HIV Transmission:

Factors that Affect Biological Risk

Contents

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INTRODUCTION

This document covers the most current scientific understandings of the factors that affect biological risk of HIV infection and transmission. There have been significant scientific advancements in understanding the biomedical aspects of HIV risk and prevention since the publication, *HIV Transmission: Guidelines for Assessing Risk (Transmission Guidelines)* was last updated in 2005. This document primarily focuses on the risk of transmission through sexual contact. It summarizes the scientific evidence about the biomedical aspects of risk and transmission, without commenting on social or behavioural factors which are equally important but are beyond the scope of this document. Information about vertical transmission and risk due to drug use is covered in the *Transmission Guidelines*.

This document is designed for reference and use by educators, counsellors, health care providers and others who provide information and support about safer sex and HIV transmission in various community settings. It is assumed that the reader will have a degree of familiarity with scientific and technical language about HIV transmission and risk reduction.

Please consult the appendices. They contain a glossary of technical terms used in this document, as well as a brief discussion and list of suggested reading on various types of studies (meta-analyses, randomized controlled trials, observational studies, etc.) mentioned in this document.

1. BIOLOGY OF HIV TRANSMISSION[1]

As discussed in Chapter 3 of the *Transmission Guidelines,* there are five conditions for HIV transmission:

1. **There must be a source of infection.**

2. **There must be a means of transmission.**

3. **There must be a host susceptible to infection.**

4. **There must be an appropriate route of entry to the target cells of the body.**

5. **There must be a sufficient level of virus delivered to establish infection.**

1.1 BODILY FLUIDS

For an HIV exposure to pose a risk of infection, specific bodily fluids from a person living with HIV need to come into contact with specific body parts of an HIV-negative person. This can happen during anal, vaginal or oral sex.

We know that if a person is living with HIV, only some of their bodily fluids contain enough virus to transmit HIV sexually—these include semen and pre-ejaculatory fluid (pre-cum), vaginal fluid and rectal fluid (Zuckerman et al., 2004). Blood also contains enough virus to transmit HIV, but it is not commonly involved in the sexual transmission of HIV.

The *Transmission Guidelines* did not include a discussion of rectal fluid as one of the bodily fluids involved in HIV transmission. The rectum keeps itself moist and supple by secreting mucus. These secretions provide lubrication to help solid waste move out through the rectum and anus. Rectal secretions have been found to contain higher levels of virus than other bodily fluids (Zuckerman et al., 2004).

1.2 MUCOUS MEMBRANES

▶ *The mucous membranes are the main routes of sexual HIV transmission.*

▶ *They are more vulnerable to HIV and other germs because they lack a "dry" layer of skin that covers most of the body.*

The HIV in blood, semen, pre-cum, vaginal fluid and rectal fluid (Zuckerman et al., 2004) may cause infection if it enters the body of a sex partner. Most of the body's surfaces are "dry" skin (for example, on the arms and legs). These surfaces don't allow HIV to enter the body unless a cut or sore is present. However, other parts of the body are covered by "wet" skin, also known as mucous membranes, which are more vulnerable to HIV.

The mucous membranes are found at the entrances into the body and line the gastrointestinal tract (the passageway from the mouth to the anus), the reproductive system, the urogenital tract and the lungs.

These parts of the body play important roles that help the body work properly. They are involved in exchanging substances between the body and the outside environment. For example, the gastrointestinal tract secretes chemicals to break down food and absorb nutrients into the body. Mucous membranes need to stay wet to help them work as they are supposed to work. All mucous membranes secrete mucus, a slimy fluid that helps keep them wet and lubricated.

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[1] Some of this section is adapted from CATIE's Prevention in Focus article *"From exposure to infection : The biology of HIV transmission"*: http://www.catie.ca/en/pif/fall-2011/exposure-infection-biology-hiv-transmission

HIV Transmission: Factors that Affect Biological Risk

The mucous membranes involved in the sexual transmission of HIV include the:

- foreskin and urethra on the penis
- cervix and vagina
- anus and rectum
- mouth and throat

Most of our skin is a thick layer of tightly packed epithelial cells that is protected by a dry outer layer of protein called keratin which blocks HIV from the immune cells that it targets (see figure 1). The mucous membranes don't have such a protective layer because it would make it difficult for them to absorb and secrete different substances. The lack of a "dry" layer helps the mucous membranes do their jobs but also makes them more vulnerable to infection. Without this protective layer, mucous membranes are often the main "routes" that viruses or bacteria use to enter the body. Figures 1-3 (HIV i-Base, 2012) show the various arrangements of epithelial cells in skin and mucous membranes.

The mucous membranes are vulnerable to infection because they lack the keratin layer, the epithelial cells are loosely packed, have fewer layers (just one layer in the case of the rectum and part of the cervix), have a high concentration of a certain kind of immune cell that HIV likes to infect (known as HIV target cells), and the tissues are much easier for HIV to penetrate.

Figure 1:

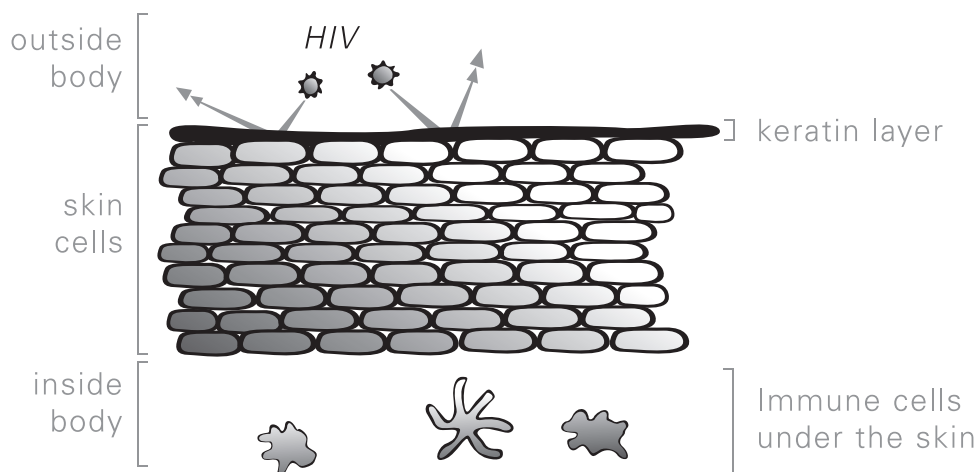## Skin – tightly packed cells act as a barrier to HIV

Figure 2:
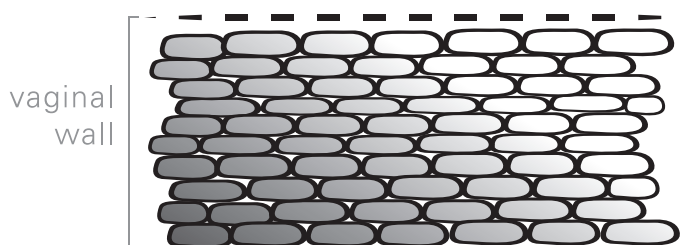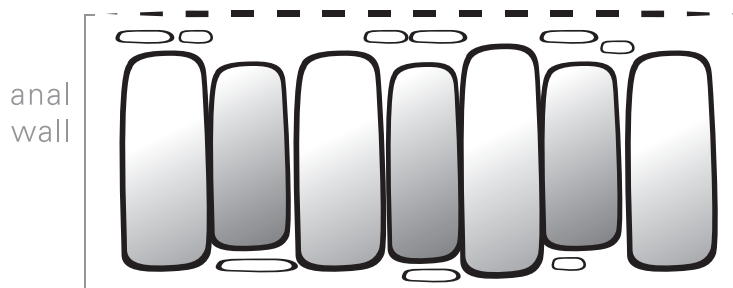
Cells in the wall of the vagina

Figure 3:

Cells in the wall of the rectum, part of the cervix and the inner foreskin

1.3 MUCOSAL IMMUNITY

▶ *Mucous membranes have mucosal immunity that protects body from germs, including mucus, epithelial cell layer, and immune cells.*

Infection isn't automatic if an exposure to a bacteria or virus occurs. When a pathogen comes into contact with one of the mucous membranes of an uninfected person, the bacteria or virus is not always able to overcome the immune system of the mucous membrane, also known as "mucosal immunity". While the mucous membranes are vulnerable, they are not defenceless. These membranes are covered with epithelial cells that help to prevent bacteria or viruses from entering the body and causing an infection. Some mucous membranes (such as the rectum, the inner surface of the foreskin and part of the cervix) have a single layer of more "fragile" columnar epithelial cells (see figure 3) while others (such as the urethra, mouth and vagina) have multiple layers of "sturdier" squamous epithelial cells (see figure 2). The more layers, the more protection there is. The mucus itself also contains chemicals and antibodies that can disable bacteria and viruses.

Even if a virus or bacteria manages to pass through the mucus and the layer of cells, there are still ways the body can prevent an infection. Under the cell layer, a large concentration of immune cells is responsible for attacking and killing bacteria and viruses that manage to find their way past the cell layer.

In some cases, the virus or bacteria may not be able to either cross the cell layer or win its battle against the immune cells in the tissue below. This explains why some exposures to pathogens do not lead to infection.

1.4 THE PROCESS OF HIV INFECTION

▶ *To cause infection after an exposure, HIV must overcome mucosal immunity.*

▶ *Not all exposures lead to HIV infection because HIV is not always able to overcome mucosal immunity.*

▶ *There are several biological factors that can either increase or decrease chances that HIV can overcome mucosal immunity and cause HIV infection.*

HIV infection occurs once HIV moves past the mucous membrane into the body's tissues. For infection to occur, HIV must first cross the epithelial cell layer and then avoid being destroyed by the immune cells below. If the virus overcomes these defences, it can enter the body and then spread past the site of infection to other parts of the body, by entering the blood and lymphatic vessels in the mucous membrane tissue (Fox & Fidler, 2010). Once HIV has spread throughout the body, the infection becomes permanent (see Figure 4). There are several factors determining whether or not the virus is able to cross the cell layer and enter the immune cells, and whether or not HIV overtakes the immune cells, as described in Section 2: Biological factors that may affect risk.

Once HIV has successfully crossed the cell layer, the virus must overcome the defences of the immune cells waiting in the tissue below. Over a span of one to three days, many types of immune cells in the mucous membranes attack HIV in an effort to rid the body of the virus. Although some of these cells can kill the virus quite well, HIV is able to infect certain types of target immune cells (CD4 cells, macrophages and dendritic cells), make copies of itself and release more virus. If HIV is able to replicate faster than the immune cells are able to kill copies, then HIV may be able to spread throughout the body. Once this happens, the immune system is defeated and the infection becomes permanent. However, if the immune cells are able to eradicate the virus in the mucous membrane, then infection does not occur.

A few weeks after permanent infection, the body's immune system begins to fight back against the virus. An important part of this immune response includes the production of HIV antibodies—small proteins made by certain immune cells, which can destroy HIV and prevent HIV from multiplying. Once antibodies to HIV have been produced, HIV replication begins to slow down and the amount of virus in the body (also known as

the viral load) gradually decreases. Unfortunately, antibodies cannot fully eliminate HIV infection (Wu, 2008). Within two weeks after HIV has entered the body, the virus becomes well-established in many cells throughout the body as well as in lymph nodes and tissues. This is known as the HIV reservoir.

Antibodies are not produced immediately after infection. The amount of time it takes for the body's immune system to produce them varies from person to person. In most people, it is possible to detect HIV antibodies in their blood within approximately 34 days of infection, although this can take up to three months in some individuals (Zetola & Pilcher, 2007). The presence of antibodies in the blood marks the end of the first stage of HIV infection—known as acute HIV infection—and the beginning of the next stage, chronic HIV infection.

Figure 4:
From exposure to infection: sexual transmission of HIV

1. Exposure to HIV

2. HIV crosses the epithelial layer of the mucous membrane

3. HIV infects the immune cells and starts replicating

4. HIV enters the blood and lymph vessels

5. HIV spreads to other parts of the body

6. Permanent HIV infection
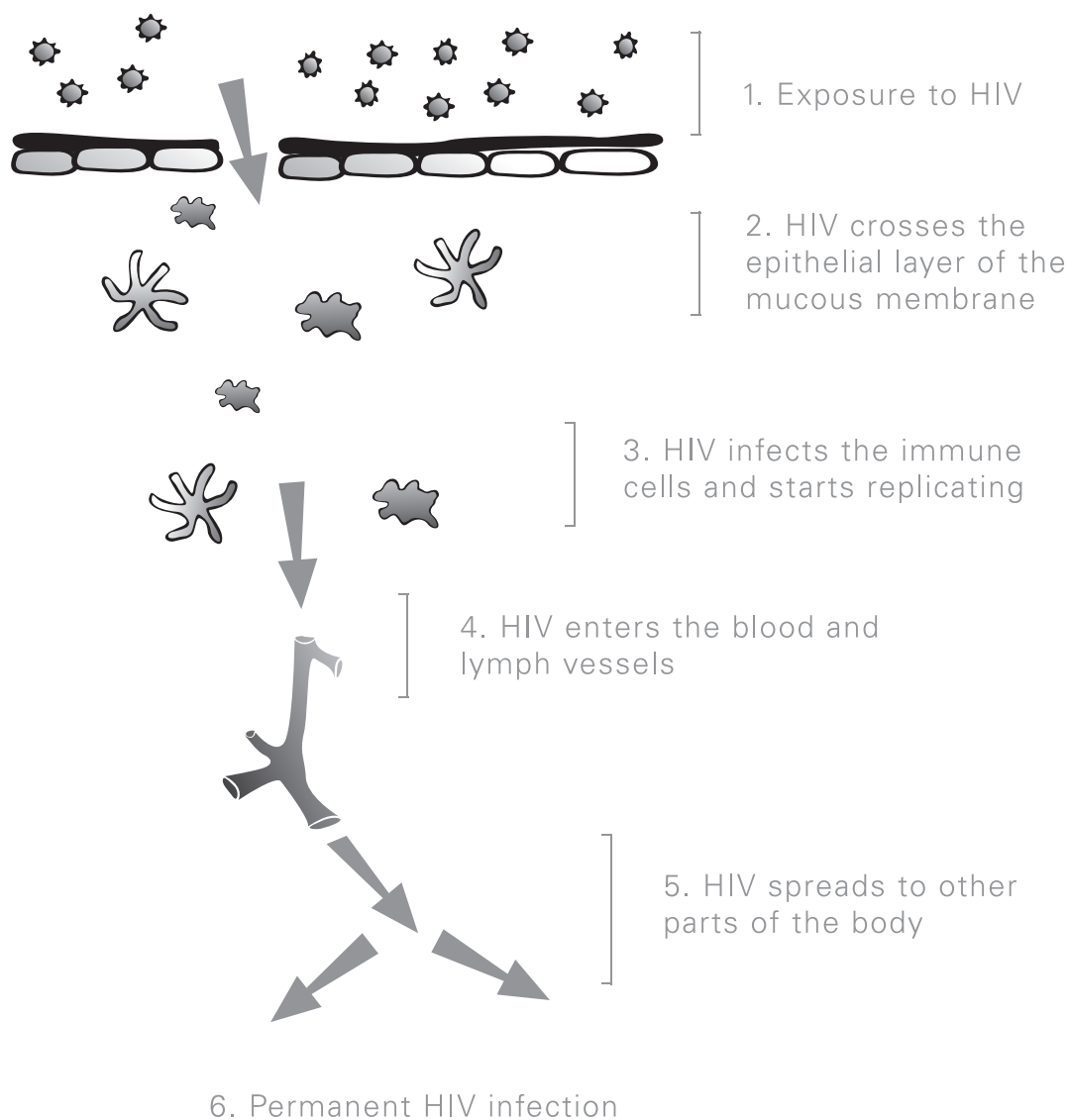
2. BIOLOGICAL FACTORS THAT MAY AFFECT RISK

There are many biological factors that affect risk of HIV transmission during sexual contact. This section describes factors that either increase or decrease the chance that HIV passes through the mucosal cell layer, and factors that increase or decrease the chance that HIV is able to overcome the defences of the immune system.

On average, some types of sex carry a higher risk of HIV transmission than others. Some studies have attempted to quantify the average risk of HIV transmission from one exposure to HIV. Numbers from studies should be viewed with caution and considered the average risk in the absence of biological factors that can increase risk. These studies show that, on average:

- Receptive anal sex carries a much higher risk of HIV infection than receptive vaginal sex.
- Receptive anal sex is riskier than insertive anal sex.
- Receptive vaginal sex is riskier than insertive vaginal sex.
- While the risk from oral sex is not zero, it is considerably lower than the risk associated with either vaginal or anal sex.

Table 1: Risk of HIV transmission from different types of condomless sex

(Baggaley, White, & Boily, 2008; Baggaley et al., 2010; Boily et al., 2009; Wawer et al., 2005)

	Number of individual studies	Range of estimates	Meta-analysis estimate
Receptive anal	4	0.4%-3.38%	1.4%
Insertive anal	2	0.06%-0.62%	-
Receptive vaginal	10	0.018%-0.150%	0.08%
Insertive vaginal	3	0.03%-0.09%	0.04%

2.1 TYPE OF SEXUAL EXPOSURE[2]

There are several reasons why, on average, some types of activities carry a higher risk of HIV transmission. The size of the surface area of mucosal membranes that are in contact is one key factor that explains why some types of sex are higher risk than others. Levels of risk also depends on a number of factors discussed in this section, including viral load, sexually transmitted infections (STIs), the concentration of "activated" target immune cells at the mucous membrane (research suggests the rectum has more of these), number of cell layers, and how long the fluid is able to stay in contact with the mucous membrane.

The larger the surface of the cell layer exposed to HIV, the more likely it is that HIV will be able to find a way to cross it. The surface area of the mucous membranes on the penis (the urethra and foreskin) is much smaller than the surface area of the rectum or vagina. This partly explains why for an HIV-negative person, insertive (anal or vaginal) sex with someone who is living with HIV is generally less risky than receptive sex. For example, insertive anal sex (inserting the penis into the anus, also known as "topping" among gay men) is generally less risky than receptive anal sex (receiving the penis into the anus, or being the "bottom"). Similarly, insertive vaginal sex is generally less risky than receptive vaginal sex (Baggaley, White, & Boily, 2010; Boily et al.,

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2009). Although potentially less risky than its receptive counterpart, insertive sex (both vaginal and anal) is still considered "high risk" in these guidelines. Surface area also partly explains why male circumcision reduces the risk of HIV infection for men who participate in vaginal sex (Templeton, 2010). As described in more detail in Section 2.6, Circumcision status, removal of the foreskin can decrease the risk of HIV infection because it reduces the surface area of the mucous membrane cell layer that HIV can use to enter the body.

Several studies have aimed to estimate the average risk of HIV transmission from a specific type of condomless sex (for example, vaginal/anal/oral; insertive/receptive). Due to the difficulties of calculating this risk, these studies have produced a wide range of numbers. To come up with a more accurate estimate for each type of condomless sex, some researchers have combined the results of individual studies into what is known as a meta-analysis. The results of several meta-analyses suggest that some types of sex carry, on average, a higher risk of HIV transmission than others. Table 1 shows estimates from meta-analyses that have combined the results of studies conducted in high-income countries. For types of sex where meta-analysis estimates do not exist, numbers from individual studies are provided.

It is important to note that any risk estimates provided below should be viewed as average risks in the absence of additional factors that can increase or decrease risk. Also, these are risks of one act of sex with someone who is living with HIV and that risk can accumulate over time.

2.1

Risk Summary:

For the HIV-negative person, insertive (anal or vaginal) sex is generally less risky than receptive sex.

2.1.1 ANAL SEX

A meta-analysis exploring the risk of HIV transmission through condomless anal sex was published in 2010 (Baggaley et al., 2010). The analysis, based on the results of four studies, estimated the risk through receptive anal sex (receiving the penis into the anus, also known as "bottoming") to be 1.4%. (This means that an average of one transmission occurred for every 71 exposures.) This risk was similar regardless of whether the receptive partner was a man or woman. No meta-analysis estimates currently exist for insertive anal sex (inserting the penis into the anus, also known as "topping") but two individual studies were conducted to calculate this risk. The first, published in 1999, calculated the risk to be 0.06% (equivalent to one transmission per 1,667 exposures) (Vittinghoff et al., 1999). However, due to the design of the study, this number likely underestimated the risk of HIV transmission. The second study, published in 2010, was better designed and estimated the risk to be 0.11% (or 1 transmission per 909 exposures) for circumcised men and 0.62% (1 transmission per 161 exposures) for uncircumcised men (Jin et al., 2010).

Another study estimated that the risk of HIV associated with condomless receptive anal intercourse for women is 1.7% per act, whereas it is only 0.08% during condomless vaginal intercourse (Boily et al., 2009). This situation is partially due to the rectal environment. A single layer of columnar epithelium and a high concentration of target CD4 cells provide a uniquely vulnerable environment for HIV acquisition (Anton et al., 2000).

Rectal secretions also play a key role in HIV transmission. The mucus normally produced in the rectum to help move solid waste may have higher viral load than any other bodily fluid. One study found that levels of HIV RNA in rectal mucosal secretions in gay men were higher than those in blood or semen – by about 500% in the case of blood and 2500% in the case of semen (Zuckerman et al., 2004).

2.1.1

Risk Summary:

The risk of HIV transmission from receptive anal sex is up to 18 times higher than from receptive vaginal sex.

The risk of HIV transmission from receptive anal sex is about 6 times higher than from insertive anal sex.

2.1.2 VAGINAL SEX

A meta-analysis of 10 studies exploring the risk of transmission through vaginal sex was published in 2009 (Boily et al., 2009). It estimated the risk of HIV transmission through receptive vaginal sex (receiving the penis in the vagina) to be 0.08% (equivalent to 1 transmission per 1,250 exposures). A meta-analysis of three studies exploring the risk from insertive vaginal sex (inserting the penis into the vagina) was estimated to be 0.04% (equivalent to 1 transmission per 2,500 exposures) (Boily et al., 2009).

2.1.2 **Risk Summary:**

The risk from receptive vaginal sex is about twice as high as that from insertive vaginal sex.

2.1.3 ORAL SEX

No meta-analysis estimates exist for oral sex (vaginal or penile) because too few good-quality studies have been completed. This is because it is difficult to find people whose only risk of HIV transmission is condomless oral sex. A review of the studies that are available was published in 2008 and concluded that vaginal and penile oral sex pose a "low but non-zero transmission probability" (Baggaley, White, & Boily, 2008).

In the three studies aimed at calculating the risk of HIV transmission from one act of oral sex, no transmissions were observed among three different populations—lesbian sero-discordant couples, heterosexual serodiscordant couples and single gay men—who reported oral sex without a condom as their only risk for HIV transmission. However, these studies enrolled only a small number of people and followed them for only a short period of time, which may explain the lack of HIV transmissions and makes it impossible to conclude that the risk from oral sex is zero (Baggaley et al., 2008).

2.1.3 **Risk Summary:**

Oral sex is not as risky as vaginal or anal sex, but it's not completely risk-free.

2.2 INFLAMMATION, TEARS AND IRRITATION OF MUCOUS MEMBRANES[3]

Damage to the epithelial cell layer can make it easier for HIV to get across. Also, inflammation can make it easier for HIV to win its battle against the immune system.

▶ *Some sexually transmitted infections can cause sores or ulcers on the mucous membranes.*

▶ *Microabrasions in the mucous membranes due to friction during sex, enemas, douching, dental work, brushing teeth and flossing can damage an intact cell layer and have the potential to increase the risk of infection.*

▶ *While lubricants may reduce the risk of tearing during sex, some types of sexual lubricants may cause damage to the epithelial cell layer. However, more research is needed to be certain.*

▶ *Tears and inflammation are not needed for HIV infection to occur.*

2.2.1 TEARS AND IRRITATION

The mucous membranes are made more vulnerable to HIV infection by tearing or damage (including that caused by sex, douching, enemas, dental work, brushing teeth, flossing, etc). Ulcers, sores, tears or microabrasions (microscopic cuts) on genital tissue (of the penis, or of the vaginal or anal lining) can increase the chances HIV can pass the epithelial cell layer. Some mucous membranes are more vulnerable to tearing, either because they are covered by a thinner cell layer or because they do not produce extra lubrication to reduce friction during sex. This partly explains why receptive anal sex (receiving the penis into the anus, also known as "bottoming" among gay men) with someone who is living with HIV is generally the riskiest type of sex (Dosekun & Fox, 2010). The rectum's cell layer is thin and does not naturally produce extra lubrication during sex.

As shown in Figure 5, a cut or tear in the mucous membranes, even at the microscopic level, makes it easier for HIV to reach the target immune cells. Microabrasions in the epithelial layer, which commonly occur during sex, can increase the risk of HIV infection. Some STIs such as herpes and syphilis can cause sores or ulcers ("holes") on the mucous membranes (Ward & Ronn, 2010).

Figure 5:

Tiny cuts or tears create an easy route to HIV to enter the body

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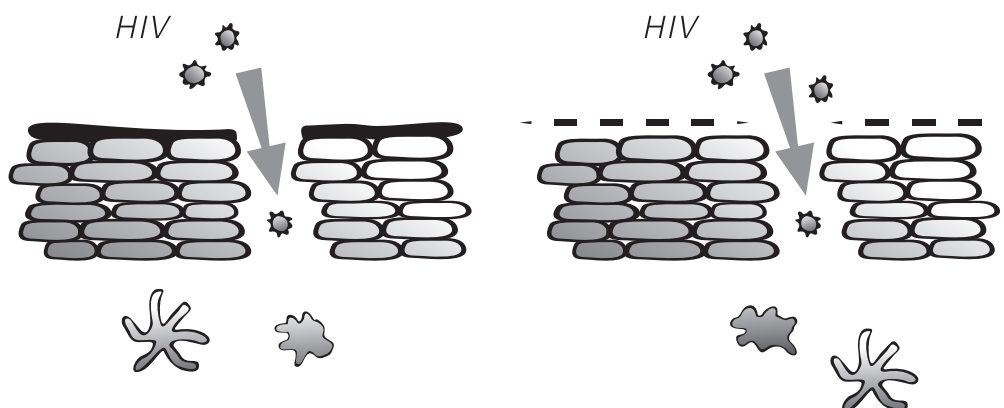
[3] Some of this section is adapted from CATIE's Prevention in Focus articles *"From exposure to infection: The biology of HIV transmission"*: http://www.catie.ca/en/pif/fall-2011/exposure-infection-biology-hiv-transmission and *"STIs: What role do they play in HIV transmission?"*: http://www.catie.ca/en/pif/spring-2012/stis-what-role-do-they-play-hiv-transmission

The rougher or more vigorous the sex, the more likely abrasions, tears, cuts and friction will damage the surface. This is why lubrication may be important during sexual intercourse, both vaginal and anal, as it helps to reduce friction and decreases the chances of tearing and irritation in the sensitive mucosal tissues. Condoms and lubricants may be especially important for anal sex, as rectal secretions carry higher concentrations of HIV, and the tissue lining the anus and rectum is very delicate.

Although lubricants are often promoted to reduce the risk of tearing during sex, preliminary research suggests that some types of sexual lubricants may cause damage to the epithelial cell layer, and therefore may increase the risk of HIV transmission (Dezzutti et al., 2012; Begay et al., 2011; Fuchs et al., 2007). More research is needed before we can change our recommendations regarding the use of lubricants.

It is important to note that while tears and irritation increase risk of HIV infection, tears and disruptions to the mucous membranes are not necessary for HIV to pass the epithelial cell layer. There are several other ways HIV can pass the cell layer. For example, some immune cells in the mucous membrane tissue called dendritic cells can squeeze between epithelial cells (especially single-layer columnar epithelium), "grab" a virus and pull it across the epithelial layer.

2.2.2 INFLAMMATION

Inflammation is part of the body's immune response to infection or tissue damage (including tearing of the mucous membranes as described above). The inflammatory response is usually protective: it brings more immune cells to an infected or damaged area to help clear bacteria or viruses or repair damaged tissue. However, HIV targets some of these immune cells, including the CD4 cells. A higher number of these immune cells in the mucous membranes can allow HIV to make copies of itself more quickly and help the virus win its battle against the immune cells. The inflammatory process "activates" our immune cells to fight the pathogens and recruits more target immune cells to the site of the infection, helping the body clear the pathogen. For example, if someone has a vaginal STI, then the inflammatory response will recruit more "activated" immune cells to the lining of the vagina (Atashili, Poole, Ndumbe, Adimora, & Smith, 2008; Cohen et al., 2012).

Therefore, anything that causes inflammation of the mucous membranes may increase the risk of HIV infection if the inflamed area is exposed to HIV. Inflammation of the mucous membranes can be caused by sexually transmitted infections (STIs) and other infections, such as bacterial vaginosis and gum disease.

2.3 SEXUALLY TRANSMITTED INFECTIONS (STIs)

STIs cause inflammation in the mouth, genitals or rectum. This recruits more activated immune cells to the inflamed area. Some STIs also increase risk of HIV transmission by creating holes or ulcers in the epithelial cell layer. Therefore, STIs increase the risk for:

▶ *HIV-negative individuals to become infected with HIV through anal sex, vaginal sex and oral sex.*

▶ *People living with HIV to transmit HIV to someone else through anal or vaginal sex.*

Since many people who have an STI are asymptomatic, testing is the only way to know for sure if you have an STI. Prompt treatment of STIs can reduce risk.

Research suggests that sexually transmitted infections (STIs) can increase both an HIV-negative person's risk of becoming infected with HIV and the likelihood that a person living with HIV will transmit HIV to someone else (Ward & Ronn, 2010). While there are many different types of STIs, the more common ones include gonorrhea, chlamydia, Trichomonas vaginalis, human papillomavirus (HPV), herpes and syphilis. Some of these (such as herpes and syphilis) cause ulcers on the genitals or rectum, while others (such as gonorrhea, chlamydia, and Trichomonas vaginalis) can cause painful urination and/or discharge. HPV can cause the growth of genital warts on or around the genitals or rectum. Most STIs can also infect the mouth and throat.

STIs can cause swelling, redness and pain in the infected area. However, many people who have an STI are asymptomatic, so neither they nor their partner may realize they are infected. Although all STIs are treatable, only some can be cured through treatment and completely cleared from the body. STIs that can be cured through treatment include gonorrhea, chlamydia, syphilis and Trichomonas vaginalis. STIs that can be managed through treatment, but not cured, include HPV, herpes and HIV.

STIs may increase the risk of HIV transmission through the inflammation they cause in the mouth, genitals or rectum. Sexually transmitted infections are caused by bacteria, viruses and parasites. Upon entering the body, these pathogens are recognized by the immune system, which, as part of the body's response to infection, starts a process known as inflammation. This leads to the symptoms associated with many STIs, such as redness, swelling and pain.

The inflammatory process "activates" our immune cells to fight the pathogens and recruits more immune cells to the site of the infection, helping the body to clear the pathogen. For example, if someone has a vaginal STI, then the inflammatory response will recruit more "activated" immune cells to the lining of the vagina (Wilton, 2012). Although the inflammatory response is meant to help fight the sexually transmitted infection, HIV likes to infect some of these recruited immune cells, also known as CD4 cells. Also, HIV finds it easier to infect, and replicate in, CD4 cells that are "activated". Therefore, if someone has an STI in the mouth, genitals or rectum, and that area is exposed to HIV, the higher concentration of "activated" CD4 cells facilitates HIV infection, replication and spread throughout the body.

Figure 6, depicting the mucous membranes of the vagina (on the left) and the rectum (on the right), shows that when an STI is present, target immune cells are sent to the tissue, moving them closer to the surface. An STI inflammation brings more of these immune cells, making it easier for HIV to establish an infection in the very immune cells that it targets (HIV i-Base, 2012). Also,

some types of STIs increase the risk of HIV infection through ulcers, which create "holes" or ways for HIV to enter the body through the mouth, genitals or rectum (Wilton, 2012).

Research suggests that HIV-positive individuals with an STI may be at increased risk of passing HIV to someone else through anal or vaginal sex (Johnson & Lewis, 2008). If a person living with HIV has an STI, then inflammation will "activate" and recruit more immune cells to the infected genitals or rectum. Some of the immune cells in a person living with HIV are already infected with HIV, therefore the inflammatory response brings more HIV (contained in the infected immune cells) to the site of the STI in the genitals or rectum. Consequently, more HIV enters the bodily fluids in that area. For example, a vaginal STI increases the amount of the virus (viral load) in the vaginal fluid. Research shows that the more virus there is in the bodily fluids of a person living with HIV, the higher the risk of passing HIV to someone else (Quinn et al., 2000). HIV also replicates, or makes more HIV, quicker in immune cells that have been "activated" through inflammation, compared to immune cells that are not "activated."

Figure 6:
Some STIs increase the risk of HIV

Vagina   Rectum
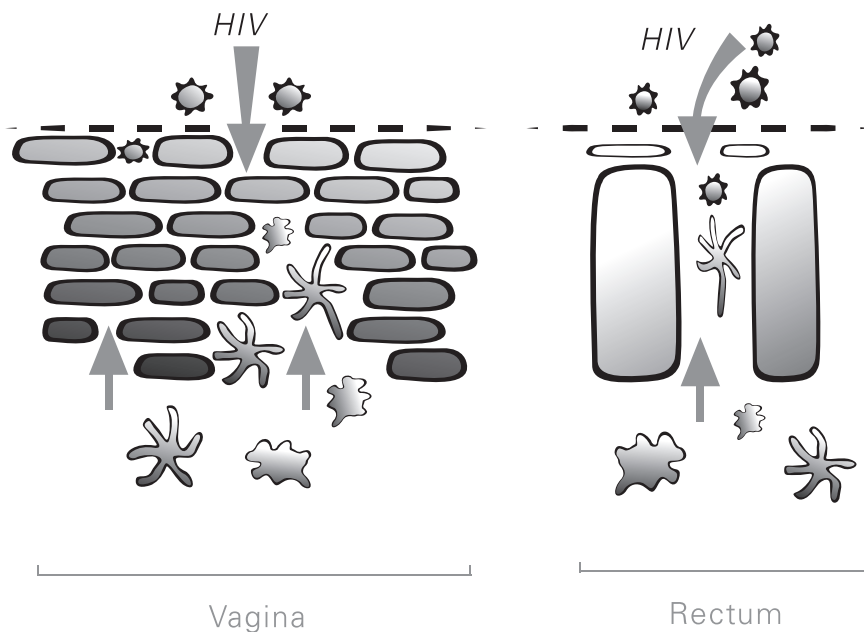
2.4 VIRAL LOAD

▶ *Viral load is the number of copies of the virus in the bodily fluids of a person living with HIV.*

▶ *A higher viral load generally increases the risk of transmission from an exposure, while a lower viral load reduces risk. The amount of virus in the bodily fluids is highest during the acute HIV infection stage.*

▶ *Antiretroviral treatment (ART) decreases the amount of virus in bodily fluids, and can reduce the risk of transmitting HIV to others.*

▶ *Several factors can affect the viral load in bodily fluids, such as the stage of HIV infection, the presence of STIs, whether someone is on ART, and the type of antiretrovirals (ARVs) a person is taking.*

▶ *Undetectable viral load means that the viral load in a bodily fluid is below the limit that our viral load tests can detect.*

Although the risk is lowered, there is a general consensus that there may still be a risk of HIV transmission when the viral load is undetectable. This is because even if blood viral load is undetectable, a person living with HIV can still have detectable (although lowered) amounts of virus in the genital and rectal fluids, particularly if there is inflammation due to an STI. This may increase the risk of HIV transmission when the viral load is undetectable in the blood.

Viral load is the amount of HIV in blood. Viral load test results are reported as the number of copies of HIV in one millilitre of blood. The lower the number, the less virus there is in the blood. Numbers can range from about one million copies to as few as 40 copies. Viral load can be measured by several different lab tests.

The more HIV the epithelial cell layer is exposed to, the greater the chance that one or more virion particles will be able to find a way past the layer, enter the tissue below and cause infection. Therefore, things that increase the viral load in the fluids of someone who is living with HIV may increase their risk of transmitting HIV. Anything that causes inflammation – including tearing, bacterial vaginosis or STIs (such as gonorrhea, chlamydia, herpes and syphilis), can increase the viral load in the bodily fluid at the site of the inflammation (Ward & Ronn, 2010). The stage of

HIV infection can also affect the amount of virus in the body of a person living with HIV. The viral load is very high during the first 10 to 12 weeks after a person becomes infected and also when a person has AIDS (Miller, Rosenberg, Rutstein, & Powers, 2010).

The amount of virus in the bodily fluids is highest during the acute HIV infection stage. After antibodies are produced, the viral load slowly decreases but does not stabilize at a lower level until up to six months after infection (Pilcher, Eron, Galvin, Gay, & Cohen, 2004; Schacker, Hughes, Shea, Coombs, & Corey, 1998).

Decreasing the viral load in the genital or rectal fluids can reduce the risk of HIV transmission. Therefore, treating STIs in a person living with HIV reduces their risk of transmitting HIV to their sex partner(s). Also, treating a person's HIV with antiretrovirals —which we know can decrease the amount of virus in their bodily fluids—can reduce their risk of transmitting HIV to others (Cohen et al., 2011).

Hormonal changes as a result of menstrual cycle, pregnancy, and hormonal contraceptives may also affect viral load (as explained in Section 2.7: Women's biological vulnerabilities).

2.4.1 UNDETECTABLE VIRAL LOAD

Undetectable viral load means that the number of copies of the virus (also known as the viral load) in a bodily fluid is below the limit that our viral load tests can detect. When a person is living with HIV and is linked to clinical care, they will have their blood's viral load (sometimes called plasma viral load) regularly measured in order to monitor disease progression and how well treatment is suppressing viral replication. Generally, successful antiretroviral treatment (ART) can reduce the blood viral load to undetectable levels within a few months of starting.

However, having an undetectable viral load does not mean that an individual has been cured of HIV or that it cannot be transmitted to others. It just means that there is not enough HIV for the test to measure. It is also important to know that labs that test viral load have different cut-offs below which they cannot detect HIV. In Canada, an undetectable viral load normally means that there are less than 40 copies of the virus per millilitre of blood.

Tests to detect the amount of virus in other bodily fluids such as semen, vaginal fluid, and rectal fluid, are not commonly available to people living with HIV but have been developed for research purposes. As outlined in Section 3.1.1: Treatment as prevention, there is a growing amount of research indicating that a lower viral load in the blood is generally associated with a lower risk of HIV transmission. Although blood isn't a fluid that's often involved in the sexual transmission of HIV, the viral load in the blood is generally correlated with the viral load in the fluids that are, such

as semen, vaginal fluid, and rectal fluid. In other words, if the viral load is controlled in the blood, it's also generally controlled in those other bodily fluids (Wilton & Leahy, 2012).

However, this isn't always the case and some people living with HIV can have detectable amounts of virus in the genital and rectal fluids even though the viral load is undetectable in the blood. Even if HIV is suppressed by ART to achieve undetectable viral load, currently available ART suppresses but does not eliminate shedding of HIV in genital secretions, including vaginal fluids (Fiore et al., 2003), semen (Coombs, Reichelderfer, & Landay, 2003; Xu et al., 1997) or in the rectum (Lampinen et al., 2000). Anywhere from 3% to 48% of men can still have a detectable (although lowered) viral load in their semen despite having an undetectable plasma viral load (Coombs et al., 2003; Xu et al., 1997). However, the significance of this viral load in terms of likelihood of HIV transmission is unknown.

Even if viral load in the blood is undetectable, risk of transmission can be increased if the individual has a sexually transmitted infection (Xu et al., 1997; Coombs et al., 2003). It is still unknown how high the viral load in genital fluids must be for transmission to occur.

The choice of antiretroviral (ARV) drugs may make a difference. Although most ARVs can penetrate the genital tract, protease inhibitors (one class of antiretrovirals) achieve limited concentration in genital secretions (Cohen & Gay, 2010). More research is needed to understand how viral load in the genital fluids can be controlled.

A review showed that no HIV transmissions occurred within serodiscordant couples where the HIV-positive partner was on treatment and the viral load was undetectable. The review concluded that when the viral load is undetectable, there may be a 1% risk of HIV transmission per 10 years of relationship and sexual activity. However there are caveats to this finding: condoms may have played a role in preventing the HIV transmissions; the majority of couples enrolled in these studies were heterosexual and were (likely) having mostly vaginal sex; and the studies reviewed did not provide data on the presence of STIs other than HIV (Loutfy et al., 2013). As a further caveat, there has been one case report of transmission when the viral load is undetectable (Sturmer, Doerr, Berger, & Gute, 2008).

2.5 RECENT HIV INFECTION[4]

▶ *Some people with acute HIV infection develop symptoms. However, many people who have recently become infected do not know they are HIV infected.*

▶ *The high viral load during recent HIV infection can increase the risk of HIV transmission from an exposure.*

▶ *Many HIV transmissions happen during the first few months after someone becomes infected with HIV. This period of acute HIV infection represents a period of very high risk for transmission because this is when viral load is very high and also when individuals are likely engaging in high-risk practices.*

After an individual becomes infected with HIV, the virus begins to replicate rapidly and the amount of virus in the body and bodily fluids (such as the blood, semen, vaginal fluid and rectal fluid) rises quickly. In some individuals, symptoms of acute infection are experienced such as fever, fatigue, night sweats, headache, diarrhea, sore throat and/or a rash. These symptoms (sometimes called seroconversion illness) generally appear about two weeks after infection occurs (Lindback et al., 2000). Other individuals who become infected notice no symptoms at all during this period. This first stage of HIV infection is known as acute HIV infection.

It is possible for HIV to be transmitted through condomless sex at any time when someone is HIV-positive. However, emerging research suggests that a disproportionate number of HIV transmissions—perhaps more than half—may occur during the first few months after someone becomes infected with HIV (Miller, Rosenberg, Rutstein, & Powers, 2010; Brenner et al., 2007; Zetola & Pilcher, 2007).

This period of acute HIV infection represents a period of very high risk for transmission because this is when viral load is very high (Wawer et al., 2005; Haase, 2010). The higher the viral load, the greater the risk is of transmitting HIV to others through

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condomless sex. Researchers estimate that the risk of transmitting HIV to another person from one act of condomless sex may be up to 26 times higher during the first three months after infection than during the months and years that follow (Hollingsworth, Anderson, & Fraser, 2008).

A high viral load alone is not enough to transmit HIV to another person; a recently infected individual also needs to be engaging in activities that can lead to the transmission of HIV, such as condomless sex. Unfortunately, a person who has recently been infected with HIV is more likely to be engaging in high-risk behaviours than a person who has been infected for a longer period of time (Moore, McCoy, Kuruc, Hilton, & Leone, 2009; Colfax et al., 2002). There are two possible explanations for this. First, individuals may be experiencing a time in their lives during which they are engaging in high-risk behaviours, which led to their own HIV infection. Second, many recently infected individuals are unaware of their HIV status and therefore may not realize the importance of having safer sex.

Figure 7:

Viral load levels as HIV infection progresses (HIV i-Base, 2012)
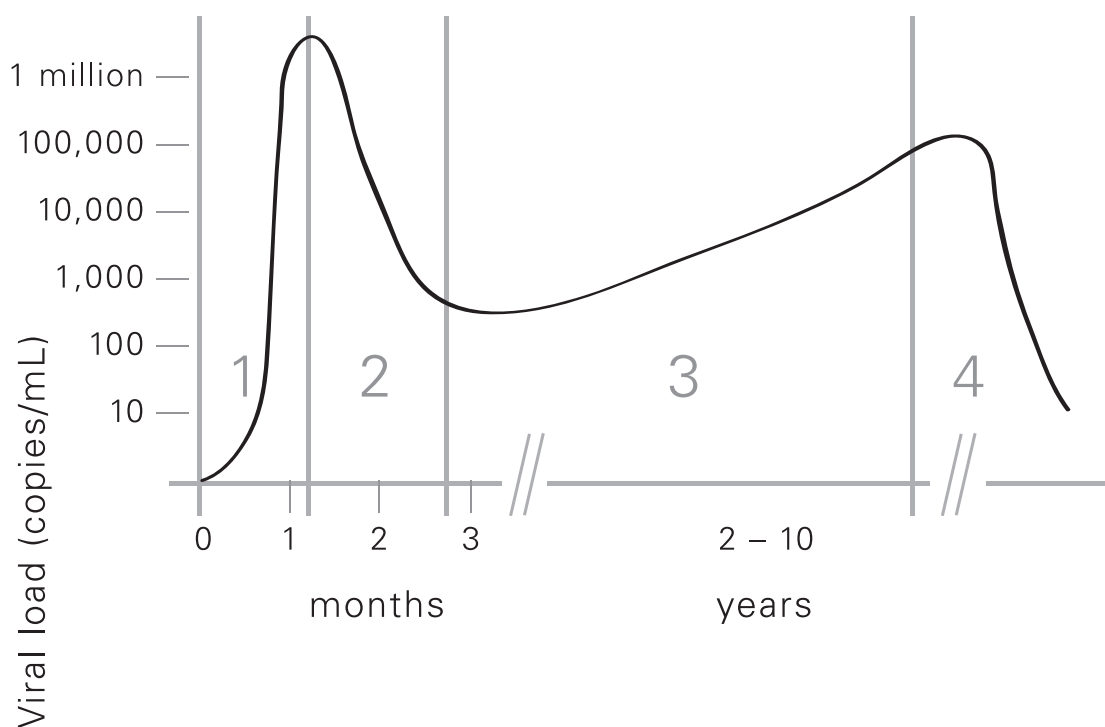
1. A few weeks after infection, HIV viral load increases to very high levels. This can be many millions of copies/mL. This makes someone extremely infectious.

2. As the immune system fights back, viral load usually drops to lower levels.

3. Over 2-10 years, viral load increases. It is usually between 50,000-100,000 when HIV treatment is started.

4. Treatment should reduce viral load to less than 50copies/mL within 3 months. All body fluids become dramatically less infectious.

2.6 CIRCUMCISION STATUS[5]

Removal of the foreskin through circumcision makes it more difficult for HIV to find a way into the male body. However, it does not provide complete protection because HIV can also enter through the urethra.

▶ *Circumcision can reduce the risk of HIV infection for men who have vaginal sex with women. In other words, circumcision can reduce the risk of HIV infection from an exposure to HIV through insertive vaginal sex.*

▶ *Circumcision does not provide protection for HIV-negative women who are at risk of infection through vaginal sex with HIV-positive men. In other words, circumcision does not reduce the risk of HIV infection from an exposure to HIV through receptive vaginal sex.*

▶ *It is not clear what degree of protection circumcision offers for men who engage in anal sex.*

Circumcision is the surgical removal of the foreskin—a retractable fold of skin that covers the head of the penis. Circumcision is most commonly performed on infants, although it can be done later in life too. It is performed for a variety of social, religious, cultural and health reasons. As one of the body's mucosal tissues, the foreskin is a major route that HIV can use to enter the body and cause infection. There are two reasons for this. Firstly, the foreskin is a delicate tissue that can tear during sex. These tears can make it easier for the virus to enter the body. Secondly, the foreskin has a high number of a certain kind of immune cell that HIV likes to infect, known as HIV target cells. The more HIV target cells there are, the more likely HIV will find one to infect. Therefore, the removal of the foreskin through circumcision makes it more difficult for HIV to find a way into the body and to cause infection.

For men who have vaginal sex with women: Circumcision provides protection for HIV-negative men who are at risk of HIV infection through vaginal sex with HIV-positive women. Three randomized controlled trials conducted in Eastern and Southern Africa found that circumcised men were approximately 50% to 60% less likely to become infected with HIV than uncircumcised men (Auvert et al., 2005; Bailey et al., 2007; Gray et al., 2007). These studies suggest that circumcision can reduce the risk of HIV infection for men in countries that have high rates of HIV among heterosexual people. The circumcised men were also at reduced risk of herpes, syphilis and human papillomavirus (HPV) (Fankem, Wiysonge, & Hankins, 2008; Krieger, 2012; Templeton, 2010; Templeton, 2010).

We also know that there is a cumulative benefit of circumcision for men over time, with 67% fewer HIV infections documented five years after trials. High effectiveness of circumcision for HIV prevention was maintained for almost 5 years following trial closure (Gray et al., 2012).

For women who have vaginal sex with men: Penile circumcision does not provide protection for HIV-negative women who are at risk of infection through vaginal sex with HIV-positive men. An HIV-positive circumcised man is not less likely to transmit HIV through condomless vaginal sex (Wawer, 2012).

For men who have anal sex with men: While circumcision may also reduce the risk of HIV infection for men who participate in insertive anal sex, there is not yet conclusive evidence to say this definitively. Although one would expect that, in the same way that circumcision provides some protection to HIV-negative men who have insertive vaginal sex, circumcision would provide some protection to HIV-negative men who have insertive anal sex (also known as "topping"). However, many men who have sex with men (MSM) are not exclusively tops (the insertive partner)—but also bottoms (that is, they also have receptive anal sex). Circumcision would not protect an HIV-negative man when he bottoms because in this case HIV would enter through the anus or rectum, and not the foreskin of the penis. Because the risk is so much higher when a man bottoms than when he tops (Jin et al., 2010), circumcision may not protect him even if he bottoms only occasionally.

The few studies among MSM that have been completed to date have been inconclusive—with some studies suggesting that circumcision is protective for men who only top, while other studies suggest otherwise (Templeton, Millett, & Grulich, 2010). However, a recent review that combined the results of several studies suggests that circumcision is protective for men who only top, but not for gay men who top and bottom (Wiysonge et al., 2011). The degree of protection (if any) has yet to be determined (Wilton, 2012).

2.7 WOMEN'S BIOLOGICAL VULNERABILITIES[6]

Biologically speaking, women are twice as vulnerable to HIV infection through vaginal intercourse than are men. Certain parts of the cervix and uterine walls have only a very thin layer of epithelial cells and imbalances in the vaginal flora can make HIV infection more likely. Women may be at more risk during various phases of their reproductive lifespan:

▶ *Adolescent girls have immature genital tracts and their cervixes are even more vulnerable to HIV and other STIs.*

▶ *Pregnant women may be at an increased risk of both infection and transmission due to hormonal changes.*

▶ *Postmenopausal or post-hysterectomy women may have vaginal atrophy due to low levels of estrogen, making the uterus and vagina more vulnerable to infection.*

Women are generally more biologically vulnerable to HIV infection through vaginal intercourse than are men. One estimate is that transmission of HIV is about two times more likely from man to woman than from woman to man (European Study Group on Heterosexual Transmission of HIV, 1992). Several plausible biological explanations have been proposed to account for this disparity (Coombs et al., 2003). There is a much larger surface area in the vagina and cervix compared to the areas of the penis where transmission can happen (foreskin, urethra and small tears on the head of the penis). In addition, women are exposed to considerable amounts of seminal fluid during sex, if ejaculation occurs. Women are exposed to infectious fluids for longer periods during sexual intercourse than men are; they also face increased risk of tissue injury during intercourse (Chersich & Rees, 2008).

2.7.1 VULNERABILITY OF THE VAGINA AND CERVIX

▶ *Vaginal conditions, such as bacterial vaginosis (BV) and yeast infections, can cause inflammation of the vagina and increase risk of becoming infected with HIV and transmitting HIV.*

The vagina is particularly vulnerable to invasion by bacteria, viruses and other pathogens. It is an ideal place for bacteria to grow, as it is warm and moist and provides an easy entrance into the body (Sheth & Thorndycraft, 2009).

The vagina has many "friendly" bacteria that are thought to play a role in the health of the female genital tract. Changes in the vaginal bacteria (a decrease in good bacteria and an increase in bad bacteria) have been found to increase a woman's risk of HIV infection by as much as 2.5 times (Sheth & Thorndycraft, 2009). This alteration in the vaginal bacteria is referred to as altered vaginal flora (AVF) or bacterial vaginosis (BV) (Wasserheit, 1992; Cohen, 1998; Sheth & Thorndycraft, 2009). It is very common and sometimes has no symptoms, but symptoms may include abnormal discharge and a "fishy" odour. Other imbalances to the vaginal flora – such as yeast infections and trichomoniasis – can cause genital inflammation that makes it easier to get infected with the HIV virus, or to pass the HIV virus on to a sex partner (CDC, 2012).

The cells lining the surface of the cervix may also be especially susceptible to HIV infection (Moench, Chipato, & Padian, 2001). Unlike the vagina, the mucous membranes on certain parts of the cervix and uterine walls have only a very thin layer of epithelial cells (often just one layer thick) and so it is much easier for viruses like HIV to cross into the body through the cervix and possibly the uterus (Coombs et al., 2003). Because the cervix acts as a barrier to protect a potential fetus, it is home to a large number of immune cells. Many of those immune cells are CD4 cells, which are the cells that HIV is most able to infect (Sheth & Thorndycraft, 2009).

A woman's risk for HIV infection during vaginal sex is affected by the general health of her genital tract, as well as her age and hormones (Sheth & Thorndycraft, 2009). Women have specific risks of HIV acquisition at different phases of the lifespan (adolescence, reproductive age and menopause) (U.S.Department of Health and Human Services, 2011). Each of these phases will be discussed in more detail below.

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[6] Some of this section has been adapted from the CATIE factsheet *"Women and the biology of HIV transmission"*:

http://www.catie.ca/en/fact-sheets/epidemiology/women-and-biology-hiv-transmission

2.7.2 ADOLESCENCE

Young women, particularly below the age of 24, appear to be much more vulnerable to HIV. This is because their genital tracts are not mature and may be more prone to tears and abrasions during sexual intercourse.

Up until the age of 18, a woman's cervix is still developing. During this time, the thinner cells that line the cervix are found further down into the vagina than they are in older women. This is called "cervical ectopy" or an "immature cervix," and means that the columnar epithelium (cells lining the transition zone of the cervical opening) extends onto the face of the cervix. Cervical ectopy has been associated with increased risk of HIV infection, possibly because it facilitates greater exposure of target cells to trauma and pathogens in the vagina (Moench et al., 2001; Royce, Sena, Cates, Jr., & Cohen, 1997). Since the cells lining the cervix provide a thinner and weaker barrier to HIV, young women with cervical ectopy have a much greater risk of HIV infection (Sheth & Thorndycraft, 2009).

Rupture of the hymen, such as during first sexual intercourse, also makes the vagina vulnerable to HIV infection (Bouvet, de, I, Ancelle, & Vachon, 1989).

2.7.3 MENSTRUATION

Another possible but unconfirmed contributing factor to women's vulnerability to HIV during vaginal intercourse is menstruation (de Vincenzi, 1994). Although the impact of the menstrual cycle and hormonal changes on the female genital tract is not clear, animal studies have suggested that the lining of the vagina gets thinner closer to menstruation than during other periods of a woman's cycle. It has also been found that women's vaginal epithelium may thin slightly during the luteal phase of the menstrual cycle (when a woman's natural progesterone levels are highest) (Martin, Jr. et al., 1998). This suggests that the risk of HIV infection over the course of her menstrual cycle may change (Sheth & Thorndycraft, 2009).

Women who are living with HIV may be more likely to pass HIV to their sexual partners during menstruation. Because HIV is more easily passed from blood cells than from genital secretions, a higher quantity of viral particles may be present in the vagina of women living with HIV during menses (European Study Group on Heterosexual Transmission of HIV, 1992; Vogt et al., 1987).

2.7.4 PREGNANCY

Some researchers have found that pregnant women may be more at risk for HIV infection. However, more research is needed to understand the degree to which risk is increased, and what mechanisms may be the cause—for example, hormonal changes affecting the genital tract mucosa or immune responses that help protect a fetus (Gray et al., 2005).

2.7.5 MENOPAUSE

In a large study of heterosexual partnerships, women over 45 years of age were infected significantly more often by their HIV-positive male partners than younger women (44% aged above 45 vs. 20% aged 45 or below) (European Study Group on Heterosexual Transmission of HIV, 1992). This finding supports the hypothesis that perimenopausal women have an increased fragility of the genital mucosa, in turn increasing their risk of infection.

Vaginal atrophy is the thinning and inflammation of the vaginal walls due to a decline in estrogen. Vaginal atrophy occurs most often after menopause, but it can also develop during breast-feeding or at any other time a woman's estrogen production declines. Women with low levels of the hormone estrogen, such as during menopause, may be at increased risk for transmission of HIV because low estrogen levels directly affect the vaginal wall, making it thinner so HIV can more easily pass through the wall. Women who have gone through menopause are also at a higher risk of HIV infection, because the lining of the uterus thins, and the vagina becomes drier (Sheth & Thorndycraft, 2009).

2.8 GENDER TRANSITIONING

▶ *There has been some speculation about potential factors that may affect the biological risk of HIV transmission among transgender individuals. However, in the absence of relevant research, it is speculation.*

Most of the literature on HIV risk among transgender individuals is from behavioural or epidemiological studies. There is very little published research describing how various elements of gender transitioning (e.g., hormone replacement therapy, surgery) may affect the biological HIV risk of transgender individuals.

There has been some speculation about potential factors that may affect the biological risk of HIV transmission among transgender individuals. For example, transgender men on testosterone and/or who have had a hysterectomy may experience frontal (vaginal) dryness and a thinning of the mucosal lining. This could increase their risk for frontal (vaginal) trauma during penetration, thus increasing their risk for STIs, including HIV (University of California San Francisco, 2010). Some transgender women will have vaginoplasty (formation of a vagina and labia), usually created by the inversion of the skin of the penis. This creates a canal that may be used for intercourse but that does not include mucosal membrane or a cervix. It remains unclear how this affects the risks of HIV infection.[7] As discussed below (see 3.2 Hormonal Contraceptives), there are questions about whether injectable hormone contraceptives may increase biological risk of HIV transmission and acquisition. The implications for transgender individuals who undergo hormone replacement therapy are unknown. However, in the absence of relevant research, all this is speculation (Asia Pacific Transgender Network & UNDP, 2012).

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[7] **Personal communication with Marcus Greatheart, MSW, RSW, MD Candidate (McMaster University, 2015), author of** *Transforming Practice: Life Stories of Transgender Men that Change How Health Providers Work* **(Ethica Press, 2013).**

HIV Transmission: Factors that Affect Biological Risk

3. ANTIRETROVIRAL DRUGS, OTHER PRODUCTS AND INTERVENTIONS: HOW THEY MAY AFFECT BIOLOGICAL RISK

A broad range of interventions, products and practices have an impact on the biological risk of HIV transmission. Some have been shown to reduce risk, while others may increase risk. Some of these products and interventions are currently available, while other interventions which hope to reduce risk are still in development.

This section includes antiretroviral-based HIV prevention strategies (treatment-as-prevention, pre-exposure prophylaxis, post-exposure prophylaxis, most microbicides) and non-antiretroviral based strategies (vaccines, some microbicides, cures). Some of these interventions help the immune cells in the mucous membrane destroy HIV before the virus spreads throughout the body. These interventions need to act quickly because HIV needs to replicate for only one to three days before it is able to spread beyond the mucous membrane and cause a permanent infection (Haase, 2010).

Also included are a range of other products and practices that may have an impact on biological risk, including hormonal contraceptives, vaginal practices, douches/enemas, sexual lubricants, spermicides and some recreational drugs.

Barrier methods of reducing risk are covered in the *Transmission Guidelines*.

3.1 ANTIRETROVIRAL DRUGS

Antiretrovirals (ARVs) developed and used for treatment of HIV can also work in a variety of ways to prevent HIV infection. Antiretroviral drugs prevent HIV from creating copies of itself in immune cells. If an HIV-negative person is exposed to HIV but is taking ARVs, this may reduce the ability of the virus to create more copies of itself and help the immune cells clear it from the body before permanent infection occurs. The five main ways that antiretroviral drugs could be used to prevent HIV transmission are in the form of prevention of vertical transmission,[8] pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), microbicides and reducing the viral load of people living with HIV (known as treatment-as-prevention or TasP).

Pre-exposure prophylaxis (PrEP) (Mayer & Venkatesh, 2010), post-exposure prophylaxis (PEP) (Barber & Benn, 2010) and microbicides are three prevention methods that involve HIV-negative people taking ARVs to reduce their risk of infection.

Treatment-as-prevention describes the prevention benefits that come from people living with HIV taking ARVs for treatment.

3.1.1 TREATMENT-AS-PREVENTION

▶ *Treatment-as-prevention seems highly effective at reducing risk at an individual level. A person living with HIV on ART may be 96% less likely to transmit HIV than someone not on ART.*

▶ *HPTN 052 included few male-male couples. Therefore it is unclear whether the risk of transmission through anal sex is also reduced by 96%. HIV transmission risk through anal sex likely still remains higher than through vaginal sex.*

As a concept and a strategy, treating people living with HIV to improve their health and to reduce the risk of onward transmission – known as treatment-as-prevention – refers to the personal and public health benefits of using ARVs to continuously suppress HIV viral load in the blood and genital fluids, which decreases the risk of transmitting the virus to others.

Combination antiretroviral therapy (ART) decreases the replication of HIV and decreases mortality rates of people living with HIV (Ray et al., 2010). Such therapy has been shown to reduce the amount of HIV in genital fluids (Vernazza et al., 2000; Graham et al., 2007). Because the sexual transmission of HIV is strongly correlated with concentrations of HIV in blood and in the genital tract of HIV-positive people (Quinn et al., 2000; Baeten et al., 2011), ART reduces sexual transmission of the virus.

Several observational studies have reported decreased HIV infection rates in sexual partners of patients receiving ART (Reynolds et al., 2011; Donnell et al., 2010). A meta-analysis of 11 cohort studies (Attia, Egger, Muller, Zwahlen, & Low, 2009) found that heterosexual transmission of HIV was reduced by 92% in patients on ART when comparing transmission rates to patients not on ART. This analysis was confirmed by the HIV Prevention Trials Network (HPTN) 052 study, a

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Box 1: Deciphering HPTN 052 Results (Wilton & Leahy, 2012)

The HPTN 052 study demonstrated that early initiation of treatment by an HIV-positive partner reduces the risk of transmission to the HIV-negative partner by 96% (Cohen et al., 2011). Unfortunately, biomedical HIV prevention trials such as the HPTN 052 study are not designed to provide information on an individual's absolute risk of HIV transmission, and the results of this particular trial are not necessarily translatable to non-heterosexual couples.

Even if relative risk-reduction calculations are the same for gay men, the absolute risk of HIV transmission while on treatment may be higher for anal sex than for vaginal sex. Condomless receptive anal sex is up to 20 times more likely to lead to HIV transmission than condomless receptive vaginal sex. Therefore, the higher initial risk associated with anal sex may mean that the absolute risk of HIV transmission when undetectable is much higher for anal sex than for vaginal sex.

The 96% relative-risk reduction from being on treatment is equivalent to approximately a 20-times reduced risk of HIV transmission. Furthermore, when not on treatment, we know that the risk of HIV transmission through "bottoming" is up to 20-times higher than vaginal sex. Therefore, if being on treatment reduces the risk of HIV transmission through "bottoming" by 20 times, the absolute risk of HIV transmission after this reduction in risk may still be in the same range as vaginal sex when not on treatment. These hypothetical 'calculations' emphasize the confusion generated.

randomized clinical trial designed to evaluate whether starting ART early can prevent the sexual transmission of HIV among 1763 (mostly) heterosexual serodiscordant couples (couples in which one partner is HIV-infected and the other is not). HPTN 052 found that early initiation of ART for the HIV-positive partner resulted in a relative reduction of 96% in the number of HIV transmissions, when compared to delayed ART (Cohen et al., 2011). See Box 1 for a discussion of the HPTN 052 results.

HPTN 052 included few male-male couples. Therefore it is unclear whether the risk of transmission through anal sex is also reduced by 96%. Fortunately there are some ongoing studies that are trying to answer this question, such as the Opposites Attract study in Australia and the PARTNER study in Europe.

3.1.2 PRE-EXPOSURE PROPHYLAXIS

▶ *Overall, studies suggest that the use of daily oral Truvada as PrEP can reduce the risk of sexual transmission of HIV for HIV-negative men and women, including gay and bisexual men, and heterosexual men and women.*

▶ *Additional studies are needed to determine if daily oral Truvada can also protect people who are at risk of HIV infection from injection drug use.*

▶ *A key finding from all studies is that PrEP effectiveness is strongly linked to adherence; PrEP is more effective when taken consistently, and less effective when not taken consistently.*

▶ *Daily oral Truvada as PrEP has been approved by the U.S. FDA, but has not been submitted for approval to Health Canada. PrEP can be prescribed by doctors as "off-label" use.*

▶ *The WHO and U.S. CDC have issued guidance on PrEP.*

Pre-exposure prophylaxis (PrEP) is another way that ARVs can be used for HIV prevention. It involves an HIV-negative individual taking ARVs in an effort to reduce their risk of becoming infected with HIV. PrEP involves taking anti-HIV medications on a regular basis – starting before exposure to HIV and continuing afterwards.

Results from five trials testing the efficacy of PrEP were reported from 2010 to 2013 (see Table 2 below). Three of the studies provided strong evidence that HIV-negative men who have sex with men, transgender women, and heterosexual men and women can significantly reduce their risk of HIV infection when they consistently take a daily ARV pill: either tenofovir/emtricitabine (TDF/FTC; brand name Truvada) or tenofovir (TDF; brand name Viread). The trials also showed that risk was most reduced among the most consistent users. (Baeten et al., 2012; Grant et al., 2010; Thigpen et al., 2012; Anderson et al., 2012). Two other studies failed to demonstrate efficacy among women, most likely due to the fact that most participants were not using the study product (Marrazzo et al., 2013; Van Damme et al., 2012).

Another clinical trial by the US Centres for Disease Control, called CDC 4370, is assessing the safety and efficacy of daily tenofovir to prevent HIV infection among injection drug users (IDUs). The trial is scheduled to be completed in June 2013.

There are also other studies underway in 2013, each looking at the safety and effectiveness of a particular type of PrEP (such as pills and gels) in a specific population (such as gay and bisexual men, injection drug users, or heterosexual men and women), used at different times (daily or around the time of sexual intercourse).

Based on the study findings to date, in July 2012, the U.S. Food and Drug Administration approved the combination medication Truvada for use as PrEP among sexually active adults at risk for HIV infection. As of March 2013, however, PrEP has not been submitted for approval by Health Canada. Although anti-HIV drugs have not been approved for the prevention of HIV (as PrEP), they have been approved for the treatment of HIV. Once a drug has been approved, it can be prescribed by doctors for other conditions. This practice is called "off-label" use of prescription drugs. PrEP can be prescribed by doctors in this way.

Both the WHO (World Health Organization, 2012) and the U.S. CDC (CDC, 2012) have issued guidance on PrEP, which include a wide range of recommendations for using PrEP.

Table 2: Summary of PrEP Studies

Trial name (product tested)	Reduction in transmission risk	Trial population	Trial countries
iPrEx (Truvada pill)	43.8% overall 73% among consistent users	2,499 gay men and other MSM; transgender women	Brazil, Ecuador, India, Peru, South Africa, Thailand, US
TDF2 or CDC 4940 (Truvada pill)	63% overall 78% among consistent users	1,219 heterosexual men and women	Botswana
Partners PrEP (Truvada or tenofovir pill)	62% overall for tenofovir 73% overall for Truvada	4,758 serodiscordant couples (heterosexual men and women)	Kenya, Uganda
FEMPrEP (Truvada pill)	N/A – trial stopped early	2,120 women	Kenya, South Africa, Tanzania
VOICE (Truvada or tenofovir pill or tenofovir gel)	N/A for tenofovir or Truvada pill (arms were stopped early) 14.7% for tenofovir gel (not statistically significant)	5,029 women	South Africa, Uganda, Zimbabwe

3.1.3 POST-EXPOSURE PROPHYLAXIS

▶ *PEP can lower the risk of HIV infection for occupational and non-occupational exposure when taken soon after an exposure.*

▶ *Effectiveness of PEP depends on how quickly it is taken after an exposure, how well it is adhered to, and whether additional exposures are avoided while taking it.*

▶ *Access to, and financial coverage of, PEP varies greatly across the country.*

Post-exposure prophylaxis (PEP) is a prevention intervention which consists of administering a combination of two or three ARVs within 72 hours after an HIV exposure (the sooner, the better), and continuing daily treatment for four weeks. PEP can be used for occupational exposures when people are exposed in the workplace to bodily fluids that may contain HIV (for example, a healthcare worker who accidently suffers a needle-stick injury). PEP can also be used after exposure to HIV in other situations (non-occupational exposure) to reduce the chances of infection, such as after condomless sex, a condom breaking during sex, needle sharing or sexual assault.

Several animal studies have provided proof of principle for PEP (Buchbinder & Liu, 2011). Although no randomized controlled trial of PEP has been conducted in humans, an observational case–control study in health care workers with occupational exposures demonstrated a significantly lower rate of HIV infection among those who took AZT compared to those who did not (Cardo et al., 1997).

Although there are clear guidelines across Canada for access to PEP for occupational exposures, the guidelines are less consistent for non-occupational exposures. Access and coverage varies greatly across the country. Provincial and territorial policies should be checked for more detail.

3.2 HORMONAL CONTRACEPTIVES

▶ *Some injectable hormonal contraceptives, notably Depo-Provera, may increase an HIV-negative woman's risk of acquiring HIV and an HIV-positive woman's risk of transmitting HIV. Depo-Provera is not commonly used in Canada.*

▶ *WHO/UNAIDS has concluded that data are insufficient to change current guidelines, but emphasize the need to use condoms to reduce HIV risks.*

Hormonal contraceptives are a popular method of reducing the risk of unplanned pregnancy in Canada. Oral contraceptive pills, more commonly called birth control pills, are taken daily and normally contain both progesterone and estrogen. Hormonal injections, commonly known as Depo-Provera, contain progesterone alone and are given once every three months. A national survey in 2006 found that among women who reported using contraception, approximately 44% used the oral contraceptive pill and 2.5% used hormonal injections (Black et al., 2013). Depo-Provera is not commonly used in Canada.

While the results of epidemiological studies have been conflicting, the majority of studies have observed at least a modest increase in risk of HIV infection in women using hormonal contraceptives (Martin, Jr. et al., 1998); (Ungchusak et al., 1996). A 2012 study found that HIV-negative women in Eastern and Southern Africa who used Depo-Provera were two times more likely to become infected with HIV, compared to women who did not use Depo-Provera (Heffron et al., 2012). The study also found that HIV-positive women who used Depo-Provera were two times more likely to pass HIV on to their partners. There were not enough women in the study using birth control pills to make any conclusions about this contraceptive method.

The positive association between hormonal contraceptives and HIV infection could be explained by the local effects of hormones on the genital tract, the interaction of hormones with the immune system, the direct effects of hormones on HIV, and effects on other factors known to increase a woman's

susceptibility to HIV (Martin, Jr. et al., 1998). According to various studies, progesterone-based contraceptives, such as Depo-Provera may:

- increase the amount of virus (or viral load) in the vaginal fluid of women living with HIV, making them more likely to transmit HIV to others (Mostad et al., 1997).

- increase risk of acquiring other sexually transmitted infections, such as gonorrhoea, and we know that having an STI increases risk of HIV infection (See Section 2.3: Sexually transmitted infections).

- cause irregular vaginal bleeding, which may potentially increase the risk of acquiring and transmitting HIV

- cause cervical ectopy, thereby increasing the number of susceptible cells in the genital tract or reduce the thickness of the vaginal lining, weakening the defensive barrier of the vagina (Sheth & Thorndycraft, 2009)

- increase the susceptibility of potential target cells by boosting the cellular proteins required for HIV to replicate or enter immune cells (Mostad et al., 1997)

- weaken the cell-mediated immune response in women, perhaps to prevent rejection of a fetus (Martin, Jr. et al., 1998)

A consultation was held on this topic by WHO/UNAIDS in February, 2012. After reviewing the evidence, they determined that the data were not sufficiently conclusive to change current guidance—women living with HIV, or at high risk of HIV, can continue to use hormonal contraceptives to prevent pregnancy, but emphasized the need to also use condoms to prevent HIV acquisition and transmission (World Health Organization, 2012).

3.3 SEXUAL LUBRICANTS

▶ *Condom-compatible lubricants facilitate the use of condoms and help ensure they don't slip or break during sexual intercourse.*

▶ *Laboratory studies and one study in humans suggest some lubes may damage mucous membranes.*

▶ *There are no studies among humans that directly show lubes can increase the risk of HIV transmission.*

▶ *At this point, there are limited data on how commercially available lubricants affect the rectal mucosa or the female genital tract. It is unclear whether any particular type or brand of lubricant might increase, decrease or have no effect on acquiring HIV and/or STIs.*

A vital part of preventing HIV transmission is the use of condoms for both vaginal and anal sex, and lubricants may help to reduce the risk of condoms breaking or slipping during sex. Some lubricants (water- and silicone-based) are safe to use with condoms; others (petroleum-based products) are not safe to use with condoms. Many people use personal lubricants for enhancing pleasure and reducing dryness. As discussed in Section 2.2.1: Tears and irritation, preventing microabrasions is known to be an important part of protecting the mucosal tissues. Lubricants may also become important as a form of microbicide delivery, as discussed in more detail in Section 3.8.1: Microbicides.

Very little literature exists on preferences and practices regarding vaginal lubrication during sex and very little is known about the safety of lubricants for vaginal or anal intercourse.

Direct and indirect links between vaginal lubrication and vulnerability to HIV may exist. For instance, there is some evidence that lack of lubrication may increase condom breakage, while excessive lubrication may increase condom slippage. Some lubricants will break down latex condoms and increase the chances of breakage. Some lubricants may increase vulnerability for HIV by damaging the vaginal walls and disrupting the vaginal flora, and also by interfering with the acceptability and use of barrier methods (Braunstein & van de Wijgert, 2003).

Only a few studies have examined the safety of lubricants in a laboratory setting, but those that did showed mixed results. Most water-based lubricants tested in these studies were shown to be damaging to cells. However, some lubricants were more damaging than others (Begay et al., 2011; Dezzutti et al., 2012).

Only one study has tested the effect of lubes on rectal tissue in humans. This one study found that many commonly used lubricants are hyperosmolar, meaning that they tend to attract and absorb water from cells lining the rectum. This has the potential to damage these cells. This had the potential to reduce the layer of mucus that coats the rectum (Fuchs, 2007).

Furthermore, in one socio-behavioural study, the use of lube for anal intercourse was associated with the presence of rectal sexually transmitted infection (STI), although a cause-to-effect link was not established as part of the study (Gorbach, 2012).

3.4 VAGINAL PRACTICES

▶ *A wide range of practices, including washing, douching and drying the vagina, are reported by women. These practices may undermine the body's innate defences against pathogens.*

▶ *Researchers have suggested a link between such vaginal practices and increased risk of infection with HIV and other STIs. However, data on the association between vaginal practices to promote vaginal drying and HIV are inconclusive.*

Globally, there is a wide variety of vaginal practices and products used by women to tighten, dry, warm and clean the vagina. Women's efforts to change their genital environment can undermine the body's innate defences against pathogens. In particular, vaginal practices have been linked to loss of lactobacilli and disruption of the vaginal epithelium. A wide range of practices, including washing, douching and drying the vagina, are reported by women. These practices may undermine the body's innate defences.

A number of studies from a variety of settings have suggested that vaginal practices, especially douching, are associated with bacterial vaginosis. As described in Section 2.7.1: Vulnerability of the vagina and cervix, bacterial vaginosis is itself linked to an increased risk of HIV infection. It is also possible that vaginal practices, especially those involving foreign substances, disrupt the vaginal and cervical mucosa, either through physical trauma or chemical irritation.

Data on the association between vaginal practices to promote vaginal drying and HIV are inconclusive, primarily because of the lack of prospective studies designed to study this association. Researchers have suggested a link between such vaginal practices and increased risk of infection with HIV and other STIs. A number of cross-sectional studies have found associations between vaginal practices and HIV infection, but these studies cannot demonstrate which comes first - that is, whether intravaginal practices increase susceptibility to HIV infection or whether HIV infection leads to increased intravaginal practices. The latter is a possibility, because vaginal infections such as trichomoniasis, bacterial vaginosis and thrush are common in some groups of HIV-positive women. It is plausible that intravaginal practices may be used to help relieve the symptoms of vaginal infection, including discharge and itching (AIDSmap, 2013).

Three mechanisms for the link have been proposed: (1) such vaginal practices may dry and irritate the vaginal and cervical mucosa, causing inflammation; (2) such vaginal practices may disturb the normal vaginal flora and eliminate lactobacilli that form a natural barrier against colonization by STI pathogens and transmission of HIV; and (3) such vaginal practices may interfere with the acceptability and efficacy of barrier methods for HIV/STI prevention (Braunstein & van de Wijgert, 2003).

A number of vaginal practices have been described (AIDSmap, 2013):

- External washing: Cleaning of the external area around the vagina and genitalia using a product or substance with or without water, normally using the hand. Products used vary from soap and water to traditional and chemical detergent-like substances.

- External application: Placing or rubbing various substances or products on to the external genitalia (the labia, clitoris, and vulva). Included is the 'steaming' or 'smoking' of the vagina, by sitting above a source of heat (fire, coals, hot rocks) on which water, herbs or oils are placed to create steam or smoke.

- Intravaginal cleansing ('washing'): Internal cleansing or washing inside the vagina include wiping the internal genitalia with fingers and other substances (e.g., cotton, cloths, paper) for the purpose of removing fluids. It also includes douching, which is the pressurised shooting or pumping of water or solution (including douching gel) into the vagina.

- Intravaginal insertion: Pushing or placing something inside the vagina (including powders, creams, herbs, tablets, sticks, stones, leaves, cotton, paper, tampons, tissue, etc.) regardless of the duration it is left inside.

- Oral ingestion: Drinking or swallowing of substances perceived to affect the vagina and uterus, for example to dry or lubricate the vagina. Substances may be dissolved in water or other liquids.

3.5   DOUCHING AND ENEMAS

▶ *Use of douches and enemas, either vaginally or rectally, has been associated with an increased risk of HIV and other STIs during condomless sex.*

Some women douche or wash the vagina before or after sex. Women use various combinations that include water, soap, lemon juice, vinegar and antiseptics. The most common reasons given by women as to why they douche are to clean the vagina, to rinse away menstrual blood, to get rid of odour from the vagina, to prevent pregnancy, and to reduce the risk of sexually transmitted infections (Sheth & Thorndycraft, 2009).

Research has shown that douching is not an effective method to prevent pregnancy nor does it provide protection from sexually transmitted infections. In fact, studies have shown that women who douche typically have more sexual health problems than those that do not. One reason for this may be that douching can alter or kill the "friendly" bacteria that protect the vagina. In addition, the use of antiseptic or acidic liquids such as rubbing alcohol or lemon juice can irritate the lining of the vagina, causing inflammation, and can create microscopic tears that HIV can pass through (Sheth & Thorndycraft, 2009).

Links have been found between vaginal practices and abnormal vaginal flora and bacterial vaginosis, which may explain why some vaginal practices can increase HIV risk (Braunstein & van de Wijgert, 2003). Associations have been found between vaginal douching and chlamydial infection, pelvic inflammatory disease, and other STIs (Martino & Vermund, 2002).

Links have also been found between the use of rectal enemas or douches and HIV as well as other sexually transmitted infections (Carballo-Dieguez et al., 2008; Schmelzer, Schiller, Meyer, Rugari, & Case, 2004). The use of enema solutions (soapsuds, tap water) results in surface epithelium loss. Products that result in loss or damage to the epithelium may facilitate HIV transmission, one of the main reasons for which nonoxynol-9, a detergent that results in epithelial sloughing, was discarded as a possible rectal microbicide (Phillips et al., 2004). HIV-uninfected or infected men who have condomless receptive anal intercourse and douche in preparation for sex or following sex could unwittingly be increasing their chances of HIV transmission.

3.6   SPERMICIDES

▶ *Spermicides may increase the risk of acquiring HIV and other STIs when used vaginally more than once daily or when used rectally even once.*

Spermicides are a form of contraception that are sometimes added to condoms, diaphragms and cervical caps. Spermicides are also available in foams, jellies, creams and suppositories (small capsules of medicine that are inserted into the vagina). They work by killing sperm before it has a chance to reach the cervix. Spermicides are only about 70 per cent effective in preventing pregnancy and offer no protection against HIV and other sexually transmitted infections (CATIE, 2009).

Some spermicides may increase the risk of HIV transmission by irritating the mucosa in the vagina and rectum. They should not be used as a means of preventing HIV transmission.

Nonxynol-9 (N-9) is the active ingredient found in most over-the-counter spermicides on the market today. Study results showed that N-9 can increase risk of acquiring HIV when used vaginally more than once a day (Van et al., 2002). A separate study showed that even small doses of N-9 used rectally even one time can be highly damaging to rectal tissue in the period shortly after use. However, damage shown at 15 minutes after exposure to N-9 had completely healed by 2 hours (Phillips et al., 2004).

Generally, it is recommended that although N-9 is still a viable option for contraception, it should not be used more than once a day vaginally and should never be used rectally (IRMA, 2010).

3.7   RECREATIONAL DRUGS

▶ *Recreational drugs may increase the risk of HIV transmission either directly or indirectly. Some drugs may affect the biological risk of HIV transmission through a variety of mechanisms.*

Recreational drug use can increase the risk of HIV transmission either directly (for example, through shared injection or inhalation equipment) or indirectly (for example through elevated risk-taking). Also, for people taking antiretroviral medications (ARVs) to fight HIV, there can be some serious interactions between recreational drugs and ARVs. We focus here on the more direct biological impact of recreational drugs on the risk of HIV transmission, rather than the indirect impact through increased risk-taking behaviour.

Based on individual case reports, and what we know about how the body processes these drugs, some recreational drugs may be dangerous when combined with HIV medications. These interactions can lead to under- or overdoses of ARVs or recreational drugs. In the worst case, ARVs may stop working because there are not enough of them in the body. Also, the drug interactions can cause a serious, possibly fatal increase in the level of recreational drugs. If the drugs interfere with the effectiveness of treatment, this could increase the risk of transmission by affecting viral load.

Actual risk assessments of individual situations are hard to make. Most ARVs are processed by the liver. All protease inhibitors use this pathway and caution is necessary as the levels of recreational drugs metabolized in the liver can be changed significantly. If an individual takes recreational drugs while also taking a protease inhibitor, he or she may end up with a stronger dose than expected (CATIE, 2012).

Some specific drug interactions that we know about include:

• Cocaine may have relatively few potential drug interactions with anti-HIV drugs, but it may make immune cells more vulnerable to HIV, as well as increase cocaine toxicity. This could make HIV disease progress faster (CATIE, 2012), and also affect the risk of HIV transmission.

• Chronic and heavy alcohol use could affect the way the body uses ARV medications, thereby interfering with HIV treatment. Alcohol can also increase blood levels of abacavir (Ziagen) and amprenavir (Agenerase) (The Body, 2011).

• Some studies (Macdonald et al., 2008; Ostrow et al., 2009) have suggested that using poppers during condomless receptive anal intercourse increases the risk of acquiring HIV. This is probably due to a combination of biological and behavioural factors, which the studies generally are unable to untangle—so determining whether, and to what extent, poppers have an impact on the biological risk of HIV infection remains difficult. The most likely biological factor is that poppers may increase blood flow to the rectum.

3.8 INTERVENTIONS UNDER INVESTIGATION

Research into new biomedical HIV prevention options evolves quickly. For the latest information, please consult www.avac.org.

3.8.1 MICROBICIDES

▶ *One ARV-based gel has proven to be effective in one trial, but another trial of the same product failed to show efficacy. Other products are in development, including vaginal- and rectal-specific products, ARV-based and non-ARV-based products, and products formulated as gels or rings.*

▶ *No vaginal or rectal microbicide is currently available on the market.*

The term microbicide refers to substances being studied that could be used in the vagina or rectum to reduce the risk of HIV transmission during sex. Microbicides could come in a number of forms, including creams, gels, films, slow-release vaginal rings, enemas and suppositories that could be used vaginally or rectally.

The most advanced candidate—and the only candidate to show efficacy to date—is 1% tenofovir gel, a topical formulation of the antiretroviral drug tenofovir. One trial showed that the product reduced risk of HIV and Herpes simplex virus (HSV-2) acquisition among women (Abdool Karim & Baxter, 2012).[9] However, another trial testing the same product was unable to demonstrate efficacy (Microbicides Trial Network, 2011).[10] Another trial of the same product will provide results in 2014 (Celum & Baeten, 2012).[11] A rectal-specific formulation of the same product is also being tested (McGowan, 2012).[12]

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[9] The CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 trial among 889 South African women found that 1% tenofovir gel reduced women's risk of HIV infection via vaginal sex by 39 percent overall (Abdool et al., 2010). The protective effect was higher among women who used the product more consistently. The microbicide also reduced risk of herpes simplex virus (HSV-2) by 51%. Women in the trial were counselled to use the gel within 12 hours before and after sex.

[10] The VOICE trial, which was designed to test both oral (pill form) and topical (gel form) ARV-based prevention found that 1% tenofovir gel did not reduce risk in women counselled to use the gel on a daily basis. This was due to lack of adherence—most participants did not use the study product (Microbicides Trial Network, 2011).

[11] FACTS 001 is a large-scale trial of tenofovir gel in South African women, which began enrolling in 2011, and is testing the same dosing strategy evaluated in CAPRISA 004 (Celum & Baeten, 2012).

[12] MTN 017 is the first-ever Phase II trial of a rectal microbicide candidate, a rectal-specific formulation of 1% tenofovir. It is scheduled to start in 2013. Over 200 MSM will be enrolled at sites in Peru, South Africa, Thailand and the United States (McGowan, 2012).

The majority of microbicide candidates in testing today are formulated with antiretroviral (ARVs) drugs and many current and past microbicide candidate products have been gels. For the first time, a vaginal ring will be tested in large-scale microbicide safety and effectiveness trials for HIV prevention. Some of these studies began in 2012 and should yield results in 2015 (AVAC, 2013). There is also research into non-ARV-based microbicides. Most of these trials are in the earlier stages.

No vaginal or rectal microbicide is currently available on the market.

3.8.2 VACCINES

▶ *One preventative vaccine has shown modest efficacy in reducing HIV risk. Further research is planned for this vaccine to improve its efficacy. It is unlikely to be made available in its current form. Other preventative vaccine candidates are being pursued.*

▶ *Therapeutic vaccines are also being investigated.*

▶ *No preventative or therapeutic vaccines are currently available on the market.*

A preventive HIV vaccine is not yet available but its goal would be to prepare the immune cells in the mucous membrane to respond more quickly to HIV if an exposure were to occur. If the immune cells can react more quickly and with greater strength, this may give them a better chance of clearing the virus before it spreads throughout the body.

Over the years, investigators have made numerous attempts to develop an HIV vaccine. Several recent advances have led to a degree of cautious optimism in the field of HIV vaccine research (Dieffenbach, 2012).

In 2009, a clinical trial conducted in 16,000 relatively low-risk participants (predominantly heterosexual men and women) in Thailand showed that the vaccine being tested had a modest 31% efficacy in preventing HIV infection (Rerks-Ngarm et al., 2009). This result was the first indication of any degree of efficacy in HIV vaccine trials and researchers are working to understand how the vaccine may have prevented HIV infection in some vaccine recipients (Rolland & Gilbert, 2012). At the September 2011 AIDS Vaccine Conference, researchers announced they

had found an antibody produced by the immune system of some Thai vaccine recipients, which may have protected them from HIV infection. Those who received the vaccine and produced this specific antibody were 43% less likely to become infected with HIV than those vaccine recipients whose immune system did not produce this antibody (Hankins, Glasser, & Chen, 2011). Additional studies of the Thai vaccine are planned.

There is a general consensus that 31% protection is too low to make this vaccine widely available. Also, we don't know if the Thai vaccine can reduce the risk of HIV infection among populations that were not included in the trial, such as men who have sex with men and people who use injection drugs. Since many of the new HIV infections that occur each year in Canada are among these groups, it is difficult to predict the impact of the vaccine on the epidemic in Canada (Wilton, 2012). Until we know more about the Thai vaccine, it is unlikely that the vaccine will be made available in Canada.

Other possible HIV vaccines are also being studied, including one large trial in the United States among men and male-to-female transgender persons who have sex with men. Results are expected in 2015. Several vaccine candidates are also in earlier stages of development; however, these may not proceed to larger trials for several years (AVAC, 2013).

Although most vaccines are designed to protect people from infection in the first place, people living with HIV may also one day benefit from a type of vaccine called a therapeutic vaccine. Therapeutic vaccines are compounds designed to stimulate the immune response to HIV in a person already infected with the virus, in order to control the infection. Also referred to as immunotherapeutic vaccines, these vaccines could potentially reduce risk of transmission, by acting to reduce viral load (much like treatment-as-prevention).

3.8.3 CURES

▶ *Researchers are pursuing two types of cures: sterilizing cures and functional cures.*

▶ *So far, only one case of a sterilizing cure (the "Berlin patient") has been documented.*

▶ *One case of a functional cure has been reported in a baby. However, researchers from the French VISCONTI study have reported 14 patients that they describe as "post-treatment controllers", and they suggest that up to 15% of people living with HIV may be able to achieve the same results.*

When we talk about a "cure" for HIV infection, there are two possible lines of research: 1) development of a true sterilizing cure with complete eradication of the virus, and 2) a functional cure, which is a permanent suppression of the virus without significant replication in the absence of ART. Research has shown that despite years of effective ART, which consistently suppressed HIV to undetectable levels, the HIV virus can hide in resting memory T-cells and resurge if ART is stopped (Finzi et al., 1997; Pierson, McArthur, & Siliciano, 2000). This hiding out is known as a persistent or latent reservoir, and is the main stumbling block to finding a true cure for HIV infection.

Various strategies for eliminating the persistent reservoir, and achieving a sterilizing cure, have been attempted or are being tested (Chun, Davey, Jr., Engel, Lane, & Fauci, 1999; Strain et al., 2005; Richman et al., 2009; Pierson et al., 2000). Unfortunately, after ART was discontinued, all participants in these studies experienced some rebound of HIV replication.

However, it has been claimed that one HIV-infected patient was "cured" after receiving a stem cell transplant to treat a complicating case of leukemia. The transplanted cells expressed a genetic defect that did not allow the replication of HIV (Allers et al., 2011; Hutter et al., 2009). Although this case does not present a practical approach for treatment of the millions of HIV-infected persons, it does prove in concept that, under certain circumstances, HIV can be controlled in the absence of ART.

A functional cure is achieved when the immune system can control the virus from replicating even after ART is discontinued. There is a significant amount of information available on HIV-infected persons whose immune responses effectively control, but do not clear, their HIV infection. This population, known as "elite controllers," provides convincing evidence that it may be possible for the immune system to reduce HIV to low or undetectable levels while also maintaining high CD4 cell counts (Walker, 2007). These elite controllers share a genetic profile that allows them to achieve a functional cure, but the challenge for researchers is to determine whether this elite controller ability can be induced in persons without the genetic predisposition.

To achieve this, investigators are combining and evaluating many strategies, including early treatment of HIV infection to both minimize the size of the viral reservoir and preserve anti-HIV immunity, together with "therapeutic" vaccination to bolster the immune response to a level where adequate control of viral replication is possible. Such strategies, if successful, could establish and maintain effective immunologic control of virus replication in the absence of ART so that HIV infection does not progress and transmission of HIV is highly unlikely. Patients in whom such a regimen could be successfully implemented might avoid the inevitability of lifelong ART (Dieffenbach, 2012).

A case of a functional cure was reported in March 2013 in a child infected with HIV who began ART within 30 hours of birth. Even after being off ART for a year, and although HIV DNA is still detectable at very low levels in the child's cells (representing a latent reservoir of HIV-infected cells), the virus has not been replicating (Persaud et al., 13 A.D.).

Also in March 2013, researchers reported that 14 patients from the French VISCONTI study who had initiated ART early (all within 10 weeks of infection), remained on ART for three years on average, and subsequently discontinued ART are now generally able to maintain undetectable viral load in the absence of ART. They have been off ART for an average of 7.5 years. The researchers have suggested that up to 15% of people living with HIV may be able to achieve the same results, which they refer to as "post-treatment controllers" (Saez-Cirion et al., 2013).

4. CO-INFECTION WITH HIV AND HEPATITIS C VIRUS

The effectiveness of ART can be affected by different types of co-infections and their related treatments, including Hepatitis C virus (HCV). Some drug interactions for treatment of HIV and HCV may affect their effectiveness. Since effective ART can significantly reduce the risk of HIV transmission, these interactions stemming from co-infections and other treatments may have an indirect effect on HIV risk.

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APPENDIX A: A NOTE ON TYPES OF STUDIES MENTIONED IN THE DOCUMENT

It is generally accepted that there is a hierarchy of quality of evidence from research. The hierarchy indicates the relative weight that can be attributed to a particular study design. At one end lies the meta-analysis, synthesizing the results of a number of similar trials to produce a result of higher statistical power. At the other end of the spectrum lie observational studies and expert opinion, thought to provide the weakest level of evidence.

This is one of the most widely accepted hierarchies:

Multi-study reviews	1. Systemic Reviews and meta-analyses
Experimental design	2. Randomized controlled trials (RCT)
Observational studies	3. Cohort studies 4. Case-control studies 5. Cross-sectional surveys 6. Case reports
Expert advice	7. Expert advice

Research studies often set out to investigate a link between one or more factors. Sometimes additional factors (other than those the study set out to examine) can make it seem like there is a link between two factors, when there actually isn't (or make it seem like there is a strong link when, in reality, the link is weaker). These additional factors are known as confounders and can lead to biased results. There are many types of studies and some are better than others at reducing bias and the effect of confounders. Reducing bias is important in order to understand the true relationship between two factors.

For a description of each study design, and a discussion of the advantages and disadvantages of each, please consult some of the following resources:
- The hierarchy of research evidence - from well conducted meta-analysis down to small case series, publication bias (http://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/hierarchy-research-evidence)
- Study designs (http://www.med.uottawa.ca/sim/data/Study_Designs_e.htm)
- Study designs (http://www.cebm.net/?o=1039)
- Types of study designs: from descriptive studies to randomized controlled trials (http://www.scribd.com/doc/19101103/Types-of-Study-Designs)

GLOSSARY

Acute HIV infection – A stage of HIV infection which occurs 2-4 weeks after infection and is marked by influenza–like symptoms which last anywhere from 1 to 4 weeks in duration; also known as acute seroconversion syndrome or primary HIV infection.

AIDS – Acquired immunodeficiency syndrome – final stage of HIV infection, a condition marked by low CD4 counts and the presence of certain opportunistic infections in humans, causing progressive failure of the human immune system's ability to defend against these infections.

Altered vaginal flora (AGF) – also known as bacterial vaginosis (BV); describes changes in vaginal bacteria where there is a decrease in helpful bacteria, and an increase in problematic bacteria. There may be no symptoms of this change; however, some common symptoms that may appear include an abnormal discharge or a strong odour from the vagina.

Antibody – part of the immune system which binds to antigens on the surface of viruses, preventing them from multiplying. Antibodies may be developed after exposure to a foreign antigen, usually by infection, but humans also have natural antibodies which are produced before any exposure to a foreign antigen.

Antigen – part of viruses, bacteria and other microorganisms that, if foreign to the immune system, causes the immune system to generate antibodies to match that antigen and bind to it upon a subsequent exposure. If the immune system already has antibodies that match that antigen, the antigen will bind to the antibody and the virus will be prevented from multiplying.

Asymptomatic – term used when a person has an infection, but is not affected by the symptoms or disease associated with that infection; opposite of symptomatic.

Bacterial vaginosis – see Altered vaginal flora (AGF) above

Cervical ectopy – also know as immature cervix; cells lining the transition from the interior of the cervix to the cervical opening extend onto the face of the cervix.

Circumcision – removal of foreskin from the penis.

Chlamydia – a sexually transmitted infection caused by bacteria. This infection may not generate noticeable symptoms in women; men may notice a milky discharge from the penis. If untreated, the infection may spread to other parts of the reproductive organs with serious short and long term consequences.

CD4 – white blood cell, one of the cells which help the immune system, and a target cell for HIV to use in viral replication. CD4 cells are destroyed by HIV in the viral replication process, as well as by other mechanisms, such as when targeted by a CD8 cell. A reduction of CD4 cells in the blood is one marker of an immune system in decline.

CD8 – white blood cell, helps the immune system by identifying and killing infected, damaged or cancerous cells, including CD4 cells infected with HIV.

Effectiveness – how well a product works in practice, such as in "real life", outside of a controlled testing environment, where ideal conditions may not always be present. Example: The efficacy of condoms may be nearly 100% when used correctly, but their effectiveness is less than 100% because they may not be used correctly or consistently in practice.

Efficacy – how well a product works under ideal conditions, such as in the context of a controlled testing environment. Example: The efficacy of condoms may be nearly 100% when used correctly, but their effectiveness is less than 100% because they may not be used correctly or consistently in practice.

Epithelium – a layer of cells that line hollow organs and glands, and that make up the outer surface of the body. The epithelial layer acts to secrete and absorb substances, to transport elements through cells, and to protect cells from transporting or absorbing foreign substances. These cells may be arranged in two ways: columnar (arranged like upright columns) or squamous (arranged flat and overlapping, like scales). Each arrangement serves a different purpose and makes transport, secretion and absorption of substances more or less direct.

Gonorrhea – a sexually transmitted infection caused by bacteria. This infection may or may not generate noticeable symptoms in women; vaginal discharge and pelvic pain may indicate an infection. Men may notice pain while urinating and/or a discharge from the penis. If untreated, the infection may spread to other parts of the reproductive organs with serious short and long term consequences.

Herpes – a sexually transmitted infection caused by the herpes simplex virus (HSV). Often asymptomatic, common symptoms include pain, itching, burning, discharge, and sores or lesions on the genitals, thighs, buttocks or anus. These sores may resemble cold sores that appear around the mouth, another form of herpes infection.

HIV – human immunodeficiency virus; this virus attacks the human immune system, decreasing its effectiveness over time, such that many common infections become life-threatening.

HPV – human papillomavirus; a sexually transmitted infection. This virus infects the skin or mucous membranes. Certain types of this virus may generate no symptoms, but other types do, with the most common symptoms being genital and anal warts. Serious complications may arise, including cancer of the cervix, vulva, vagina, anus, throat and penis.

Hyperosmolar – Osmolarity is a measure of the concentration of the soluble components—or solutes—present in a solution. Products can be iso-osmolar, hypo-osmolar or hyperosmolar. Iso-osmolar products have the same osmolarity as normal cells. Hypo-osmolar products tend to make cells swell up with water, which can lead to cells bursting. Hyperosmolar products have a higher concentration of solutes than normal human cells. Therefore, when in contact with the cells of the rectum or vagina, they tend to "suck" away water from inside cells, making them shrink in size.

Latent HIV infection - a stage of HIV infection which occurs after acute HIV infection and before AIDS, and is marked by a period with few or no symptoms that can last as few as 2 weeks to 20 years or more, depending on the individual; also known as secondary or chronic HIV infection.

Luteal phase of the menstrual cycle – Refers to the latter stage of the menstrual cycle, when progesterone levels are significantly higher than in other phases.

Meta-analysis – Meta-analysis is a statistical technique for combining the findings from independent studies. Meta-analysis is most often used to assess the clinical effectiveness of healthcare interventions; it does this by combining data from two or more randomized control trials.

Microabrasions – cuts or openings too small to be seen by the human eye without the use of a microscope.

Mucosal immunity – part of the immune system which protects the mucous membrane from infection, controls immune responses to, and prevents uptake of, foreign materials.

Mucous membrane – linings in the body that act to absorb and secrete different substances. They are found at the entrances into the body and line various tracts supporting different body systems. Unlike the dry surface of skin on the outside of the human body, mucous membranes are wet, moist or slimy.

Pathogen – A biological agent (for example, a virus, bacterium or fungus) that causes disease or illness to its host.

Reservoir – within two weeks after HIV has entered the body, the virus becomes well established in many cells throughout the body as well as in lymph nodes and tissues. This is known as the HIV reservoir.

Risk – Generally, risk refers to the probability that a chosen action or inaction will result in an undesirable result, with the implication that a different choice sometimes exists that may influence the outcome. In this document, risk refers to the likelihood of infection with HIV occurring during the performance of activities and behaviours, based on clinical evidence.

Seroconcordant - grouping where all partners have the same HIV status, i.e all have tested positive for HIV antibodies or all have tested negative for HIV antibodies.

Serodiscordant - grouping where partners do not all share the same HIV status, i.e. one or more partner(s) has tested positive for HIV antibodies and one or more partner(s) has tested negative for HIV antibodies.

Sexually transmitted infection (STI) – illnesses whose transmission between humans commonly occurs through human sexual behaviour. Humans may transmit the infection without displaying the symptoms of disease. Some STIs may also be transmitted in other ways, such as through sharing IV needles, childbirth or breastfeeding.

Symptomatic – term used when a person has an infection and is affected by the symptoms or disease associated with that infection; opposite of asymptomatic.

Syphilis – a sexually transmitted infection caused by bacteria. The disease is notable for having four stages: primary, secondary, latent (asymptomatic) and tertiary, and for the severe neurological complications which may arise should the infection progress to the tertiary stage.

Target immune cells – Certain types of cells in the immune system (CD4 cells, macrophages and dendritic cells) that HIV is able to infect and use to make copies of itself and release more virus.

Trichomoniasis – a sexually transmitted infection caused by trichomonas vaginalis, a parasitic microorganism. Its symptoms include vaginitis in women, and urethritis in men. Untreated trichomoniasis can lead to serious complications.

Undetectable viral load – describes a measure of viral severity that falls below the lowest measurable amount a test can confirm; see viral load. Different tests may have different points at which the viral severity is determined to be undetectable.

Vaginal atrophy – A thinning and inflammation of the vaginal walls due to a decline in estrogen. Vaginal atrophy occurs most often after menopause, but it can also develop during breast-feeding or at any other time a woman's estrogen production declines.

Viral load – a marker of the severity of a viral infection. Viral load is usually documented by the estimated amount of virus in a body fluid. HIV viral load is measured by the number of copies of HIV per millilitre of blood.

Virion – refers to a single viral particle that is released from a cell and is capable of infecting other cells