Hot News

HIV load in plasma and semen – do they match each other?

Earlier this year, the Swiss Federal Commission for HIV/AIDS sparked controversy when they suggested that HIV-infected individuals on antiretroviral therapy who are fully adherent and maintaining undetectable plasma viremia (< 50 HIV RNA copies/ml) for at least six months and having no concurrent sexually transmitted infections, essentially cannot transmit HIV through heterosexual vaginal intercourse. A recent French study (Marcelin, et al. AIDS. 2008;22:1677-9), however, found that 5% of men in serodiscordant couples had intermittently detectable HIV in their semen, despite meeting the criteria specified in the Swiss statement. One possible reason for detectable semen viral load despite undetectable HIV in the blood is that antiretroviral drugs may fail to reach the genital compartment. Like the brain, the testes are isolated by a physical barrier that prevents certain substances, including many drugs, from passing through.

At the XVII International AIDS Conference, held in Mexico last August, Australian researchers presented one study looking at how well different antiretroviral agents penetrate the semen (Chan, et al. XVII IAC, Mexico City, August 3-8, 2008. Abstract TUPE0077). Their analysis included data from a cross-sectional cohort of 119 HIV-positive men divided into treated (n = 81) and untreated groups (n = 38). Participants had well-controlled HIV, with undetectable plasma viremia, a median CD4 count of 595 cells/mm^3, and a median treatment duration of about 30 months. Blood and semen were collected concurrently to provide paired samples. The investigators assessed semen viral load using an assay with a limit of detection of 250 HIV RNA copies/ml. They used high-performance liquid chromatography to measure antiretroviral drug concentrations in the blood and semen.

All treated individuals had undetectable HIV RNA in both their blood plasma and their semen. Median blood and semen concentrations for atazanavir were 630 and 87.5 mg/l, respectively (the latter below the therapeutic concentration of 150 mg/l). Corresponding concentrations for lopinavir were 7,428 and 465 mg/l, respectively (again, the semen level was below the therapeutic concentration of 1,000 mg/l). In contrast, 80% of patients taking nevirapine exceeded the therapeutic blood concentration (> 3,450 mg/l), and the mean semen concentration was right about this level (3,462 mg/l). All participants taking efavirenz attained therapeutic blood concentrations (at least 1,000 mg/l), but no efavirenz penetrated the semen. The investigators concluded that antiretroviral agents that suppress blood viral load also suppress seminal viral load, despite differential drug penetration of semen. Based on these findings, they suggested that "fully suppressive antiretroviral therapy may significantly reduce the risk of sexual transmission of HIV-1".

This study adds to the evidence that HIV transmission is likely to be very rare if an HIV-positive individual is on effective antiretroviral therapy for at least six months (Barreiro, et al. J Acquir Immune Defic Syndr. 2006;43:324-6), but does indicate the potential for a small residual risk, which perhaps could be further minimized using nevirapine. This information is relevant since a substantial number of heterosexual HIV-serodiscordant couples are currently seeking reproductive counseling using procedures other than *in vitro* fertilization, which is expensive, has a relatively low success rate, and raises ethical concerns (Barreiro, et al. Hum Reprod. 2007;22:2353-8). In this regard, heterosexual vaginal intercourse during a woman's fertile days following prior confirmation of fertility in both partners should be considered a valid option.

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No longer room for valproic acid as anti-HIV therapy

Highly active antiretroviral therapy (HAART) can reduce and maintain plasma HIV RNA levels below the limit of detection (< 50 copies/ml) in most adherent patients. Despite its benefits, antiretroviral therapy cannot eliminate HIV infection since there is an early establishment of a latent HIV reservoir, mainly constituted by a pool of "resting" CD4$^+$ T-cells, following acute infection. Hypothetically, the use of compounds that selectively induce the expression of quiescent proviral genomes might allow reducing the size or even eliminating the latent HIV reservoir in patients with long-term suppression of viremia.

The histone deacetylase (HDAC) is a critical enzyme involved in the regulation of HIV latency. It introduces an acetyl group in the N-terminal domain of histones, increasing their affinity for the DNA, which then is no longer substrate for transcription. Therefore, HDAC inhibits DNA replication and transcription, favoring HIV latency. Valproic acid is an anticonvulsant and mood-stabilizing drug, extensively used in the treatment of epilepsy, bipolar disorders, or migraine prophylaxis. Valproic acid acts

as a non-selective HDAC inhibitor and may induce viral and cellular gene expression from resting CD4+ T-cells. In 2005, Lehrman, et al. (Lancet. 2005;366:549-55) tested the ability of valproic acid to deplete HIV infection of resting CD4+ T-cells. These authors selected four HIV-infected patients on HAART with long-term suppression of viremia (< 50 HIV RNA copies/ml) for > 2 years. After intensifying the effect of HAART with enfuvirtide during 4-6 weeks, patients received valproic acid (500-750 mg twice daily) for three months. A significant decline in the number of resting CD4+ T-cells was noticed. However, this observation could not be confirmed by Siliciano, et al. (J Infect Dis. 2007;195:833-6) who did not observe any ancillary effect on the decay of the latent HIV reservoir. The apparent discordance between these results was attributed to differences in study design: (i) the prior use of enfuvirtide by Lehrman, et al., which could have driven a more intensive suppressive effect on viral replication and new cellular infections, (ii) the different valproic acid doses used in the two studies, or (iii) differences in the methodologies used to measure the number of resting CD4+ T-cells.

Two recent reports (Sagot-Lerolle, et al. AIDS. 2008;22:1125-9; and Archin, et al. AIDS. 2008;22:1131-5) had ended the controversy about the potential role of valproic acid for accelerating the decay of the HIV reservoir on HAART. Both studies agreed that the effect of adding valproic acid to conventional HAART seems to be negligible and does not impact significantly on the size of the HIV reservoir.

Alternative approaches using drugs such as enfuvirtide, maraviroc, or raltegravir, which by themselves reduce new HIV infections and potentially the size of the HIV reservoir, along with more potent HDAC inhibitors are currently under evaluation. Therefore, the opportunity to find a way to eradicate HIV infection, although extremely difficult, is still open.

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Clinical impact of minor drug-resistant virus populations on treatment response

Transmitted drug-resistant HIV can compromise initial antiretroviral therapy; therefore, its detection is important for patient management, and accordingly, guidelines recommend drug resistance testing before initiating HAART (Hirsch, et al. Clin Infect Dis. 2008;47:266-85). The absence of drug pressure in antiretroviral-naive persons may cause transmitted drug-resistant viruses to decline to levels undetectable by conventional bulk sequencing, persisting only as minority drug-resistant variants (Briones and Domingo. AIDS Rev. 2008;10:93-109). In a recent study, CDC researchers used sensitive tests to investigate evidence of transmitted drug resistance in antiretroviral-naive persons and assessed the clinical implications of minority drug-resistant variants (Johnson, et al. PLoS Med. 2008;5:1112-22). The authors examined 508 newly diagnosed HIV-positive persons in North America who had no detectable (wild-type) or one or more resistance-associated mutations by conventional sequencing. Eight validated real-time PCR-based assays were used to test for minority drug resistance mutations (protease L90M and reverse transcriptase M41L, K70R, K103N, Y181C, M184V, and T215F/Y). The sensitive real-time PCR testing identified 1-3 minority drug resistance mutation(s) in 34/205 (17%) newly diagnosed persons who had wild-type virus by conventional genotyping. On the other hand, at least one minority drug-resistant variant was identified among 30/303 (10%) samples with bulk genotype resistance mutations.

In a second step, CDC investigators performed a case-control study to assess the impact of three relevant drug resistance mutations at baseline from a separate group of 316 previously antiretroviral-naive persons with no evidence of drug resistance on bulk genotype testing who were placed on efavirenz-based regimens. Interestingly, 7/95 (7%) persons who experienced virologic failure had minority drug resistance mutations at baseline, while minority resistance was found in only 2/221 (0.9%) treatment successes ($p = 0.004$). Based on these results, the authors concluded that a considerable proportion of transmitted HIV-1 drug resistance may be missed using conventional bulk genotyping and that minority drug resistance mutations can have clinical consequences.

The results of this study, however, contrast with findings from a recent French report (Peuchant, et al. AIDS. 2008;22:1417-23), which has not recognized any significant clinical impact of minority drug-resistant viruses on treatment outcomes when examining 172 antiretroviral-naive HIV patients who initiated HAART. Differences in methodology as well as in antiretroviral regimens used could account for the discordant results between the studies. Clearly, further work is warranted to clarify whether the use of more sensitive tools for drug resistance testing could improve antiretroviral treatment outcomes and therefore should be implemented in clinical settings.

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