

Plasma HIV-1 RNA Levels During Antiretroviral Therapy: How Low Is Low Enough?

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Antiretroviral therapy prevents human immunodeficiency virus type 1 (HIV-1)-related complications by suppressing viral replication [1]. To forestall virologic rebound and treatment failure, a regimen must reduce the plasma HIV-1 RNA to a threshold below which the virus does not evolve and develop drug resistance. Although this threshold has not been precisely defined, it is probably near the level of quantification for the conventional assays used in the past decade (ie, <50–75 copies/mL), and hence most clinicians have aimed to maintain a viral load that is “undetectable.” This goal can easily be achieved with many modern regimens [2, 3]. Recently, the sensitivity of these assays has improved, resulting in a lower threshold for undetectability. This change has led to a clinical quandary: Should patients who have very low but detectable viremia be considered as having failed therapy?

To address this question, Doyle and colleagues performed an analysis of patients on therapy who had viral loads below 50 copies/mL as measured by the Abbott RealTime HIV-1 assay [4]. The lower limit of quantification of this test is 40 copies/mL; below this threshold, the assay detects HIV-1 RNA, but only qualitative results (detectable or non-detectable) are reported. Given the lack of clarity regarding the significance of these low RNA levels, the treating clinician was informed only that the patient’s viral load was below 50 copies/mL, and, hence, the actual results did not affect the clinician’s decision making. Based on their unreported results, patients were retrospectively divided into 3 groups: those with viral load of 40–49 copies/mL, those with a detectable but unquantifiable viral load (RNA^{pos}), and those with an undetectable viral load (RNA^{neg}). Of 1247 patients, 19% had an initial viral load of 40–49 copies/mL, 41% had a detectable but nonquantifiable viral load <40 copies/mL, and 40% had a truly undetectable viral load. Most patients who had viral load between 40–49 copies/mL had only recently achieved virologic suppression (median 0.2 years), whereas those who were RNA^{pos} and RNA^{neg} had been suppressed much longer (median 1.3 years and 2.8 years, respectively). Among the

subset of patients for whom information was available, those who had a viral load of 40–49 copies/mL were significantly less likely to have perfect adherence, as assessed by pharmacy records, than those in the RNA^{neg} group.

So what were the virologic outcomes over the subsequent 12 months? Compared with those who were RNA^{neg}, a higher percentage of patients who had a viral load of 40–49 copies/mL had a subsequent viral load above 50 copies/mL (4% vs 34%). This finding is not surprising; patients who had a viral load just <50 copies/mL might have random variation in RNA levels resulting in intermittent values above this line [5]. When Doyle and colleagues focused on a level of viremia more clearly associated with treatment failure (>400 copies/mL), those who had a viral load of 40–49 copies/mL were still more likely to have virologic rebound (13%) than those whose viral load was below 40 copies/mL (3.8% in the RNA^{pos} and 1.2% in the RNA^{neg} group). Based on these results, the authors conclude that “the goal of [highly active antiretroviral therapy] may need to be revised to a lower cutoff than 50 copies/mL.”

There are reasons to pause before adopting this recommendation. Even though the investigators performed appropriate analytic adjustments, it is

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difficult to exclude the possibility that the results may have been at least partially affected by survivor bias. Patients who have had virologic suppression for longer periods of time are less likely to have rebound than those suppressed for shorter durations [6, 7]; in this regard, patients in the current study who were RNA^{neg} had been on therapy much longer than those who had a viral load of 40–49 copies/mL. In fact, many if not most of the patients whose viral load was 40–49 copies/mL may have been in the third phase of viral decay, which is estimated to have a half-life of 9–15 months after initiation of therapy [8], and hence not yet at a steady state. Because one would expect all patients to have a low but detectable HIV-1 RNA level during the first several months of suppressive therapy, any successful regimen might be considered as having failed if the test were performed during the third phase of decay. This supposition is borne out by the observation that, in a subanalysis, a substantial proportion of patients who had a detectable initial viral load did *not* have a detectable viral load when measured 3–4 months later. Moreover, the risk of virologic failure was most clearly associated with persistently detectable viremia: Only patients who had 2 consecutive detectable viral load measurements had a significantly higher hazard ratio for virologic rebound above 400 copies/mL.

So, how low is low enough? The U.S. Department of Health and Human Services recommends using a threshold of 200 copies/mL to define virologic success versus failure [9]. This recommendation is based in part on the lack of evidence that HIV-1 replicates and evolves when RNA levels are below this threshold and the observation that virologic failure was uncommon once viremia reached these levels [10]. The findings of the current study suggest that this threshold may be too high for a patient who has quantifiable and persistently detectable viremia, but confirmatory studies are needed.

Until such studies are available, a careful assessment of adherence should be the first response to low levels of viremia. Whether treatment for such individuals should be modified or intensified is currently unknown.

Of note, having 2 consecutive low but quantifiable plasma HIV-1 RNA levels was uncommon in this cohort. The more common scenario was having a detectable but unquantifiable viral load. Among individuals who had a single detectable but unquantifiable viral load, the risk of subsequent virologic failure to above 400 copies/mL over the following year was 3.8%; this was only slightly higher than the 1.2% risk among those who had a truly undetectable viral load. Detectable viremia below 40 copies/mL may not be clinically important with regard to risk of subsequent virologic outcomes.

Several factors might contribute to persistent viremia during effective therapy, including release of virus from latent reservoirs or cycles of viral replication. Based on a series of intensification studies [11–14], viral replication is clearly not an important cause of viremia among those with very low plasma HIV-1 RNA levels (ie, below 3 copies/mL). Controlled studies using intensification as a probe may be needed to determine whether viral replication is a cause of low but more readily detectable levels of viremia, as was suggested by a small intensification study of individuals with viremia between 3–23 copies/mL [15]. The results of this latter study—which needs confirmation—are generally consistent with those of the current study.

We believe that the implications of low-level viremia for treatment outcomes—including the extent of immune reconstitution and rates of non-AIDS morbidity—are among the more important issues for clinical research. Until such studies are performed, clinicians and their patients are advised to pay careful attention to adherence and regimen potency if the viral load is consistently detectable and quantifiable using modern

sensitive assays. To advance emerging work on HIV-1 eradication, we also need to understand the origin of low-level viremia [16] in treated patients and to determine whether there is ongoing viral replication in tissue reservoirs that might prevent a durable response to those curative interventions now being considered.

Notes

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