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The debate continues: does ‘undetectable’ mean ‘uninfectious’?

“Now that the Pandora’s box has been opened, we have to discuss the statement but we also need to learn more about the consequences.”

When the Swiss Commission on AIDS issued a statement in January last year, regarding the risk of sexual transmission of HIV under HAART, a multifaceted debate was launched that rapidly involved hundreds of individuals and institutions worldwide [1]. The issue under debate immediately polarized the scientific community as well as people living with HIV/AIDS (PLWHA). On one side there was a sound support from numerous people, especially from the PLWHA community. Infected individuals stated the report allowed them to no longer consider themselves as a threat to others. Such fears, as we learned, were much more common than anticipated.

On the other polarized side of the debate were individuals and public health officials who were concerned that the information could be wrongly misinterpreted as a signal indicating HIV-prevention efforts are no longer necessary. This worry is quite understandable. If, in fact, HIV-infected individuals were told not to be concerned at all and have no (shared) obligation to protect their partner, such information could have detrimental consequences.

When the debate began in February 2008 these two standpoints created opposite fronts that were difficult to bring together. However, over the past year we have learned that both fronts have legitimate concerns and that it is actually not only possible but also essential to combine the two positions in such a way that the statement can be used for future policy making and prevention efforts.

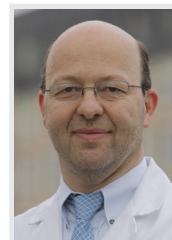
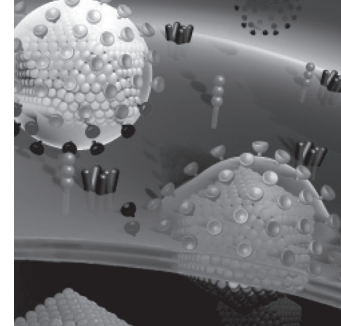
The original Swiss statement

However, at the beginning of the debate, quite some information about the statement was misleading. The CDC, as an example, issued a response to the Swiss statement on their internet pages with the title: “The risk is not zero!” In fact, this was exactly what the Swiss statement was all about: it clearly stated that the risk associated with

sex without condom under HAART is not zero. But it also made clear that the Swiss HIV physicians considered the risk to be in the same range as for condom protected sex (without treatment) and in the same range as other generally well-accepted risks of daily life. Some misleading interpretations might have resulted from the nature of the statement itself. It was issued by the Swiss Commission on AIDS to inform Swiss physicians and other professionals how to counsel HIV-positive patients and their partners. Thus, the original version of the text was in German and French. Abbreviated, non-official translations were unfortunately distributed that were part of the confusion.

The statement was delivered to Swiss physicians to help them discuss sexual risk-taking with their patients together with the steady partner. To understand the motivation for such a statement one also has to consider the counseling situation at the time. For the past few years, we have learned that the strongest determinant of transmission risk is the blood viral load. We have learned that reduction of blood viral load to undetectable levels during pregnancy and delivery prevents vertical transmission. Current Swiss guidelines for postexposure prophylaxis no longer proposed prophylaxis after unprotected sexual intercourse with a partner under fully suppressive antiretroviral therapy (sART).

The appreciation of this information by patients and physicians has led to a general perception that there is limited risk of HIV transmission under sART. Given the lack of standardized counseling, physicians informed their patients in a very unsystematic way about the limited risks of transmission. While some physicians assured their patients that unprotected sex was safe to conceive, others were much more conservative with their ascertainment. In the past, many patients and physicians felt that sART was associated with a limited risk of



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transmission. The Swiss statement made a more precise description of situations associated with sART that had theoretically a lower risk.

More specifically, the statement defined a status of negligible risk as a risk that is similar or smaller than many other risky situations of daily life. But more importantly, the statement clearly specified that it can only be the negative partner who decides how to deal with the limited or negligible risk of transmission under sART.

The basis of the Swiss statement regarding negligible risk was not only the epidemiological evidence obtained in the Rakai-partner project [2] or the biological findings of limited HIV-RNA detection in genital secretions under HAART; more importantly, the Swiss statement was based on the lack of documented case reports of HIV transmission under sART. We based our estimates on the fact that more than 300,000 patients have been under sART alone for more than 5 years in Europe. Our estimates were further based on the average sexual activity among couples of 2.5 times per month, a 20% rate of couples not adhering to safe sex recommendations and a report rate of one in a hundred for such a case of HIV-transmission under HAART. We concluded that the finding of no reported cases would lead to an upper confidence interval for the risk of transmission associated with unprotected sex of less than 1:100,000. This estimate confirmed the biological estimates using mathematical models [3]. Since a large proportion of unprotected sex acts in Europe occur among men having sex with men we did not restrict our statement to heterosexual contacts.

Despite the lack of documented cases of transmission under HAART the Swiss statement did make a distinction between situations with a higher or lower risk among all patients under sART. The statement was restricted to a very special situation where the risk was considered to be at the lowest: stable HIV RNA under less than 40 cp/ml for at least 6 months, no change in antiretroviral therapy, regular follow-up by a trained physician, perfect drug adherence and last but not least, absence of sexually transmitted diseases (STDs).

Notably, the STD was not included based on evidence for transmission under sART in the presence of STDs but rather because of its theoretic potential to increase transmission risk. Thus, the statement described a very well defined situation of lowest risk in order to limit potential harm if patients and physicians would continue to consider antiretroviral therapy in general as low risk.

The criticism

The major criticisms that were put forward against the Swiss statement could be grouped into three areas: one group of criticism focused on the basis of the evidence. Of course, we are deficient in definitive randomized, controlled trials to confirm our estimates. But given the fact that it will take another 7 years to get more definitive results [4] from a randomized study, there is no reason why we should not start to consult our patients and their partners in a standardized manner and give them advice that they could use in order to make their own decision today. For many couples who have already postponed their wish to conceive a child, the option to wait for another 7 years might be impossible.

The second criticism focused on the limitation of the epidemiological evidence on heterosexual transmission [2]. However, as mentioned above, the Quinn study was only one part of the issue. The lack of documented cases applies to all forms of sexual contact, including anal sex between men as well as among heterosexuals.

The third group of criticism came from individuals who were not principally opposed regarding the definition of the limited risk but who felt this information should not be delivered to the patients. It is a valid concern that the information about the infectiousness under HAART could be misconceived by some individuals. This concern was also shared by the Swiss commission. That is why the information was delivered primarily to physicians and other professionals. The commission felt it was important that all individuals involved in counseling were informed together, so that all professionals from different disciplines would give the same information to their clients. The commission further emphasized the importance of having only one valid version of information as opposed to the situation prior to the statement, where some physicians, other professionals, as well as some internet pages gave information to patients that was completely inconsistent with information obtained from other sources. The commission felt that inconsistent information is a poor guide for prevention measures.

Perhaps some evidence already lends support to this argument. Since the publication of the Swiss statement and the following debate, a large group of patients in Europe started to talk about the additional risk of STDs, a theme that was much less covered in the years before. In addition, an anonymous survey among HIV-infected patients in several Swiss HIV clinics indicated

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that the Swiss statement produced less behavioral changes than previously thought [5]. Among 134 patients who have heard about the statement, only 11 patients indicated that the statement resulted in change of their sexual behavior with their HIV-negative partner. Interestingly, four patients mentioned that they already had sex without a condom with their HIV-negative partner prior to the statement.

Our impression of much higher awareness of STDs in the HIV setting is only one additional collateral benefit among others. Some patients mentioned that they were much more motivated to maintain optimal adherence while some of the negative partners also indicated that they are now more vigilant about the patient's medication.

A further criticism was that it was too dangerous to communicate such information in resource-poor countries with high HIV incidence. We made very clear that our analysis was intended for Switzerland – a highly developed country with a low-level concentrated epidemic. In fact, at the Mexico World AIDS Conference, a call to increase the availability of antiretroviral therapy worldwide was made [101] – a positive echo to our statement. Currently, only 1 in 10 of the estimated 33 million HIV-positive people receive treatment. If everybody in need could receive a therapy and have a fully suppressed viral load, then new infections will dramatically drop, as a recent mathematical model demonstrated [6].

More evidence to support or reject the statement

The debate will continue on a scientific level. The Swiss statement provoked a number of studies. Wilson *et al.* presented a mathematical model that challenged the low risk of transmission in a partnership arguing that the cumulative risk of transmission might have been underestimated by the Swiss [7]. However, the model assumed several questionable assumptions [8]. One was that there is no threshold level for transmission. Second, the transmission risk is constantly increased 20-fold among homosexuals independent of blood viral load. Based on the authors' assumptions, transmission risk in the absence of HAART would be unrealistically high (1% transmission risk after a single anal sex act, over 60% risk after 100 anal sex acts) [8,9]. Furthermore, based on Wilson's assumption the risk of anal sex with a condom was higher than the risk with sART [9], which in fact is what the Swiss statement said ('similar risk').

In addition, more studies have been put forward to suggest that there might be detectable virus in the genital tract under sART, albeit at a very low level [10,11]. But other studies have not been able to support this observation [10,12,13]. These studies fail to discuss or examine the replicative capacity of these viruses. Coombs *et al.* have previously demonstrated absence of replication competent viruses in semen samples with an HIV-RNA concentration below 3.8 log₁₀ copies/ml [14].

Shortly after the Swiss statement, a case report of assumed HIV transmission under sART was published [15]. A partner of an HIV-positive patient who started antiretroviral therapy in 2000 was shown to be HIV-positive with the same virus in 2005. The partner claimed to have had a negative anonymous test performed more than a year after full suppression. However, this test result was not documented so the case lacks important documentation of the time of transmission, since the partnership already started just around the time of treatment initiation [16].

What's next?

The Mexico Manifesto that was published at the World AIDS Conference in July 2008 called for "the representatives of science, medicine, economy, governments and WHO and UNAIDS to recognize the Swiss Statement and not to suppress information" [102]. Now that the Pandora's box has been opened, we have to discuss the statement but we also need to learn more about the consequences. The statement has stimulated a significant number of research teams to improve and evaluate counseling in HIV prevention, to understand the consequences of exaggerated fears of transmission among PLWHA and also to investigate the risk of transmission associated with anal sex. We have learned that counseling must also include risk management and that reduction of stigma might in fact simplify HIV prevention efforts, including efforts for early diagnosis and treatment of HIV. However, 1 year after opening this box, we have not yet seen any clear disadvantage of doing so.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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