



The Effects of Viral Load and Antiretroviral Medications on Sexual Transmission of HIV



Questions

1. Is there a difference between viral loads in blood plasma vs. genital fluids? If so, what factors contribute to this difference?
2. When viral load is higher in genital fluids than blood plasma, how likely is this to result in HIV transmission?
3. How are viral load measurements affected by Highly Active Antiretroviral Therapy (HAART)?
4. What is the impact of antiretroviral medications on the risk of HIV transmission?

Key Take-Home Messages

- Several studies have noted differences in viral load levels when comparing blood plasma to semen, cervicovaginal secretions and rectal mucosa.(1-18)
- Despite an undetectable blood plasma viral load (i.e. <50 copies/ml) a percentage of people living with HIV (as observed in cross-sectional studies), ranging from 5% (18) to 25% (4), still have detectable viral loads in genital secretions. (1-17)
- Despite an undetectable blood plasma viral load, the presence of genital inflammation including sexually transmitted infections (STIs) and, for women, the use of hormonal contraceptives, correlates with a detectable viral load in genital secretions. (1;3;5-9;12)
- Some drugs included in Highly Active Antiretroviral Therapy (HAART) are not able to penetrate the genital tract; of those that can, only a small number do so effectively (i.e. suboptimal drug levels). This lack of penetration can be problematic as drug-resistant strains of HIV can replicate in the genital tract, which can act as separate compartment in the body, which means that virologic failure may not be detected in blood. (1-3;5;6;8;11)
- Rectal secretions were found to contain the highest levels of virus compared to blood plasma, vaginal and seminal fluids. (4;13)
- As blood plasma viral load was found to not accurately predict seminal

EVIDENCE INTO ACTION

The OHTN Rapid Response Service offers HIV/AIDS programs and services in Ontario quick access to research evidence to help inform decision making, service delivery and advocacy. In response to a question from the field, the Rapid Response Team reviews the scientific and grey literature, consults with experts, and prepares a brief fact sheet summarizing the current evidence and its implications for policy and practice.

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vaginal and rectal mucosa viral loads, condom use is recommended during intercourse, even when people living with HIV have undetectable blood plasma viral loads. (1-17)

- Unprotected sexual intercourse among heterosexual serodiscordant couples in monogamous relationships, where the HIV-infected partner has full virologic suppression, carries minimal risk of HIV transmission. (19-21)
- Antiretroviral therapy is recommended for people with HIV in serodiscordant relationships to reduce the risk of HIV transmission to their uninfected partner. (22)

The Issue and Why It's Important

Some studies have concluded that people living with HIV (PHAs) on HAART with undetectable blood plasma viral loads, have a minimal risk of sexually transmitting HIV through unprotected intercourse. However, HIV transmission has been known to occur under these conditions as genital tract and rectal mucosal viral loads are not always in perfect correlation with blood plasma viral loads.(4) In fact, several studies have found that viral loads in the genital secretions and rectum of both male and female PHAs (e.g., seminal, vaginal, ectocervical, endocervical, rectal mucosa) could still be detected, even when blood plasma viral loads are undetectable (i.e. <50 copies/mL). (1;2;5;8-10;14).

Standard care for PHAs measures blood plasma viral load regularly (i.e., every three months) (3), and does not measure the viral load in genital secretions. As a result, it is not clear if being on HAART and having an undetectable blood plasma viral load can be considered a reasonable alternative to condom use in reducing HIV transmission among serodiscordant sexual partners.

It is important to understand the conditions and factors that can allow for the sexual transmission of HIV despite an undetectable blood plasma viral load.

What We Found

The Difference between Viral Loads in Blood and Genital Fluids

Ten studies based in North America, Europe and Sub-Saharan Africa explicitly measured the differences between blood plasma and genital fluid and/or rectal mucosa viral loads and found that when blood plasma viral load was undetectable, the viral load in the genital tract and rectum could still be detectable. (1-5;8-10;13-15;18) Due to the biological differences, each of these measures of viral load will be examined separately.

Some studies that specifically looked at viral loads in vaginal secretions found that HIV was detectable even when a participant's blood plasma viral load was undetectable and participants were on HAART. (5;8;15) The incidence of detection varied widely from 9% to 25%. (5;15) Cu-Uvin et al's longitudinal study (5) further revealed the complexity of what is known as viral shedding (i.e. presence and replication of HIV in a body fluid). If the blood and genital tract can be viewed as separate compartments in the body, then the female genital tract is further divided into three subcompartments: vagina, endocervix (cervix on the side of the uterus) and ectocervix (cervix on the side of the vagina). The authors explained

how shedding in one sub-compartment did not correlate with shedding in another. In fact, shedding could occur in only one sub-compartment without the others being affected. The authors also found that for women who were persistent shedders, the sub-compartment which shed often rotated at random. (5) Even though most study participants were on HAART, 22 of the 59 participants (37%) had levels of virus in their genital secretions, which classified their viral shedding as persistent (7%), intermittent (31%) or not at all (46%). (5) Non-shedders were defined as participants who had no detectable genital viral load, when the blood plasma viral load was undetectable.

An Italian study that sampled the blood and cervicovaginal viral loads in 122 women found that genital viral load was positively but weakly correlated to blood plasma viral load. (15) However, the authors cautioned that blood plasma viral load is not an accurate marker of the infectivity of genital secretions, as 25% of the participants who had an undetectable blood plasma viral load were found to shed the virus in their genital secretions. Again, the authors concluded that the virological differences between the blood and the genital tract suggests they can be considered separate compartments. (15)

Several studies specifically examined the presence of HIV viral load in seminal fluid in HIV-positive males. (2-4;9-11;17;18) In a cross-sectional study of sexually active men who have sex with men (MSM) who were currently on HAART for more than three months, overall 30% had a detectable seminal viral load, with a range of 80 to 2560 copies/mL (median = 200 copies/mL), and 18% solely had a detectable blood plasma viral load. (4) Twenty-five percent of the 83 participants that had an undetectable blood plasma viral load had a detectable seminal viral load; however the authors concluded that this was likely due to the presence of STIs and genital inflammation (leukocytospermia). (4)

Five percent of 145 HIV-1 infected men enrolled in an assisted reproductive technology program had detectable HIV-1 RNA in semen, although they had no other sexually transmitted disease and their blood viral load was undetectable for at least 6 months under antiretroviral treatment. (18)

A 10-year cohort study on HIV-positive heterosexual males in monogamous relationships examined the occurrence of HIV in seminal fluid when their blood plasma viral load was undetectable (2). Patients were on HAART and had an undetectable blood plasma viral load, yet 7% of patients were found to have detectable levels of HIV in their seminal fluid, with titers ranging from 135copies/mL to 2365 copies/mL. (2)

A prospective longitudinal Canadian study that looked at men starting antiretroviral therapy also found that 12 of the 25 participants (48%), had more than one record of HIV shedding in their semen, and four participants (16%) had seminal viral load of >5000 copies/mL. (10) All participants had an undetectable blood plasma viral load at the time of the visits.

A few studies reported higher HIV viral loads in the rectal mucosa compared to the blood and seminal fluid of men. (4;13) One of these studies, based in the US and Peru, found that median HIV viral loads in rectal secretions, blood and semen were as follows: (13)

- Rectal Viral Load: 4.96 log₁₀ copies/mL (>79,433 copies/mL)
- Blood Plasma Viral Load: 4.24 log₁₀ copies/mL (>15,849 copies/mL)
- Seminal Viral Load: 3.55 log₁₀ copies/mL (>3,162 copies/mL)

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The Authors' opinions differed on the proportions of PHAs who may shed HIV in their genital fluid despite having an undetectable blood plasma viral load. (2-4) However, when comparing the methodology of studies, it was clear that all longitudinal studies found that a proportion of their sample had detectable levels of HIV in the genital secretions and/or anal mucosa when the blood plasma viral load was undetectable. (2) Cross-sectional studies (i.e. studies which took only one measurement) varied in the detection of HIV in genital secretions and/or anal mucosa. This is important for the medical care of PHAs as it will not be known if a patient is a persistent, intermittent or a non-shedder of HIV in their genital secretions, unless consistent measurements are taken over time.

HIV Transmission Risks When Viral Loads Differ

Although some authors have noted that further research is required to set viral load thresholds of genital secretions or rectal mucosa that allow for transmission (1;10;15), others have noted that low titers of HIV in seminal fluid (<1000 for male to female, <200 for male to male) could be sufficient to cause HIV transmission to sexual partners.(3;4;16)The estimated titer number for male-to-male transmission is lower, as the thin rectal epithelium layer allows HIV to be transmitted more easily to a receptive partner through unprotected anal intercourse than vaginal intercourse. (13) As stated before, rectal mucosa typically has a higher viral load than other body fluids and a male's urethra may be a primary HIV infection site, which may also explain why unprotected anal intercourse is extremely efficient for HIV transmission at low but detectable viral loads for both partners. (4;13)

A few studies that examined the correlation and predictive ability of blood plasma viral load found poor correlations between blood and semen, and blood and vaginal fluids (2;14;16). Regarding the risk of transmission, Baeten et al (2011) found a stepwise association between genital viral load and HIV incidence. (16) In addition, Lambert-Niclot et al (2012) reported that blood plasma viral load was unable to predict seminal viral load. (2) Furthermore, since there is a poor correlation between the two fluids, and seminal shedding is known to occur both persistently and in 'blips' (ie. transient viral increases), despite the use of HAART and undetectable blood plasma viral load, the study encouraged heterosexual couples to use safer sex measures, or at least be aware of the risk of transmission, when engaging in unprotected intercourse.(2)

A Ugandan study published in 2000 identified that, when PHAs were not on HAART and their blood plasma viral load was less than 1500 copies/mL, the risk of heterosexual transmission is negligible. Its findings were based on blood plasma viral load levels alone and did not take into account viral load levels in genital secretions.(23) A cross-sectional study with male PHAs on HAART found that even with an undetectable blood plasma viral load (i.e. medically controlled), 2 out of 33 participants (6%) had a seminal viral load of 700 copies/mL and 1100 copies/mL respectively. (3) Both participants had been diagnosed HIV-positive three or more years prior and had successive undetectable blood plasma viral load readings for over two years. Previous studies had also noted that between 7% and 15% of men with an undetectable blood plasma viral load had seminal shedding. (3) They concluded that an undetectable blood plasma viral load does not guarantee a PHA being sexually non-infectious. (3) A study from Malawi that examined males with both acute and chronic HIV infection found that seminal viral load was the highest in acute HIV infection and "late stages" of chronic HIV infection with low CD4 cell counts (compared with the "early stage" chronic HIV infection) and posed the greatest risk for HIV transmission. (9)

One paper stated that, from their results, it was not clear if isolated seminal shedding of HIV can result in sexual transmission of HIV, but noted that their study may underestimate the infectious potential of semen. (10) Given there are such differences between individuals, even in how seminal HIV shedding occurs, they concluded that some HIV-positive males can be sexually infectious despite having an undetectable blood plasma viral load. (10) Another study that looked at rectal mucosa viral loads (RVL) in HIV-positive MSM with an undetectable blood plasma viral load found similar discrepancies. They also recommended that condoms be used, given the reservoir of infected rectal cells that can still replicate, even though a PHA's blood plasma viral load is undetectable. (14)

Factors That Contribute to Differences in Viral Loads

One of reasons for differences in viral load between the blood plasma and genital fluids is the fact that the blood and the genital tract are separate compartments in the body. (15) A study that reviewed the literature on various viral loads (14) found that, as HIV infects multiple cell types in the genital tract, HIV replication occurs differently in the genital tract than in the blood. This may account for the variations in HIV strains even between the fluids of the same person (1), and explain why HAART is not as effective in reducing genital viral load. (1)

Several studies found that despite an undetectable blood plasma viral load, the presence of genital inflammation including STIs and the use of hormonal contraceptives in women correlate with a detectable viral load in genital secretions (1;3;5-9;12) For male PHAs, HIV detected in semen was found to be attributable to poor HAART adherence and virologic HAART failure, as well as STIs and genital inflammation. (7;9;15) Cu-Uvin et al (2000) found that, although there was a weak relationship between blood plasma viral load and vaginal genital viral load, blood plasma viral load drives the presence of HIV in the genital tract. (5)

Furthermore, authors found that with every log₁₀ unit increase in blood plasma viral load the odds of genital shedding were 2.6 times more likely to occur. (5) Another study noted that HIV viral loads may increase either first in the plasma, or concurrently with the genital tract viral load. Regardless, genital shedding can occur without a detectable blood plasma viral load or virologic failure. (14)

Another Kenya-based study that looked at the relationship between genital inflammation and vaginal viral load found that inflammation was significantly associated with vaginal viral load, independent of blood plasma viral load. (7) The researchers suggest that there are limits to using blood plasma viral load as a marker for transmission risk, as local inflammation could moderate transmission as well.(7) They also suggest that inflammation markers in the blood should not be used to predict genital inflammation or shedding. (7) As noted in other studies, the use of hormonal contraceptives by female PHAs is associated with an increase in concentration of pro-inflammatory messengers in the vaginal tract, which are associated with shedding; however the latter association is weak. (7)

In a study from Malawi, Pilcher et al (2007) found that for men with acute HIV infection (AHI) not on HAART, the blood viral load peaked at 17 days, while the seminal viral load peaked at 30 days. (9) The authors noted, as others did, that seminal viral load was higher when CD4+ cell counts were lower (9), but other studies found no relationship between CD4+ count and genital viral load. (6) The Malawi study also noted that the greatest changes in seminal viral load were observed in males with acute HIV infection, compared to males who were chronically infected with HIV. (9) A Kenya-based study by Graham et al (2010), found that having genital herpes was associated with genital HIV shedding while taking HAART(6), and the authors reported that higher genital viral loads are associated with a risk of HIV transmission through insertive male-to-female

intercourse among serodiscordant couples. (6) Similar to other studies, the authors noted that this could be a biomarker for HIV infectivity. (6;16) A US-based study that examined the correlation between blood plasma viral load and rectal viral load (RVL) among MSM, found that in men with rectal gonorrhoea or chlamydia, the correlation between the two viral loads was stronger in the presence of one of the STIs. (12) The authors surmised that with ongoing viral replication, rectal shedding may be enhanced by the STIs. In addition to gonorrhoea and chlamydia, genital herpes (HSV-2) shedding also increased rectal viral load. (12) Valacyclovir, the treatment for genital herpes, was found to reduce rectal viral load. Authors also noted that HAART may mitigate the effect of STIs on rectal viral load and, thus, HIV transmission through unprotected insertive anal intercourse. However recurrent STI infections are associated with a higher risk of HIV seroconversion in HIV-negative MSM. (12)

Impact of HAART on Genital and Rectal Viral Loads

HAART has been demonstrated to be effective in reducing blood plasma viral loads; however, it can be less efficacious in reducing genital and rectal viral loads. Fiore et al (2003) found genital shedding of virus in 25% of women with undetectable plasma viral load. (15) The authors noted that, as a rule, antiretroviral treatment can suppress HIV viral shedding at the genital site and should be considered as a tool to reduce HIV transmission. However, they echoed the findings of other authors that an undetectable blood plasma viral load is not an accurate indicator of the absence of genital shedding in females. (8;15)

Both cross-sectional and longitudinal studies reveal that not all HAART regimens have the same effect on the genital tract and rectum. A cohort study documented the HAART regimens of male participants, and found that the drugs indinavir, tenofovir, and darunavir had good penetration of the male genital tract; however, seminal shedding still occurred. (2) The authors also noted that the male genital tract was found to be virtually impenetrable by the drug lopinavir, similar to the findings of a French study that examined drug concentrations in semen. (11) The latter study also found that ritonavir was also undetectable in semen, even when it and lopinavir were detectable in the blood, and they were used as standalone treatments or in combination with other drugs. (11) The authors explicitly noted that these findings cannot be extended to the entire protease inhibitor class. (11)

A Canadian cross-sectional study found that efavirenz had poor penetration into the male genital tract, and concluded that this fact may explain why there can be detectable seminal viral load levels in spite of an undetectable blood plasma viral load. (3) Poor penetration by antiretrovirals, at sub-therapeutic levels, means that the drugs do not work as effectively in suppressing the seminal viral load, although they can ensure undetectable blood plasma viral load. (3)

Furthermore, several authors have noted that sub-therapeutic levels of ARV drug concentration in seminal fluid is probably the reason for the increased incidence of drug-resistant HIV strains. (1;3;11) In a Toronto-based prospective study of men starting ART, Sheth et al (2009) found no association between isolated seminal viral shedding and being on a specific HAART regimen, and HIV already within genital tract cells may persist in spite of HAART therapy. (10)

None of the reviewed studies focused on the ability of specific antiretrovirals to penetrate the female genital tract or the rectum. However, a literature review by Canadian researchers found that HAART medications do not effectively enter the genital tract from the blood, and that viral loads in the genital secretions of some women were still detectable even after being on HAART for six months. (1)

The authors also observed that PHAs who are pregnant and on HAART with undetectable viral loads are given supplemental zidovudine (AZT) during delivery, in case a viral load 'blip' occurs. (1) Furthermore, they caution that even though naturally occurring low blood plasma viral loads correlated with a reduced likelihood of HIV transmission, HAART induced low blood plasma viral loads cannot ensure the same correlation. (1) Like other authors, they conclude that HAART may not be sufficient to ensure a negligible risk of HIV transmission. (1) A Kenya-based study found adherence to HAART to be a strong and consistent predictor of genital viral load suppression in women who were HIV-positive; however, having drug-resistant strains of HIV in one's blood was associated with higher genital viral load due to a higher blood plasma viral load. (6) Women who continuously shed HIV in their genital secretions were also found to shed drug-resistant strains of the virus. (6)

Specifically pertaining to the viral load of rectal mucosa (RM), a US-based study found that, for MSM on HAART (irrespective of whether a protease inhibitor was used or not), HIV was less detectable in the rectal mucosa. (14) In terms of the impact of HAART, it can reduce HIV that is outside of the cell, but has little impact on the reservoir of infected cells, which have the ability to replicate. (14) The US-Peru study found that HAART was associated with a 1.3 log₁₀ reduction in rectal viral load, and a >1 log₁₀ decrease in seminal viral load when blood plasma viral load was undetectable (14). The same study found that HAART regimens varied widely across participants, but 100% of participants who were on HAART were taking a nucleoside reverse transcriptase inhibitor (NRTI). (13)

Overall, HAART does have a significant impact in reducing genital viral load for most PHAs; however, under certain conditions, 'blips' in genital viral load can occur. It is important to note that detection limits for measuring viral loads in blood plasma and genital secretions are often different. In blood the detection limit is 40 or 50 copies/mL, however in genital secretions it is usually about 10 times higher (around 400 copies/mL), thus "undetectable" viral load has different meanings depending on the source fluid, making HIV transmission rates difficult to assess. As a result, more research is needed to determine what procedures should be introduced into the standard of care model for PHAs to best inform them of the potential risk for transmitting HIV to sexual partners.

The Impact of Antiretroviral Medications on HIV Transmission

There have been intensive discussions about the impact of antiretroviral medications on the risk of HIV transmission since the Swiss National AIDS Commission issued a statement in January 2008 specifying that HIV-infected individuals could be considered non-infectious if they: were adherent to cART and under the care of an HIV physician, showed virologic suppression below the level of detection for at least six months, and had no presence of concomitant sexually transmitted infections (STIs). (21)

Cohen et al. (20) in a widely publicized randomized controlled trial, known as HTPN 052, compared effectiveness of antiretroviral therapy either immediately (early therapy) or after a decline in the CD4 count or the onset of HIV-1-related symptoms (delayed therapy) among 1763 serodiscordant overwhelmingly heterosexual (97%) couples in 13 sites in 9 countries. A total of 39 HIV-1 transmissions were observed; of these, 28 were virologically linked to the infected partner. Among HIV-1-infected participants, a mean of 96% of those in the early-therapy group and 95% of those in the delayed-therapy group reported 100% condom use during the study. Of the 28 linked transmissions, only one occurred in the early therapy group, meaning that all linked transmissions in the delayed-therapy group occurred while the HIV-1-infected participant was not receiving antiretroviral therapy. The study concluded that early initiation of antiretroviral

therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy. But it should be emphasized that this study was conducted in mostly heterosexual stable HIV-1-discordant couples who reported using condoms as well as treatment, and that only blood plasma viral load levels were measured. It is not clear how many of the people who seroconverted did so while using condoms. (20)

Another widely known randomized-controlled trial, iPrex, (24) evaluated the safety and efficacy of once-daily oral combination of two nucleoside reverse transcriptase inhibitors (NRTIs) - emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) - compared to placebos for the prevention of HIV acquisition among men and transgender women who have sex with men. Participants were followed for 3324 person-years (median 1.2 years). Ten were found to have been infected with HIV at enrollment, and 100 became infected during follow-up (36 in the FTC-TDF group and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV. The protective effect of FTC-TDF was significant but not as high as the 92% reduction originally hypothesized during the design of the study.(24)

The latest systematic review by Loutfy et al (19) analyzed the findings from five observational studies and one randomized-controlled trial (20) and suggested minimal risk of sexual HIV transmission for heterosexual serodiscordant couples when the HIV-positive partner has full viral suppression on cART with caveats regarding information on sexual intercourse type (anal vs. vaginal), STIs, and condom use. These findings have implications when counseling heterosexual serodiscordant couples on sexual and reproductive health. The authors noted that this systematic review contributes to the emerging body of literature expanding on the position put forth by the Swiss National AIDS Commission (21) that unprotected sexual intercourse represents a low risk of HIV transmission for heterosexual serodiscordant couples in monogamous relationships if the HIV-infected partner has full virologic suppression on cART, where both parties understand the limitations of the available data.(19)

Finally, according to the guidance on couples HIV testing and counseling - including antiretroviral therapy for treatment and prevention in serodiscordant couples, published by the World Health Organization in 2012, people with HIV in serodiscordant couples and who are started on antiretroviral therapy for their own health should be advised that ART is also recommended to reduce HIV transmission to the uninfected partner. (22) HIV-positive partners with >350 CD4 cells/ μ L in serodiscordant couples should be offered ART to reduce HIV transmission to uninfected partners.(22)

Factors that May Impact Local Applicability

As the studies primarily focus on the biological aspects of HIV transmission, geographical context was not explored; however HAART/medication availability may be limited in specific countries. Another issue is that the majority of studies focused on either gay men or men who have sex with men, or the heterosexual risk of HIV transmission regarding males transmitting the virus to females. A few studies focused on the vaginal viral load, but even fewer actually focused on the risk of females transmitting the virus to males.

What We Did

We conducted related articles search in Medline for the two articles: Lambert-Niclot et al (2012) (2) and Politch et al (2012) (4). We also reviewed references in the studies found and searched Cochrane Collaboration HIV/AIDS review group for relevant systematic reviews. Experts in the field, including Drs. Rupert Kaul and Paul MacPherson were also consulted.