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HIV DNA Decay During Antiretroviral Therapy - Lessons from a Clinic-based Cohort Study

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Antiretroviral therapy (ART) suppresses HIV replication which leads to plasma viral loads (pVLs) below the limit of quantification in the majority of treated people. Despite suppression of plasma viremia, however, a latent HIV reservoir persists that prevents eradication of the infection (reviewed in [1, 2]). Even when plasma HIV RNA is suppressed, HIV DNA is detectable in infected cells; indeed, HIV DNA levels have frequently been used to evaluate the size of the HIV reservoir. For this reason, determining the factors that affect the decay and levels of HIV DNA in people on ART has been a focus of many studies.

To address this question, Golob *et al.* describe the decay of total HIV DNA in a clinic-based cohort of 111 people with HIV who had been virally suppressed on ART for at least 5 years [3]. The subsequent decay of total HIV DNA in peripheral blood mononuclear cells (PBMC) was assessed over a median of 1.4 years. There was a wide range in baseline HIV DNA levels and the median half-life for decay was approximately 12 years. There was no evidence for an association between HIV DNA and gender, race, antiretroviral drug class or risk factor for HIV infection. The only factor that was associated with HIV DNA level was age: HIV DNA was lower in participants who achieved virologic suppression at a younger age.

What accounts for the association between age at time of virologic suppression and HIV DNA level? One possibility is that younger individuals generally have higher frequencies of naïve CD4 T cells, which tend to be less prone to HIV infection than memory T cells [4].

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Alternatively, younger people may have been infected for a shorter period of time than older individuals prior to ART initiation leading to lower pre-ART HIV DNA levels. In another longitudinal study, higher HIV DNA levels before ART initiation was associated with higher HIV DNA while on ART, even after many years of virologic suppression, suggesting that early events before initiation of therapy have long-lasting consequences [5].

In the study by Golob et al, HIV DNA decay in participants with undetectable pVL at all time points was compared to those with detectable pVL, either below the limit of quantification (<40 copies/microliter) or above the limit of quantification ("viral blips"). Intriguingly, although the differences were not statistically significant, individuals with consistently undetectable pVL (n=21) appeared to have a shorter HIV DNA half-life (mean $t_{½}$=87 months) than participants with at least one episode of detectable-but-not-quantifiable pVL (n=82; mean $t_{½}$ = 145 months) or those who had viral blips (n=4; mean $t_{½}$ =264 months). A similar finding was recently reported in a study of >1000 participants in the Swiss HIV Cohort Study [6]. In that study, there was a significant correlation between viral blips and slower HIV DNA decay, perhaps reflecting lower adherence to ART among those with blips. Alternatively, people with higher HIV DNA levels and/or those with more episodic clonal proliferation of cells harboring replication-competent virus may be more likely to intermittently produce plasma virus.

What do the findings from Golob et al tell us about the mechanisms behind HIV persistence in people on ART? First, they observed wide variability in HIV DNA levels (between 0.01 and 4.8 *pol*-copies per microgram of genomic DNA and per CD4 cell number/microliter). Previous studies have also shown marked differences in HIV DNA levels in people on ART; for example, in a cross-sectional study comparing different measures of HIV persistence, HIV DNA values varied over a 2-log range [7]. This striking variability in HIV DNA "set-point" in people on ART may reflect differences that occurred before treatment was started or other factors that affect the HIV proviral landscape, including proportion of HIV DNA in different T cell subsets or differences in the amount of defective HIV DNA that has accumulated. Second, Golob et al observe a slow decay in HIV DNA levels with a median half-life of about 12 years; in this cohort, however, HIV DNA was measured after at least 5 years of ART, so HIV DNA decay before this time point could not be assessed. This gap has been filled in by previous longitudinal studies [8, 9] which found HIV DNA levels drop most rapidly during the first year of ART (approximately 7-fold), followed by a slower decline from years 1 to 4 (approximately 2-fold), and then an even slower decay from year 4 of ART onwards (half-life of 13 years for this phase [5], similar to that observed by Golob et al.) The very slow decay of HIV DNA after year 4 of ART may reflect ongoing loss of HIV-infected cells counterbalanced by clonal proliferation of infected cells, perhaps driven by specific antigens or induced by cytokines [10]. Understanding the longitudinal evolution of infected cell clones and the HIV proviral landscape over time (including in different T cell memory subsets and in relation to HIV-specific immune responses) may shed light on the forces that shape HIV persistence.

Finally, even though HIV DNA assays – such as the one in the study by Golob et al. – have often been used to assess the size of the HIV reservoir, the recognition based on sequencing studies that most HIV DNA in people on ART is defective [11, 12] highlights the need for

tests that more accurately measure the replication-competent HIV reservoir which is, after all, the main barrier to cure. Recently, a digital-droplet PCR-based assay that detects intact proviral DNA by using techniques designed to filter out defective and hypermutated HIV DNA sequences, has been developed [13]; this measure appears to more closely approximate the size of the replication-competent HIV reservoir. Careful longitudinal studies using this and other novel assays – along with comparisons to measures such as the viral outgrowth assay, assessment of the ratio of intact to total HIV DNA over time, and identification of gene expression profiles of reactivated latent cells [14] – may shed light on the mechanisms that lead to HIV persistence. Ultimately, the value of studies such as that by Golob et al will be to more precisely define the factors involved in establishing and shaping persistence so that therapeutic interventions can be rationally designed to eradicate or control the HIV reservoir.

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