

Australasian Statement on HIV Antiretroviral Therapy and Infectiousness

(A) Australasian statement on HIV antiretroviral therapy and infectiousness

Consistent use of effective antiretroviral therapy (ART) will, in most cases, lead to an undetectable viral load (VL), as measured in blood, semen and vaginal fluids. As a result, the average viral load of the community of people living with the human immunodeficiency virus (HIV) will be reduced. By reducing the VL, ART will also complement the benefits of consistent condom use and effective sexually transmitted infections (STI) detection and treatment, in preventing HIV transmission that may otherwise occur due to condom failure. However, there are no data to suggest that a population HIV prevention strategy based solely or predominately on the use of ART and associated with a reduction in condom use, will lead to fewer people becoming infected in the Australian and New Zealand populations, especially in the context of rising rates of STI.

This statement is a joint response issued by the following organisations:

- Australasian Society for HIV Medicine Inc. (ASHM), Darlinghurst, NSW 2010, Australia
- National Centre in HIV Epidemiology and Clinical Research (NCHECR), Darlinghurst, NSW 2010, Australia
- Australian Federation of AIDS Organisations (AFAO), Newtown, NSW, 2042, Australia
- National Association of People Living with HIV/AIDS (NAPWA), Newtown, NSW, 2042, Australia

(B) Background

In the January issue of the Bulletin of Swiss Medicine¹ the Swiss National AIDS Commission (EKAF) issued a report on the infectiousness of people with HIV on optimally effective ART. The statement, on behalf of the Swiss Federal Commission for HIV / AIDS was authored by four of Switzerland's foremost HIV experts: Prof Pietro Vernazza, of the Cantonal Hospital in St. Gallen, and President of the Swiss Federal Commission for HIV / AIDS; Prof 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. The report stated that after review of the medical literature and extensive discussion with experts a HIV-infected person on antiretroviral therapy with completely suppressed viraemia (effective ART) is not sexually infectious, i.e. cannot transmit HIV through sexual contact. The authors clarified the statement indicating that it was only valid if the following conditions are fulfilled:

- The person infected with HIV consistently adheres with the ART, the effects of which must be evaluated regularly by the treating physician;

- The person infected with HIV has a VL during ART that has been below the limits of detection (blood plasma level <40 copies/ml) and has been so for at least six months (i.e. viraemia is suppressed);
- The person infected with HIV has no additional STI present.

Zero infection risk

Since the publication of the Swiss report the main debate has focused on the 'zero risk' implication. It has been suggested that this concept is misleading and may easily be equated to zero HIV VL in body cells, tissues or compartments. This could add to the complexity of public health messages to positive people and the wider community resulting in confusion around HIV therapy, prevention and infectiousness.

Research to date has indicated that the eradication of human immunodeficiency virus (HIV) is unachievable with currently available ART. However, it is well documented that:

- The consistent use of effective ART will, in most cases, lead to an undetectable HIV viral load in blood, semen and vaginal fluids;
- The reduction in VL is associated with statistically significant improvements in survival and clinical outcome for the person infected with HIV;
- At the population level the average VL of the community of people living with HIV will be reduced;
- Lowered VL equates to reduced infection rate but not zero risk of infection.

The availability of ART has made HIV infection less of an obstacle in many situations. ART has already been shown to be successful in preventing HIV transmission when used as pre-exposure prophylaxis (PrEP), as post-exposure prophylaxis (PEP) and when conceiving a child for the HIV infected person and their seronegative partner. Montaner^{2,62} used the 'low VL = reduced infection rate' concept when presenting the case for expanding treatment access to curb the growth of the HIV epidemic. He suggested that the use of ART could reduce global prevalence of the virus more than 7-fold, and in reality would cause the epidemic to retract rather than to continue expanding.

A dose response effect of VL on the rate of transmission has been indicated in a number of studies. Data derived from mathematical modeling by Quinn et al³ showed that as the serum HIV RNA level increased from less than 3500 copies per milliliter to 50,000 or more copies per milliliter there was an increase in infection rate from 2.2 per 100 person-years to 23.0 per 100 person-years. Each log increase in viral load was associated with an increase by a factor of 2.45 in the risk of transmission or infectiousness. The study also found there were no instances of transmissions by seropositive subjects with undetectable viral loads or with serum HIV RNA levels of less than 1500 copies per milliliter.

Early studies estimated the rate of sexual HIV transmission to be one infection per 1,000–2,000 coital acts. However, new data indicates that the rate varies widely with the phase of the infection, and is more than 10-fold higher during acute infection.^{3,6} Wawer et al.⁶ demonstrated that the rate of HIV transmission was 0.0082 per coital act within approximately 2.5 months after seroconversion of the index partner. The rate of transmission increased again during late-stage HIV infection suggesting that individuals are more likely to transmit HIV when viral load is high. Transmission probabilities have been shown to increase from 0.0001 per coital act at viral loads of less than 1700 copies/mL to 0.0023 per act at 38 500 copies/mL or more, and were 0.0041 with genital ulceration versus 0.0011 without.⁷ These studies provide an argument for the use of effective ART during times of high VL (e.g. seroconversion) in the ART naïve person and will have a significant effect on decreasing the rates of HIV transmission.

VL is the strongest risk factor for the transmission from mother to child. In one cohort study an HIV RNA > 100,000 copies/ml, was associated with a 41 % risk of vertical transmission, 1-10,000 copies /ml was associated with a 17% risk and less than 1000 copies/ml had a zero transmission rate. Although this study showed no case of transmission at lower levels of virus, case reports suggest that there is no absolute level below which there is zero risk of mother-to-child transmission.⁸

Genital tract HIV viral load during antiretroviral therapy

Since the earliest days of the HIV epidemic it has been shown that HIV is present in both blood and genital fluids and the VL in the two compartments are related. Several studies have shown a good correlation between peripheral-blood VL and VL in seminal plasma and cervical secretions.³ Generally, effective ART has been shown to decrease HIV RNA shedding in the genital tract and the use of ART among serodiscordant couples has been associated with reduced seroconversions in partners who are HIV negative^{3,13,14,15,16,17,18,19,20,21,22} and reduced transmission of HIV from mother-to-child.^{2,4,9,21,22,24} Consequently, there is a growing number of serodiscordant couples requesting counseling regarding the options available for reproduction.²² In a review of all natural pregnancies attained by HIV-serodiscordant couples seen in three clinics in Spain, in which the infected partner had undetectable plasma viraemia while receiving ART, there were no cases of HIV seroconversion in the uninfected sexual partners. The study suggested that serodiscordant couples attaining natural pregnancy are exposed to a negligible risk of sexual transmission of HIV when the infected partner presents with and maintains complete suppression of plasma VL while receiving effective ART.²⁵

Semen

The analysis of semen samples from patients receiving Zidovudine monotherapy^{18,26} was the first to show the decreased frequency of HIV-1 in compartments other than blood with ART. This effect appeared to be associated with a significant reduction of HIV-1 positive white blood cells (seminal polynuclear cells), the principal HIV-1 cell hosts in semen. Subsequent studies on individuals receiving combination antiretroviral therapy (cART) continued to show a significant fall in the VL in semen (measured by HIV RNA and culture), which paralleled the reduction of VL in blood. More pronounced reductions of HIV RNA in semen have been observed as the effectiveness of cART on blood VL levels increases.^{13,14,15,16,17,27} However, variation amongst studies exists with some showing lower VL in semen than in blood while others have shown

levels of HIV in semen that were equal to or greater than in the infected person's blood.²⁸ Further, it is noteworthy that a number of studies have been able to recover replication-competent viruses from cells in the semen of HIV-1-infected men who are receiving cART and who have undetectable levels of HIV-1 RNA in blood plasma. For example Zhang et al¹⁹ showed that despite the long-term suppression of HIV-1 RNA in the plasma proviral DNA could be detected in cells in semen in patients on triple therapy for more than 2 years. Further, these viruses were macrophage-tropic, a feature that is characteristic of HIV-1 strains that are capable of being sexually transmitted. Choudhury et al²⁹ isolated infectious HIV virions from cells in semen, but not from blood cells, of an individual on cART. Leruez-Ville et al¹⁶ analysed 39 HIV-1-infected men in a prospective study for HIV seminal shedding after the initiation of cART. HIV RNA drastically decreased in the semen of all men, but low levels remained detectable in three men at 18 months. Proviral HIV DNA became undetectable in the cells in semen of all men after 18 months. The authors suggested that HIV-infected cells in the male genital compartment might come from the intermittent passage of blood lymphocytes, rather than constituting a major local reservoir. Results of paired blood and semen samples from a study by Bujan et al³⁰ showed that where seminal plasma results were always negative, 6 – 10% of sperm cell samples contained HIV- 1 genomes due to the presence of seminal polynuclear cells. Again, indicating that although cART may reduce blood RNA to undetectable levels, it does not follow that there are no viral genomes in the semen. Whether these viral genomes are able infect a person if transmitted is unclear. Certainly, data from Zhang et al¹⁹ suggests this may be the case, however, Nunnari et al³¹ indicated that cell associated viral genomes detected in genital secretions of those taking effective cART may not be infectious as viral LTR-circular DNA, as a sign of locally active proliferating virus, was not found.

The Swiss report recommends a 6 month period of undetectable VL before the risk of HIV transmission is negligible. However, the data above suggest that this period may be too short and that effective ART needs to be in place for at least 2 years. The discrepancy suggests further research is required in this area.

Female genital secretions

Generally, the amount of HIV-1 RNA in vaginal secretions, like that of semen, has been correlated with the plasma viral load^{32,33} and an increase in plasma viral load in infected women is associated with an increase in HIV-1 transmission to sex partners.^{32,35,36} In principle, cART capable of suppressing viral replication in blood also suppresses HIV viral shedding at the genital site. However, studies by Fiore et al³⁷, Kovacs et al³⁸ and Saracino et al³⁹, show that important exceptions to this principle do exist and that in some treated individuals with undetectable plasma VL there is continued shedding of virus in the genital tract. This indicates caution is required in judging infectivity of some women on the basis of plasma viral load alone.

Transmission during anal sex

There are relatively few studies looking at the levels of HIV RNA in secretions from the rectal mucosa in HIV-infected men who have sex with men (MSM). As an example, data from Zuckerman et al⁴⁰ found VL was often at high levels in rectal secretions, even in men receiving cART, and that VL in rectal secretions was greater than that in either the blood or seminal plasma. It was also observed that antiretroviral therapy had a greater direct effect on levels of HIV in seminal plasma than in rectal secretions. This may be due to differing levels of antiretroviral drugs or to anatomic and immunologic differences in the male genital tract versus rectal mucosa.

Relationship between viral load in blood, semen and cervical secretions

Factors identified that could potentially influence the relationship between viral load in blood, semen and cervical secretions and have a subsequent effect on infection rate include:

1. Sexually transmitted infections;
2. Antiretroviral drug concentrations;
3. Adherence with antiretroviral therapy;
4. Intermittent HIV-1 viraemia (Blips).

(1) Sexually transmitted infections

Over the past two decades, numerous observational studies have suggested that sexually transmitted infections (STIs) increase the probability of HIV-1 acquisition and/or transmission by increasing susceptibility and infectiousness, respectively. Mechanisms associated with this phenomenon are likely related to the presence of increased numbers of activated target cells for HIV (i.e., CD4+ lymphocytes and macrophages) and the expression of proinflammatory cytokines in the genital mucosa.^{41,42} These factors lead to increased mucosal shedding of HIV-1 in infected patients, causing higher concentrations of virus to be present, and micro-ulcerations in the genital mucosa of patients with genital ulcer disease such as syphilis, chancroid, and herpes simplex virus type 2 (HSV-2) allow for more efficient infection of target cells by HIV.⁴² Effective ART appeared to limit the effect of STIs, however, higher HIV VL in the genital tract compared to blood is generally observed during these infections, thus increasing the potential risk of HIV transmission.⁴³

(2) Antiretroviral drug concentrations in the genital tract

The pharmacology of ART in the male and female genital tract can be expected to affect the success of ART as a preventive intervention. It has been shown that ART agents differ considerably in their ability to concentrate in genital tract secretions.^{44,45,46} Most protease inhibitors are not found at significant concentrations in genital secretions, whereas drugs such as tenofovir or emtricitabine are highly concentrated within the genital tract.^{47,48,49,50}

Drummond et al⁴⁵ stratified antiretroviral drugs according to the female genital tract concentrations achieved relative to blood plasma: Lamivudine (concentrations achieved were 411% greater than blood plasma), emtricitabine (395%), zidovudine (235%) tenofovir (75%), ritonavir (26%), didanosine (21%), atazanavir (18%), lopinavir (8%), abacavir (8%), stavudine (5%), and efavirenz (0.4%). Kwara et al⁴⁴ have published data regarding antiretroviral drug concentrations and HIV RNA in the genital tract of HIV-infected women receiving long-term highly active ART. This group found that the concentration of tenofovir in cervicovaginal fluid was five times that in the blood. A high concentration of 3TC in cervicovaginal fluids was also observed, with levels of the drug in the genital tract being three times higher than those seen in the blood. In addition, levels of FTC (emtricitabine, Emtriva) were 50% higher in the genital tract than blood and those of ddl some nine times higher. However, concentrations in the genital tract of efavirenz (Sustiva) were only

1% of those achieved in the blood, and concentrations of protease inhibitors in cervicovaginal fluid were between 3% - 33% of those in the blood. Although both NNRTIs and protease inhibitors had poor concentrations in the genital tract compared to blood, sustained suppression of HIV RNA levels was observed in the genital tract compartment. It has been suggested by Neely et al⁵² that, overall, the choice of treatment regimen among women with low or undetectable quantities of VL in plasma is poorly matched with these observations and that some cART is associated with cervicovaginal viral shedding e.g. NNRTI-based cART.

(3) Adherence with antiretroviral therapy

Adherence is increasingly recognised as the critical factor in treatment success in most people with HIV infection. There are significant correlations between adherence to medication and virological suppression^{53,54,58}, plasma HIV RNA levels, CD4 cell count and mortality.^{57,58} In addition the possibility of transmission of drug-resistant virus is a public health concern.^{56,58} Suboptimal adherence is associated with loss of virological control, development of resistance to antiretroviral drugs (often with cross-resistance) and, ultimately, progression of HIV disease. While early reports^{54,58} suggested greater than 95% adherence (i.e. missing no more than 1 or 2 doses per month of a twice daily regimen) was required for optimal virological control, more recent data demonstrate that lower adherence rates may be effective in terms of these clinical issues.^{59,60} The latter notwithstanding, if ART is being considered as a prevention measure, its success requires maximal adherence for greatest effectiveness.

(4) Intermittent HIV-1 viraemia (Blips)

Generally a person with HIV infection and receiving ART would have viral load determined every 3 or 6 months. Although VL may be undetectable (<50 copies /ml) at these set points, the real time VL may be more difficult to predict. Many patients on ART experience intermittent episodes of detectable viraemia or 'blips'^{59, 60, 12} which raise concerns about the degree of infectivity and risk that would be associated with sexual contact if activity was based solely on ART as prevention. In a study by Nettles et al⁵⁹ patients underwent intensive sampling (every 2-3 days) over a 3 to 4 month period to define the frequency, magnitude and duration of blips and the blip association with drug levels and other clinical variables. For this study, blips were defined as HIV-1 RNA measurements greater than or equal to 50 copies/ml preceded and followed by measurements less than 50 copies/ml without a change in treatment. Patients had to have suppression of viraemia to below 50 copies /ml while receiving stable ART for 6 months or longer. Blips were detected in 9 of 10 patients, had a short duration (<3days) and low magnitude (median 79 copies/ml). Blips were marginally associated with episodes of non-adherence. The authors suggested that the blips represented random biological and statistical variation around the mean HIV level below 50 copies /ml as no resistance mutations were detected before, during and after blips. Macias et al⁶⁰ found transient rebound of HIV viraemia was associated with emergence of new drug resistant HIV variants. Individuals studied in this group presented with one blip of viraemia less than or equal to 1000copies/ml followed by two consecutive undetectable VL. Adherence was 95% or greater. However, in spite of the rebound, virological failure was not observed during the follow-up period of 2 years.

The continued release of HIV into plasma at very low levels during ART can be detected using specialized techniques, but the nature and significance of this low-level viraemia, especially as related to acquisition of drug resistance mutations, and degree of infectiousness are unclear and require further study.

Legal implications

There are mixed reports about unprotected sex among people receiving ART. For example studies have associated ART with increased¹⁰ as well as decreased¹¹ sexual risk behaviour.

Overall, the vast majority of HIV-infected people believe there continues to be significant health risk (to partner or self) associated with unprotected sex when on ART.²³

At the present time in Australia, the obligation on the person infected with HIV to disclose their HIV status prior to sexual intercourse varies from state to state. For example, in NSW prior to engaging in sex is the one time when disclosure is required by law under the *Public Health Act* and the *Crimes Act* (Summary available from the AFAO website by following the link in⁵). This applies whether you are intending safe sex or not.

The Swiss consensus statement will have interesting implications for all public health policies not only in Switzerland but for all jurisdictions that have HIV exposure laws, including Australia. The definitions of effective ART, HIV exposure, risk perception and the importance of viral load in the risk and grievous bodily harm equations will need to be updated. The Australian community perception of HIV infection as a terminal condition no longer applies, but instead a person with HIV receiving effective ART with an undetectable VL has a chronic illness. Updating of laws should reflect this evolutionary change in the control of the virus so that every person with HIV can live a normal life within the framework of the community.

Adapting and Upgrading Prevention Strategies.

HIV prevention, like treatment, is for life. Instead of short-term or isolated prevention initiatives, effective national programmes need to sustain essential programmatic and policy actions at a sufficient scale over the long term, adapting them as the epidemic evolves, responding to changes in infection patterns and social environments. In recognition of the inherent long-term nature of the HIV prevention enterprise, implementation and scaling up of available prevention strategies should be coupled with longer term efforts to address human resource challenges and to develop new prevention technologies, including the ultimate prevention tool, a preventive vaccine.

Source: 2006 Report on the Global AIDS Epidemic Comprehensive HIV Prevention UNAIDS Global Report
http://data.unaids.org/pub/GlobalReport/2006/2006_GR_CH06_en.pdf

Recommendations by organizations in the light of the Swiss report.

Despite the position being adopted by the Swiss Report, most AIDS researchers insist safe sex is the only way to prevent HIV spread. UNAIDS and the World Health Organisation have come out strongly in favor of recommending continued use of a comprehensive package of HIV prevention approaches, including correct and consistent use of condoms.³⁴ The CDC (Centers for Disease Control and Prevention) continues to underscore its recommendation that people living with HIV who are sexually active use condoms consistently and correctly with all sex partners.⁵¹

In light of the literature which indicates suppression of HIV on one hand, but also indicates continued presence of replication-competent virus in some patients receiving effective ART, ASHM, NCHECR, NAPWA and AFAO support the recommendations made by UNAIDS, WHO and the CDC. For the present and in light of our current knowledge, safe sex 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.

Further research is required on: the dynamics of viral suppression after the initiation of ART in male and female genital tract, the mucosa of colorectal and cervicovaginal tissue; and the degree to which latently infected lymphocytes are sequestered in the prostate or the seminal vesicles. Studies on viral kinetics in the genital tract should assess the impact of different antiretroviral regimens, and monitor changes in cellular proviral DNA and replication-competent virus over a longer period of time. Researchers also need to consider other related factors that contribute to HIV transmission, including co-infection with other sexually transmitted diseases. Finally, analysis also needs to consider homosexual as well as heterosexual modes of transmission.

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