Semen as the Way Forward to Understand HIV-1 Transmission

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(See the major article by Imaz et al on pages 1512–9.)

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The central role of semen in sexual transmission of human immunodeficiency virus (HIV) type 1 infection is well established. Of the estimated 2.1 million new HIV-1 infections worldwide in 2015, the overwhelming majority occurred by sexual transmission, and semen is the most important genital fluid for such transmission events [1].

The simplest mathematical model for male-associated HIV-1 forward transmission includes 3 variables: (1) the probability of transmission within a partnership (transmission per sex act and number of sex acts); (2) the duration of seminal infectiousness (i.e., time above a critical threshold level of infectivity); and (3) the number of sexual partners. The product of these 3 variables defines the basic reproductive number ($R_o$), which is the average number of secondary cases of infection generated by a primary case in a susceptible population [2]. If $R_o$ remains $>1$, then transmission of HIV-1 increases. Thus the goal is to effect both behavioral changes and therapeutic interventions to decrease $R_o$ to $<1$.

Two major public health measures have been proved to diminish the forward transmission of HIV-1 from men to men and from men to women. The first is the implementation of safe sexual practices along with antiretroviral preexposure (and to a lesser extent postexposure) prophylaxis for HIV-1-seronegative at risk persons. Preexposure prophylaxis (PrEP) is highly effective in preventing transmission if the current antiretroviral drug combination with tenofovir and emtricitabine is used consistently [3]. The second public health measure relies on antiretroviral therapy (ART) for systemic viral suppression among persons already infected with HIV-1 [4]. Importantly, among serodiscordant couples, the integrated delivery of both ART and PrEP is associated with almost no viral transmission to the susceptible partner [5].

The caveat to these public health messages is that a small proportion of HIV-1-infected men (<10%) achieve viral suppression in their blood but continue to shed HIV-1 episodically in their semen, albeit at levels that are very low (<1000 HIV-1 RNA copies/mL of seminal plasma in 80% of shedding episodes) [6, 7]. Such low-level viral shedding in semen might be below a threshold necessary for sexual transmission; however, it is not known to what extent this low-level shedding in semen contributes to the residual HIV transmission risk that persists after the first 6 months of ART [8]. Thus, for HIV-serodiscordant couples in which the infected partner starts ART, other prevention options are needed, such as PrEP, until systemic viral suppression is achieved. Demonstrating the rapid suppression of seminal HIV-1 shedding after ART initiation would represent an important contribution toward decreasing the infectious level, shortening the duration of transmissible infectivity, and quickly decreasing $R_o$.

In this issue of The Journal of Infectious Diseases, Imaz et al [9] provide reassuring data from 15 ART-naive men who started abacavir, lamivudine, and dolutegravir once per day. Dolutegravir, a new integrase strand transfer inhibitor, reduces HIV-1 RNA in semen and in blood plasma. Dolutegravir (and the integrase strand transfer inhibitor agents as a class) is a potent antiretroviral agent but is highly bound to albumin and is also a substrate for the efflux transporter P-glycoprotein and breast cancer resistance protein, which are both known to limit penetration of dolutegravir into the semen, similarly to findings reported elsewhere for the protease inhibitor atazanavir [10]. In semen, the favorable viral decay kinetics and dolutegravir concentration of protein-unbound fractions, exceeding the in vitro median inhibitory concentration by 214-fold, are indeed reassuring because of the recommendation to use dolutegravir as first-line ART [11].

As discussed by Imaz et al [9], the association between seminal dolutegravir levels and viral suppression was weak. Furthermore, 4 of 5 participants with the lowest total dolutegravir concentrations had rapid suppression of seminal HIV-1 RNA even before suppression in blood plasma. These observations raise some important questions about interpreting...
semen and the seminal antiretroviral drug concentrations, the potential sources of HIV-1 RNA in semen, and compartmentalization of HIV-1 in the genital tract.

The effect of ART on seminal HIV-1 RNA levels is complicated. A variety of mechanisms contribute to poor tissue penetration of ART, and multiple sources of HIV-1 contribute to the final HIV-1 RNA levels measured in seminal plasma [12]. The hypothesis that tissue penetration of ART through the blood-testes-barrier can be blocked by P-glycoprotein and breast cancer resistance protein–like mechanisms and thus, contribute to a drug-impermeable sanctuary for HIV-1 replication and recrudescence is attractive but simplistic, given that there are multiple genital tract sources of HIV-1 that may contribute to the differences in HIV-1 RNA first-phase decay rates noted between plasma (half-life, 4.5 days) and semen (8.6 days) in this study and others [9, 13, 14].

For example, the contribution of testicular-associated HIV-1 to semen is generally considered minimal because vasectomy has no effect on the HIV-1 RNA level in seminal plasma [15], and other sources of virus from the more distal genital tract glandular structures (eg, prostate, seminal vesicles, bulbourethral glands, urethral glands of Littre, and periurethral submucosal and semen-associated mononuclear cells) are probably more important sources of semen virus. HIV-1 RNA levels measured in urethral swab fluid and voided urine after prostatic massage are independent predictors of seminal HIV-1 RNA level, which supports a urethral mucosal (or submucosal) or periurethral source for a good portion of the semen-associated virus [12]. Taken together, these observations suggest that antiretroviral drug levels in seminal plasma may underestimate the levels in any of the aforementioned genital tract sites that contribute HIV-1 to seminal plasma.

Despite the limitations associated with semen studies, including small sample sizes, difficulty in obtaining repeated semen samples, limited seminal fluid volume, and the complex biological sources of HIV-1 in semen, there is a need to replicate the pharmacokinetic study by Imaz et al [9] with the new, longer-acting ART drugs on the clinical horizon. These agents offer the potential to improve first-line ART and simplify PrEP, to decrease ART through the blood-testes-barrier can be blocked by P-glycoprotein and breast cancer resistance protein–like mechanisms and thus, contribute to a drug-impermeable sanctuary for HIV-1 replication and recrudescence is attractive but simplistic, given that there are multiple genital tract sources of HIV-1 that may contribute to the differences in HIV-1 RNA first-phase decay rates noted between plasma (half-life, 4.5 days) and semen (8.6 days) in this study and others [9, 13, 14].

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