Suppressed but still infectious

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The majority of HIV in the USA is transmitted through sexual intercourse. In 2011, diagnosed infections attributed to male-to-male sexual contact (65%) and those attributed to heterosexual contact (27%) accounted for approximately 92% of new HIV infections in the USA [101]. The current prevention paradigm suggests that early identification of HIV-infected individuals (‘test’) and early initiation of antiretroviral therapy (ART; ‘treat’) could lead to dramatic reductions in the incidence of HIV infection [1,2], and this ‘test-and-treat’ strategy for HIV prevention is supported by mathematical models and epidemiological data [2–4]. Additionally, data from a large randomized trial demonstrated a 92% reduction in HIV transmission within sero-discordant couples when the HIV-infected partner was placed on ART [3]. Nevertheless, incomplete engagement in HIV care is still common in the USA and the most recent estimate from the CDC is that only 66% of the 1.1 million Americans living with HIV are linked to care and only around one quarter have HIV RNA suppressed in plasma [102]. These incompletely engaged individuals continue to contribute to the ongoing transmission of HIV infection and pose substantial barriers to the achievement of optimal treatment outcomes. Additionally, high-risk individuals that understand the protective effect of ART on HIV transmission [5–7], and who are receiving ART (regardless of viral suppression) [8–10], have demonstrated increased risk behaviors – several studies have reported an increasing incidence of HIV among men who have sex with men (MSM), despite the widespread availability of ART [11–13]. Finally, sexual HIV transmission [14,15] and intermittent seminal HIV shedding [16] can occur even in treated individuals with undetectable HIV RNA levels in blood; it remains unclear how much of the residual risk of transmission is contributing to sustain the HIV epidemic at a population level.

Seminal HIV shedding during effective ART is intermittent, and the prevalence ranges from

2% up to 48% (most studies have rates between 6 and 8%) [17–23], depending on the characteristics of the observed population. Prevalence estimates increase when repeated longitudinal sampling is employed [17]. In addition, since most studies only measured cell-free HIV RNA in seminal plasma, the detectable rate of HIV in genital secretions may actually double if cell-associated HIV DNA and RNA transcripts are also measured [18].

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These reported isolated seminal HIV shedding events in ART-treated individuals might be a consequence of viral compartmentalization [24] with poor drug penetration within the genital tract [16,25], or may arise from stimulation by concurrent sexually transmitted infections (STIs) and genital inflammation [17,18,26–28]. Our group has focused on identifying factors associated with HIV seminal shedding in asymptomatic MSM with and without ART [29–32]. In ART-naïve MSM, we identified that seminal shedding of CMV, EBV and human herpes virus 8 were associated with increased HIV seminal shedding [29]; CMV and EBV were also associated with HIV transmission [30]. More recently, we reported that 6% of asymptomatic HIV-infected MSM on ART had detectable HIV RNA in semen, despite completely suppressed HIV RNA levels in blood, and the presence of bacterial STIs was not a major contributor to these viral shedding episodes [31]. In our study, the only independent predictor of seminal HIV RNA shedding was the concurrent detection of high-level CMV DNA in the genital tract. Another recent study on treated MSM with suppressed HIV RNA in the blood [23] observed a similar frequency of 7.6% seminal HIV shedding, which was

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associated with the size of the latent HIV reservoir in blood, but not with presence of STIs. The composition of the agents in the antiretroviral regimen has not generally been associated with differential shedding rates, with the exception of regimens containing raltegravir [31,33]. In our study, 4.8% of subjects on suppressive raltegravir regimens had seminal shedding compared with 9.9% on nonraltegravir-containing regimens, but this difference was not statistically significant [31].

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An important point, which remains to be determined, is whether the presence of detectable HIV RNA in semen at low levels while on ART (mostly found at levels <1000 copies/ml) represents a real risk of viral transmission during sexual intercourse. In addition, since the origin of transmitted virus (cell free vs cell associated) is still unresolved, the contribution of cell-associated HIV to sexual HIV transmission during suppressive ART needs to be studied further [34,35]. One study estimated heterosexual transmission using a probabilistic model for a seminal viral load of <1000 copies/ml to be 3/10,000 sexual episodes [36], and this estimate is likely to be higher during anal intercourse. Another recent study described a stepwise association between levels of genital HIV RNA and HIV transmission risk among heterosexual couples [37], with a 1 log₁₀ increase in genital HIV RNA resulting in a 1.79–2.20-fold increased risk of HIV transmission. In this study the risk of HIV transmission was estimated at 1.4–4.4 per 100 person-years when HIV RNA in genital secretion was <3 logs. Interestingly, a total of 11 transmissions (incidence <1% per year) occurred from individuals with undetectable genital HIV RNA. However, all these subjects had detectable plasma HIV RNA levels, and the median time between collection of the genital sample from the source partner and HIV seroconversion was 4.6 months. Independently from HIV RNA levels in the genital tract, one study calculated a transmission rate of 0.37 (95% CI: 0.09–2.04) per 100 person-years for ART-treated source partners, compared with 2.24 (95% CI: 1.84–2.72) from ART-naïve heterosexual partners, corresponding to a 92% reduction [3]. This is similar to a

pooled estimate of transmission from heterosexuals on ART of 0.46 (95% CI: 0.19–1.09) per 100 person-years [38].

Translating the individual estimates of HIV transmission risk into estimates of the overall effect of HIV spread among the growing number of ART-treated individuals is currently a challenge. We previously attempted to estimate the potential impact of HIV transmission in the USA related to MSM on ART with suppressed HIV RNA viral load [39], which gave a figure of approximately 3500 cases in 1 year. However, there are many factors that could significantly impact this estimate, and these should be accounted for. First, we used a probability of transmission of 0.00136 per act (92% reduction from the estimate in untreated men of 0.017 [40]). However, the true transmission per act during suppressive ART has not been well defined for MSM, and the 92% reduction applied to the empirically derived estimates of transmission with anal sex are higher than the mathematically modeled estimate of transmission with a seminal viral load <1000 copies/ml. Additionally, while it is relatively straight forward to estimate the number of ART-suppressed MSM living in the USA (as 25% of the 489,121 HIV-infected MSM [102,103]), there is much less certainty regarding the number of unprotected anal sex acts per year these MSM are having with serodiscordant partnerships. Changes in risk behavior (i.e., risk compensation) may also be expected to increase with further dissemination of the belief in the protective effect of ART and use of pre-exposure prophylaxis [41].

“...current scientific priorities should be concerned with HIV transmission from individuals on suppressive antiretroviral therapy...”

Similar problems would exist when attempting to calculate the transmissions in heterosexual and injection drug users. Better accuracy and precision in the future will require a more definitive estimate of transmission probability and transmission risk behavior derived from empirical data. The point remains that with a growing number of individuals living with HIV and suppressed on ART, this group may still contribute substantially to the HIV epidemic.

In conclusion, there is accumulating evidence suggesting that HIV RNA can be detected in the semen of men, despite being on suppressive ART [17–23,31]. However, the clinical significance and contribution of the detected virus

to ongoing HIV transmission remains unclear. One first step to investigate the clinical significance would be to determine the threshold of detectable seminal HIV RNA associated with culture-competent virus, but these studies would be confounded by the sensitivity of viral growth assays. There are very few observational data on transmission partner pairs where the sources are receiving ART and, although difficult, this research would greatly inform the topic. For example, some important open questions to be addressed would be: is there a threshold (and what is it) or a linear relationship for seminal viral load that is associated with HIV transmission, and how is this different for heterosexual and MSM sexual transmission? What is the origin of transmitted virus (cell free vs cell associated)? Given our recent observations on asymptomatic viral coinfections [31], especially CMV, could there be important cofactors that need further consideration? Interventional research should be performed to determine whether better genital tract-penetrating ART drugs or the suppression of CMV is effective in reducing HIV shedding in semen and eventually also impacting the risk of HIV transmission. Thus, current scientific priorities should be concerned with HIV transmission from individuals on suppressive ART and how such transmission can be prevented; this agenda will require a better

understanding of the attributable proportion of HIV transmission that comes from treated HIV-infected subjects, and which factors contribute to enhancing the risk of HIV RNA shedding in semen during ART.

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