Towards a UK Consensus on ART and HIV Transmission Risk

Edwin J Bernard

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NAT, New City Cloisters, 196 Old Street, London EC1V 9FR
T: +44 (0)20 7814 6767 F: +44 (0)20 7216 0111 E: info@nat.org.uk

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Executive Summary

This briefing paper explores the impact of antiretroviral therapy (ART) on HIV transmission risk, highlighting key matters of clinical and scientific contention and exploring the policy implications of HIV treatment for HIV prevention on an individual and population level.

Chapters 1 and 2 examine the details of the Swiss National AIDS Commission's statement on individual risk of sexual transmission on effective ART ('the Swiss statement') as well as initial reactions from unilateral and multilateral public health authorities; the scientific community; and the communities of people living with HIV.

Chapter 3 explores subsequent national statements and guidance within Switzerland around the world, including Australia, Germany, France, the United Kingdom and the United States.

Chapter 4 examines the use of ART in combination with existing prevention methods in order to reduce new infections on a population level which is currently being studied around the world using four different models:

- Increased treatment uptake
- Increased testing with linkage to care and treatment based on clinical need
- Early versus deferred treatment
- Universal voluntary testing and treatment at any CD4 count

It also includes a discussion of the rationale and controversy behind the implementation of a version of the fourth model in San Francisco.

Chapter 5 examines key issues of clinical, social and scientific contention regarding the use of ART for prevention on an individual or population including:

- A lack of randomised controlled studies to show a direct correlation between reduced viral load due to ART and a reduction in new infections;
- The unknown threshold of viral load below which transmission cannot occur;
- The residual risks due to differences in viral load between the blood and sexual fluids, and variations in viral load between clinic visits;
- Incomplete data for anal sex and sex between men; and the
- Unknown impact on sexual behaviour.

Chapter 6 explores some of the policy implications of the impact of ART on HIV transmission risk for individuals and individual-focussed prevention and for public health/population-focussed prevention, and identifies some initial questions for consideration. Policy implications for assisted conception, criminal prosecutions, occupational restrictions and post exposure prophylaxis are also briefly discussed.

1. The Swiss statement

In January 2008, the Swiss National AIDS Commission (Eidgenössische Kommission für Aids-Fragen, EKAF) issued a statement in French and German[1] aimed at clinicians in Switzerland. It has since become known as 'the Swiss statement'.

The Swiss statement was co-authored by four of Switzerland's foremost HIV experts: Professor Pietro Vernazza, of the Cantonal Hospital in St. Gallen, and President of EKAF; Professor Bernard Hirschel from Geneva University Hospital; Dr Enos Bernasconi of the Lugano Regional Hospital; and Dr Markus Flepp, President of the Swiss Federal Office of Public Health's Sub-committee on the clinical and therapeutic aspects of HIV/AIDS.

This expert assessment of the biological, epidemiological and ecological evidence to date on the impact of reduced viral load due to ART on the individual risk of sexual transmission stated:

"An HIV-infected person on antiretroviral therapy with completely suppressed viraemia ("effective ART") is not sexually infectious, i.e. cannot transmit HIV through sexual contact."

It went on to say that this statement was valid as long as:

- *The person adheres to antiretroviral therapy, the effects of which must be evaluated regularly by the treating physician; and*
- *The viral load has been suppressed below the limits of detection (i.e. below 40 copies/ml) for at least six months; and*
- *There are no other sexually transmitted infections (STIs).*

Subsequent clarification has established the Swiss did not actually mean to state there is zero risk under these circumstances, but that the risk of HIV transmission is similar to the efficacy of condoms when having sex with an untreated individual. They have estimated the risk to be in the region of 1-in-100,000.[2]

The statement did not recommend any change in policy regarding the use of treatment to prevent new infections on a population level.

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[1] Vernazza P et al. *Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitment antirétroviral efficace ne transmettent pas le VIH par voie sexuelle.* Bulletin des médecins suisses 89 (5), 2008. [English translation. (including translator's affidavit) *HIV-positive individuals not suffering from any other STD and adhering to an effective antiretroviral treatment do not transmit HIV sexually* .]

[2] Bernard EJ. *Swiss statement that 'undetectable equals uninfectious' creates more controversy in Mexico City*. Aidsmap.com, August 5, 2008.

2. Initial reactions

Although never intended for an audience outside of Switzerland, the statement's contents were nevertheless quickly circulated globally[3] and immediately polarised the international public health and scientific community.

2.1 Initial public health response

The statement received immediate short shrift from unilateral and multilateral public health agencies – including the United States Centres for Disease Control and Prevention (CDC)[4], the Joint United Nations Programme on HIV and AIDS (UNAIDS) and the World Health Organization (WHO)[5] – concerned that the information could be wrongly misinterpreted as a recommendation that treatment should replace condoms as a prevention strategy.

2.2 Initial scientific response

Although there was general agreement that a reduced viral load due to ART greatly reduces the risk of HIV transmission, initial criticism from the international scientific community highlighted concerns regarding exactly under what circumstances an individual might be counselled (or consider themselves) to be effectively uninfectious.

These criticisms highlighted the residual individual risks that remain due to three essential areas of concern:

2.2.1 The potential for viral load in sexual fluids and the rectal lining to be greater than that measured in the blood due to:

- variability of individual antiretroviral drugs penetrating into genital and rectal regions;
- genital and rectal lining inflammation (notably caused by an infection with an STI, which is often unrecognised); and
- menstruation (in women).

2.2.2 The potential for small variations in viral load on an ongoing basis and the potential for a larger increase in viral load going unnoticed in the gap following treatment failure (due to systemic drug levels not being high enough caused by a variety of factors including poor adherence, poor gut absorption, and drug-drug interactions) and the next scheduled clinical visit .

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[3] Bernard EJ *Swiss experts say individuals with undetectable viral load and no STI cannot transmit HIV during sex*. Aidsmap.com, January 30 2008; Associated Press *AIDS experts: Unprotected sex OK for some*, January 31, 2008; IRIN. *GLOBAL: Positive people on ARVs not sexually infectious say experts,* February 1, 2008; Park A. *Are Some HIV Patients Non-Infectious?* Time, February 4, 2008.

[4] Press Release. *CDC Underscores Current Recommendation for Preventing HIV Transmission*, February 1, 2008.

[5] Press Release. *Antiretroviral therapy and sexual transmission of HIV*. UNAIDS/WHO, February 1,2008.

2.2.3. Limited data regarding the links between viral load in the rectal lining and the blood, and the inherently higher HIV transmission risks of anal sex.

2.3 Initial community response

Leaders of communities of people living with HIV cautiously welcomed the statement, with some considering it a "pivotal" and "liberating" moment.[6]

Positive responses highlighted:

- the stigma-reducing aspects of reduced infectiousness, including the positive impact this may have on testing, uptake of treatment and on legal frameworks that criminalise HIV exposure/transmission;
- the potential for couples of different HIV status to have children in the absence of access to assisted reproduction methods such as IVF and sperm washing;
- reducing unrealistic fears of transmission for sexual partners with different (or unknown) HIV status when condoms fail if the HIV-positive partner is on effective ART;
- the recognition that people living with HIV and their partners are able to appreciate and understand individual transmission risks beyond overly simplistic 'condom only' guidance.

The statement also brought concern by some advocates of communities of people living with, and at risk of HIV, however. These concerns highlighted:

- the limited number of people living with HIV who actually fulfilled the strict criteria of the Swiss statement
- the potential to confuse current safer sex messages;
- the impact on individuals (notably women, who may be unable to negotiate condom use) with HIV who prefer to continue to use condoms with HIV-negative partners;
- the potential to create a perception that sexual and reproductive health is perceived only in terms of HIV transmission risk;
- the lack of guidance for gay men and injecting drug users.

Many of the above public health, scientific and community concerns are analysed in greater detail in **Chapter 5: Key matters of scientific, clinical and social contention**.

[6] Quoted in Bernard EJ. *Does undetectable really mean uninfectious?* HIV Treatment Update, April 2008.

3. Subsequent national statements and guidance

Following the Swiss statement, a number of national HIV organisations in well-resourced countries around the world have produced their own statements on the impact of ART on individual transmission risk and/or produced counselling guidance for individuals that highlighted this issue.

3.1 Individual counselling guidance in Switzerland

The week of the publication of the Swiss statement, EKAF provided more detailed guidance for physicians and other healthcare workers and community-based counsellors in collaboration with the civil society organisation, Swiss AIDS Federation (Aids-Hilfe Schweiz) about how to counsel people with HIV in Switzerland as regards the impact of ART on their individual infectiousness and how to reduce their risk of HIV transmission in ways other than 100% condom use.[7] The guidance covered detailed information covering a variety of situations.

3.1.1. Couples of different HIV status are required to undergo intensive couples counselling regarding the risks and benefits of unprotected sex when the HIV-positive partner is on effective ART.

- Physicians should deliver detailed information (covering preconditions for potent ART, medical check-up frequencies, residual risks, STIs, contraception) to both partners.

- Further information regarding psychological issues, ART adherence issues, the legal situation, and shared responsibility within the partnership for HIV transmission (although it also stressed that the HIV-negative partner should make the final decision to forgo condoms possibly due to concerns over Swiss public health and criminal law which places 100% responsibility for safer sex on the HIV-positive partner) should be delivered as part of community-based counselling.

- When having sex outside of the relationship with casual contacts, anonymous sex or in a new relationship where neither is certain of the other's HIV status, condoms should still be used.

3.1.2. HIV-positive couples are required to undergo similar couples counselling to couples of different HIV status with the added discussion of reinfection risk and a focus on shared responsibility for deciding whether or not to forgo condoms.

3.1.3. HIV-positive, HIV-negative or untested individuals who are having sex outside of relationships should be counselled to continue to rely on condom use to protect themselves. The counselling guidelines highlight that

[7] Swiss AIDS Federation. Advice Manual: 'Doing without condoms during potent ART' January 30, 2008.

individuals are responsible for their own protection in such circumstances and cannot rely on the credibility of information they receive from their sexual partners regarding serostatus, therapy and its success.

3.2 Australasian statement

In July 2008 a joint statement by the Australian public health agency (National Centre in HIV Epidemiology and Clinical Research), an Australasian HIV clinicians association (Australasian Society for HIV Medicine) as well as two civil society organisations representing people with HIV (Australian Federation of AIDS Organisations and National Association of People Living with HIV/AIDS) summarised the available knowledge on the effect of treatment on transmission and weighed the pros and cons of making a public statement that encourages individuals with an undetectable viral load to forego condoms under certain circumstances.

Focusing primarily on the public health risks, as opposed to providing an individual risk-benefit analysis as per the Swiss statement, it concluded that, “for the present and in light of our current knowledge, safe sex (*sic*) is the only way to prevent HIV spread. Safer sex includes correct and consistent male and female condom use, and early and effective detection and treatment for STIs."

3.2.1. Australian mathematic model and UK editorial response

The Australasian statement was accompanied by the publication in *The Lancet* of a mathematical model from the National Centre in HIV Epidemiology and Clinical Research highlighting the public health implications if their assumptions and calculations were to hold true. The model assumed that HIV transmission is possible at any viral load, rather than assuming, like the Swiss, that there is a threshold below which transmission cannot occur. It compared the residual transmission risk of a viral load below 10 copies/ml on ART *plus* condoms with a viral load below 10 copies/ml on ART *minus* condoms over ten years and 10,000 serodiscordant couples.

Their findings suggested that if condoms were abandoned by all couples where the HIV-positive individual was on effective ART there would be "an increase in incidence of four times compared with incidence under current rates of condom use.”[8] They concluded: "Although we agree that effective antiretroviral treatment which leads to undetectable viral load is likely to have a substantial effect on reducing infectiousness, our analyses suggest that it should not replace condoms.” EKAF President, Pietro Vernazza, criticised the model's assumptions as "biased".[9]

In the discussion section of *The Lancet* paper, however, the model's authors point out that “under our assumptions, the effectiveness of treatment in reducing the risk of HIV transmission per sexual act was about the same as

[8] Wilson DP et al. *Relation between HIV viral load and infectiousness: a model-based analysis.* Lancet 372: 314-20, 2008.
[9] Vernazza P. *HIV-Transmission under HAART - Lancet study rather supports "Swiss Statement" than challenging it.* Infekt.ch, July 25, 2008

has been reported for condoms." An editorial in same issue of *The Lancet*[10] by two highly respected UK clinicians, Professor Geoffrey Garnett and Professor Brian Gazzard, notes that the model did not compare ART plus condoms with condoms alone. They highlight this finding through the use of a table that compares the model's assumptions with 80% and 100% condom use. This is relevant because a meta-analysis of real-life epidemiological studies in heterosexuals show that even 100% condom use probably reduces the risk of HIV transmission by around 80% compared to not using condoms (i.e 100% condom use results in 80% efficacy). This is because condoms can fail or slip off.[11] Limited data suggest that condoms have similar efficacy in gay men.[12]

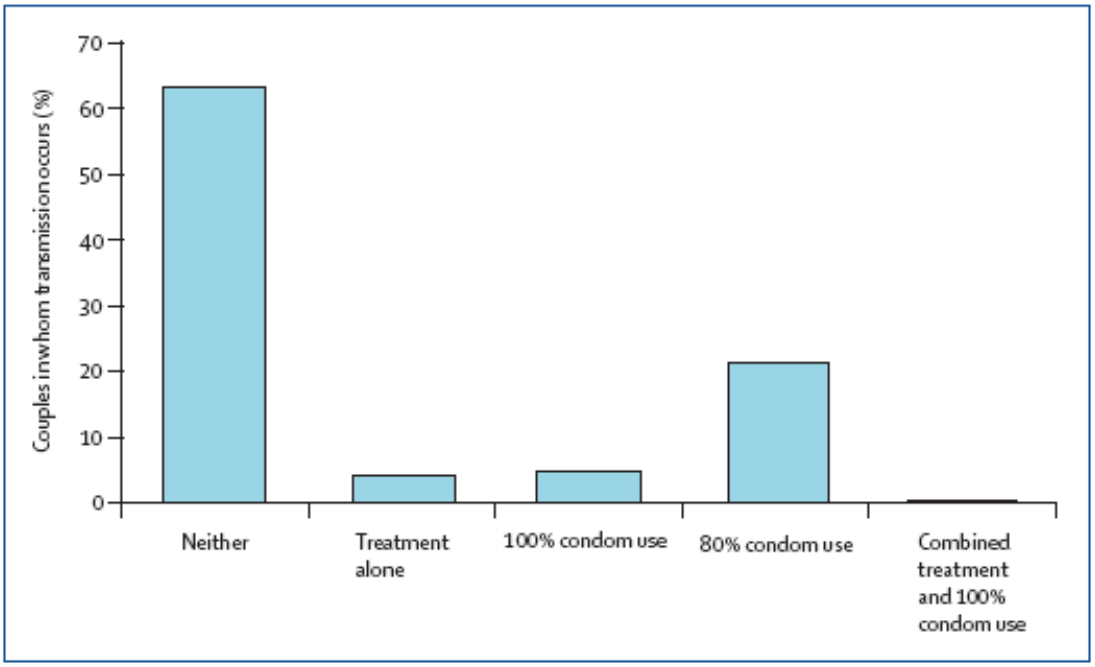

Figure 1: Risk of HIV transmission over 100 sex acts during anal sex where one partner is HIV-positive

Figure 1 (above) adapted from data in the National Centre in HIV Epidemiology and Clinical Research mathematic model, compares the risk over 100 sex acts of HIV transmission during anal sex between men where one partner is HIV-positive: with condoms; with an undetectable viral load on HIV treatment; with both; and with neither. The table illustrates that an undetectable viral load on ART is likely to be as effective in reducing HIV transmission risk as 100% condom use without ART and that combining the two almost eliminates any residual risk.

“Denying an effect of treatment on risk of transmission would be dishonest and futile, because well-informed patients will assume an effect,” write Professors Garnett and Gazzard who welcome the Swiss statement. “In many

[10] Garnett GP and Gazzard B. *Risk of HIV transmission in discordant couples.* Lancet 372: 270-71, 2008.
[11] Weller SC and Davis-Beaty K. *Condom effectiveness in reducing heterosexual HIV transmission.* Cochrane Database of Systematic Reviews Issue 1, 2002.
[12] Condom efficacy in gay men, HIV transmission and testing, NAM, 2009.

ways," they argue, "the Swiss statement provides the opportunity for positive public health messages, by promoting adherence to treatment and concern over other sexually transmitted infections. The use of condoms, in addition to antiretrovirals, to further reduce risk and prevent other sexually transmitted infections can then also be promoted."

3.3. German civil society response

Deutsche AIDS-Hilfe (DAH), the largest HIV voluntary sector organisation in Germany issued a position paper in April 2009 which broadly echoed the Swiss statement. Notable, however, is the lack of endorsement by the public health agency (Robert Koch Institute) or expert HIV clinicians. It is believed that such stakeholders were originally part of discussions, but withdrew because they could not agree with DAH's position.

To correspond with the demographics of the German HIV epidemic, DAH focuses more attention on anal sex and sex between men. The paper acknowledges that there are few available data on the effect of viral load on transmission risk during anal sex and sex between men, states that such evidence is unlikely to be produced in the foreseeable future and argues that it is logical to assume that gay men on effective treatment also experience dramatic reductions in their infectiousness. However, it highlights the rare case report[13] of a German man who was apparently infected by his long-term male partner while the partner was maintaining an undetectable viral load on ART and had no STIs.

Nevertheless, the position paper describes HIV transmission on effective ART as "improbable", comparable to the consistent use of condoms, and argues for a "realistic" HIV prevention approach, recognising a balance of risk reduction against sexual desires, and suggesting that individuals can make their own decisions depending on their own circumstances and priorities.

In addition to STIs, the main cause of genital and rectal inflammation, the paper draws attention to other causes of damage to mucosal surfaces such as anal or vaginal fistulas or chronic gastro-intestinal diseases that can affect the lower end of the large intestine such as ulcerative colitis or Crohn's disease.

3.4. Conflicting French statements

Within a week of each other, two expert bodies in France provided conflicting statements regarding the impact of treatment on infectiousness on an individual level and on prevention on a population level.

[13] Sturmer M et al. *Is transmission of HIV-1 in non-viraemic serodiscordant couples possible?* Antiviral Therapy 13: 729 – 732, 2008.

3.4.1 On April 30th, the Conseil National du Sida (CNS) issued a position paper essentially supporting the science behind the Swiss statement but stressing the residual risk for individuals that remain (previously explored in section 2.2.). The paper additionally highlighted some of the policy repercussions if ART were to be used for prevention purposes on a population level.

This included concern that:

- ART used for prevention may reframe shared responsibility for HIV prevention and imply that the HIV-positive partner "wholly bears the responsibility to contain the risk for the other";
- coercion may be introduced into HIV testing and treatment; and
- ART may replace condoms as a prevention tool rather than being offered in addition to condoms and other 'combination prevention' methods.

3.4.2 On May 7th, the French government's public health department, Direction générale de la santé (DGS), issued a press statement responding to the CNS position paper undermining much of its support for treatment as prevention on both an individual and population level. The DGS stated that the CNS position would instead feed into an expert review of HIV prevention strategies.

The DGS insisted that only male or female condom use could guarantee maximum protection against HIV and other STIs, and stressed that condoms must be used consistently during casual sex or when the HIV status of a stable partner was not known.

It also stressed the lack of evidence of ART's effectiveness in preventing transmission during anal sex and in sex between men and additionally highlighted the increased risks of resistance due to non-adherence should treatment be offered to individuals for its public health impact and if they do not require for their own health. However, it supported the CNS' position that early detection of HIV-positive status as one of the pillars of HIV/STI prevention.

3.5 UK guidelines for the sexual and reproductive health (SRH) of people living with HIV

Published in October 2008[14], guidelines on the sexual and reproductive health (SRH) of people with HIV, produced by the British HIV Association (BHIVA), the British Association of Sexual Health and HIV (BASHH) and the Faculty of Sexual and Reproductive Health of the Royal College of Obstetricians and Gynaecologists (FSRH), include a section discussing some of the individual HIV transmission risk issues raised by the Swiss statement.

[14] Fakyoa A, et al. *British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008.* HIV Medicine 9 (9), 2008.

The short section addressing the Swiss statement acknowledges the "compelling evidence" concerning effective ART reducing individual risk for vaginal or oral sex, but notes that the writing committee "cannot fully endorse the Swiss consensus statement" for anal sex due to a lack of scientific evidence.

It recommends that detailed individual counselling focusing on harm reduction (rather than harm elimination) should be available for all HIV-positive individuals in long-term relationships who wish to consider unprotected sexual intercourse with people of the same or different status relationships, for example, for the purposes of natural conception. However, in most circumstances, counselling and advice should continue to promote the use of condoms to reduce the transmission risk of HIV and other STIs.

(The entire relevant section of the 2008 BHIVA, BASHH, FSRH guidelines on the sexual and reproductive health of people with HIV are reproduced in the Appendix.)

3.6 Department of Health Expert Advisory Group (EAGA)

The Swiss statement and its repercussions have been discussed in great detail by EAGA. Although minutes of the two meetings discussing this topic are in the public domain[15], no public statement has been made.

3.7. CDC Guidance on ART and its Effect on Sexual Transmission of HIV

In August 2009, the United States Centres for Disease Control and Prevention (CDC) issued a statement clarifying its initial brief response to the Swiss statement on individual risk, and discussing the population benefits of treatment as prevention.

While recognising that "treatment of the infected partner with effective ART and suppression of viral load to undetectable levels should greatly reduce the risk of transmission to the uninfected partner" it stresses that "this risk is not eliminated" and "it is important that individual couples recognize the risk, and use additional preventive methods (e.g., condoms) in order to further minimize the chance of transmission." It also recommends condoms for HIV-positive couples to reduce the risk of reinfection (also known as superinfection).

Nevertheless, the CDC notes that "clinicians may consider the potential benefit of decreased risk of HIV transmission to others in deciding whether to initiate ART in infected patients (even at CD4 counts of >350 cells/μL)."

[15] EAGA 81 Public minutes. MINUTES OF THE 81st MEETING OF THE EXPERT ADVISORY GROUP ON AIDS, 11 JUNE 2008; EAGA 82 Public minutes. MINUTES OF THE 82nd MEETING EXPERT ADVISORY GROUP ON AIDS, 5 November 2008.

In addition, the CDC is more upbeat regarding the use of treatment for prevention on a population level:

> *"Use of ART may be a promising tool for slowing the transmission of HIV within populations if prevention benefits are not offset by increases in risk behavior. Success of such a program will depend critically upon 1) widespread testing and early identification of infected persons, 2) ongoing counseling to support maintenance of safer sexual behaviors , 3) adequate clinical follow-up to monitor for adverse effects of ART, and 4) geographic and financial accessibility of treatment for affected persons."*

4. Treatment as Prevention

The CDC guidance reflected a major global policy shift in population-based HIV prevention strategies, one that emerged from the XVII International AIDS Conference held in Mexico City in August 2008. Since then there has been increasing recognition – first postulated eight years earlier in a mathematical model that suggested increasing ART uptake in San Francisco could substantially reduce new infections as long as HIV risk behaviour did not increase[16] – of the potential of ART to greatly reduce HIV transmission on a population level.

In November 2008, prominent members of staff of the World Health Organization (WHO) published a theoretical mathematical model in the *Lancet*[17] that examined the potential impact of universal voluntary HIV testing followed by immediate ART, irrespective of clinical stage or CD4 count. The model assumed that treatment in combination with current prevention methods would greatly reduce new infections, and concluded that transmission could be reduced 100-fold in a heterosexual epidemic of southern African severity and eventually reduce HIV prevalence to less than 1% within 50 years.

An international consultation on ART for HIV prevention convened by WHO in November 2009,[18] featured the latest research on the impact of ART on a population level including new data from Vancouver (publically presented at major scientific meeting in February 2010) that appeared to show an association between increased ART coverage and a lower 'community viral load' resulting in reduced HIV incidence.[19]

The consultation heard that a potential benefit of such an approach would be earlier access to treatment for people living with HIV in resource-limited settings. However, 'universal' voluntary HIV testing would be a major challenge that could not be achievable without changes in both policy and social conditions. Representatives of people living with HIV stressed the potential for human rights violations in the absence of a supportive policy and legal environment, such as involuntary testing and/or treatment for

[16] Blower SM et al. *A tale of two futures: HIV and antiretroviral therapy in San Francisco.* Science 2000; 287: 650-654

[17] Granich RM, Gilks CF, Dye C, et al. *Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.* Lancet 373 (9657); 48 - 57, 2009.

[18] Agenda and presentations available at: http://www.who.int/hiv/events/artprevention/en/index.html

[19] Montaner J et al. *Association of expanded HAART coverage with a decrease in new HIV diagnoses, particularly among injection drug users in British Columbia, Canada*. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 88LB, 2010.

marginalised and/or disempowered populations, including pregnant women, men who have sex with men, sex workers and people who use drugs.[20]

The consultation also heard that the scale-up of both testing and treatment would require a substantial and sustained scale-up of infrastructure and resources. Such an approach would also rely on a lifetime of ART adherence, which may not be sustainable for individuals, or for countries' healthcare systems.

The meeting was welcomed in a statement by the International AIDS Society[21] that recognised the benefits of such an approach in galvanising a renewed commitment towards universal access. A statement from UNAIDS focused on how such an approach might impact individuals living with, and at risk of, HIV and reiterated:[22]

> *"Antiretroviral therapy will play several roles in combination prevention strategies, along with other key strategies including, but not limited to, social and behavioral change communication to delay sexual debut, promote mutual fidelity and reduction of the number of sexual partners, promote safer sex including correct and consistent male and female condom use, harm reduction programmes for people who use drugs, prevention of vertical transmission, and other biomedical, behavioural and structural prevention programmes."*

At the XVIII International AIDS Conference held in Vienna in July 2010, UNAIDS proposed a new strategy known as Treatment 2.0[23] which includes treatment as prevention as one of its five pillars (see figure 2). It suggests that simpler, cheaper and less-toxic treatment would increase access to the many people who are currently in need of treatment in low- and middle-income countries. It assumes that filling the treatment gap would also result in significantly fewer new infections:

> *"Treating everyone in need of treatment according to the current treatment guidelines could result in a one third reduction in new infections globally."*

[20] Press Release. *Statement on ART as Prevention: Scaling down HIV requires scaling up human rights, testing and treatment*, ICASO, October 2009.
[21] Press Release. *IAS URGES NEW FOCUS ON ART AS PREVENTION, CALLS FOR IMMEDIATE GLOBAL ACTION AND FUNDING FOR UNIVERSAL ACCESS TO HIV THERAPY*, November 4, 2009.
[22] Press Release. *Antiretroviral treatment for prevention*, UNAIDS, November 6, 2009.
[23] UNAIDS. *Treatment 2.0 - Is this the future of treatment?* UNAIDS Outlook, July 2010.

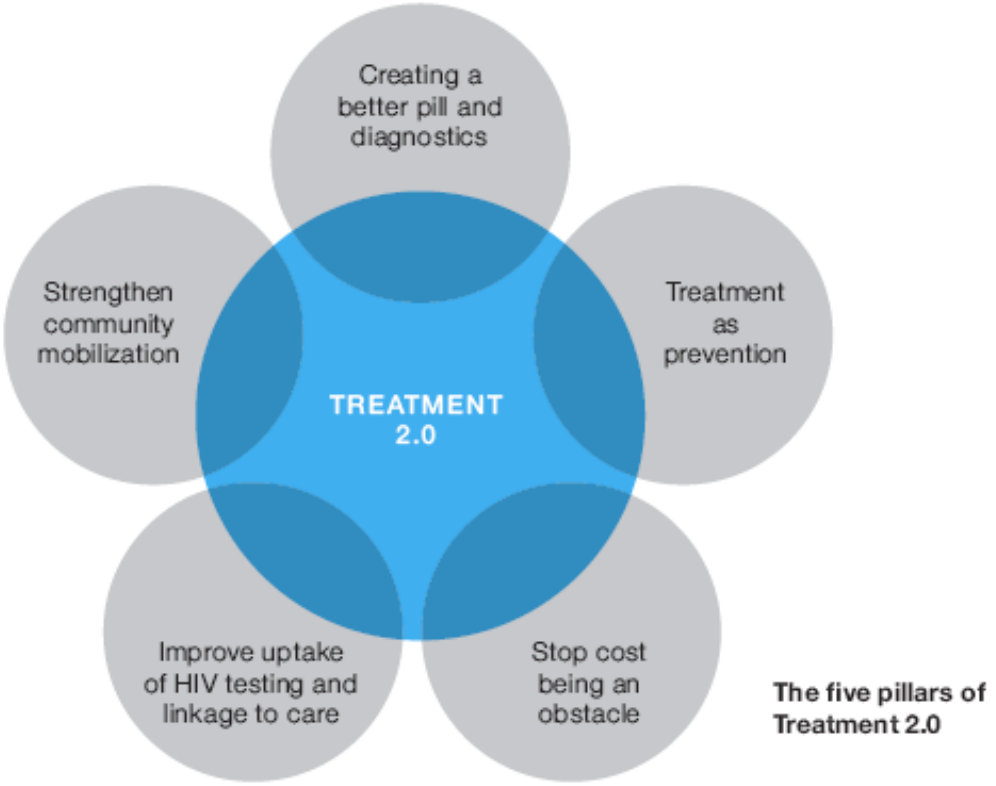

Figure 2: The five pillars of Treatment 2.0 Source: UNAIDS

4.1 Treatment as prevention models

The use of ART in combination with existing prevention methods in order to reduce new infections on a population level is currently being studied around the world. There are, in fact, four different models of such an approach:

- Increased treatment uptake
- Increased testing with linkage to care and treatment based on clinical need
- Early versus deferred treatment
- Universal voluntary testing and treatment at any CD4 count

4.1.1 Increased treatment uptake

Even in settings – such as Canada and the United Kingdom – with universal, free access to HIV treatment, not all individuals who have previously tested HIV-positive remain in care and access and adhere to ART based on national treatment guidelines. A strategy to increase treatment uptake under these circumstances, commonly known as 'seek and treat', is thought to have benefits for both individual and public health.

A pilot study, STOP HIV & AIDS (Seek and Treat to Optimally Prevent HIV & AIDS), by the British Columbia Centre for Excellence in HIV/AIDS, supported by the US National Institute for Drug Abuse, is underway in Vancouver to assess the impact on new infections over five years by increasing treatment

uptake in hard to reach populations including people who use drugs.[24] The impact on the health of individuals with HIV targeted under this strategy will be secondary endpoints of the study.

4.1.2 Increased testing and linkage to care with treatment based on clinical need

Previous studies from the CDC have concluded that untested individuals are the most significant source of new infections and are more likely to engage in sex that risks transmission than those who know their status and are accessing care and treatment.[25] [26] A strategy to increase knowledge of HIV status with linkage into care and treatment, previously known as 'Test and Treat' (TNT) but now characterised as Testing & Linkage to Care Plus (TLC+) following community consultation[27], is also thought to have benefits for both individual and public health.

Two high prevalence sites in the United States – the Bronx and Washington DC - have been chosen by the US Federal Government for a pilot study for such an approach. The study has four components:

- Expanding HIV testing
- Strengthening linkages with care allowing for prompt ART initiation according to current DHHS guidelines
- Promoting adherence to maximise viral suppression
- Decreasing high-risk sexual behaviour based on the CDC's 'prevention for positives' model.

4.1.3 Early versus deferred treatment

One of the patient-centred concerns regarding treatment as prevention is the optimal CD4 count to initiate treatment which appropriately balances the needs of both individual and public health.

HPTN052 is an international, randomised, seven-year study taking place in eight low-and middle-income countries as well as in Boston, USA.[28] 1750 individuals with HIV who are partnered with an HIV-negative individual have been enrolled. The two arms of the study will compare the rate of HIV acquisition in the partners of people who are immediately given antiretrovirals on enrolment (when their CD4 count is between 350 - 550 cells) with the rate in partners of people who are only given ART when their CD4 counts decline to between 200 - 250 cells.

The trial enrolled prior to the updated WHO treatment guidelines which now recommend treatment at 350 cells. Results are not anticipated until 2014 and

[24] British Columbia Centre for Excellence in HIV/AIDS website
[25] Marks G et al. *Meta-analysis of high-risk sexual behaviour in persons aware and unaware they are infected with HIV in the United States.* JAIDS, 39(4):446-53, 2005.
[26] Marks, G et al. *Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA*. AIDS 20(10):1447-50, 2006
[27] Press Release. *Project Inform and CHAMP lead Think Tank to develop an integrated approach to HIV testing, linkage to care & treatment to further control US epidemic.* December 14, 2009
[28] HIV Prevention Trials Network website

not enough gay couples have enrolled in the study for any meaningful results for anal sex.

4.1.4 Universal test and treat at any CD4 count

The concept of 'universal test and treat', as proposed in the mathematical model by WHO staff will be tested in two feasibility studies currently in preparation: PopART[29] in Uganda and Zambia and TasP in South Africa. These cluster-randomised trials to 'test and treat' entire communities and begin ART at any CD4 count will examine the impact on reducing community viral load, incidence of new infections, cost-effectiveness and safety.

4.2 'Treatment as prevention' implementation

A population-based 'treatment as prevention' approach is currently being implemented in San Francisco, although it is not being labelled as such by its implementers. In addition, STOP AIDS NOW! a partnership between Aids Fonds and four Dutch organisations providing international development aid is proposing to implement a 'universal test and treat' programme in Africa with funding from the Clinton Foundation.[30]

4.2.1 San Francisco: rationale and controversy

In March and April 2010, the San Francisco Department of Public Health (SFDPH) announced new HIV prevention[31] and treatment[32] policies for the city. The prevention goal is focused on increasing testing frequency for key populations – primarily gay men – to every six months with most of its budget being used to scale-up testing and for its 'prevention with positives' programme. In a radical move, no part of the HIV prevention budget is aimed at HIV-negative men. The treatment goal is to treat everyone who tests HIV-positive regardless of their CD4 count.

The prevention policy is based on emerging data from San Francisco which found an association between reduced HIV incidence as individuals commenced ART, thereby reducing community viral load,[33] and mathematical modelling that predicts a 91% reduction in new infections over ten years if such a policy were implemented.[34]

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[29] Imperial College London website
[30] Personal communication, unpublished.
[31] Hemmelgarn S. *HIV prevention effort shifts to 'status awareness'.* Bay Area Reporter, March 25, 2010. http://ebar.com/news/article.php?sec=news&article=4652
[32] Highleyman L. *SF health officials advise early treatment for people with HIV*. Bay Area Reporter, April 15, 2010. http://ebar.com/news/article.php?sec=news&article=4709
[33] Das-Douglas M et al. *Decreases in Community Viral Load Are Associated with a Reduction in New HIV Diagnoses in San Francisco*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 33, Feb 2010.
[34] Charlebois E et al. *Effect of Expanded ART Strategies on the MSM HIV Epidemic in San Francisco*. Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 33, Feb 2010.

Current treatment guidelines from the US Department of Health and Human Services (DHHS)[35] and the International AIDS Society - USA Panel[36] recommend treatment for everyone with a CD4 count below 350 and strongly encourage treatment at CD4 counts below 500; treatment is considered optional for those with CD4 counts over 500 due to unresolved concerns regarding the individual health risks and benefits of commencing treatment at higher CD4 counts. The Strategic Timing of Antiretroviral Treatment (START) study, conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), currently enrolling at 90 sites in nearly 30 countries, seeks to answer this question.

While SFDPH officials are recommending treatment at CD4 counts over 500 as a benefit to an individual's health, they are underselling the potential of such a policy on reduced transmission risk on a population level, and do not appear to be counselling individuals about the potential for treatment to reduce individual transmission risk,[37] which some advocates consider disingenuous.[38] "An undetectable viral load on an individual level reduces the risk of transmission—this is supported by the data. But rolling out early treatment as a public health policy is different. An individual taking treatment primarily has to derive personal benefit, given that they face an individual risk from treatment. The discussion for individual treatment and public health cannot just be lumped together," argues Simon Collins of HIV-iBase and START's Community Advisory Board (CAB).[39]

[35] Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* Department of Health and Human Services. December 1, 2009.
[36] Thompson MA et al. *Antiretroviral Treatment of Adult HIV Infection 2010 Recommendations of the International AIDS Society–USA Panel.* JAMA 304 (3), July 21, 2010
[37] Highleyman L. *SF health officials advise early treatment for people with HIV.* Bay Area Reporter, April 15, 2010.
[38] Strub S. *Medical ethics and the rights of people with HIV under assault*. Poz Blogs, April 28, 2010.
[39] Quoted in Horn T. *Start Wars*, POZ Magazine, May 5 2010.

5. Key matters of scientific, clinical and social contention

The use of treatment as prevention on an individual or population level remains controversial due to the following concerns:

- Lack of randomised controlled studies to show a direct correlation between reduced viral load due to ART and a reduction in new infections
- Unknown threshold of viral load below which transmission cannot occur
- Residual risks due to differences in viral load between the blood and sexual fluids
- Residual risks due to variations in viral load between clinic visits
- Incomplete data for anal sex and sex between men
- Unknown impact on sexual behaviour

5.1 Lack of randomised controlled studies to show a direct correlation between reduced viral load due to ART and a reduction in new infections

HPTN052, with results due in 2014, will be the first randomised controlled study to show if there is a direct correlation between ART reducing viral load and individual transmission risk. Currently, all studies examining ART's impact on new infections that have been published or presented at conferences are limited because they are either prospective, observational or not originally designed to measure the impact of ART on transmission.

In 2009, Attia and colleagues undertook a meta-analysis of all studies to date that had estimated the impact of viral load on transmission risk. The meta-analysis confirmed that a high viral load can significantly increase the risk of transmission, and that a low viral load significantly reduces the risk. They calculated that out of 1,000 HIV-positive individuals with a viral load *below 400 copies/ml* regularly engaging in vaginal sex with an HIV-negative partner, only one transmission could be expected to occur in the course of a year. In contrast, among 1,000 HIV-positive individuals with a viral load *above 50,000 copies/ml*, at least 90 transmissions could be expected to occur in the course of a year.

Only a small proportion of these studies included individuals with an undetectable viral load due to ART. For these studies, they calculated that with zero transmissions over a total of 291 person years of follow-up, the transmission rate was zero, but state that “the data were also compatible with one transmission per 79 person-years”, based on their upper 95% confidence limit of 1.27 per 100 person-years.[40]

[40] Attia S et al. *Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis.* AIDS 23 (online edition), 2009.

Castilla and colleagues recently published an update to an earlier study (included in the above meta-analysis) that observed no transmission where the HIV-positive partner was on antiretroviral therapy with a viral load below 50 copies/ml.[41] In this update, which observed 648 heterosexual couples between 1989 and 2008 during regular clinic visits, in the 149 couples where the HIV-positive partner was on ART no HIV transmission was observed, compared to a rate of transmission of 9.2% among partners of untreated patients.[42]

The most recent study to report on the preventative effect of ART was presented at a major scientific meeting in February 2010[43] and published in *The Lancet* in May 2010.[44] The main purpose of the trial, which involved 3,381 heterosexual couples in Africa in which one partner was HIV-positive and the other negative, was to investigate the impact on HIV transmission of suppressing herpes simplex virus infection with aciclovir. This *post hoc* analysis looked at the number of HIV transmissions according to whether or not the HIV-positive partner was on ART. Out of 103 cases of transmission that were documented, 102 occurred in couples where the positive partner was not using ART. In the remaining case, ART had only very recently been initiated. This was equivalent to a 92% reduction in the risk of transmission, the highest ever recorded of any prevention method.

Reaction to the results of this study have been very positive. A recent joint statement by UNAIDS and the United Nations Development Programme (UNDP) to the Human Rights Council[45] not only highlights the results of this study but also refers, uncritically, to the Swiss statement in footnote that follows the phrase "even greater impacts for individuals":

> *"It is even more critical to get those living with HIV on treatment as the latest science shows that treatment reduces HIV transmission by 92% at the population level, and can have even greater impacts for individuals."*

The study was also referred to in UNAIDS' proposed new treatment paradigm, Treatment 2.0 (see: 4. Treatment as Prevention, above).

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[41] Castilla J et al. *Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV*. J Acquir Immune Defic Syndr 40: 96-101, 2005.
[42] Del Romero G et al. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. BMJ 2010;340:c2205.
[43] Donnell D et al. *ART and risk of heterosexual HIV-1 transmission in HIV-1 serodiscordant African couples: a multinational prospective study.* Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 136, 2010.
[44] Donnell D et al. *Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis*. Lancet 375 (9731): 2092-2098, 2010.
[45] *Statement by the Secretariat of the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the United Nations Development Programme (UNDP)*
14th Session the Human Rights Council, June 7, 2010

5.2 Unknown threshold of viral load below which transmission cannot occur

It is currently unknown whether there is a viral load threshold below which transmission is not possible. The Swiss statement refers to a viral load below the limits of detection (40 copies/ml) but elsewhere assumes a blood viral load threshold of 1000 copies/ml below which transmission is extremely unlikely to occur.

If this lower threshold does not exist, an Australian mathematical model suggests that over time this would result in a low but definite number of transmissions within a monogamous partnership even if the HIV-positive individual on ART achieved a viral load of 10 copies/ml. [46]

Other studies have used the threshold of 400 copies/ml. Attia and colleagues' meta-analysis estimated that the transmission rate for people with a blood plasma viral load below 400 copies/ml is 0.16 per 100 person years. The lowest threshold of sexual transmission (in an individual not on ART) included in the meta-analysis occurred at a viral load of 362 copies/ml.

5.3. Residual risks due to differences in viral load between the blood and sexual fluids

Most studies conducted so far have shown that the majority of men and women successfully treated with antiretrovirals experience parallel declines in viral load in both the blood and sexual fluids.[47] [48]

However, a minority of the men and women in these studies had more HIV in their sexual fluids than in their blood. This may be due to:

- drug levels not being high enough in sexual fluids;
- inflammation (notably caused by an infection with an STI);
- in women, menstruation.

5.3.1 ART penetration into genital compartments

Recent studies have confirmed that there appear to be several patterns of drug penetration into the male and female genital tract. In addition, there appear to be different patterns of genital shedding under ART. However, the importance of drug penetration into genital tract on transmission risk is still not completely understood.[49]

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[46] Wilson DP. *Data are lacking for quantifying HIV transmission risk in the presence of effective antiretroviral therapy*. AIDS 23 (11): 1431-1433, 2009.

[47] Kalichman SC et al. *Human immunodeficiency virus load in blood plasma and semen: review and implications of empirical findings*. Sexually Transmitted Diseases 35: 55 – 60, 2008.

[48] Kwara A et al. *Antiretroviral drug concentrations and HIV RNA in the genital tract of HIV-infected women receiving long-term highly active antiretroviral therapy*. Clin Infect Dis 46: (Online edition), 2008.

[49] Taylor S and Davies S. *Antiretroviral drug concentrations in the male and female genital tract: implications for the sexual transmission of HIV*. Curr Opin HIV AIDS. 5(4):335-43, 2010.

5.3.2 Impact of STIs

It is well-established that diagnosed and undiagnosed STIs increase the risk of acquiring HIV and, in those who are HIV-positive, increase the risk of onward HIV transmission. STIs that can cause ulcers – typically herpes simplex virus (HSV-2) and syphilis – as well as those that can cause inflammation – typically gonorrhoea and chlamydia – are both associated with increased HIV shedding in the genital tracts of people with HIV.[50]

There are relatively few data on the impact of STI co-infection in individuals on suppressive ART. Among 17 HIV-positive men with symptomatic urethritis (caused by either gonorrhoea or chlamydia) and undetectable viral loads in the blood, two had detectable HIV in seminal plasma which became undetectable following treatment for urethritis.[51]

Asymptomatic (and, therefore, undiagnosed) urethritis may be a particular concern. A small study of five men examining the effect of asymptomatic urethritis on seminal viral load found that although the three men not on ART had a higher seminal viral load than those on ART, the two men on ART still had potentially infectious seminal viral loads (2.11 and 1.98 log(10) copies/mL).[52]

The role of HSV-2 in increasing the risk of HIV transmission in the presence of ART is currently unclear. A small study examining the impact of ART on blood and seminal viral load up to 24 weeks following ART initiation found isolated semen HIV shedding in 12 of 25 (48%) participants. Although none were diagnosed with a symptomatic STI at any visit, 9/25 (36%) were chronically infected with HSV-2.[53]

A recent large, randomised control trial which involved 3,381 heterosexual couples in Africa in which one partner was HIV-positive and chronically infected with HSV-2 found no impact on HIV transmission risk in the HIV-positive partners whose HSV-2 was treated with daily aciclovir.[54] However, this same study found that ART reduced sexual HIV transmission risk by 92%, suggesting that chronic HSV-2 may not necessarily result in a significant increase in transmission risk.

5.3.3 Impact of menstruation

There are conflicting data on the role of hormonal fluctuations and their effect on viral load in the blood and genital tract. Although a 2004 study of viral load changes during the menstrual cycle found that viral loads in vaginal fluid tended to peak at the time of menstruation and fell to the lowest level just prior

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

[51] Sadiq ST et al. *The effects of antiretroviral therapy on HIV-1 RNA loads in seminal plasma in HIV-positive patients with and without urethritis*. *AIDS* 16: 219–225, 2002.

[52] Rieg G et al. *Seminal plasma HIV levels in men with asymptomatic sexually transmitted infections*. Int J STD AIDS. 21(3):207-8, 2010.

[53] Sheth PM. *Persistent HIV RNA shedding in semen despite effective antiretroviral therapy.* AIDS: 23 (15): 2050-2054, 2009.

[54] Celum C et al. *Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2*. N Engl J Med 362:427-39, 2010.

to ovulation,[55] several other studies have shown no significant effect of menstrual cycle on the detection of HIV in the genital tract and in the blood.[56] Consequently, not only there is a lack of consensus as to the effect of hormonal changes during the menstrual cycle on HIV shedding in the genital tract, there are no data on the impact of ART on such shedding.

5.4 Residual risk due to transient variations in viral load between clinic visits

The Swiss statement acknowledges that it may take up to six months following ART initiation for viral load to reach stable, undetectable levels, notwithstanding suboptimal adherence, and to a lesser extent, gut absorption issues, drug-drug interactions, and acquired resistance. It specified that an individual must remain under regular follow-up in order to monitor viral load and the factors that may affect it.

However, critics have pointed out that between clinic visits viral load may temporarily rise from undetectable levels to detectable levels ("blips") potentially increasing transmission risk, and that maintaining optimal adherence over the long-term may be limited. Since the publication of the Swiss statement, several studies examining the length of time it takes to reach a stable, undetectable viral load; the incidence of transient variations in viral load between clinic visits; and factors associated with long-term optimal adherence have been published.

A Danish study found that risk of transmission was especially high during the first six months of ART, when 8% of the time was spent with a viral load above 1000 copies/ml. This reduced to 1% for the following six months. Thereafter, viral load was above 1000 copies/ml for an average of 0.6% of the follow-up period. However, amongst patients who had been taking suppressive HIV treatment for over five years, only 0.03% of the follow-up period was spent with a viral load above 1000 copies/ml.

Noting that “HIV-infected patients have, however, an increased risk of abrupt viraemia in not just the first six months but the first twelve months of episodes with undetectable viral load”, the investigators recommend “there would be a substantial gain in reducing the risk of infecting the sexual partner, if the time limit recommended by the Swiss…was extended from six months to at least twelve months.”[57]

A Swiss study estimated a 99% probability that HIV would remain suppressed below 1000 copies/ml in the period between routine viral load tests. Although viral load rebounded to above 50 copies/ml on at least one occasion in 43% of

[55] Benki S et al. Cyclic shedding of HIV-1 RNA in cervical secretions during the menstrual cycle. J Infect Dis 189(12): 2192-2201, 2004.
[56] Cu-Uvin, S. *Effect of the Menstrual Cycle on Virological Parameters*. JAIDS 38: S33-S34, 2005.
[57] Engsig FN et al. *Risk of high-level viraemia in HIV-infected patients on successful antiretroviral treatment for more than 6 months*. HIV Medicine 11 (7): 457-461, 2010.

patients, only 7% experienced a transient viral load above 1000 copies/ml during the 3 1/2 year study period. The probability of suppression was correlated with the reported level of adherence.[58]

An analysis of over 2000 patients at London's Royal Free Hospital with a median of 4.5 years and to up to nine years of follow-up found that most (79%) maintained an undetectable viral load for the duration of follow-up. The majority (92%) of individuals remained adherent to their antiretroviral therapy throughout the study and the chances of remaining adherent increased by about 2% a year. It found that being a black heterosexual man was associated with poorer adherence and increasing age was significantly associated with better adherence. “Adherence to antiretroviral therapy is generally high in routine practice and does not have a tendency to decline over … long periods, providing encouragement that maintenance of adherence for a lifetime may well be possible," the investigators conclude.[59]

5.5 Incomplete data for anal sex and sex between men

All of the prospective and observational studies cited in the Swiss statement were based on heterosexual couples. Although the Swiss did not differentiate between the risk of vaginal and anal sex in their statement, much of the criticism and confusion that followed related to the relevance for anal sex and sex between men.

Anal sex is inherently a higher HIV transmission than vaginal sex due to biological differences between the vagina and the anus. Receptive anal sex may be 8x (if the HIV-positive male does not ejaculate) and 18x (with ejaculation) more risky than receptive vaginal sex. Insertive anal sex appears to be 2.75x (if the HIV-negative male is circumcised) and 7.75x (uncircumcised) more risky than insertive vaginal sex.[60] Limited data suggest some beneficial impact of male circumcision in gay men but only if the insertive partner is exclusively a 'top'.[61]

In addition, there are not enough to data to reliably state that reductions of viral load in the blood are paralleled in rectal secretions. Limited data suggest that HIV may be higher in rectal secretions than either blood or semen, and

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[58] Combescure C et al. *How reliable is an undetectable viral load?* HIV Medicine 10: 470-76, 2009.

[59] Cambiano V et al. *Long-term trends in adherence to antiretroviral therapy from start of HAART*. AIDS. 24(8):1153-62, 2010.

[60] Boily MC et al. *Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies*. Lancet Infect Dis 9: 118-29, 2009; Jin F et al. *Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART*. AIDS 24(6):907-13, 2010.

[61] Millett G et al. *Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis*. Journal of the American Medical Association 300(14):1674-1684, 2008; Templeton DJ et al. *Circumcision and risk of HIV infection in Australian homosexual men*. AIDS 23: 2347-51, 2009.

can still be shed in the rectum despite successful ART.[62] This may have an impact upon the logic behind a risk reduction strategy known as 'strategic positioning' (i.e. where the HIV-positive man is the receptive partner in anal sex) which appears to be practiced by a significant number of gay men.[63] A substudy within the Medical Research Council's PIVOT (Protease Inhibitor monotherapy Versus Ongoing Triple-therapy in the long-term management of HIV infection) study which closes enrolment in November 2013 will examine the effect of ART on rectal secretions.

A prospective study examining the determinants of HIV transmission in a cohort of 1144 gay men attending an HIV clinic Brighton between 2000 and 2006, is the first to explore the role of viral load, and ART use, in a cohort of gay men.[64] The investigators used clinical and epidemiological information to identify the factors involved in new HIV infections in these men, and by performing phylogenetic analysis on the HIV from 859 individuals, 41 'likely transmitters' were identified, 29 (70%) of which had never taken HIV treatment and nine of which had interrupted their treatment at the time of transmission. As expected, the study found an association between a higher viral load and a greater risk of HIV transmission, with each $\log_{10}$ increment in viral load increasing the risk of HIV transmission by 61%.

Two suspected transmissions occurred from individuals with a blood plasma viral load below 50 copies/ml at their most recent clinic visit. The investigators note: "For one individual, the next available viral load was above detection, suggesting that transmission may actually have occurred with detectable viraemia. For the other, there is no evident explanation for apparent transmission while undetectable on ART." However, they caution at over-interpretation. "Given that the data were unlinked prior to phylogenetic analysis, it was not possible further to evaluate this case with the rigor necessary to determine whether transmission truly occurred while 'undetectable'...Nevertheless, given the large size of the cohort – of whom approximately 70% (circa 800) were receiving ART – the absolute risk of transmission associated with an undetectable viral load was low."

In a case report from Germany[65](previously highlighted by Deutsche AIDS Hilfe: see Section 3.3) published in August 2008, a gay man who had maintained an undetectable viral load on treatment since 2000 apparently infected his partner between 2002 and 2004 after reporting unprotected anal intercourse on a number of occasions. Neither partner reported a sexually transmitted infection and both reported that their relationship was monogamous. The author of the report has been unable to confirm the sexual

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[62] Zuckerman R A et al. *Higher concentrations of HIV RNA in rectal mucosa secretions than in blood and seminal plasma, among men who have sex with men, independent of antiretroviral therapy*. J Infect Dis 189: 156-161, 2004.
[63] Crepaz N et al. *Prevalence of unprotected anal intercourse among HIV-diagnosed MSM in the United States: a meta-analysis*. AIDS 23: 1617-1629, 2009.
[64] Fisher M et al. *Determinants of HIV-1 transmission in men who have sex with men: a combined clinical, epidemiological and phylogenetic approach*. AIDS 24 (11): 1739–1747, 2010.
[65] Sturmer M et al. *Is transmission of HIV-1 in non-viraemic serodiscordant couples possible?* Antiviral Therapy 13: 729 – 732, 2008.

position of each partner (i.e. whether or not the HIV-positive partner on ART was the receptive partner during anal sex).[66]

5.6 Unknown impact on sexual behaviour

Since the advent of highly active antiretroviral therapy (HAART) in 1995-6, there have been concerns that gay men in particular have relaxed 'safer sex' behaviours due to fewer concerns over the consequences of becoming HIV-positive (known as 'treatment optimism'). A 2004 meta-analysis found that this was not necessarily the main reasoning behind an increase in unprotected anal sex amongst gay men that had been observed from the mid-1990s.[67]

Mathematical models provide conflicting evidence of 'treatment optimism' on a population level. A recent study from the Netherlands[68] suggested that sexual disinhibition amongst gay men had offset the benefits of ART on viral load, resulting in an overall increase in HIV incidence at population level. However, recent modelling in a similar population in San Francisco[69] suggests that even though unprotected sex remains highly prevalent ART appears to have reduced the incidence of new infections on a population level.

Specific concerns raised following the publication of the Swiss statement involve two separate but related changes in sexual behaviour: risk compensation (replacing a prior reliance on condoms or other proven 'safer sex' methods with a reliance on undetectable viral load) and/or behavioural disinhibition (having more unprotected sex due to a belief that an undetectable viral load is protective).

A 2008 anonymous questionnaire distributed to 185 HIV-positive individuals in several Swiss cities found that 18 of the 134 individuals who had heard of the Swiss statement had changed their sexual behaviour – eleven said they now had sex without condoms with their current HIV-negative partner and seven said they now had condomless sex with their HIV-positive partner. An additional four individuals stated that they had already practised sex without condoms with their HIV-negative partner. A further two said that the Swiss statement had motivated them to start antiretroviral therapy even though they currently did not have a regular sexual partner.[70]

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[66] Personal communication with Nikos Dedes, EATG.
[67] Crepaz N et al. *Highly active antiretroviral therapy and sexual risk taking*. JAMA: 292: 224 – 236, 2004.
[68] Bezemer D et al. *A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy.* AIDS. 22(9):1071-1077, 2008.
[69] Das-Douglas M et al. *Decreases in community viral load are associated with a reduction in new HIV diagnoses in San Francisco.* Seventeenth Conference on Retroviruses and Opportunistic Infections, San Francisco, abstract 33. 2010.
[70] Wasserfallen FM *Swiss statement for PLWHA on effective ARV treatment.* XVII International AIDS Conference, Mexico City, abstract MOPE0212, 2008.

The impact of the Swiss statement in sexual behaviour elsewhere in the world is unclear. Even prior to 2008, a subset of HIV-positive gay men in Sydney considered their viral load when deciding whether or not to use a condom for anal sex with an HIV-negative partner.[71] However, in studies undertaken prior to, and after the Swiss statement, this is not necessarily the case amongst other populations in Sydney or amongst gay men elsewhere in the world.

A 2009 qualitative study of 42 British HIV-positive gay men who admitted to at least one episode of unprotected anal sex in the previous year found that while most considered the HIV status of their partners before unprotected anal sex (known as 'sero-sorting') none considered their own, or partner's viral load as a means of reducing the risk of HIV transmission. Several men suggested that to attend to viral load prior to unprotected anal sex would be considered "too calculating".[72]

A 2008 survey of responses to the Swiss statement from well-informed gay men in high-income countries suggested that the statement resonated more strongly for men who already had a problematic relationship with condoms – primarily because they perceived that sex without condoms provides greater intimacy – but concluded that the statement itself had not significantly changed sexual practices.[73]

A study of HIV-positive heterosexual men and women in New South Wales first undertaken between 2004 and 2006, and again in 2009, found that although unprotected sex did take place between some couples where the positive partner was on treatment and had an undetectable viral load, no couple stated that an undetectable viral load was their reason for having unprotected sex. "In fact," suggested the researchers, "unprotected sex appeared less driven by calculations of risk, than by complex dynamics around gender, intimacy, reproduction and a desire for 'normality'."

Furthermore, the Swiss statement appeared to have had little impact on their sexual behaviour.

> *"Interviews in 2009 revealed that hardly any participant had read, heard or been informed about the Swiss Statement. In the interview, all participants were given information about the Swiss Statement and articles outlining the debate. Most found it very interesting. But, regardless of their own sexual practice, nearly all were sceptical of its prevention message, and described it as having little direct relevance to their sexual decision making. Most argued they would need a lot more evidence before they believed its claims or, in the case of those*

[71] Van de Ven P et al. *Undetectable viral load is associated with sexual risk taking in HIV serodiscordant gay couples in Sydney*. AIDS 19: 179 – 184, 2005.
[72] Bourne A et al. *Relative safety II: risk and unprotected anal intercourse among gay men with diagnosed HIV.* Sigma Research, London, 2009.
[73] Bernard EJ. *BHIVA Community Symposium: Undetectable = Uninfectious*? BHIVA Autumn Conference, London, 2008.

who had protected sex, before they would consider changing their sexual practice."[74]

This parallels a 2008 survey of British heterosexual women's responses to the Swiss statement which suggested that, for some, the statement supported existing practices that included unprotected sex (primarily for intimacy or conception). However, it did not appear to significantly change sexual practices. Similar to the findings in New South Wales, many of the women consulted were unaware of the statement.[75]

[74] Persson A. *Heterosexuals living with HIV and the Swiss Consensus Statement*. Talkabout, Oct-Nov 2009.
[75] Petretti S. *BHIVA Community Symposium: Undetectable = Uninfectious*? BHIVA Autumn Conference, London, 2008.

6. ART and HIV transmission risk - issues for policy consideration

> *"All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."*[76]

The HIV prevention paradigm has forever changed, and the lines have now become significantly blurred between prevention and treatment. The concept of 'combination prevention,' which emerged from AIDS 2008 in Mexico City accepts that focusing primarily on behavioural change is overly simplistic. [77]

Combination prevention appreciates the realities of sexual dynamics, addresses societal and structural issues, and embraces biomedical interventions as prevention tools. Such tools may soon include the use of antiretrovirals - in the form of oral (pre-exposure prophylaxis or PrEP[78]) or topical agents (microbicides[79]) – for people at risk of acquiring HIV.

The impact of ART on HIV transmission risk has many implications for policy in the United Kingdom. No matter how unresolved matters of scientific, clinical and social concern may make consensus difficult to reach, denying an effect of ART on HIV transmission risk "would be dishonest and futile". [80] Tackling the issue head-on as a unified HIV sector may be an ideal opportunity to face the challenge of this forever-changed HIV prevention paradigm today as we prepare for a future of increasingly complex and individualised prevention choices.

Q: Is it possible for the UK HIV sector to agree on a policy that harmonises the benefits of ART on transmission risk for both individuals and public health?

Following the Swiss statement, outside of Switzerland only the German civil society explicitly agreed with the specific claims of the Swiss statement in relation to the individual risk of transmission on ART. But the Swiss statement

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[76] Bradford-Hill, A. *The environment and disease: association or causation?* President address at January 14 meeting. Proceedings of the Royal Society of Medicine163 (seriesB): 295-300, 1965.
[77] See Pebody R. *Prevention – there will be no magic bullet, we need 'combination prevention'*. Aidsmap.com, August 6, 2008.
[78] See: PrEP section of NAM's 'HIV transmission testing' manual
[79] See: Microbicide section of NAM's 'HIV transmission and testing' manual.
[80] Garnett GP and Gazzard B. *Risk of HIV transmission in discordant couples.* Lancet 372: 270-71, 2008.

only provides guidance on individual risk reduction and does not recommend the use of 'treatment as prevention' for public health purposes.

More recent treatment guidance from the United States[81], as well as implementation of 'treatment as prevention' within the San Francisco Public Health system stresses the public health benefit of 'treatment as prevention' but provides neither guidance nor recommendations regarding individual risk reduction counselling for individuals on ART. In fact, as discussed above, the CDC continues to recommend against the use of ART for individual risk reduction benefit.

However, current international enthusiasm for 'treatment as prevention' on a population level implies an acceptance that ART reduces HIV risk on an individual level, but by not addressing this issue suggests a disconnect between approaches to individualised risk and population based-risk.

Might it be possible for the UK to be the first place in the world to address to the individual and population-based impact of ART on HIV transmission risk with honesty, clarity and transparency?

6. 1 Policy implications for individuals and individually-focussed prevention

6.1.1. What information should be provided to individuals?

2008 BHIVA, BASHH and FSRH sexual and reproductive health (SRH) guidance for individuals with HIV were produced in 2006-2007, prior to the Swiss statement, and although an additional section was added in May 2008 during the final review process, the rest of the guidance was not amended. The section was conceived as interim guidance pending fuller UK guidelines. Forthcoming 2010 BASHH and BHIVA UK national guidelines on safer sex advice[82] more fully address the issue of ART and HIV transmission risk in dedicated section aimed at individuals living with diagnosed HIV.

The forthcoming guidelines highlight "the reported discordance between plasma and genital viral loads, the possibility of STIs increasing transmission risk, and the lack of data for sexual transmission in anal sex both for heterosexual and MSM populations." Nevertheless, they recognise that "couples may wish to consider discontinuing use of condoms for a number of reasons" and recommend "detailed expert counselling and support on the transmission risks and other relevant issues".

[81] Current treatment guidelines from the US Department of Health and Human Services (DHHS) list one of the primary goals of treatment to "prevent HIV transmission" but do not make any specific recommendations based on these assertions. However, the most recent treatment guidelines from the International AIDS Society - USA Panel recommend that "[t]herapy should be considered where there is a heightened risk of HIV transmission (ie, HIV-serodiscordant couples) without supplanting traditional prevention approaches."

[82] All recommendations are taken from draft three of the guidance, dated January 2010, and updated on February 23 2010 (not in the public domain)

According to the HPA, in 2009, 65,319 individuals were seen for HIV care in the UK..[83] of whom (44,028) are on triple drug-based ART and of whom (82%[84]) currently have an undetectable viral load .This leaves approximately 36,500 individuals. who may require such counselling, although it is currently unclear how many individuals are in relationships that might fulfil the criteria laid down by the Swiss statement. Notwithstanding the human and financial resources required, the following question should be addressed.

Q: Since the draft guidelines do not appear to provide detailed information for those counselling such individuals (or couples) on their specific situation might clinicians, health advisers, lay counsellors and people with HIV benefit from more detailed guidance, similar in form (if not content) to the Swiss AIDS Federation's Advice Manual: 'Doing without condoms during potent ART' ?

Examples of the kinds of ethical, social and scientific issues that might be addressed on an individual level include:

- Is the aim of counselling to reduce risk realistically (harm reduction) or to remove risk altogether (harm elimination)?
- Who would actually undertake this counselling? HIV clinicians, Health Advisers and/or community-based organisations? What are the resource implications?
- Under what circumstances should condoms and ART be relied upon together and when should they be considered individually efficacious prevention tools?
- Under what circumstances might an individual with HIV be counselled that ART provides a similar protection to their sexual partner as condoms?
- Should individuals with HIV who are in relationships be counselled alone or with their partners? What is the definition of a relationship?
- What are the pyschosocial implications in terms of understanding risk and responsibility for HIV prevention? For example, who helps individuals cope with unrealistic fears of infecting a partner and/or not wanting to be considered overly-calculating?
- Whose responsibility is the reliance of ART for prevention - the person with HIV on ART or their partner? Can responsibility truly be shared without disclosure? How does that compare with reliance on condoms?
- Are all reasons equally valid for discontinuing use of condoms? For example, is the inability to achieve erection with a condom or a desire for intimacy within a relationship as valid a reason as procreation for such a discussion?
- What should people with HIV who are not in relationships be told? Are the risks different if they do not practise anal sex?

[83] HPA. Numbers accessing HIV care: National Overview. HPA website (accessed August 18 2010).
[84] Bansi L et al. *Trends over calendar time in antiretroviral treatment success and failure in HIV clinic populations*. HIV Medicine 11: 432-38, 2010.

- What should people with HIV who practise anal sex be told? Are the risks different if they are in a relationship?
- According to the HPA, in 2008 only 79% of individuals with a CD4 cell count <350/mm^3 were on ART.[85] What are the implications in terms of an added incentive for diagnosed individuals not currently on treatment, but who are currently eligible under BHIVA guidelines, to commence ART?
- What are the implications in terms of an added incentive to adhere to ART?
- What are the implications for frequency of clinic visits in terms of monitoring viral load?
- What are the implications for STI detection and treatment?
- What are the implications for non-sexual transmission, notably through injecting drug use?

6.2 Implications for public health/population-focussed prevention

Currently there appear to be no plans for 'treatment as prevention' interventions on a population level in the United Kingdom. The implementation of this policy in San Francisco (see 4.2.1 San Francisco: rationale and controversy) and the results of ongoing clinical trials may provide important lessons for the future, in particular for addressing sexual transmission between men in UK.

In the meantime, however, addressing the implications of ART on HIV transmission risk has important consequences on a population level for information provision, as well as testing and treatment initiation policies, and requires an appreciation of complex ethical, social and scientific issues.

Q: If the UK provides information to people with diagnosed HIV on their individualised risk, should the same kind of detailed information regarding the impact on ART on infectiousness be provided to wider at-risk communities (as a further incentive for increased testing and treatment uptake, and to reduce HIV-related stigma) and how will this be balanced with concerns over increased community-wide risk behaviour?

Discussions regarding the feasibility of a UK policy to reduce transmission on a population level might also include:

- the financial and human resource implications (i.e. is it cost-effective?)
- how to increase voluntary HIV testing rates while protecting human rights, in particular informed consent
- the role of primary infection
- whether possible increases in sexual risk-taking by at-risk populations outweigh the potential benefits of early or universal ART

[85] Health Protection Agency. *HIV in the United Kingdom: 2009 Report*. November 2009.

- how ART might be positioned as *an addition* to condoms and where it fits with other behavioural and biomedical 'combination prevention' technologies
- how ART used for prevention may reframe the concept of shared responsibility for HIV prevention and imply that the diagnosed HIV-positive individual (and whomever advises them) bears more responsibility than, for example, when using condoms
- reframing the policy debate around legal and social obstacles to people taking up and adhering to treatment

Q: What are the implications for guidance on initiating treatment, and how might this benefit the individual as well as public health?

Existing BHIVA treatment guidelines[86] only refer to the potential benefit of ART in terms of reduced transmission risk in the section on treatment during primary infection. It is unclear what impact this recommendation has had in clinical practice. The BHIVA treatment guidelines writing committee is presently working on the next revision of the guidelines, and the 'when to start' section will likely include reference to impact on transmission risk.

The forthcoming BASHH and BHIVA UK national guidelines on safer sex advice 2010[87] in their current draft form recommend the following:

> *"Discussion regarding the early initiation of antiretroviral therapy to reduce the risk of HIV transmission may be appropriate as part of safer sex counselling for some people living with HIV."*

According to the HPA, in 2008 55% of adults were diagnosed with a CD4 count <350 mm^3, below the current threshold recommended for treatment initiation and 32% were diagnosed with a CD4 cell count <200 per mm^3, making the issue of earlier initiation moot. However, a significant proportion of individuals are diagnosed with CD4 counts above the current threshold, including the majority of gay men (See Figure 3: Estimated CD4 count at HIV diagnosis by prevention group, 2008.)

[86] British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008

[87] All recommendations are taken from draft three of the guidance, dated January 2010, and updated on February 23 2010 (not in the public domain)

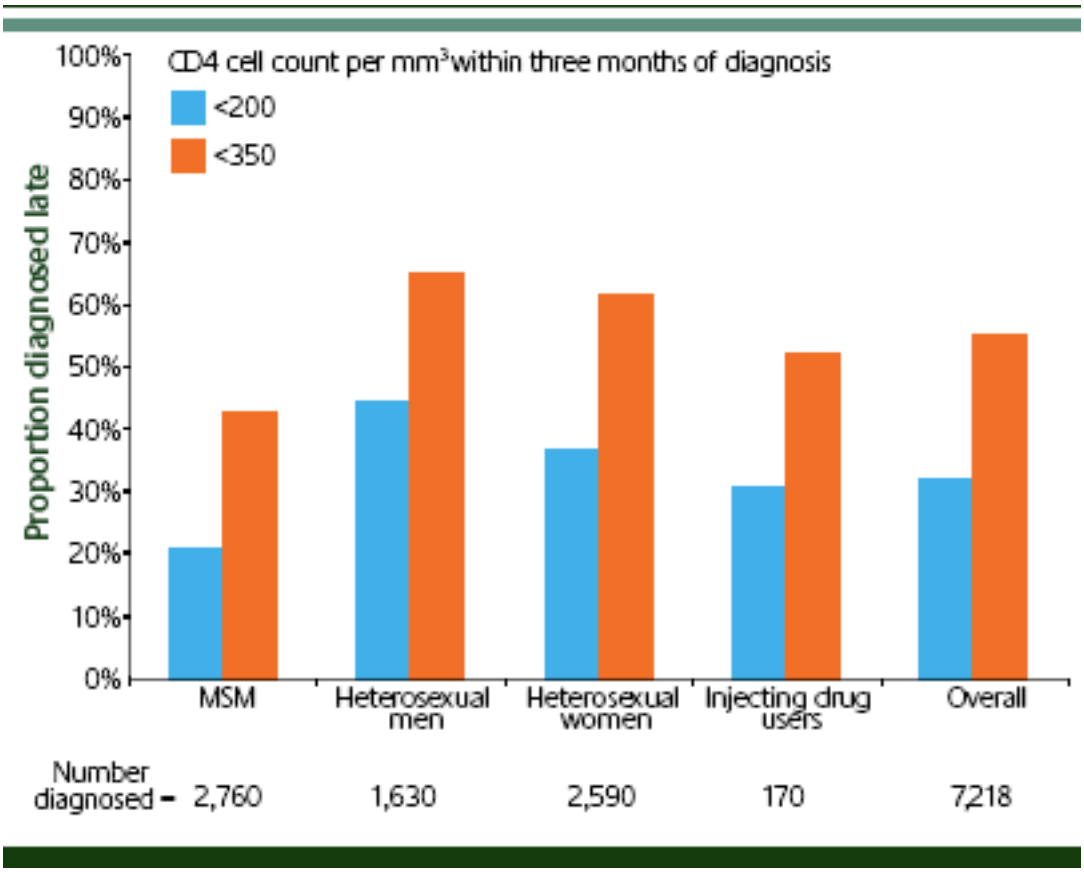

Figure 3: Estimated CD4 count at HIV diagnosis by prevention group, 2008. Source, HPA.

Currently the best time to initiate ART for individual benefit is unknown. Consequently, the individual risks and benefits of commencing treatment at CD4 counts above 350 cells/mm^3 also requires some considered discussion.

Given the continuing uncertainties as to the longer-term impacts of treatment on the individual how do we balance the interests of individual and public health where starting earlier may bring no individual benefit, and might conceivably harm both the individual (in terms of adverse affects and reduced treatment options should resistance occur) and public health (in terms of the potential of transmitted resistance)?

Q: Is it desirable – and ethical – for BHIVA treatment guidelines to recommend a two-tier approach to the initiation of treatment: one that clearly benefits the individual and one that provides an option of earlier treatment where there are concerns around onward transmission?

6.3 Other policy implications

6.3.1 Conception issues

2008 BHIVA, BASHH and FSRH sexual and reproductive health (SRH) guidance for individuals with HIV explore the risks and benefits of natural versus assisted conception in great detail, and include reference to the Swiss statement. It makes the following recommendations.

HIV-positive men and women and their partners planning to have children should receive pre-conceptual counselling on all their conception options including HIV transmission risks associated with each case so that they can make an informed choice.

Detailed comprehensive pre-conceptual counselling should be available for couples considering conceiving. This should review the available options and the possible risks of each method. All discussions should be documented clearly in clinical notes.

Clinics advising serodiscordant couples on risk reduction strategies for natural conception should obtain signed consent that both parties understand and accept the small risks of HIV transmission.

Q: Might further detailed guidance, similar to the Swiss AIDS Federation's Advice Manual: 'Doing without condoms during potent ART' be of benefit in assisting counsellors, PLHIV and their partners to discuss under what circumstances the benefits of natural conception may outweigh the risks?

6.3.2 Criminal prosecutions

One of the principal reasons for the issuance of the Swiss statement was Switzerland's overly-draconian criminal laws relating to HIV exposure and transmission which do no not allow HIV-negative individuals to consent to the risk of unprotected sex following disclosure and mutual agreement, and which hold the HIV-positive individual completely liable.

The statement specifically addressed the legal implications noting that unprotected sex between a positive person on antiretroviral treatment and without an STI, and an HIV-negative person, does not comply with the criteria for an “attempt at propagation of a dangerous disease” in the Swiss penal code nor for “an attempt to engender grievous bodily harm”.

In February 2009, the Geneva Court of Justice quashed an HIV exposure conviction after hearing expert testimony from one of the authors of the Swiss Federal AIDS Commission’s statement regarding the lack of infectiousness of individuals on effective treatment and accepting that the risk of HIV exposure during unprotected sex from a person undergoing successful antiretroviral therapy is so low that it is only hypothetical. Although HIV-exposure charges for people on effective treatment may still be laid in Switzerland’s 25 other

cantons, there have been no further reports of prosecutions for HIV exposure – or transmission – since the ruling.[88]

Crown Prosecution Guidance for England and Wales has clarified some of the uncertainties created by two Appeal Court judgements regarding under which circumstances people living with HIV could be charged for grievous bodily harm under the Offences Against the Person Act 1861: either Section 18, 'intentional transmission' or Section 20, 'reckless transmission'.[89]

The section of the guidance relating to 'Safeguards against transmitting infection' is left open to allow for a 'safer sex' defence to charges of 'recklessness' other than the use of condoms. It notes that each case will be decided on its own merits based on testimony from "medical experts" regarding whether "appropriate safeguards to prevent the transmission of their infection throughout the entire period of sexual activity" are "reasonable in light of the nature of the infection."

There is no prosecutorial guidance for legal situation in Scotland, which is closer to the situation in Switzerland, since it currently remains unclear whether disclosure in the absence of condoms is a legitimate defence to accusations under the Scottish common law offence of 'culpable and reckless conduct' which allows for prosecutions for both HIV exposure and transmission are offences.

Q: Might a UK consensus statement on ART and risk of HIV transmission help clarify the situation for individuals living with HIV, those counselling them on transmission risks, as well as those working with, and in, the criminal justice system?

6.3.3 Occupational restrictions on PLHIV

Current guidance from the Department of Health states that since "there is a low risk of BBVs [blood borne viruses, including HIV] transmission during EPPs [exposure prone procedures] healthcare workers who are infected with BBVs are not allowed to carry out EPPs, as injury to the worker could result in their blood contaminating their patient's open tissues."[90]

EPPs include "procedures where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (eg spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hands or fingertips may not be completely visible at all times. Such procedures occur mainly in surgery, obstetrics and gynaecology, dentistry and some aspects of midwifery."

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[88] See Switzerland section in NAM's HIV and the criminal law resource

[89] Crown Prosecution Service. *Intentional Or Reckless Sexual Transmission Of Infection.* CPS website, updated 21 June 2010.

[90] Department of Health. *Health clearance for tuberculosis, hepatitis B, hepatitis C and HIV: New healthcare workers*. March 2007

A working group comprising members of the Expert Advisory Group on AIDS, the Advisory Group on Hepatitis and UK Advisory Panel for Healthcare Workers Infected with Bloodborne Viruses is considering the implications of ART on infectiousness on healthcare workers living with HIV.

Q: Might a UK consensus statement on ART and HIV transmission risk further clarify the situation for individuals living with HIV and working in these areas?

6.3.4. PEP guidance

UK guidelines for post-exposure prophylaxis (PEP) specifically aimed at preventing HIV transmission taking place following non-occupational exposure to HIV were last produced in 2006 by the British Association for Sexual Health and HIV (BASHH)[91].

The guidelines recommend PEP following possible HIV exposure after receptive or insertive anal or vaginal intercourse when the source individual is known to be HIV-positive. It may also be considered following receptive oral sex (fellatio) with ejaculation and/or mucous membrane exposure (e.g. splash of semen into the eye).

Updated PEP following sexual exposure (PEPSE) guidelines from BASHH and BHIVA are currently in development.

Q: Might a UK consensus statement on ART and HIV transmission risk further clarify the when PEP might be warranted following sexual exposure from a known HIV-positive individual on successful ART?

[91] Fisher M et al. *UK Guideline for the use of post-exposure prophylaxis for HIV following sexual exposure*. International Journal of STD & AIDS 17: 81–92, 2006.

Appendix

Reproduced here are relevant excerpts from *UK guidelines for the management of sexual and reproductive health (SRH) of people living with HIV infection 2008.* Produced jointly by the British HIV Association (BHIVA), the British Association for Sexual Health & HIV (BASHH) and the Faculty of Sexual and Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists (FSRH)

Authors: A. Fakoya, H Lamba, N. Mackie, R Nandwani, A. Brown, EJ Bernard, C Gilling-Smith, C Lacey, L. Sherr, P Claydon, S Wallage, B Gazzard.

HIV sexual transmission on HAART

Introduction

There have been several advances in the field of HIV transmission science which have implications for the counselling and clinical management of PLHA. Patients need evidence-based information and advice in order to make important decisions in developing and maintaining long-term meaningful relationships.

In general, and in short-term casual relationships, advice and support on safer sex and the use of condoms to reduce the transmission or acquisition of HIV or other sexually transmitted infections is still recommended.[92] However, couples in long-term monogamous relationships may wish for information in order to make decisions about whether or not to cease using barrier protection. This may be for couples who are either sero-different or sero-same.

There is currently no UK guidance on counselling on HIV transmission in the era of HAART and it is envisaged that because this is an increasingly important and controversial area, detailed guidance on this will be developed in the near future. In the interim, we present the currently available evidence, which may be useful in guiding consultations and discussions.

Risks of HIV transmission on ART

Studies have shown that the risk of HIV transmission correlates with the level of plasma HIV RNA for sexual [93] [94] and mother to child [95] [96]transmission. It is

[92] UNAIDS, WHO. Antiretroviral therapy and sexual transmission of HIV, 2008.
[93] Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. 2000 Mar 30;342(13):921-9.

now well established that treatment with HAART reduces HIV infectiousness [97] [98]. Extrapolations from epidemiological and biological data have led Swiss experts to the opinion that individuals with chronically suppressed viral loads taking HAART and with no sexually transmitted infections are not sexually infectious if certain key criteria are met. [99]. The Swiss experts state that viral load suppression must be for at least six months and the person must be on effective suppressive therapy under regular clinical follow-up.

Although the precise transmission risk on suppressive ART is not known, prospective studies have shown no transmissions between sero-different couples if viral loads were undetectable [100]. Similarly, during therapy the concentration of HIV diminishes in both semen [101] and cervico-vaginal fluid. [102] [103] Mathematical modelling of transmission data by Chakraborty et al shows that as the viral load in semen reduces, the transmission rate per sexual act reduces exponentially to approach zero [104]. Although there is compelling evidence to reach similar conclusions to the Swiss where oral and vaginal intercourse are concerned, gaps in currently-available evidence, regarding the transmission risk of anal intercourse, which is not only practised by MSM but also by a significant minority of heterosexuals, who may be unwilling to disclose this to healthcare workers. There would also be concern about the interpretation of this statement by individuals who might make

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[94] Tovanabutra S, Robison V, Wongtrakul J, Sennum S, Suriyanon V, Kingkeow D, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. J Acquir Immune Defic Syndr. 2002 Mar 1;29(3):275-83.

[95] Garcia PM, Kalish LA, Pitt J, Minkoff H, Quinn TC, Burchett SK, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. N Engl J Med. 1999 Aug 5;341(6):394-402.

[96] Rousseau CM, Nduati RW, Richardson BA, Steele MS, John-Stewart GC, Mbori-Ngacha DA, et al. Longitudinal analysis of human immunodeficiency virus type 1 RNA in breast milk and of its relationship to infant infection and maternal disease. J Infect Dis. 2003 Mar 1;187(5):741-7.

[97] Vettore MV, Schechter M, Melo MF, Boechat LJ, Barroso PF. Genital HIV-1 viral load is correlated with blood plasma HIV-1 viral load in Brazilian women and is reduced by antiretroviral therapy. J Infect. 2006 Apr;52(4):290-3.

[98] Lalani T, Hicks C. Does antiretroviral therapy prevent HIV transmission to sexual partners? Curr HIV/AIDS Rep. 2007 May;4(2):80-5.

[99] Vernazza P, Hirschel B, Bernassconi E, Flepp M. HIV-positive individuals without additional sexually transmitted diseases (STD) and on effective anti-retroviral therapy are sexually non-infectious. Bulletin des medecins suisses. 2008;89:5.

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

[101] Vernazza PL, Troiani L, Flepp MJ, Cone RW, Schock J, Roth F, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. AIDS. 2000 Jan 28;14(2):117-21.

[102] Vettore MV, Schechter M, Melo MF, Boechat LJ, Barroso PF. Genital HIV-1 viral load is correlated with blood plasma HIV-1 viral load in Brazilian women and is reduced by antiretroviral therapy. J Infect. 2006 Apr;52(4):290-3.

[103] Cu-Uvin S, Caliendo AM, Reinert S, Chang A, Juliano-Remollino C, Flanigan TP, et al. Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA. AIDS. 2000 Mar 10;14(4):415-21.

[104] Chakraborty H, Sen PK, Helms RW, Vernazza PL, Fiscus SA, Eron JJ, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. AIDS. 2001 Mar 30;15(5):621-7.

decisions about their infectiousness based on incorrect assumptions, e.g. about the presence of STIs if they were asymptomatic, or who have multiple casual partners.

Nevertheless, providing information on HIV transmission to HIV-positive individuals is vital, and clear information based on the evidence must be provided in ways where the possibility of ambiguity does not arise. Time should be made available for detailed counselling and information provision which can support PLHA to develop and maintain healthy and fulfilling sexual relationships, including the choice of procreation. Key areas of discussion are included below with a summation of the evidence to date in each case.

… *[A substantial section on HIV reinfection risk between HIV-positive couples is omitted here because it does not address the impact of ART on reinfection risk]…*

HIV transmission in HIV discordant couples

As mentioned above there is increasing evidence that HAART reduces the risk of sexual transmission and this will play an increasing role in HIV prevention in the future. The fact that almost two thirds of PLHA on HAART in the UK have an undetectable viral load means that information on the risks of HIV transmission on HAART is relevant to many. However given that the average time for remaining undetectable on a ART is limited there are important considerations which need to be taken into account regarding the public health implications of any recommendations or advice given to patients. Similar to other national and international positions this current guideline cannot fully endorse the Swiss consensus statement. However, it is acknowledged that in many instances long-term serodiscordant partners may seek advice about risk reduction in certain instances such as natural conception. Information on risk reduction should be provided as it has been shown that many couples who cannot access fertility services eventually conceive.

Pre conception, pre exposure prophylaxis in sero-different couples

The number of centres that provide conception services is limited and in many instances the procedure is costly. Although the exact number of couples who practice unprotected sex in order to conceive is not known, it is likely to be underestimated. It has been reported that up to one third of couples who have been on waiting lists for fertility clinics do not attend and a significant number of these conceive naturally [105]

Data on the use of pre exposure prophylaxis with tenofovir and risk reduction counselling has been recently presented by Vernazza and colleagues.[106] Within counselling discussions on minimising the transmission risks whilst

[105] Vernazza PL, Hollander L, Semprini AE, Anderson DJ, Duerr A. HIV-discordant couples and parenthood: how are we dealing with the risk of transmission? AIDS. 2006 Feb 28;20(4):635-6.

[106] Vernazza P. HAART improves quality of life: should we care about the quality of spermatozoa? AIDS. 2008 Mar 12;22(5):647-8.

trying to conceive, 22 couples where the male partner had fully suppressed viral load (< 50) were offered the option of timed intercourse with tenofovir pre exposure prophylaxis. With 50% of women conceiving after 3 cycles the conception rate was higher than with artificial conception techniques and all of the women tested negative 3 months after last exposure. This preliminary data and results from pre- exposure animal studies suggests that harm reduction strategies such as this will be important for the future but currently no recommendation on the use of pre conception prophylaxis for sero – discordant couples can be made.

Key points and recommendations

- HAART reduces the risk of HIV sexual transmission and for individuals with chronically suppressed viral loads the transmission risk may be negligible in the absence of sexually transmitted infections II
- In most circumstances counselling and advice should continue to promote the use of condoms to reduce the transmission risk of HIV and other STIs III
- Detailed individual counselling including the use of harm reduction should be available for individuals in sero- different and sero-same long term relationships who wish to consider unprotected sexual intercourse IV
- The risk of HIV superinfection may diminish with the time from initial infection. Although it appears more likely in the first three years following seroconversion, a risk persists after this – II.
- HIV-positive individuals should be counselled regarding the low but possible risk of superinfection, particularly those who choose to serosort (i.e. have unprotected intercourse with partners who are also HIV-positive) – II.

Levels of evidence

I = high quality meta-analyses, systematic reviews of randomized control trials (RCTs) or RCTs;

II = other good quality trials such as case control or cohort studies;

III = non-analytic studies such as observational studies, case reports or case series;

IV = consensus or expert.