The Journal of Infectious Diseases
EDITORIAL COMMENTARY

Mucosal HIV Shedding During ART

Aida Sivro[1,2] and Lyle R. McKinnon[1,2,3]

[1]Centre for the AIDS Programme of Research in South Africa, Durban; [2]Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada; and [3]Department of Medical Microbiology, University of Nairobi, Kenya

(See the major article by King et al, on pages 1534–40.)

Keywords. HIV; mucosal; viral shedding; antiretroviral therapy; Africa.

Viral load (VL) of human immunodeficiency virus (HIV) in the HIV-infected partner is the best described correlate of heterosexual HIV transmission, with each order of magnitude of VL associated with a 2- to 3-fold increased risk for the HIV-uninfected partner (both male-to-female and female-to-male) [1]. While antiretroviral therapy (ART) can dramatically reduce the rate of HIV transmission [2], placing this at the forefront of HIV prevention strategies, its effectiveness is contingent on consistent VL suppression [3]. Because a large proportion of HIV transmission occurs via sexual intercourse, the assumption was that by reducing plasma VL (PVL), ART is in parallel reducing genital VL (GVL). However, if this was not the case, the hypothesis was that suppressed PVL might not predict instances of onward HIV transmission due to "isolated" mucosal HIV shedding (PVL negative but GVL positive). Studies in semen have demonstrated that local shedding can be persistent and at levels corresponding to "transmissible" virus [4]. Indeed, although PVL has correlated with GVL in studies of both male and female genital secretions [5], this correlation was typically modest, and many found that a proportion of individuals are GVL positive even though PVL is undetectable, suggesting that local factors could influence the risk of transmission [6]. This was further supported by evidence that GVL also correlated with HIV transmission risk, independent of PVL [7]. Together these studies have suggested that a better understanding of how often, and in what circumstances, mucosal shedding of HIV occurs during effective HIV treatment might have important HIV-prevention implications.

In this issue of *the Journal of Infectious Diseases*, King et al report a large prospective study of >1100 African women on ART carried out to better understand the extent of, and potential contributors to, genital HIV shedding. This large study utilized specimens from 3 HIV clinical trials spanning several central and southern African countries. Genital HIV RNA was detected in 6% of >1400 visits made by women with undetectable PVL and 24% of approximately 400 visits by women with detectable PVL. Both of these estimates are well below those observed in untreated HIV infection, where approximately three-quarters of individuals are GVL positive. Importantly, <1% of women with suppressed PVL shed GVL consistently. Although there was no change in the magnitude of viral shedding, there was a decrease in the proportion of visits with genital shedding with increased ART duration in those with undetectable PVL. This is consistent with a previous report that showed a decline in shedding up to 18 months on ART [8], and suggests that the source of HIV mucosal shedding may decrease relative to the rate of PVL suppression. The observed rate of genital shedding of 6% is slightly lower, but generally consistent with, rates reported in previous studies (typically 10%–15%) that have had more limited power (n = 100–200) [9–11]. It is also consistent with studies that have suggested that ART leads to a rapid decline in GVL (more rapidly than PVL) [12], suggesting that ART is highly effective in reducing GVL levels.

One important contribution added by this study is the large sample size and inclusion of multiple study cohorts. While this increases the accuracy and generalizability of reported shedding rates, it also allows better characterization of predictors of shedding, which could be key to future interventions. The main predictors of genital shedding among women with undetectable PVL included advanced WHO classification of HIV disease stage and presence of genital ulcers or cervical tenderness, followed by type of ART regimen. The extent of HIV disease was found to influence HIV shedding in previous work [13], and may be indicative of increased systemic immune activation and immune dysregulation during chronic HIV infection. One might infer that with earlier ART initiation, as per all current guidelines, the rate of HIV shedding may decline further.

A long-standing hypothesis has suggested that local events may influence HIV shedding, as is supported by the finding that HIV shedding was associated with surrogates of genital inflammation (which are also a risk factor for HIV acquisition [14]). Indeed, this finding is supported

Received 11 October 2017; editorial decision 11 October 2017; accepted 12 October 2017; published online December 12, 2017.

Correspondence: L. R. McKinnon, PhD, 504-745 Bannatyne Ave, Winnipeg MB R3E 0J9 (lyle.mckinnon@umanitoba.ca).

The Journal of Infectious Diseases® 2017;216:1484–6

DOI: 10.1093/infdis/jix551

by several early, smaller studies that have suggested associations between cervical HIV shedding and increased frequencies of immune cells [15–18], higher mucosal cytokine levels [19, 20], cervical infections, herpes simplex type 2 reactivation, and/or vaginal dysbiosis [21–24]. Although the authors did not observe any effect of chlamydia and gonococcal infections on HIV shedding, this is likely due to low prevalence of these STIs. One weakness of the study is that many potential biological correlates of shedding were not measured, resulting in inability to determine the impact of these and whether they may have confounded the other predictors. One potential focus of future studies could be cytomegalovirus (CMV), an important opportunistic pathogen in HIV-infected individuals. In individuals with ART-suppressed HIV infection, CMV often reactivates asymptomatically and contributes to persistent immune activation and ongoing inflammation [25, 26]. However, because the HIV shedding observed by King et al was relatively uncommon, even if the specific factors predicting HIV shedding were to be identified, intervening may not carry significant public health impact if the predicted event is relatively rare because of the effectiveness of ART itself.

Another open question, related to local drivers of HIV shedding, is the underlying source of HIV in the genital mucosa. The extent to which viral shedding is due to the blood supply to the mucosa and/or due to local viral reservoirs is still unclear and likely depends on both the extent of viral replication at different anatomical sites and on levels of local and systemic inflammation. Blood flow could deliver cell-free virus to tissues and/or enhance the infection of local CD4 T cells. A case can also be made for compartmentalization of virus, as has been observed in virologic differences between the genital and systemic compartments [27]. One interpretation of the data, including the modest correlation between PVL and GVL, coupled with the observation of local drivers of HIV shedding, might suggest that HIV shedding can result from both infected tissue and new virus that is introduced from systemic circulation.

This study also addresses the question of the degree to which different ARVs are able to access different tissues. One recent study in SIV-infected nonhuman primates has suggested that extensive SIV RNA can be detected in multiple organ systems [28]. Suboptimal tissue penetration of the ARVs may not fully suppress viral production in the tissues, a result that is dependent on physiochemical properties of the ARVs as well as levels of tissue inflammation [29]. There are mixed reports in the literature regarding ART regimen and HIV mucosal shedding, and this issue is not entirely clarified by the current study. Future studies that do not rely on self-reported ART adherence data and instead female reproductive tract and plasma drug level measurements may provide more clarity. The choice of regimen could also be a confounding factor, if patients with different outcomes are given different regimens in the clinic; this is not really addressed by King et al. Finally, this issue will need to be re-evaluated as newer ART regimens become available, particularly those containing integrase inhibitors.

Finally, although these results support the concept that women on ART with suppressed PVL may still be at risk of transmitting HIV, the extent to which HIV shedding defined by GVL contributes to actual HIV transmission remains unclear. No HIV transmissions to HIV uninfected partners were observed by King et al (all participants were in an HIV-discordant couple). This supports a previous report in which approximately 14000 exposures did not lead to HIV transmission despite detection of shedding [13], evidence from an HIV Prevention Trials Network study (HPTN 502), where the only transmission was in a person yet to suppress PVL [2], and the lack of HIV transmission from PVL-suppressed individuals in the PARTNER study [30]. Therefore, the low rates of HIV shedding observed by King et al should be reassuring to those who are implementing test-and-treat strategies of HIV prevention. These data combined with previously published studies suggest that because HIV shedding is relatively uncommon and not associated with significant rates of HIV transmission, efforts to address the major challenges of increasing rates of HIV testing and achieving sustained ART adherence may be most critical for success in combination HIV prevention [31]. That being said, the development of additional therapeutic modalities to reduce mucosal inflammation, microbial dysbiosis, and other genital infections—the burden of which is higher in HIV-positive individuals and which contribute to significant morbidity—would be a major benefit to women globally, regardless of whether there are any implications for HIV transmission.

Note

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med **2000**; 342:921–9.
2. Cohen MS, Chen YQ, McCauley M, et al.; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med **2011**; 365:493–505.
3. Hughes JP, Baeten JM, Lingappa JR, et al.; Partners in Prevention HSV/HIV Transmission Study Team. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. J Infect Dis **2012**; 205:358–65.
4. Sheth PM, Kovacs C, Kemal KS, et al.; Toronto Mucosal Immunology Group. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. AIDS **2009**; 23:2050–4.
5. Kovacs A, Wasserman SS, Burns D, et al.; DATRI Study Group; WIHS Study Group. Determinants of HIV-1

shedding in the genital tract of women. Lancet **2001**; 358:1593–601.
6. Kaul R, Pettengell C, Sheth PM, et al. The genital tract immune milieu: an important determinant of HIV susceptibility and secondary transmission. J Reprod Immunol **2008**; 77:32–40.
7. Baeten JM, Kahle E, Lingappa JR, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. Sci Transl Med **2011**; 3:77ra29.
8. Launay O, Tod M, Tschöpe I, et al.; ANRS EP24 GYNODYN Study Group. Residual HIV-1 RNA and HIV-1 DNA production in the genital tract reservoir of women treated with HAART: the prospective ANRS EP24 GYNODYN study. Antivir Ther **2011**; 16:843–52.
9. Ondoa P, Gautam R, Rusine J, et al. Twelve-month antiretroviral therapy suppresses plasma and genital viral loads but fails to alter genital levels of cytokines, in a cohort of HIV-infected Rwandan women. PLoS One **2015**; 10:e0127201.
10. Fiore JR, Suligoi B, Saracino A, et al. Correlates of HIV-1 shedding in cervicovaginal secretions and effects of antiretroviral therapies. AIDS **2003**; 17:2169–76.
11. Venkatesh KK, DeLong AK, Kantor R, et al. Persistent genital tract HIV-1 RNA shedding after change in treatment regimens in antiretroviral-experienced women with detectable plasma viral load. J Womens Health (Larchmt) **2013**; 22:330–8.
12. Graham SM, Holte SE, Peshu NM, et al. Initiation of antiretroviral therapy leads to a rapid decline in cervical and vaginal HIV-1 shedding. AIDS **2007**; 21:501–7.
13. Prazuck T, Chaillon A, Avettand-Fènoël V, et al. HIV-DNA in the genital tract of women on long-term effective therapy is associated to residual viremia and previous AIDS-defining illnesses. PLoS One **2013**; 8:e69686.
14. Masson L, Passmore JA, Liebenberg LJ, et al. Genital inflammation and the risk of HIV acquisition in women. Clin Infect Dis **2015**; 61:260–9.
15. Jaspan HB, Liebenberg L, Hanekom W, et al. Immune activation in the female genital tract during HIV infection predicts mucosal CD4 depletion and HIV shedding. J Infect Dis **2011**; 204:1550–6.
16. Anderson BL, Wang CC, Delong AK, et al. Genital tract leukocytes and shedding of genital HIV type 1 RNA. Clin Infect Dis **2008**; 47:1216–21.
17. Homans J, Christensen S, Stiller T, et al. Permissive and protective factors associated with presence, level, and longitudinal pattern of cervicovaginal HIV shedding. J Acquir Immune Defic Syndr **2012**; 60:99–110.
18. Coleman JS, Hitti J, Bukusi EA, et al. Infectious correlates of HIV-1 shedding in the female upper and lower genital tracts. AIDS **2007**; 21:755–9.
19. Herold BC, Keller MJ, Shi Q, et al. Plasma and mucosal HIV viral loads are associated with genital tract inflammation in HIV-infected women. J Acquir Immune Defic Syndr **2013**; 63:485–93.
20. Mitchell C, Balkus JE, Fredricks D, et al. Interaction between lactobacilli, bacterial vaginosis-associated bacteria, and HIV Type 1 RNA and DNA Genital shedding in U.S. and Kenyan women. AIDS Res Hum Retroviruses **2013**; 29:13–19.
21. Gitau RW, Graham SM, Masese LN, et al. Effect of acquisition and treatment of cervical infections on HIV-1 shedding in women on antiretroviral therapy. AIDS **2010**; 24:2733–7.
22. Cu-Uvin S, Hogan JW, Caliendo AM, Harwell J, Mayer KH, Carpenter CC; HIV Epidemiology Research Study. Association between bacterial vaginosis and expression of human immunodeficiency virus type 1 RNA in the female genital tract. Clin Infect Dis **2001**; 33:894–6.
23. LeGoff J, Weiss HA, Gresenguet G, et al. Cervicovaginal HIV-1 and herpes simplex virus type 2 shedding during genital ulcer disease episodes. AIDS **2007**; 21:1569–78.
24. Rebbapragada A, Wachihi C, Pettengell C, et al. Negative mucosal synergy between Herpes simplex type 2 and HIV in the female genital tract. AIDS **2007**; 21:589–98.
25. Nason MC, Patel EU, Kirkpatrick AR, et al. Immunological signaling during herpes simplex virus-2 and cytomegalovirus vaginal shedding after initiation of antiretroviral treatment. Open Forum Infect Dis **2016**; 3:ofw073.
26. Smith DM, Nakazawa M, Freeman ML, et al. Asymptomatic CMV replication during early human immunodeficiency virus (HIV) infection is associated with lower CD4/CD8 ratio during HIV treatment. Clin Infect Dis **2016**; 63:1517–24.
27. Kemal KS, Foley B, Burger H, et al. HIV-1 in genital tract and plasma of women: compartmentalization of viral sequences, coreceptor usage, and glycosylation. Proc Natl Acad Sci U S A **2003**; 100:12972–7.
28. Estes JD, Kityo C, Ssali F, et al. Defining total-body AIDS-virus burden with implications for curative strategies. Nat Med [published online ahead of print 2 October, 2017]. doi: 10.1038/nm.4411.
29. Fletcher CV, Staskus K, Wietgrefe SW, et al. Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues. Proc Natl Acad Sci U S A **2014**; 111:2307–12.
30. Rodger AJ, Cambiano V, Bruun T, et al.; PARTNER Study Group. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA **2016**; 316:171–81.
31. Grobler A, Cawood C, Khanyile D, Puren A, Kharsany ABM. Progress of UNAIDS 90-90-90 targets in a district in KwaZulu-Natal, South Africa, with high HIV burden, in the HIPSS study: a household-based complex multilevel community survey. Lancet HIV [published online ahead of print 2 August, 2017]. doi: 10.1016/S2352-3018(17)30122-4.