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Transmission Rates of HIV on Antiretroviral Therapy (ART): Unanswered Questions

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BACKGROUND

People on ART with low viral load have markedly reduced infectiousness through sexual intercourse. Although the full extent of this is uncertain, there is clear potential for use of ART to prevent transmission as is successfully done to prevent mother-to-child transmission. There is increased interest in ART as a prevention strategy following the results of the HPTN 052 randomised controlled trial which demonstrated a reduction in HIV transmission risk due to ART use of 96% [1]. We know however that condom use is also highly effective at preventing HIV transmission, with a meta-analysis placing the reduction of transmission through the use of condoms alone in the region of 85% (95% CI: 60% - 96%)[2]. Similar results were obtained from the Partners in Prevention study which found that self reported condom use reduced HIV transmission to negative partners by 78% (95% CI: 58% - 89%)[3]. A key factor therefore to understand the effectiveness, (and hence cost-effectiveness) of an ART for prevention strategy is what is the absolute risk of HIV transmission through condom-less sex when the HIV-positive partner is on ART with a suppressed plasma viral load (VL). We aimed to evaluate the extent of existing evidence.

METHODS

We reviewed studies that reported risk of HIV transmission through condom-less sex when the HIV-positive partner is on ART with a suppressed VL.

RESULTS

The HPTN 052 trial – which randomised 1,763 serodiscordant couples to early or delayed ART - is the only RCT to evaluate the effect of ART on prevention of HIV transmission to uninfected sexual partners. The 052 study reported 1 linked transmission with suppressed VL (although even this may have been at higher VL) in 1585 couple-years in the early ART arm (0.1 per 100PY [0.0, 0.4]) and 27 transmissions in the delayed therapy group (1.7 per 100PY [95%CI: 1.1,2.5]), a reduction of 96% in the risk of HIV transmission in the early ART group [1], *table 1*. Similar findings have been reported in observational studies with a 2009 meta-analysis [4] reporting 0 transmissions in 291 couple-years on ART (from 2 studies [5,6]) with VL<400 and a reduction in heterosexual transmission through the use of ART of 92% from 5.64 to 0.46 per 100PY. Similarly the Partners in Prevention Study [7] reported 1 transmission in 273 couple-years on ART (0.37 per 100PY [95% CI: 0.09, 2.004]) and the Rakai study [8] reported 0 transmissions in 53.6PY (0 per 100PY [95%CI: 0, 5.98]) .

However it remains unclear what the risk of HIV transmission on ART when condoms are not used . In studies to date [1,4,7,8] most of the couple years were without reported condom-less sex, so the low observed transmission risk is partly due to consistent condom use. Accounting for proportions having condom-less sex (around 4% [1], 75% [4], 7% [7] and 46%5 [8] in the four studies, respectively), only approximately 329 couple-years of condom-less sex with VL suppression have been observed over all studies combined. Even with no transmissions (the two observed may have not been with viral load suppression), this gives an upper 95% confidence for transmission rate of 1.1/100 couple-years. At least (if 0 transmissions) another 500 couple-years are needed to establish that the rate is below 0.5/100 couple-years.

In MSM, receptive and to a lesser extent insertive unprotected anal intercourse with a HIV positive man is the major risk factor for HIV transmission. There have been studies documenting per act estimates of HIV transmissibility per anal intercourse [9-12], but to date no data are available from observational cohorts or RCTs following serodifferent MSM couples to determine risk of HIV transmission through anal intercourse when the HIV positive partner is on ART.

A further question is how low a risk of HIV transmission is considered an acceptable risk to promote a strategy of condom-less sex when the positive partner is on ART. The data from Attia et al reports that the upper limit of the confidence interval from their analysis of heterosexual transmission on ART was equivalent to one new infection per 79 years of follow up (or one per 7900 sex acts if the yearly average is 100 contacts) [4]. The Swiss Statement quoted risks of much lower than 100,000 acts of sexual intercourse when the index was on ART with an undetectable VL and no STI [13]. It is likely that an acceptable risk will be one that is at least twice that of an individual's life span i.e. 1 transmission per 200 years. If the true transmission rate is < 1 per 1000 person years of unprotected sex partnerships with viral load < 50, then 2000 person years of observation with viral load < 50 will enable the upper 95% confidence limit for the transmission rate to be < 0.0044 (i.e. 1 per 227 person years of unprotected sex).

Table 1: HIV transmission in serodiscordant coupes on ART and PY of follow up of condom less sex

Author, Journal, Year	Type of study	Setting	VL lower limit of detection	PY follow up index case on HAART	Transmissions on ART	Estimated HIV transmission per 100PY (95% CI)	Proportion couples having condom-less sex	PY follow up index case on ART and having condom-less sex
Cohen [1] NEJM, 2011	Randomised controlled trial	Heterosexual couples, 13 sites in 9 countries	<400 copies/ml	1585.0	1	0.1 (0.0, 0.4)	4%	63.4
Attia, [4], AIDS, 2009	systematic review and meta analysis	2 cohort studies included of sero-discordant heterosexual couples on ART with VL<400 [5,6]	<400 copies/ml	291.0	0	0 (0, 1.27)	75%	218.25
Donnell [7], Lancet, 2010	Observational cohort	Heterosexual couples, 14 sites in 7 African countries	240 copies per mL	273 .0	1 genetically linked HIV-1 transmission	0.37 (0.09, 2.04)	7%	19.1
Reynolds [8], AIDS, 2011	Observational cohort	Heterosexual couples, Rakai study, Uganda	<400 copies/ml	53.6	0	0 (0, 5.98)	46%	29.9

CONCLUSION

We know that transmission risk is reduced in people on ART with plasma viral load < 50 c/mL but it is critical to estimate how low this risk is – in both heterosexual and MSM couples - if we are to understand the potential for widespread ART to reduce HIV incidence. Therefore further information in several areas is needed. Firstly more extensive study is required of sero-different couples having condom-less vaginal sex with suppressed VL on ART in order to more precisely estimate the risk of HIV transmission using ART alone and secondly there remains no data for anal sex in serodifferent MSM couples, which are likely to be different to vaginal sex, and ongoing studies that include MSM are critical.

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