

## Commentary

# Further research needed to support a policy of antiretroviral therapy as an HIV prevention initiative

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The results from the HPTN 052 trial have increased the focus on use of antiretroviral therapy (ART) for prevention of HIV transmission; however, condom use also effectively prevents HIV transmission. Studies in heterosexual serodiscordant couples with viral suppression have so far only reported

follow-up data for 330 couple-years when condoms were not being used. Data are even more limited for anal sex in men who have sex with men. Additional data on the effectiveness of ART as prevention when practicing condom-less sex is urgently needed.

People on ART with low plasma HIV viral load (VL) have markedly reduced infectiousness for sexual transmission [1–3]. The HPTN 052 randomized controlled trial (RCT) demonstrated a reduction in HIV transmission risk due to antiretroviral therapy (ART) use by 96% [1]. However, as the HPTN 052 trial was performed in a population where condom use was actively promoted, the low absolute rate of transmission in the ART arm was due to both ART and condom use, although there was evidence of non-condom use in HPTN 052, including pregnancies and sexually transmitted infection acquisition. The use of several HIV prevention interventions at the same time is likely to increase protection, but studies such as HPTN 052 are often unable to report the independent impact from each intervention. It is important that this is understood to prevent the assumption that the results of HPTN 052 indicate that ART alone without the use of condoms is completely protective.

Condom use is highly effective at preventing HIV transmission, with estimates of efficacy of 85% (95% CI 60, 96) [4] and 78% (95% CI 58, 89) [5], although underestimation of efficacy due to failure to report lack of condom use in some people who acquired HIV means that condom efficacy in a single act when used properly is likely to be close to 100%. As the benefits of

reduced transmission as a result of ART become more widely disseminated, condom use may be reduced. Therefore, a key factor in assessing the effectiveness and cost-effectiveness of ART as a prevention strategy is to understand what the absolute risk of HIV transmission through condom-less sex is when the HIV-positive partner is on ART with a suppressed VL. In this paper we review the extent of existing evidence.

The HPTN 052 trial, which randomized 1,763 serodiscordant couples to early or delayed ART, is the only RCT to prospectively evaluate the effect of ART on prevention of HIV transmission to uninfected sexual partners. Only one linked transmission was reported in the ART-treated group (although even this occurred shortly after treatment initiation and may have been while the VL was detectable) over 1,585 couple-years in the early ART arm (0.1 per 100 person-years [PY]) and 27 transmissions in the delayed therapy group (1.7 per 100 PY). A reduction of 96% in the early ART group [1] was observed (Table 1). Similar findings have been reported in observational studies with a meta-analysis [6] reporting no transmissions in 291 couple-years on ART from two studies [7,8] with VL<400 copies/ml and a 92% reduction in heterosexual transmission through the use of ART from 5.64 to 0.46 per 100 PY. Similarly, the Partners

**Table 1.** HIV transmission in serodiscordant couples on ART and PY of follow-up of condom-less sex

Reference	Type of study	Setting	VL lower limit of detection, copies/ml	Transmissions on ART, <i>n</i>	Estimated HIV transmission per 100 PY (95% CI)	Proportion of couples having condom-less sex, %	Follow-up index case on ART and having condom-less sex, PY
Cohen, <i>et al.</i> [1]	Randomized controlled trial	Heterosexual couples; 13 sites in 9 countries	<400	1	0.1 (0.0, 0.4)	7	63.4
Attia, <i>et al.</i> [6]	Systematic review and meta-analysis	Two cohort studies including serodiscordant heterosexual couples on ART with VL<400 copies/ml [7,8]	<400	0	0 (0, 1.27)	25	218.25
Donnell, <i>et al.</i> [3]	Observational cohort	Heterosexual couples; 14 sites in 7 African countries	240	1 <sup>a</sup>	0.37 (0.09, 2.04)	7	19.1
Reynolds, <i>et al.</i> [9]	Observational cohort	Heterosexual couples; Rakai Study, Uganda	<400	0	0 (0, 5.98)	46	28.9

<sup>a</sup>Genetically linked HIV-1 transmission. ART, antiretroviral therapy; PY, person-years; VL, viral load.

in Prevention Study [3] reported one transmission in 273 couple-years on ART regardless of viral load suppression (0.37 per 100 PY) and the Rakai study [9] reported no transmissions in 53.6 PY (0 per 100 PY). However, it remains unclear what the risk of HIV transmission is on ART when condoms are not used. In studies to date [1,3,6,9], most couple-years were without reported condom-less sex, so the low observed transmission risk is partly due to consistent condom use (Table 1).

Accounting for proportions having condom-less sex (approximately 7% [1], 25% [6], 7% [3] and 46% [9] in the four studies), only approximately 330 couple-years of condom-less sex on suppressive ART have been observed over all studies combined. Even with no transmissions (the two observed may have not been with VL suppression), this gives an upper 95% CI for transmission rate of 1.1/100 couple-years (calculated using exact methods assuming a Poisson distribution for numbers of transmission events). At least another 500 couple-years are needed to establish that the rate is below 0.5/100 couple-years.

In men who have sex with men (MSM) receptive and, to a lesser extent, insertive condom-less anal intercourse is the major risk factor for HIV transmission [10]. There have been studies documenting per act estimates of HIV transmissibility for anal intercourse [11–14], but to date no data are available from observational cohorts or RCTs to determine HIV transmission rates for anal sex in MSM when the HIV-positive partner is on ART. As the risk of HIV transmission is greater for anal sex

than for vaginal sex, the degree to which the HPTN 052 results in heterosexual couples can be extrapolated to MSM is unknown as only 2% of couples enrolled in HPTN 052 were MSM.

A further question is how low a risk of HIV transmission is considered tolerable such that condom-less sex can be considered acceptable. The data from Attia *et al.* [6] reports the upper limit of the confidence interval for heterosexual transmission on ART was equivalent to one new infection per 79 years of follow-up or one per 7,900 sex acts if the yearly average is 100 contacts. The Swiss Statement quoted risks of much lower than 1 per 100,000 acts of sexual intercourse when the index was on ART with an undetectable VL and no sexually transmitted infections [15]. For HPTN 052, it is believed that no transmissions occurred with an undetectable HIV VL in the absence of condom use, but this is difficult to interpret when the number of couple-years in the absence of condom use – the denominator for calculating the rate – is unknown.

An acceptable risk may be one that is at least twice an individual's life span, that is, 1 transmission per 200 years. If the true transmission rate is <1 per 1,000 PY of unprotected sex providing that VL<50 copies/ml, then 2,000 PY of observation with VL<50 copies/ml will enable the upper 95% CI limit for the transmission rate to be <0.44 per 100 PY (that is, 1 per 227 PY of unprotected sex). As it is unlikely that any new RCTs will be performed in this area, we can only perform observational studies to further lower the upper 95% CI boundary.

In conclusion, we know that transmission risk is reduced in people on ART with plasma viral load <50 copies/ml, but it is important to estimate how low this risk is with and without concomitant use of condoms, in both heterosexual and MSM couples, if we are to more fully understand the potential for widespread ART to reduce HIV incidence. Ongoing observational studies such as the PARTNER study [16,17], which aims to study the rate of HIV transmission in serodiscordant heterosexual and MSM couples on ART who do not use condoms, will provide missing information in several key areas. First, to more precisely estimate the absolute risk of HIV transmission using ART alone in serodiscordant couples having condom-less vaginal sex with suppressed VL on ART and second, to provide data on rates of transmission for anal sex in serodiscordant couples (including MSM), which are likely to be different than vaginal sex.

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