

Position statement on the use of antiretroviral therapy to reduce HIV transmission, January 2013: The British HIV Association (BHIVA) and the Expert Advisory Group on AIDS (EAGA)

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Definition: This statement refers to the use of antiretroviral therapy (ART) by HIV-positive individuals to reduce the risk of transmission of HIV.

- 1 There is now conclusive randomized clinical trial evidence, from heterosexual couples where one partner has HIV infection and the other does not, that if the partner who is HIV positive is taking effective ART, transmission of HIV through vaginal sex is significantly reduced (by 96%) [1]. The observed reduction in HIV transmission in a clinical trial setting demonstrates that successful ART use by the person who is HIV positive is as effective as consistent condom use in limiting viral transmission.
- 2 The risk of a person living with HIV, who is taking effective ART, passing HIV on to sexual partners through vaginal intercourse is extremely low, provided that the following conditions are fulfilled.
 - There are no other sexually transmitted infections (STIs) in either partner*.
 - The person who is HIV positive has a sustained plasma viral load below 50 HIV-1 RNA copies/mL for more than 6 months and the viral load is below 50 copies/mL on the most recent test.
 - Viral load testing to support the strategic use of ART as prevention should be undertaken regularly (3–4-monthly)*.
- 3 The published data are largely from heterosexual couples and there are insufficient data to conclude that successful

ART use can provide similar levels of protection in relation to other sexual practices, including unprotected anal intercourse between men or between men and women. However, it is expert opinion that an extremely low risk of transmission can also be anticipated for these practices, provided that the same conditions stated above are met.

- 4 With the level of evidence available, it is recommended that health care professionals discuss with all people living with HIV the impact of ART on the risk of viral transmission to sexual partners. For those not yet taking ART and wishing to reduce the risk of transmission, the possibility of starting ART for this purpose should be discussed. Such discussion should establish that there is no evidence of coercion and that the person with HIV infection is fully informed of the need to commit to long-term adherence to ART, frequent STI screening (3–6-monthly dependent on risk)* and regular viral load measurements, and is aware of the potential side effects of therapy.

It must be noted that no single prevention method can completely prevent HIV transmission. ART reduces the risk of transmission only of HIV. Irrespective of ART, condoms remain the most effective way to prevent the spread of other STIs.

Notes

- (a) *STIs within a couple can only be reliably excluded if:
- both partners have had a comprehensive STI screen and all results are negative;

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- neither partner has had sex with anyone else since the screen;
 - the screen is repeated for each individual following sexual exposure with every new sexual partner and a negative result is obtained within the relevant 'window' period for each STI before the couple have sex again.
- (b) These conditions can only apply if there is complete disclosure within the couple about sexual relationships outside the partnership.
- (c) STIs can increase susceptibility to HIV acquisition, and may increase genital tract HIV viral load in an HIV-infected individual from previously undetectable levels, so leading to an increased risk of HIV transmission. An undetectable HIV viral load in the plasma does not always mean that there is an undetectable viral load in the genital tract. If the possibility of STIs is not excluded, being on ART may still bring protective and public health benefits in reducing transmission risk, but under these circumstances it is not advisable to rely on treatment alone to prevent HIV transmission, and condoms continue to be recommended.
- (d) *If ART is being used as a strategy to reduce the risk of viral transmission, more frequent viral load testing than is currently recommended for standard clinical care may be necessary.

Explanatory notes

The above position statement by BHIVA and EAGA summarizes extensive discussion about various aspects of the scientific data and it was felt that some explanatory notes would be helpful, particularly where there are areas of controversy.

ART vs. condoms for prevention of HIV transmission

The mechanisms by which condoms and ART prevent HIV transmission are fundamentally different. Condoms prevent contact with genital fluids and their efficacy is reduced by factors that compromise the integrity of the physical barrier, such as non-use, slippage and breakage. ART prevents HIV transmission by stopping viral replication and lowering the amount of virus within the genital compartment; its value will be reduced by nonadherence, poor absorption and the presence of other STIs. The observed reduction in HIV transmission between couples (assumed to be having vaginal sex) in the HIV prevention trials network (HPTN) 052 trial [1] was 96%, when the HIV-positive partner took ART. We do not yet know, however, how ART use affects HIV transmission between

couples in 'real-world' settings outside a clinical trial. Conversely, there has never been a randomized controlled trial of the efficacy of condom use *vs.* no use. However, several meta-analyses of observational and cohort studies of HIV infection in couples who maintained 100% condom use have found that this strategy is about 80% (79–93%) effective in reducing HIV infections [2]. It must be noted, though, that it is not possible to make a direct comparison of these two strategies: HPTN 052 was a prospective randomized controlled trial enrolling HIV-serodiscordant couples where HIV transmission was the primary outcome, whereas the condom evaluation was a meta-analysis of multiple observational studies, and as such may underestimate the effect of condoms.

Communicating the level of risk

BHIVA and EAGA believe that giving an actual figure for the risk of transmission for one episode of sex in a serodiscordant couple is not currently meaningful for an individual and that any figure proposed would be misleading, for the reasons outlined below. In the absence of such a figure, BHIVA and EAGA have therefore adopted the term 'extremely low' whilst recognizing the difficulty inherent in the imprecise nature of such a term.

Risk assessment

The studies conducted to date in heterosexual serodiscordant couples indicate that there have been no confirmed transmissions from people whose HIV infection is virologically undetectable (< 50 copies/mL). The small number of documented HIV transmissions in these studies occurred from HIV-positive individuals who had only recently started therapy and in whom, therefore, it is unlikely that an undetectable HIV viral load had been achieved or sustained for the 6-month time period recommended by this statement. However, to be certain that the risk of transmission approaches zero in defined circumstances, a much larger number than the 1763 serodiscordant couples enrolled in HPTN 052 would have to be studied. This will be tested in the PARTNER study [9].

Questions and answers

What does 'extremely low risk' mean?

There was a 96% reduction in HIV transmission risk demonstrated in the HPTN 052 study, which can be considered as 'extremely low risk'. Within the study partnerships, there was only one genotypically confirmed HIV transmission from an HIV-infected participant on ART. In this case, an individual randomized to immediate ART had not yet

achieved an undetectable viral load at the time of viral transmission. The BHIVA and EAGA statement requires evidence of confirmed HIV viral load < 50 copies/mL for 6 months, which would exclude a comparable risk to that observed in the trial, hence justifying the 'extremely low' statement; although this does not mean zero risk.

What is the estimated relative risk of HIV transmission for different sex acts?

The nature of sexual exposure does influence the actual risk of acquisition/transmission. The actual relative risk for each individual sex act is not certain, as multiple factors are at play [3–5]. Biologically, the integrity of the exposed mucosal surface is important as well as the presence of concomitant mucosal infections. The latter influence membrane integrity, attract inflammatory target cells and affect HIV shedding by the genital tract. Estimates of risk of HIV acquisition per coital act are largely influenced by \log_{10} viral load of the HIV-infected partner; whilst the majority of these data are from African heterosexual couples reporting vaginal sex [3,4,6], the assumption from these trials is that the majority of sex acts were vaginal sex. The concept that the HIV-positive partner's viral load is the key determinant of risk of transmission is pertinent for all sex acts, although the absolute risk is affected by the nature of exposure.

Because the risk of transmission through anal sex is higher than that through vaginal sex [7], and because of the lack of high-grade evidence that ART prevents viral transmission through this route, it is not possible at this time to confirm the same level of protection by ART as for vaginal sexual exposure. The data overall show that, for each \log_{10} increase in plasma HIV-1 RNA, the per-act risk of transmission increased 2.9-fold [95% confidence interval (CI) 2.2–3.8] [5,6]. Whilst HIV viral load is the most significant contributor to risk of onward viral transmission, there is an order of magnitude difference in risk of transmission between insertive and receptive anal sex, with transmission by receptive anal sex around 10-fold more likely than transmission by insertive sex [5–7]. Insertive anal sex carries a similar level of risk to insertive or receptive vaginal sex (estimated at 5–6/10 000 exposures), whilst receptive anal sex carries an estimated 10-fold higher risk of viral transmission (estimated at 50/10 000 exposures) [5–8]. UK data from Fisher *et al.* [8] correlated the risk of onward transmission via anal sex to viral load, recent HIV infection and recent STI (rate ratio 5.32; 95% CI 2.51–11.29). The PARTNER study [9] will evaluate risk of viral transmission through anal sex when the HIV-positive partner is on suppressive ART, although this study will not report until 2015.

Although HIV viral load may be < 50 copies/mL in blood tests, does this always mean there is no detectable virus in the genital tract?

For sexual transmission of HIV, reduction in genital tract HIV viral shedding is a critical factor that determines the overall risk of onward viral transmission. Generally, the plasma level of HIV RNA is a good surrogate marker for genital tract viral burden, but this is not always the case. HIV resides within anatomical 'sanctuary sites', meaning sites that are not directly part of the blood system, where local drug exposure and viral dynamics may differ significantly. Antiretroviral drug penetration varies by gender and may be drug (as opposed to class) specific, with high inter-individual variability [10].

How was the 6-month timeframe of undetectable viral load mentioned in the statement reached?

The HPTN 052 study reported a 96% reduction in the risk of onward viral transmission, measured from the time of randomization into the study, when the plasma viral load of the HIV-infected partner was below the limit of detection [1]. For individuals initiating ART, it can be anticipated that the majority of people starting an effective regimen based on their pretreatment viral genotype (i.e. their virus is sensitive to all the drugs taken) will achieve an undetectable viral load within 6 months of initiating therapy [11].

What is the actual risk of HIV transmission if there is an STI when HIV viral load is fully suppressed?

Overall, there are insufficient data to clearly respond to this question. Models have explored the role of specific STIs and onward HIV transmission risk. Observational and biological data provide compelling evidence of the importance of STIs in HIV transmission, but only one of nine STI treatment intervention trials has shown an effect [12]. Overall, trial evidence strongly supports the concept that STI treatment reduces HIV infection. However, issues in trial design and conduct, including HIV epidemic phase, STI prevalence, efficacy of the intervention (especially in the herpes trials [12,13]) and statistical power, have affected five of the six trials. In addition, these studies were undertaken prior to general availability of ART, and the significantly higher impact of HIV viral burden on risk of transmission than that conferred by the STI(s) probably also explains the lack of overall efficacy of STI treatment.

Why knowing HIV status and viral load matters when advising on sexual practices

In the pivotal HPTN 052 study of serodiscordant heterosexual couples, 28% of transmissions were not from the enrolled infected partner [1]. This was demonstrated by the absence of a virological link between the newly acquired infection and the partner who was infected at enrolment. This provides conclusive evidence that there were concurrent partnerships, not just the one protected by ART but at least one other that was unprotected, reinforcing the need for condom use outside long-term partnerships. The vast majority of HIV transmission in the UK is via casual sex and sex between new partners. If individuals plan on having sex without condom use, it is important to consider waiting until the HIV and STI statuses and the HIV viral load of the sexual partner(s) are known.

How frequently should viral load be tested?

If an HIV-positive individual chooses to rely on ART as the main method of prevention of HIV transmission, then viral load monitoring should be recommended more frequently than every 6 months.

Adherence to ART and what happens if ART is stopped

Full adherence to ART with continued suppression of plasma viral load is critical for the strategic use of ART to continue to prevent onward transmission. Stopping ART is usually accompanied by a significant increase in HIV viral load and hence an increase in the risk of onward sexual transmission. If ART is stopped for any reason, continued use of other prevention strategies is required to reduce the risk of transmission.

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