourse: a neglected risk factor in heterosexual AIDS prevention. Poster Exhibition: The XIV International AIDS Conference: Abstract no. ThPeC7438.
6. Joint United Nations Programme on HIV/AIDS. *HIV Prevention Fast Facts*. UNAIDS website, www.unaids.org/en/KnowledgeCentre/Resources/FastFacts/. Accessed February 2010.
7. Morrow G, Vachot L, Vagenas P and Robbiani M. (2007). Current concepts of HIV transmission. *Curr HIV/AIDS Rep.* Feb;4(1):29-35.
8. European Study Group on Heterosexual Transmission of HIV. (1992). Comparison of female to male and male to female transmission of HIV in 563 stable couples. *BMJ*. Mar 28;304(6830):809-13.
9. Fox J, and Fidler S. (2010). Sexual transmission of HIV-1. *Antiviral Res*. Jan;85(1):276-85.
10. Higgins JPT and Green S (editors). (updated 2009). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0*. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org. Accessed January 2010.
11. Centers for Disease Control and Prevention. (2010). Oral sex and HIV Risk. *CDC HIV/AIDS Facts*, June 2009. www.cdc.gov/hiv/resources/factsheets/oralsex.htm. Accessed January 2010.
12. National AIDS Trust. (2010). *HIV The Basics*. National AIDS Trust, UK website, www.nat.org.uk/HIV-Facts/The-basics.aspx. Accessed January 2010.
13. Vittinghoff E, Douglas J, Judson F, McKirnan D, MacQueen K and Buchbinder SP. (1999). Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *Am J Epidemiol.* Aug 1;150(3):306-11.
14. Leynaert B, Downs AM and de Vincenzi I. (1998). Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. European Study Group on Heterosexual Transmission of HIV. *Am J Epidemiol.* Jul 1;148(1):88-96.
15. Macdonald N, Elam G, Hickson F, Imrie J, McGarrigle CA, Fenton KA, Baster K, Ward H, Gilbart VL, Power RM and Evans BG. (2008). Factors associated with HIV seroconversion in gay men in England at the start of the 21st century. *Sex Transm Infect*. Feb;84(1):8-13.

16. Jin F, Jansson J, Law M, Prestage GP, Zablotska I, Imrie JC, Kippax SC, Kaldor JM, Grulich AE and Wilson DP. (2010). Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. *AIDS.* Mar 27;24(6):907-13.

17. DeGruttola V, Seage GR 3rd, Mayer KH and Horsburgh CR Jr. (1989). Infectiousness of HIV between male homosexual partners. *J Clin Epidemiol*. 42(9):849-56.

18. Jacquez JA, Koopman JS, Simon CP and Longini IM Jr. (1994). Role of the primary infection in epidemics of HIV infection in gay cohorts. *J Acquir Immune Defic Syndr*. Nov;7(11):1169-84.

19. AIDS Bureau. (2008). *Guidelines for HIV Counseling and Testing*. AIDS Bureau, Ontario Ministry of Health and Long-Term Care.

20. Public Health Agency of Canada. (2007). *Protect yourself*. Public Health Agency of Canada web site, www.phac-aspc.gc.ca/aids-sida/info/3-eng.php. Accessed January 2010.

21. Centers for Disease Control and Prevention. (2010). Condoms and STDs: Fact Sheet for Public Health Personnel. US Centers for Disease Control website, www.cdc.gov/condomeffectiveness/latex.htm. Accessed January 2010.

22. Joint United Nations Programme on HIV/AIDS. *Condoms*. UNAIDS website, www.unaids.org/en/PolicyAndPractice/Prevention/Condoms. Accessed January 2010.

23. Weller S and Davis K. (2002). Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev.* 1:CD003255.

24. Silverman BG, Gross TP. (1997). Use and effectiveness of condoms during anal intercourse. A review. *Sex Transm Dis*. Jan;24(1):11-7.

25. Lavoie E, Alary M, Remis RS, Otis J, Vincelette J, Turmel B, Lavoie R, Masse BR and Le Clerc R. (2008). Determinants of HIV seroconversion among men who have sex with men living in a low HIV incidence population in the era of highly active antiretroviral therapies. *Sex Transm Dis.* Jan;35(1):25-9.

26. ~~Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, Schrager LK and Phair JP. (1998). Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA.* Nov 4;280(17):1497-503.~~

27. Mills E, Cooper C, Anema A and Guyatt G. (2008). Male circumcision for the prevention of heterosexually acquired HIV infection: a meta-analysis of randomized trials involving 11,050 men. *HIV Med.* Jul;9(6):332-5.

28. Millett GA, Flores SA, Marks G, Reed JB and Herbst JH. (2008). Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. JAMA. 2008 Oct 8;300(14):1674-84. Erratum in: *JAMA*. 2009 Mar 18;301(11):1126-9.

29. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, Meehan MO, Lutalo T and Gray RH. (2000). Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. Mar 30;342(13):921-9.

30. Tovanabutra S, Robison V, Wongtrakul J, Sennum S, Suriyanon V, Kingkeow D, Kawichai S, Tanan P, Duerr A and Nelson KE. (2002). Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr*. Mar 1;29(3):275-83.

31. Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, Mulenga J, Kasolo F, Vermund SH and Aldrovandi GM. (2001). Virologic and immunologic determinants of

heterosexual transmission of human immunodeficiency virus type 1 in Africa. *AIDS Res Hum Retroviruses.* Jul 1;17(10):901-10.

32. Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, Diaz C, Hayani K, Handelsman E, Smeriglio V, Hoff R and Blattner W; Women and Infants' Transmission Study Group. (2002). Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr.* Apr 15;29(5):484-94.

33. Burdge DR, Money DM, Forbes JC, Walmsley SL, Smaill FM, Boucher M, Samson LM and Steben M; Canadian HIV Trials Network Working Group on Vertical HIV Transmission. (2003). Canadian consensus guidelines for the care of HIV-positive pregnant women: putting recommendations into practice. *CMAJ.* Jun 24;168(13):1683-8.

34. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. (2009). *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* Department of Health and Human Services. December 1, 1-161. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed January 2010.

35. ~~Forbes J, Samson L, Alimenti A, Singer J, Money D and Lapointe N. (2006). Perinatal HIV transmission seen in the Canadian Perinatal HIV Surveillance Project (CPHSP) from 1990. Canadian Association of HIV Research Annual Conference. Abstract 302.~~ Replaced in 2016 with: Forbes JC, Alimenti AM, Singer J, Brophy JC, Bitnun A, Samson LM, Money DM, Lee TC, Lapointe ND, Read SE; Canadian Pediatric AIDS Research Group (CPARG). (2012). A national review of vertical HIV transmission. *AIDS.* Mar 27;26(6):757-63.

36. Attia S, Egger M, Muller M, Zwahlen M and Low N. (2009). Sexual transmission of HIV according to viral loa d and antiretroviral therapy: systematic review and meta-analysis. *AIDS.* Jul 17;23(11):1397-404.

37. Wilson DP. (2009). Data are lacking for quantifying HIV transmission risk in the presence of effective antiretroviral therapy. *AIDS.* Jul 17;23(11):1431-3.

38. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, et al. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* Aug 11;365(6):493-505.

39. Johnson LF and Lewis DA. (2008). The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. *Sex Transm Dis.* Nov; 35(11):946-59.

40. ~~McCormick AW, Walensky RP, Lipsitch M, Losina E, Hsu H, Weinstein MC, Paltiel AD, Freedberg KA and Seage GR 3rd. (2007). The effect of antiretroviral therapy on secondary transmission of HIV among men who have sex with men. *Clin Infect Dis.* Apr 15;44(8):1115-22.~~

41. Sheth PM, Kovacs C, Kemal KS, Jones RB, Raboud JM, Pilon R, la Porte C, Ostrowski M, Loutfy M, Burger H, Weiser B and Kaul R; Toronto Mucosal Immunology Group. (2009). Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS.* Sep 24;23(15):2050-4.

42. Lorello G, la Porte C, Pilon R, Zhang G, Karnauchow T and MacPherson P. (2009). Discordance in HIV-1 viral loads and antiretroviral drug concentrations comparing semen and blood plasma. *HIV Med.* Oct;10(9):548-54.

43.	Pasquier C, Sauné K, Raymond S, Moinard N, Daudin M, Bujan L and Izopet J. (2009). Determining seminal plasma human immunodeficiency virus type 1 load in the context of efficient highly active antiretroviral therapy. *J Clin Microbiol*. Sep;47(9):2883-7.

44.	Cu-Uvin S, Snyder B, Harwell JI, Hogan J, Chibwesha C, Hanley D, Ingersoll J, Kurpewski J, Mayer KH and Caliendo AM. (2006). Association between paired plasma and cervicovaginal lavage fluid HIV-1 RNA levels during 36 months. *J Acquir Immune Defic Syndr*. Aug 15;42(5):584-7.

45.	Fiore JR, Suligoi B, Saracino A, Di Stefano M, Bugarini R, Lepera A, Favia A, Monno L, Angarano G and Pastore G. (2003). Correlates of HIV-1 shedding in cervicovaginal secretions and effects of antiretroviral therapies. *AIDS*. Oct 17;17(15):2169-76.

46.	Nagot N, Ouedraogo A, Weiss HA, Konate I, Sanon A, Defer MC, Sawadogo A, Andonaba JB, Vallo R, Becquart P, Segondy M, Mayaud P, and Van de Perre P; Yerelon Study Group. (2008). Longitudinal effect following initiation of highly active antiretroviral therapy on plasma and cervico-vaginal HIV-1 RNA among women in Burkina Faso. *Sex Transm Infect.* Jun;84(3):167-70.

47.	Lampinen TM, Critchlow CW, Kuypers JM, Hurt CS, Nelson PJ, Hawes SE, Coombs RW, Holmes KK and Kiviat NB. (2000). Association of antiretroviral therapy with detection of HIV-1 RNA and DNA in the anorectal mucosa of homosexual men. *AIDS*. Mar 31;14(5):F69-75.

48.	Lafeuillade A, Solas C, Chadapaud S, Hittinger G, Poggi C and Lacarelle B. (2003). HIV-1 RNA levels, resistance, and drug diffusion in semen versus blood in patients receiving a lopinavir-containing regimen. *J Acquir Immune Defic Syndr*. Apr 1;32(4):462-4.

49.	Eron JJ Jr, Smeaton LM, Fiscus SA, Gulick RM, Currier JS, Lennox JL, D'Aquila RT, Rogers MD, Tung R and Murphy RL. (2000). The effects of protease inhibitor therapy on human immunodeficiency virus type 1 levels in semen (AIDS clinical trials group protocol 850). *J Infect Dis*. May;181(5):1622-8.

50.	Barroso PF, Schechter M, Gupta P, Bressan C, Bomfim A and Harrison LH. (2003). Adherence to antiretroviral therapy and persistence of HIV RNA in semen. *J Acquir Immune Defic Syndr*. Apr 1;32(4):435-40.

51.	~~Del Romero J, Castilla J, Hernando V, Rodriguez C, and Garcia S. (2010). Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. *BMJ*. January 1; 340: c2205.~~

52.	~~Melo MG, Santos BR, De Cassia Lira R, Varella IS, Turella ML, Rocha TM and Nielsen-Saines K. (2008). Sexual transmission of HIV-1 among serodiscordant couples in Porto Alegre, southern Brazil. *Sex Transm Dis*. Nov;35(11):912-5.~~

53.	~~Reynolds SJ, Makumbi F, Nakigozi G, Kagaayi J, Gray RH, Wawer M, Quinn TC, Serwadda D. (2011). HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. Feb 20;25(4):473-7.~~

54.	~~Bunnell R, Ekwaru J, King R, Bechange S, Moore D, Khana K, Were W, Coutinho A, Tappero J and Mermin J. (2008). 3-Year follow-up of sexual behavior and HIV transmission risk of persons taking ART in rural Uganda. 15th Conference on Retroviruses and Opportunistic Infections: Abstract 29.~~

55.	~~Sullivan P, Kayitenkore K, Chomba E, Karita E, Mwananyanda L, Vwalika C, Conkling M, Luisi1 N, Tichacek A and Allen S. (2009). Reduction of HIV transmission risk and~~

high risk sex while prescribed ART: Results from discordant couples in Rwanda and Zambia. 16th Conference on Retroviruses and Opportunistic Infections: Abstract 52bLB.

56.   Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, McIntyre J, Lingappa JR, Celum C, for the Partners in Prevention HSV/HIV Transmission Study Team (2010). Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. Jun 12;375: 2092-98.

57.   Castilla J, Del Romero J, Hernando V, Marincovich B, Garcia S and Rodriguez C. (2005). Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J *Acquir Immune Defic Syndr*. Sep 1;40(1):96-101.

58.   Porco TC, Martin JN, Page-Shafer KA, Cheng A, Charlebois E, Grant RM and Osmond DH. (2004). Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. *AIDS*. Jan 2;18(1):81-8.

59.   Fang CT, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, Wang JD and Chuang CY; Division of AIDS and STD, Center for Disease Control. Department of Health, Executive Yuan (2004). Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. *J Infect Dis*. Sep 1;190(5):879-85.

60.   Katz MH, Schwarcz SK, Kellogg TA, Klausner JD, Dilley JW, Gibson S and McFarland W. (2002). Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *Am J Public Health*. Mar;92(3):388-94.

61.   Dukers NH, Spaargaren J, Geskus RB, Beijnen J, Coutinho RA and Fennema HS. (2002). HIV incidence on the increase among homosexual men attending an Amsterdam sexually transmitted disease clinic: using a novel approach for detecting recent infections. *AIDS*. Jul 5;16(10):F19-24.

62.   Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, Kiwanuka N, Kigozi G, Kiddugavu M, Lutalo T, Nalugoda F, Wabwire-Mangen F, Meehan MP and Quinn TC. (2005). Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis*. May 1;191(9):1403-9.

63.   Hollingsworth TD, Anderson RM and Fraser C. (2008). HIV-1 transmission, by stage of infection. *J Infect Dis*. Sep 1;198(5):687-93.

64.   Pinkerton SD. (2008). Probability of HIV transmission during acute infection in Rakai, Uganda. *AIDS Behav*. Sep;12(5):677-84.

65.   Galvin SR, and Cohen MS. (2004). The role of sexually transmitted diseases in HIV transmission. *Nat Rev Microbiol*. Jan;2(1):33-42.

66.   Royce RA, Sena A, Cates W Jr and Cohen MS. (1997). Sexual transmission of HIV. *N Engl J Med*. Apr 10;336(15):1072-8.

67.   Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA and Hayes RJ. (2006). Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS*. Jan 2;20(1):73-83.

68.   Atashili J, Poole C, Ndumbe PM, Adimora AA and Smith JS (2008). Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. *AIDS*. Jul 31;22(12):1493-501.

69.   Wald A and Link K. (2002). Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis*. Jan 1;185(1):45-52.

70. Antiretroviral Therapy Cohort Collaboration. (2008). Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. Jul 26;372(9635):293-9.

71. Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC and Porter K; CASCADE Collaboration. (2008). Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA*. Jul 2;300(1):51-9.

72. Keiser O, Taffe P, Zwahlen M, Battegay M, Bernasconi E, Weber R, Rickenbach M; and the Swiss HIV Cohort Study. (2004). All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population. *AIDS*. Sep 3;18(13):1835-43.

73. Ewings FM, Bhaskaran K, McLean K, Hawkins D, Fisher M, Fidler S, Gilson R, Nock D, Brettle R, Johnson M, Phillips A and Porter K; UK Register of HIV Seroconverters. (2008). Survival following HIV infection of a cohort followed up from seroconversion in the UK. AIDS. Jan 2;22(1):89-95.

74. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT and Holmberg SD; HIV Outpatient Study Investigators. (2006). Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr.* Sep;43(1):27-34.

75. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, Armstrong AW, Fraser S and Wallace MR; Triservice AIDS Clinical Consortium. (2006). Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr*. Feb 1;41(2):194-200.

76. Public Health Agency of Canada. (2009). *HIV and AIDS in Canada. Surveillance report to December 31, 2008.* Available at www.phac-aspc.gc.ca/aids-sida/publication/index-eng.php#surveillance.

77. Lewden C and the Mortality Working Group of COHERE. (2010). Time with CD4 cell count above 500 cells/mm3 allows HIV-infected men, but not women, to reach similar mortality rates to those of the general population: A seven-year analysis. 17th Conference on Retroviruses and Opportunistic Infections: Abstract 527.

78. Deeks SG and Phillips AN. (2009). HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ*. Jan 31;338:288-292.

79. Lima VD, Hogg RS, Harrigan PR, Moore D, Yip B, Wood E and Montaner JS. (2007). Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. *AIDS*. Mar 30;21(6):685-92.

80. van Sighem A, Gras L, Reiss P, Brinkman K and de Wolf F, ATHENA Natl Observational Cohort Study. (2010). Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. 17th Conference on Retroviruses and Opportunistic Infections: Abstract 526.

81. Kojic EM, Wang CC and Cu-Uvin S. (2007). HIV and menopause: a review. *J Womens Health* (Larchmt). Dec;16(10):1402-11.

82. Manfredi R. (2002). HIV disease and advanced age: an increasing therapeutic challenge. *Drugs Aging*. 19(9):647-69.

83. Manfredi R. (2004). HIV infection and advanced age emerging epidemiological, clinical, and management issues. *Ageing Res Rev*. Jan;3(1):31-54.

84. Semprini AE and Fiore S. (2004). HIV and reproduction. *Curr Opin Obstet Gynecol.* Jun;16(3):257-62.

85. Bendikson KA, Anderson D, and Hornstein MD. (2002). Fertility options for HIV patients. *Curr Opin Obstet Gynecol.* Oct;14(5):453-7.

86. van Leeuwen E, Prins JM,.Jurriaans S, Boer K, Reiss P, Repping S and van der Veen F. (2007). Reproduction and fertility in human immunodeficiency virus type-1 infection. *Human Reproduction Update.* 13(2):197–206.

87. Loutfy MR, Hart TA, Mohammed SS, Su D, Ralph ED, Walmsley SL, Soje LC, Muchenje M, Rachlis AR, Smaill FM, Angel JB, Raboud JM, Silverman MS, Tharao WE, Gough K and Yudin MH; Ontario HIV Fertility Research Team. (2009). Fertility desires and intentions of HIV-positive women of reproductive age in Ontario, Canada: a cross-sectional study. *PLoS One.* Dec 7;4(12):e7925.

88. Baggaley RF, White RG and Boily MC. (2008). Systematic review of orogenital HIV 1 transmission probabilities. *Int J Epidemiol.* Dec;37(6):1255-65.

89. Canadian AIDS Society. (2004). HIV Transmission: Guidelines for Assessing Risk. Fifth edition. Canadian AIDS Society, Ottawa. Available at www.cdnaids.ca.

90. Centers for Disease Control and Prevention. (2005). Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for Postexposure Prophylaxis. *MMWR* 54(No. RR-9):1-8. Replaced in 2016 by: Kuhar DT, Henderson DK, Struble KA, Heneine W, Thomas V, Cheever LW, Gomaa A, Panlilio AL for the US Public Health Service Working Group. (2013). Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis. *Infection Control and Hospital Epidemiology*, 34(9): 875-892.

91. Leber A, MacPherson P and Lee BC. (2008). Epidemiology of infectious syphilis in Ottawa. Recurring themes revisited. *Can J Public Health*. Sep-Oct;99(5):401-5.

92. Baggaley RF, White RG and Boily MC. (2010). HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV preventions. *Int J Epidemiol.* Aug;39(4):1048-63.

93. Wiysonge CS, Kongnyuy EJ, Shey M, Muula AS, Navti OB, Akl EA, Lo YR. (2011). Male circumcision for prevention of homosexual acquisition of HIV in men. *Cochrane Database Syst Rev*. Jun 15;(6):CD007496.

94. Anglemyer A, Rutherford GW, Baggaley RC, Egger M, and Siegfried N. (2011). Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Database Syst Rev*. Aug 10;(8):CD009153. Replaced in 2016 with: Anglemyer A, Rutherford GW, Baggaley RC, Egger M, and Siegfried N. (2013). Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Database Syst Rev*. 4: CD009153.

95. ~~Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, Colfax GN. (2010). Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS One*. Jun 10;5(6):e11068.~~

96. ~~Cowan S, Christiansen AH, Haff J. (2010). New paradigm for positive prevention: "Test and treat" - testing for and treating HIV has lowered transmission rate in Denmark in spite of increased unsafe sex among MSM. XVIII International AIDS Conference, Vienna, Austria. Abstract no. MOAC0103~~

97. Baeten JM, Kahle E, Lingappa JR, Coombs RW, Delany-Moretlwe S, Nakku-Joloba E,

Mugo NR, Wald A, Corey L, Donnell D, Campbell MS, Mullins JI, Celum C; Partners in Prevention HSV/HIV Transmission Study Team. (2011). Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. *Sci Transl Med*. Apr 6;3(77):77ra29.

98. ~~Gill VS, Lima VD, Zhang W, Wynhoven B, Yip B, Hogg RS, Montaner JS, and Harrigan PR. (2010) Improved virological outcomes in British Columbia concomitant with decreasing incidence of HIV type 1 drug resistance detection. *Clin Infect Dis*. Jan 1;50(1):98-105.~~

99. ~~Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, Shannon K, Harrigan PR, Hogg RS, Daly P, and Kendall P. (2010). Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet*. Aug 14;376(9740):532-9.~~

100. Halfon P, Giorgetti C, Khiri H, Pénaranda G, Terriou P, Porcu-Buisson G, Chabert-Orsini V. (2010). Semen may harbor HIV despite effective HAART: another piece in the puzzle. *PLoS One*. May 13;5(5):e10569.

101. Cu-Uvin S, DeLong AK, Venkatesh KK, Hogan JW, Ingersoll J, Kurpewski J, De Pasquale MP, D'A quila R, Caliendo AM. (2010). Genital tract **HIV**-1 RNA shedding among women with below detectable plasma viral load. *AIDS*. Oct 23;24(16):2489-97.

102. Kalichman SC, Di Berto G, Eaton L. (2008). Human immunodeficiency virus viral load in blood plasma and semen: review and implications of empirical findings. *Sex Transm Dis*. Jan;35(1):55-60.

103. Cohen MS. (1998). Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet*. 351 Suppl 3:5-7.

104. Ward H and Rönn M. (2010). The contribution of STIs to the sexual transmission of HIV. *Curr Opin HIV AIDS*. July ; 5(4): 305–310.

105. Paz-Bailey G, Sternberg M, Puren AJ, Steele L, Lewis DA. (2010). Determinants of HIV type 1 shedding from genital ulcers among men in South Africa. *Clin Infect Dis.* 50:1060–1067.

106. Zuckerman RA, Lucchetti A, Whittington WLH, Sanchez J, Coombs RW, Margaret A, Wald A, Corey L, Celum C. (2009). HSV supression reduces seminal HIV-1 levels in HIV-1/HSV-2 coinfected men who have sex with men (MSM). *AIDS*. Feb 20;23(4):479-83.

107. Gitau RW, Graham SM, Masese LN, Overbaugh J, Chohan V, Peshu N, Richardson BA, Jaoko W, Ndinya-Achola JO, McClelland RS. (2010). Effect of acquisition and treatment of cervical infections on HIV-1 shedding in women on antiretroviral therapy. *AIDS*. Nov;24(17):2733-37.

108. Rieg G, Butler DM, Smith DM, Daar ES. (2010). Seminal plasma HIV levels in men with asymptomatic sexually transmitted infections. *Int J STD AIDS*. March; 21(3): 207–08.

109. Chan DJ, McNally L, Batterham M, Smith DE. (2008). Relationship between HIV-RNA load in blood and semen in antiretroviral-naive and experienced men and effect of asymptomatic sexually transmissible infections. *Curr HIV Res*. Mar;6(2):138-42.

110. Kelley CF, Haaland RE, Patel P, Evans-Strickfaden T, Farshy C, Hanson D, Mayer K, Lennox JL, Brooks JT, Hart CE. (2011). HIV-1 RNA rectal shedding is reduced in men with low plasma HIV-1 RNA viral loads and is not enhanced by sexually transmitted bacterial infections of the rectum. *J Infect Dis*. Sep 1;204(5):761-7.

111. Hughes JP, Baeten JM, Lingappa JR, Magaret AS, Wald A, de Bruyn G, Kiarie J,

Inambao M, Kilembe W, Farquhar C, Celum C; Partners in Prevention HSV/HIV Transmission Study Team. (2012). Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. *J Infect Dis*. Feb 1;205(3):358-65.

112. New data on male circumcision and HIV prevention: policy and programme implications: conclusions and recommendations / WHO/UNAIDS Technical Consultation on Male Circumcision and HIV Prevention: Research Implications for Policy and Programming Montreux, 6 – 8 March 2007. Available at: http://libdoc.who.int/publications/2007/9789241595988_eng.pdf (Accessed Feb 15, 2013)

113. Loutfy MR, Wu W, Letchumanan L, Bondy L, Antoniou T, Margolese S, Zhang Y, Rueda S, McGee F, Peck R, Binder L, Allard P, Rourke SB, Rochon PA. (2012). Systematic Review of HIV Transmission between Heterosexual Serodiscordant Couples where the HIV Positive Partner Is Fully Suppressed on Antiretroviral Therapy. *PLoS ONE* 8(2): e55747. doi:10.1371/journal.pone.0055747

114. Baggaley RF, White RG, Hollingsworth TD, Boily MC. (2013). Heterosexual HIV-1 infectiousness and antiretroviral use: systematic review of prospective studies of discordant couples. *Epidemiology*. Jan;24(1):110-21.

115. Rodger A, Bruun T, Weait M, Vernazza P, Collins S, Estrada V, Lunzen JV, Corbelli GM, Lampe F, Phillips A, Lundgren J; PARTNER study group. Partners of people on ART - a New Evaluation of the Risks (The PARTNER study): design and methods. *BMC Public Health*. Jun 25;12:296

116. ~~Conclusions: WHO and U.S. NIH working group meeting on treatment for HIV prevention among MSM: What additional evidence is required? Meeting report, Geneva, 26-27 October 2011. Available at:~~ ~~http://www.who.int/hiv/pub/msm_meeting_report/en/index.html~~ ~~(Accessed Feb 16, 2013)~~

117. World Health Organization. Antiretroviral Treatment as Prevention (TasP) of HIV and TB: 2012 update. Available at: http://www.who.int/hiv/pub/mtct/programmatic_update_tasp/en/index.html (Accessed Feb 17, 2013). Replaced in 2016 by: World Health Organization. (2014). Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Available at: http://www.who.int/hiv/pub/guidelines/keypopulations/en/ (Accessed March 27, 2016).

118. Vernazza P et al. (2008). Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitment antirétroviral efficace ne transmettent pas le VIH par voie sexuelle. *Bulletin des médecins suisses* 89 (5), (English translation, including translator's affidavit, available at: http://tinyurl.com/cpyt5n Date accessed: 17 February 2013)

119. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Section accessed Feb 17, 2013

120. British HIV Association (BHIVA) and Expert Advisory Group on AIDS (EAGA). (2013). Position statement on the use of antiretroviral therapy to reduce HIV transmission. Available at: http://www.dh.gov.uk/health/2013/01/eaga-bhiva-hiv-statement/ (Accessed Feb 14, 2013)

121. Eshleman SH, Hudelson SE, Redd AD, Wang L, Debes R, Chen YQ, Martens CA, Ricklefs SM, Selig EJ, Porcella SF, Munshaw S, Ray SC, Piwowar-Manning E, McCauley M, Hosseinipour MC, Kumwenda J, Hakim JG, Chariyalertsak S, de Bruyn G, Grinsztejn B, Kumarasamy N, Makhema J, Mayer KH, Pilotto J, Santos BR, Quinn TC, Cohen MS, Hughes JP. (2011). Analysis of genetic linkage of HIV from couples enrolled in the HIV Prevention Trials Network 052 trial. *J Infect Dis.* Dec 15;204(12):1918-26.

122. ~~Apondi R, Bunnell R, Ekwaru JP, Moore D, Bechange S, Khana K, King R, Campbell J, Tappero J, Mermin J. (2011). Sexual behavior and HIV transmission risk of Ugandan adults taking antiretroviral therapy: 3 year follow-up. *AIDS*. Jun 19;25(10):1317-27.~~

123. ~~Smith MK, Powers KA, Muessig KE, Miller WC, Cohen MS. (2012) HIV Treatment as Prevention: The Utility and Limitations of Ecological Observation. *PLoS Med* 9(7): e1001260. doi:10.1371/journal.pmed.1001260~~

124. Homans J, Christensen S, Stiller T, Wang CH, Mack W, Anastos K, Minkoff H, Young M, Greenblatt R, Cohen M, Strickler H, Karim R, Spencer LY, Operskalski E, Frederick T, Kovacs A. (2012). Permissive and protective factors associated with presence, level, and longitudinal pattern of cervicovaginal HIV shedding. *J Acquir Immune Defic Syndr*. 2012 May 1;60(1):99-110.

125. Lambert-Niclot S, Peytavin G, Duvivier C, Poirot C, Algarte-Genin M, Pakianather S, Meynard JL, Valantin MA, Molina JM, Flandre P, Katlama C, Calvez V, Marcelin AG. (2010). Low frequency of intermittent HIV-1 semen excretion in patients treated with darunavir-ritonavir at 600/100 milligrams twice a day plus two nucleoside reverse transcriptase inhibitors or monotherapy. *Antimicrob Agents Chemother*. Nov;54(11):4910-3.

126. Lambert-Niclot S, Tubiana R, Beaudoux C, Lefebvre G, Caby F, Bonmarchand M, Naouri M, Schubert B, Dommergues M, Calvez V, Flandre P, Poirot C, Marcelin AG. (2012). Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma on a 2002-2011 survey. *AIDS*. May 15;26(8):971-5.

127. Politch JA, Mayer KH, Welles SL, O'Brien WX, Xu C, Bowman FP, Anderson DJ. (2012). Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men. *AIDS*. Jul 31;26(12):1535-43.

128. Ghosn J, Delobelle A, Leruez-Ville M, Beaudoux C, Mascard L, Canestri A, Landman R, Zucman D, Ponscarme D, Rami A, Viard JP, Spire B, Lecuyer H, Costagliola D, Rouzioux C, Suzan-Monti M. (2012). Prevalence of HIV-1 Seminal Shedding in HIV-1 Infected Men who Have Sex with Men (MSM) and Association with the Size of Intracellular HIV-1 Reservoir (ANRS EP49). 52nd Interscience Conference on Antimicrobial Agents and Chemotherpay. San Francisco,CA. Sep 9-12, 2012. Available at: http://icaac.posterview.com/PDFs/H-1570f.pdf. Accessed Feb 17, 2013.

129. Osborne BJ, Sheth PM, Yi TJ, Kovacs C, Benko E, la Porte C, Huibner S, Le AQ, Danroth R, Baraki B, Mazzulli T, Brumme ZL, Kaul R. (2013). The impact of antiretroviral therapy duration and intensification on isolated semen HIV-1 RNA shedding. *J Infect Dis.* Jan 17.

130. Masese LN, Graham SM, Gitau R, Peshu N, Jaoko W, Ndinya-Achola JO, Mandaliya K, Richardson BA, Overbaugh J, McClelland RS. (2011). A prospective study of vaginal

trichomoniasis and HIV-1 shedding in women on antiretroviral therapy. *BMC Infect Dis*. Nov 3;11:307.

131.   Anderson BL, Firnhaber C, Liu T, Swarts A, Siminya M, Ingersoll J, Caliendo AM, Cu-Uvin S. (2012). Effect of trichomoniasis therapy on genital HIV viral burden among African women. *Sex Transm Dis*. Aug;39(8):638-42.

132.   Cohen CR, Lingappa JR, Baeten JM, Ngayo MO, Spiegel CA, Hong T, Donnell D, Celum C, Kapiga S, Delany S, Bukusi EA. (2012). Bacterial vaginosis associated with increased risk of female-to-male HIV-1 transmission: a prospective cohort analysis among African couples. *PLoS Med*. 9(6):e1001251.

133.   Graham SM, Masese L, Gitau R, Richardson BA, Mandaliya K, Peshu N, Jaoko W, Ndinya-Achola J, Overbaugh J, McClelland RS. (2011). Genital ulceration does not increase HIV-1 shedding in cervical or vaginal secretions of women taking antiretroviral therapy. *Sex Transm Infect*. Mar;87(2):114-7.

134.   Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, Delpech V, Phillips AN. (2012). Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS*. Jan 28;26(3):335-43.

135.   Helleberg M, Afzal S, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Gerstoft J, Nordestgaard BG, Obel N. (2013). Mortality Attributable to Smoking Among HIV-1-Infected Individuals: A Nationwide, Population-Based Cohort Study. *Clin Infect Dis*. Mar;56(5):727-34.

136.   Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. (2014). Estimating per-act HIV transmission risk: a systematic review. *AIDS*. Jun 19;28(10):1509-19. doi: 10.1097/QAD.0000000000000298.

137.   Scott HM, Vittinghoff E, Irvin R, Sachdev D, Liu A, Gurwith M, and Buchbinder SP. (2014). Age, Race/Ethnicity, and Behavioral Risk Factors Associated with Per-Contact Risk of HIV Infection Among Men Who Have Sex with Men in the United States. *J Acquir Immune Defic Syndr*. January 1; 65(1): 115–121. doi:10.1097/QAI.0b013e3182a98bae.

138.   Smith DK, Herbst JH, Zhang X, Rose CE. (2015). Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States. *J Acquir Immune Defic Syndr*. Mar 1;68(3):337-44. doi:10.1097/QAI.0000000000000461.

139.   Supervie V, Viard JP, Costagliola D, Breban R. (2014). Heterosexual risk of HIV transmission per sexual act under combined antiretroviral therapy: systematic review and bayesian modeling. *Clin Infect Dis*. Jul 1;59(1):115-22. doi: 10.1093/cid/ciu223.

140.   Comité sur les infections transmissibles sexuellement et par le sang (CITSS), Institut national de santé publique du Québec. (2014). Expert Consensus: Viral Load and the Risk of HIV Transmission. Available at: https://www.inspq.qc.ca/node/4027 (Accessed March27, 2016).

141.   Loutfy M, Tyndall M, Baril JG, Montaner JS, Kaul R, Hankins C. (2014). Canadian consensus statement on HIV and its transmission in the context of criminal law. Can *J Infect Dis Med Microbiol*. May;25(3):135-40.

142.   Canadian AIDS Treatment Information Exchange. (2015). CATIE statement on the use of antiretroviral treatment (ART) and an undetectable viral load to prevent the sexual transmission of HIV. Available at: http://www.catie.ca/en/prevention/statements/tasp. (Accessed: March 27, 2016).

143. Community consensus statement on the use of antiretroviral therapy in preventing HIV transmission. Available at : http://www.hivt4p.org/ (Accessed : March 27, 2016)

144. Blaser N, Wettstein C, Estill J, Salazar Vizcaya L, Wandeler G, Egger M, Keiser O. (2014). Impact of viral load and the duration of primary infection on HIV transmission: systematic review and meta-analysis *AIDS*. April 24; 28(7): 1021–1029. doi:10.1097/QAD.0000000000000135.

145. Burchell AN, Allen VG, Gardner SL, Moravan V, Tan DH, Grewal R, Raboud J, Bayoumi AM, Kaul R, Mazzulli T, McGee F, Rourke SB; OHTN Cohort Study Team. (2015). High incidence of diagnosis with syphilis co-infection among men who have sex with men in an HIV cohort in Ontario, Canada. *BMC Infect Dis*. Aug 20;15:356. doi: 10.1186/s12879-015-1098-2.

146. Low AJ, Konate I, Nagot N, Weiss HA, Kania D, Vickerman P, Segondy M, Mabey D, Pillay D, Meda N, van de Perre P, Mayaud P; Yerelon Study Group. (2014). Cervicovaginal HIV-1 shedding in women taking antiretroviral therapy in Burkina Faso: a longitudinal study. *J Acquir Immune Defic Syndr*. Feb 1;65(2):237-45. doi:10.1097/QAI.0000000000000049.

147. Champredon D, Bellan SE, Delva W, Hunt S, Shi CF, Smieja M, Dushoff J. (2015). The effect of sexually transmitted co-infections on HIV viral load amongst individuals on antiretroviral therapy: a systematic review and meta-analysis. *BMC Infect Dis*. Jun 30;15:249. doi: 10.1186/s12879-015-0961-5.

148. Grulich AE, Bavinton BR, Jin F, Prestage G, Zablotska I, Grinsztejn B, Phanuphak N, Moore R, Koelsch KK. (2015) HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. 2015 Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, USA, abstract 1019LB, 2015.

149. Rodger A, Cambiano V, Bruun T, et al. (2016) Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy: the PARTNER study. *JAMA*. 2016 Jul 12;316(2):171-81. doi: 10.1001/jama.2016.5148

150. Cairns, Gus. (2016) More confidence on zero risk : still no transmissions seen from people with an undetectable viral load in PARTNER study. http://www.aidsmap.com/More-confidence-on-zero-risk-still-no-transmissions-seen-from-people-with-an-undetectable-viral-load-in-PARTNER-study/page/3072326/ (Accessed: July 21, 2016).

151. Cohen MS, Chen YQ, McCauley M, et al. (2016) Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med*. 2016 Jul 18. [Epub ahead of print] DOI: 10.1056/NEJMoa1600693

152. Risk of Sexual Transmission of HIV from a Person with HIV who has an Undetectable Viral Load. Prevention Access Campaign. http://www.preventionaccess.org/undetectable-untransmittable (Accessed: September 7, 2016)