

hiv treatment update



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does undetectable really mean uninfected?

Earlier this year, a consensus statement from the Swiss National AIDS Commission (EKAF)¹ created global controversy. The authors of the Swiss statement (who include Professor Bernard Hirschel of Geneva University Hospital and Professor Pietro Vernazza of the Cantonal Hospital in St. Gallen) are, notes Craig McClure, executive director of the International AIDS Society (IAS), in an email to *HTU*, "amongst the foremost HIV experts in the world".

The statement said that, as long as someone has had an undetectable viral load (which they defined as less than 40 copies/ml) for at least six months; remains adherent to their antiretroviral therapy (ART); is evaluated regularly by their HIV doctor; and has no other sexually transmitted infections (STIs); then they are "not sexually infectious, i.e. cannot transmit HIV through sexual contact."

This is something that has never before been stated in public by HIV experts, although the idea that effective treatment has a major impact on transmission on a population (rather than an individual) level is not new.

We first examined the link between treatment, transmission and prevention² six years ago. And four

years ago, when we last visited this subject, studies were already finding that a significant minority of people (primarily gay men in large Western cities) were already making safer sex decisions based on viral load.

In that article, we found that:

- the link between viral load in the blood and viral load in sexual fluids is not straightforward;
- levels of some anti-HIV drugs are lower in sexual fluids;
- levels of HIV in women's sexual fluids are affected by their periods;
- levels of HIV are thought to be much higher in the rectal lining than in the blood, even in those taking anti-HIV drugs;

- sexually transmitted infections can increase levels of HIV in sexual fluids, whether or not you are on anti-HIV drugs.

Given the uncertainties surrounding the effects of ART on sexual infectiousness, the article concluded, is it really sensible to make choices about safer sex based on viral load results?³

Has enough evidence accrued over the past four years to support the Swiss statement? How have other experts reacted? What does it mean for HIV prevention and for people living with HIV?

In this special eight-page report, we'll examine the evidence put forward by the Swiss, highlighting what they have - and have not - said, and consider some of the wide-ranging implications.



Why now?

Most of the studies reviewed by the Swiss experts are at least three years old, and the Swiss had not conducted a study that provided new data - something that was not made clear in some of the mainstream reports. So why make this statement now?

The impetus, as Professor Hirschel explained last December, when he gave a series of interviews to Swiss newspapers to coincide with World AIDS Day, appears to be a frustration that privately held

beliefs regarding the effect of treatment on infectiousness by many of his colleagues around the world had not translated into published statements for fear of the potential consequences, such as increased sexual risk-taking.

He told *Le Temps*, "nobody will reproach a politician or a medical expert if he exaggerates a risk, whereas



I think it's great that some Swiss doctors have taken a risk and said in public what many have been advising their patients in private. We don't have all the evidence in yet, especially regarding anal sex, and it's important to emphasise that you have to have been undetectable for 6 months and STI-free. But I think it potentially lifts a great burden from people with HIV and couples in serodiscordant relationships, like me. I think we'll look back on it as a pivotal and liberating moment. Think of the implications for testing, treatment and criminalisation.

Gus Cairns, HIV-positive advocate

the opposite can be sanctioned very heavily. However, one cannot allow [oneself] to be paralysed by this lack of symmetry: a preventative message which exaggerates all risks and does not correspond to reality loses credibility and efficacy."⁴

Professor Hirschel outlined the specific reasons why the statement was made in an online interview with Regan Hoffman, the editor of *Poz* magazine, in February.⁵ "There are several reasons, he said. "The first is a series of [criminal] trials in Switzerland where people were accused of endangering others through sexual relations - they were HIV-positive, the partner was HIV-negative. The defence said, 'Well, there was little or no danger because my client was treated and he had undetectable viraemia.' This defence was not admitted, based on official statements saying that treatment had little influence on infectivity. And that's just plain wrong. So there needs to be some official statement to the contrary."

He also wanted to help further the reproductive rights of his HIV-positive patients. Current assisted reproduction methods, such as 'sperm-washing', may be helpful for some couples, but they are expensive, difficult to access and result in low pregnancy rates. "You have to say something about that," he said.

He also said that the recent disappointments seen in studies of prevention technologies mean that, "we need to think about other means of prevention. Treatment is such a weapon against future HIV infection. And you cannot very well defend the point of view that we should treat additional people, not only for themselves, but also for prevention of additional infections while maintaining that treated people are still infectious. It's a real problem, the error of logic."

In another document (originally Professor Hirschel's responses to a UK Community Advisory Board discussion, but now published online in a blog⁶) he said: "I'm not comfortable with the

idea that there is one truth for the initiated, and another for the masses."

Consequently, the Swiss statement should be seen as much as a political statement as a scientific one.

Examining the science

The Swiss experts reviewed recent epidemiological (studies looking at populations, not individuals) as well as biological (small studies in HIV-positive individuals) data to inform their conclusions. Let's take a closer look at the main studies they cited.

The first epidemiological study on viral load and sexual infectiousness came from a study of 415 heterosexual couples in Uganda, and was published in 2000. Quinn and colleagues found that the risk of transmission depended on viral load and that no HIV transmission was observed over a 30-month period in the 51 couples where the HIV-positive partner consistently had a blood plasma viral load under 1500 copies/ml.⁷

It wasn't until 2005 that a second study, from Spain (again, of heterosexual couples), examining this phenomenon was published. Here, Castilla and colleagues followed 393 couples between 1991 and 2003 and found that no HIV transmission was observed when the HIV-positive partner was on antiretroviral therapy, compared to a rate of transmission of 8.6% among partners of untreated patients.

Even though the study demonstrated the ability of anti-HIV therapy to reduce heterosexual transmission by 80%, the investigators cautioned that even a small increase in sexual risk-taking could cancel this out and emphasised, "the main preventative measure for HIV sexual transmission remains the avoidance of risky sexual practices."⁸

A third study, among 93 heterosexual couples in Brazil over six years, found that there was no transmission in the 41 couples where the HIV-positive partner was on anti-HIV therapy and



The phenomenon of lower virus, less chance of transmission is well known. The critical issue that gets people at the WHO, CDC and myself a little concerned is making the statement that there is essentially no risk of getting infected if you are having sex with a partner who is HIV-positive and on [ART] with virus below detectable levels. There is no such thing as zero risk.

Dr. Anthony Fauci

Director of the US NIH's National Institute of Allergy and Infectious Diseases to *Time* magazine.

six transmissions in the couples where the HIV-positive partner was not on therapy and had a viral load of 1,000 copies/ml or higher.¹⁰

The authors of the Swiss statement go on to cite a variety of biological studies (most of which were reviewed in our 2004 article) focusing on the relationship between blood viral load and viral load in semen and vaginal (but, importantly, not rectal) fluids. "These biological data indicate that *the risk is greatly diminished* [my emphasis] during effective ART," they write.

They conclude the scientific part of the article by saying that: "During effective antiretroviral therapy, free virus is absent from blood and genital secretions. Epidemiologic and biologic data indicate that during such treatment, there is no relevant risk of transmission during complete adherence to ART. The risk of HIV transmission during sex without

condoms in the context of a completely suppressed viral load is much smaller than 1 in 100,000. Although a residual risk can not be scientifically excluded, in the judgment of the Commission, it is negligibly small."

Too many variables to consider

Dr Steve Taylor, lead HIV consultant at Birmingham Heartlands Hospital wrote his PhD thesis on the sexual transmission of HIV and has co-authored many papers on HIV in the male genital tract. He questions much of the statement's reliance on biological data, since he believes there are too few studies in too few individuals to come to any firm conclusions.

"The biology surrounding the sexual transmission of HIV is incredibly complicated, controversial and a subject littered with hundreds of virological, biological and sociological variables," he tells *HTU*. "Thus producing a simple generalised statement regarding what makes someone non-infectious with regard to HIV transmission, such as the Swiss paper, is always going to be open to criticism."

"I think," he continues, "that the general principle that ART will make someone less infectious is correct. However, it is a generalisation. It is very likely that it will have a big impact on transmission on a population level *on the condition that* [his emphasis] other prevention measures

are also employed, i.e. promotion of condom use, treatment of STIs etc."

"However," he stresses, "on an individual couple level, there are so many variables to consider that I find it problematic to be so concrete as to state the transmission risk is zero."

For example, Dr Taylor suggests that the jury is still out on the effect of ART in the female genital tract. "There appears to be more variability in the female genital tract than in the male, although this is also controversial."

When asked whether the results of the epidemiological studies in heterosexual couples (who were advised to use condoms throughout the studies) could be extrapolated to mean that condoms could be abandoned during anal sex because of a belief that undetectable means non-infectious, he says, "I think this is an extrapolation too far."

So, what about anal sex?

Matthew Hodson, Head of Programmes for London-based gay men's health charity GMFA, agrees with Dr Taylor. He tells *HTU*, "While the Swiss statement will be welcomed by some heterosexual couples, the fact that anal sex was not addressed is disappointing."

"Men who have sex with men make up the greatest number of new HIV infections acquired within Europe and the statement should have made clear

the distinctions between vaginal and anal sex," he says.

"Anal mucus, a fluid secreted inside the arse, has been shown to contain much higher levels of HIV than either blood or semen, even for guys taking ART," he notes. "The infectivity of anal mucus presents an infection risk to the insertive partner, but this was not addressed. In addition, the anus is a more effective route than the vagina for infection."

There has only been one study looking at the relationship between ART and the level of HIV in rectal secretions



The real thing missing (from the Swiss advice) is about anal sex and getting a new sexually transmitted infection.¹²

Roger Pebody
Programme Development Officer,
Terrence Higgins Trust



I think practising physicians and public health workers have long understood that the earlier and aggressive use of antiretroviral treatment would probably be associated with some diminution in the size of the epidemic, as people are less infectious if they are undetectable biologically. The problem is that this is not always the case, and a small number of people will go on producing virus in the semen despite having undetectable plasma viral loads. This seems to be particularly true during other sexually transmitted infections like gonorrhoea. For the individual patient who is virologically undetectable the risk of transmission of HIV to a partner is not zero because there may be virus in the semen, either because the patient is having early virological failure or because of an intercurrent infection.

Professor Brian Gazzard

Professor of Medicine, Imperial College School of Medicine, and HIV Research Director, Chelsea and Westminster Hospital¹¹

compared with those in blood and semen, and this took place between 1999 and 2001 in the United States and Peru. Although there were 64 HIV-positive gay men in the study, only 27 were on antiretroviral treatment. Of these 27, just 18 had an undetectable viral load (in this study defined as below 400 copies/ml) as measured in the blood.¹³

The very limited information it provided is not enough to show conclusively what effect ART has on rectal secretions. However, the results do suggest that viral load appears to be much higher in rectal secretions than in blood or semen, and that it is possible that an HIV-positive person may still have a high enough viral load in the rectal mucosa to expose their (insertive) partner to HIV, even if they have an undetectable viral load in their blood.

When asked by *Poz* why they omitted to address the differences between heterosexual sex and sex between men and the differences between vaginal and anal sex (whether between men and women or between men), Professor Hirschel says, "Well, there are no data. You'd have to admit that it's speculative. Of course, one can logically assume that it would be similar because the risk of transmission - if you take out the more traumatic practices that at times are associated with anal sex - is probably similar between anal and vaginal sex. So you would expect that the effect of treatment would be similar. But this is speculation; we don't have really good data on that."

Dr Steve Taylor says that there are, in fact, major differences between the rectum and the cervix/vagina in terms of anatomy, mucosal barriers and mucosal immunity. "To state there are no differences is incorrect," he argues. "For example, the vaginal mucosal epithelium (cells covering the outside layer of the wall of the vagina) is significantly thicker than the epithelial layers within the rectum and hence more resistant to trauma."

In addition, he notes that, "the number of target cells that HIV can utilise are significantly different within the rectum, as well as the degree of co-receptor expression. Furthermore, the microbial ecosystems of the two compartments are completely different."

The trouble with STIs

"There is also the issue of undiagnosed STIs," notes GMFA's Matthew Hodson. "Many STIs can increase HIV viral load in semen and so if STIs are present, you're more infectious despite anti-HIV drugs. While the Swiss statement touches on this, it does not fully explain that many STIs can go unnoticed. You may think you are clear of STIs, but a health check could reveal otherwise. The statement does say that it is geared toward long-term monogamous couples with no risk of infection with other STIs, but they should have been more clear about the uncertainties of knowing whether you have an STI without testing."

This is one of the main concerns of the experts that we have spoken to: how can you be sure you don't have an STI? Dr Adrian Palfreeman, Consultant GU Medicine, University Hospitals of Leicester, says, "We know that many STIs, such as chlamydia, are common and asymptomatic in the UK, and that several other STIs, including syphilis, are prevalent in the UK HIV-infected population. I am not sure that this is the case in Switzerland."

"Sending out a message that those with an undetectable HIV viral load are not sexually infectious would, therefore, unwittingly risk increasing transmissions in those who also had asymptomatic STIs," he concludes.

Child benefits

As we have seen, one of the main reasons this statement was issued was to help couples who wish to conceive, particularly if it is the man who is HIV-positive. They are the people who may benefit the most from this statement because it specifically says that "insemination via sperm washing

is no longer indicated when antiretroviral treatment is efficient."

"The number of HIV-discordant couples worldwide practising unprotected sex for the purpose of conception could number in the millions," wrote Professor Pietro Vernazza in the journal *AIDS*¹⁴ two years ago. Last year, at the Fourth IAS Conference in Sydney, he presented data on 22 couples suggesting that HIV-negative women were able to conceive safely by having unprotected intercourse with their HIV-positive male partner as long as the partner's viral load was undetectable. What was recommended, however, was a combination of couples counselling, STI screening, timed intercourse and two doses of tenofovir (*Viread*) as pre-exposure prophylaxis (PrEP). This resulted in a pregnancy rate of over 70%, and no HIV transmission, albeit in this very small study.¹⁵

During the question-and-answer session that followed, Dr Vernazza said he considered PrEP to be an additional risk-lowering intervention but that it was primarily used as a "psychological safeguard. There are a lot of psychological issues in there [for the couples]," he said. "I tell them that the [HIV transmission] risk is small - between one in one hundred thousand and one in a million - but they have practiced safer sex for so many years in the belief that there is a big risk, so they want to have this safeguard."

He added that the risks and benefits of this method, compared with traditional assisted reproduction, were explained in an hour-long counselling session, and that most couples were sufficiently convinced to try it. "It is taking longer to persuade some physicians," he noted, adding, however, that there was worldwide interest in their timed intercourse methods.

Dr Vernazza told the conference that they were now planning a prospective study that would also measure the couples' subsequent condom use. "At



We are not going to be changing in any way our very clear recommendations that people on treatment continue to practice safer sex, including protected sex with a condom, in any relationship¹⁷.

Professor Charlie Gilks

Head of treatment, prevention and scale-up at the World Health Organisation (WHO)

the moment," he said, "we cannot say whether condom use has changed [following the intervention]. But it is certainly a concern."¹⁶

Professor Hirschel also tells *Poz*, "Individual decisions have to be distinguished from public health recommendations. As an individual, you may really want to put all the chances on your side; you may want to have suspenders and a belt, and have PrEP plus undetectable viraemia; that's a choice that you can make as an individual. But very probably, the risk to your partner in such a situation is nil, or negligibly small. And therefore, many couples do have children the usual way."

Safety net

The Swiss statement is very clear that prevention strategies currently taking place in Switzerland should not change. Measures to protect ones self must be followed at all times, it says, and the only exception is "stable HIV-positive couples where HIV-positivity and the efficacy of antiretroviral therapy can be established."

"Couples must understand," it says, "that adherence will become omnipresent in their relationship when they decide not to use protection, and due to the importance of STIs, rules must be defined for sexual contacts outside of the relationship."

"People who are not in a stable relationship must protect themselves," it concludes, "as they would not be able to verify whether their partner is positive or on efficient antiretroviral therapy."

Consequently, the Swiss statement doesn't provide a 'licence to bareback' to gay men with undetectable viral loads (a misinterpretation that is feared by many prevention experts), although some gay men have been using viral load as a marker for infectiousness for some time. Some HIV advocates have characterised the Swiss statement as homophobic because it appears to hold true only for heterosexual couples and vaginal sex. The problem is that there are just not enough data on gay couples or on anal sex (which could, in itself, be characterised as homophobic).

However, during the research for this piece, we heard of two apparently robust as-yet unpublished case reports (one in the United States¹⁸ and one in Germany¹⁹) where HIV-negative gay men have apparently been infected with HIV that is very closely genetically related to that of their HIV-positive partners on ART with stable undetectable viral loads and no STIs.

In the German case, the HIV-positive partner had been undetectable for several years. "The positive partner was 100% sure he could not have infected his negative partner and assumed that his partner must have got infected outside the relationship," Cologne AIDS-Hilfe said in an email. "This was disavowed by the newly infected partner, and genetic analysis proved him to be right: the newly-infected partner's virus could only have come from his positive partner."²⁰

The case in the US is similar, except that the negative partner had admitted to unprotected oral sex with at least one partner of unknown status outside of the relationship. Was he more likely



I think we must be careful not to run before we can walk with this one. It is not saying 'ditch the condoms' but that, I fear, is one interpretation that some will place on it. For this reason alone - and it is a significant one - I would really like to see similar reviews conducted by other professional bodies such as BHIVA, and then consider their findings in the light of this. That being said, the implications here are highly significant. If used wisely by activists and campaigners, they can help mitigate the more odious anti-HIV/AIDS prejudices that put HIV in the same bracket as plague/leprosy/etc. It always was unusually difficult to acquire this virus, and now it appears to be even more so. It is a further step along the long road towards 'normalisation' and has the potential to be a liberating development.¹¹

Paul Clift, HIV-positive advocate

to have been infected by his undetectable regular partner than via oral sex with a man of unknown HIV status? Could the unknown partner have been carrying a strain of HIV similar to that of the infected man's regular partner?

However, looked at another way - as an additional safety net for 'safer sex', which is, of course, safer, but not safe - knowing that the risk of transmission is substantially lowered by effective treatment may reduce the anxiety felt by couples who do use condoms, but know that condoms can occasionally fail.

The Swiss statement may also have implications for future post exposure prophylaxis (PEP) guidelines. Professor Margaret Johnson, of London's Royal Free Hospital, tells *HTU* that the Swiss statement "opens the debate on issues like risk assessment for PEP," and whether partners of diagnosed HIV-positive people on effective treatment need to be routinely offered PEP in the event of accidental exposure.

Treatment as prevention

Although all of the epidemiological studies cited in the Swiss statement were in heterosexual couples, they do actually cite a study in gay men - the San Francisco Gay Men's Health Study - which found an association between lowered HIV incidence during the period of early potent ART (1996-1999)

compared with the period before early potent ART. However, although this suggested that viral load was lowered on a community level, it said nothing about the individual level of risk.

Interestingly, the authors of the study concluded that, "the benefit in reduced HIV transmission in the community due to widespread use of ART may be offset by increases in unsafe sexual encounters. Use of ART is a potentially important HIV prevention tool, one that is likely to succeed, however, only if accompanied by a continued emphasis on avoidance of exposure."²¹

In fact, by 2000, there was a documented significant increase in unsafe sex amongst gay men in San Francisco, and although more than 70% of gay men with a prior AIDS diagnosis were on ART in 2000²², the incidence of new HIV infections doubled from approximately 2% in 1998 to around 4% in 2000.²³

But recent data presented at the recent Retroviruses Conference (CROI) in Boston does suggest that ART - when used in combination with comprehensive sexual risk behaviour and adherence support programmes - is extremely effective at reducing transmission on a community level.

The study of more than 950 individuals in Uganda, including 62 serodiscordant heterosexual couples, found that ART cut the risk of HIV transmission by

91% over a three-year period. Although the husband of a female participant became HIV-positive within the first year of the study, there were no further seroconversions.²⁵ The exact timing of the man's infection is unknown, but his wife was known to have responded particularly slowly to ART, and had taken six months to achieve an undetectable viral load.

Interestingly, in this study, although sexual activity and sexual risk-taking initially declined, then increased to (rather low, compared with, for example, gay men in San Francisco) baseline levels after three years, the study found that the benefits of ART in reducing viral load appeared to outweigh the increases in sexual risk-taking. But what may hold true for one group of people (heterosexual and African) might not hold true for another (gay and Western).

At the recent CROI feedback session at the Royal College of Physicians, Dr Ian Williams of London's Royal Free and University College Medical School pointed out that the size of the effect ART had on prevention was greater than seen in any previous studies of a prevention technology - better than circumcision, better than microbicides, and certainly better than vaccines.

However, one thing that the authors of Swiss statement makes very clear is that they are "not for the time being, considering recommendations that

Neither the San Francisco AIDS Foundation nor the [San Francisco] Department of Health endorse the Swiss AIDS Commission statement, because: all of the studies involved heterosexual intercourse and may have little bearing on intercourse among men who have sex with men; HIV-positive people with apparently undetectable viral loads can experience occasional spikes in viral load; HIV-positive people who carefully follow their treatment regimen may develop viral resistance; people with other sexually transmitted infections can be asymptomatic yet still capable of transmitting or contracting HIV; and the Swiss report, since it did not use randomized, controlled studies, has not yet verified its causal conclusions.²⁴

SFAF/SFDPH Statement on the Swiss National AIDS Commission's report on HIV transmission



HIV-positive individuals start treatment purely for preventative reasons."

Still, there *are* hopes that treatment will become the next big prevention technology. Myron Cohen of the University of North Carolina told the 2006 Retroviruses Conference, in Denver, that he thought that treating people with HIV would, in the end, provide the biggest contribution to controlling the epidemic globally. He said he had been 'charged' by the National Institutes of Health to prove that ART could reduce transmission.

The result is HPTN052 - a randomised, seven-year study with participants on ARVs for five years. It will study 1,750 serodiscordant, heterosexual couples in eight sites in Malawi, India, Thailand, Zimbabwe, Brazil and the US, and the two arms will compare the rate of HIV acquisition in the partners of people who are immediately given ART on enrolment (when their CD4s are between 300-500 cells/mm³) with the rate in partners of people who are only given ARVs when their CD4 count hits 200 cells/mm³ (or higher if they receive an AIDS diagnosis). Infections will be compared by genotype to make sure they really are from the primary partner, and the study will have a 90% power to detect a 35% reduction in HIV transmission.

"We have no option but to study the effect of antiretroviral therapy on HIV transmission," said Dr Cohen. "To do otherwise would be total folly. We should have studied this when HAART came along, and we need to start the work that hasn't been done in the last ten years."²⁶

Even if HPTN052 provides robust evidence that treatment is indeed preventative, it is unlikely to mean that future protocols will recommend the use of treatment *alone* for HIV prevention. Rather, it is likely to be seen as one of the ingredients in a prevention 'cocktail'.

Nothing is risk-free

How we balance the knowledge that effective ART reduces the risk of sexual transmission with the truism that the only kind of sex that is risk-free is no sex at all, remains to be seen.

Bernard Hirshel was insistent that there shouldn't be one truth for the informed, and another for the masses. He's certainly made sure that more people than ever understand that treatment has an effect on transmission. Whether his audience appreciate the subtleties is another matter.

The debate on the risks of unprotected sex with a stable, undetectable viral load and no STIs, has only just begun. It joins longer-standing, but still unresolved, debates over how important the risks of reinfection are when two HIV-positive individuals have unprotected sex, and whether unprotected oral sex is an important route of HIV transmission. As the IAS's Craig McClure tells *HTU*, "The question of whether people living with HIV who achieve an undetectable viral load on antiretroviral therapy and are adherent to their prescribed medication should then be considered non-infectious is a controversial one. I have no doubt that this work is going to be the topic of continued debate in the months to come, including at the upcoming International AIDS Conference in Mexico City in August 2008."

For those of us who are HIV-positive, it would indeed be a wonderful relief to be told that we are no longer infectious under certain circumstances. However, the information we have gathered over more than 25 years of the HIV epidemic is that there is no such thing as zero risk. Deciding on how acceptable any sexual risk is, ultimately, is a personal decision, and ideally one that should be shared equally between you and your partner.

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