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Reply to "Seminal HIV Blips and Structured Natural Conception In Serodiscordant Couples" by Mounzer and DiNubile

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This letter discusses the residual risk of HIV-transmission during sustained long-term suppression of plasma viremia by antiretroviral therapy (ART) due to intermittent HIV shedding in semen and the implications for serodiscordant heterosexual couples planning to conceive a child. There are several important questions that arise: 1) what is the residual risk of transmission; 2) what is the global impact of seminal HIV shedding during ART; and 3) which factors related to seminal HIV shedding are modifiable to further reduce the risk of HIV-transmission.

Among heterosexual discordant pairs, HIV viral load in seminal plasma is the most predictive factor for HIV-transmission[1]. Notably, HIV-transmission does occur from individuals with low blood viral load (<1500copies/ml) and those on successful ART [2-5]. In a recent study, only one of 103 genetically-linked HIV-transmissions was from an infected partner on ART, with a calculated transmission rate of 0.37 (95%CI 0.09-2.04) per 100 person-years compared to 2.24 (1.84-2.72) from ART-naïve partners, corresponding to 92% reduction [2]. 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 [3]. Factoring a 92% reduction in HIV-transmission during ART to the summary estimated risk of heterosexual transmission of 0.008 [6], results in a per coital act HIV-transmission risk of 0.0007 during ART. Although the risk of HIV-transmission is likely a stochastic process (related to sporadic seminal HIV shedding) rather than a specific risk per episode of unprotected sex, this average estimate can be used to inform the risk to serodiscordant couples planning unprotected sexual activity for conception. The probability of conception from a single coital act varies during the ovulatory cycle of the average woman, with a probability of conception estimated as 0.084 for day 12, 0.086 for day 13, and 0.081 for day 14[7]. If couples had sex on all three days the monthly cumulative probability of conception

would be 0.23 [calculated as 0.084+(1-0.084)*0.086+(1-0.079)*0.081], while the risk of transmitting HIV can be estimated similarly at 0.002. However, the probability of conception is highest during the first few months of trying, while the risk of HIV likely accumulates steadily over time (figure 1). This temporal probability trend should be taken into account when planning structured natural conception to minimize HIV-transmission risk.

In a broader view, the population effect of HIV shedding during ART in the United States (U.S.) will likely have the largest impact on men who have sex with men (MSM). We estimated the potential impact of transmission from MSM on ART by using a theoretical average of two unprotected anal sex acts per HIV-infected MSM per month with serodiscordant partners (unpublished data from the California Collaborative Treatment Group), at a probability of transmission of 0.00136 per act (92% reduction from 0.017 [6]). Estimating 442,000 HIV-infected MSM living in the U.S. (CDC 2009),and subsetting those on ART (59%), there are approximately 260,000 MSM on ART in the U.S. If sexually active men comprise 85% of MSM [8], we estimate approximately 7,000 transmissions in the U.S. related to MSM on ART and theoretically >1000 cases of transmitted drug resistance mutations (DRM), assuming 15% rate of transmitted DRM[9]. This suggests that a large pool of individuals on ART could still contribute substantially to the HIV epidemic.

Both in the case of serodiscordant couples trying to conceive children and in the overall HIV epidemic, additional measures for prevention of HIV-transmission are needed. Our group focused on identifying factors associated with HIV seminal shedding in MSM [10, 11]. In ART-naïve MSM, we identified that seminal shedding of cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus 8 were associated with increased HIV seminal shedding[10]; CMV and EBV were also associated with HIV-transmission[11]. We recently demonstrated that high-level seminal CMV shedding is associated with seminal shedding of HIV also in MSM receiving ART [12]. Since we only included MSM in this study, it needs to be determined if this

remains true for heterosexual individuals trying to conceive. While the treatment of bacterial sexually transmitted infections is a recognized strategy to reduce HIV-transmission[13], given our recent observations, an additional strategy might be the suppression of asymptomatic viral co-infections in the genital tract, especially CMV. Other considerations for adjunctive prevention measures include pre-exposure prophylaxis with antiretroviral medication and alternative ART regimens. As suggested by Mounzer and DiNubile, there are still limitations of current methods to prevent HIV-transmission among serodiscordant couples attempting to conceive a child, and this should lead to development of future strategies using combined approaches to minimize the risk.

Competing Interests

SG, SRM and SJLdoes not have any commercial or other associations that might pose a conflict of interest**.** DMS has received grant support from ViiV Pharmaceuticals and consultant fees from Gen-Probe.

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Legend

Figure 1: Theoretical Probability of Conception and HIV Acquisition over One Year

Theoretical cumulative monthly probability of conception and HIV acquisition over the period of one year for a serodiscordant couple with average fertility and HIV-infected male partner receiving antiretroviral therapy. Grey dots represent the cumulative probability of conception while the empty diamonds represents the cumulative probability of HIV-transmission. Note different scales in y-axis for the risk of conception (0.0-1.0) and for HIV transmission (0.0-0.1)

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