HIV RNA and Genotype in Resource-Limited Settings: Can We Do Better?

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(See the Major Article HIV/AIDS by Aghokeng et al on pages 99–109.)

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World Health Organization (WHO) recommendations to scale up antiretroviral treatment (ART) have impacted mortality, morbidity, and potentially the transmission of human immunodeficiency virus (HIV) [1, 2]. Because suppression of virus replication reduces both disease progression and transmission, virologic failure provides a surrogate biologic marker for the effectiveness of treatment. Measurement of viremia among treated and untreated individuals and summed as a “community viral load” provide a population estimate of transmissible virus and the risk of disease progression [3–5]. Similarly, the patterns, frequency, and characteristics of drug resistance mutations predict the potential effectiveness of second-line regimens, the mutations more likely to be transmitted, and susceptibility to preexposure prophylaxis and first-line regimens [6–8].

There is a wide gulf between the drugs and diagnostic testing recommended in the United States and Europe and the WHO recommendations for public health ART in resource-limited settings. How can resources best be focused on virologic monitoring for the successful scale-up of treatment in resource-limited settings? In a cross-sectional study in this issue of Clinical Infectious Diseases, Aghokeng et al contend that “limited access to virologic monitoring in developing countries is a major weakness of the current antiretroviral treatment (ART) strategy in these settings” [9]. Implementing virologic monitoring in resource-limited settings includes challenges in providing transport, laboratory and clinical infrastructure, and trained personnel [10], competing for resources for prevention and treatment [11]. Cost-effectiveness models conclude that viral load monitoring may be feasible and affordable only as the cost is reduced below $20 [12–14]. New lower-cost point-of-care viral load tests may address some of these concerns [15–17]; however, benefit and cost will vary among different settings [18]. With another 9.7 million people eligible for ART in resource-limited settings, every aspect of public health ART delivery deserves scrutiny to improve adherence, effectiveness, and the long-term delivery of services.

Aghokeng et al, for the Agence Nationale de Recherches sur la SIDA (ANRS) 12186 study, analyzed virologic failure and drug resistance in a cross-sectional sample of public health ART among nearly 4000 individuals in 7 programs in Africa and Asia [9]. The individuals sampled were consecutive, consenting participants in ART programs, excluding those lost to follow-up and drop-outs from HIV treatment and prevention [19, 20]. Among these as-treated cohorts, they describe a striking heterogeneity in the frequency of virologic failure, varying from a site with <3% to one with >20% virologic failure after 12 months of ART. These differences among sites are not associated with geography (Asia vs Africa), HIV type 1 subtype (CRF01AE vs CRF02AG), non-nucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitor combination regimens, or patient demographics. Rather, they hypothesize that HIV drug resistance early warning indicators—antiretroviral prescribing practices, on-time ART drug pickup and clinic appointment keeping, percentages of patients lost to follow-up, and antiretroviral drug stock-outs and shortages—are more likely to account for these differences [21]. Unfortunately, these parameters were not systematically collected from the 7 sites, so associations cannot be drawn between rates of virologic failure and these less expensive and less technically demanding programmatic measures [22].
As resources are allocated to monitor viral load, the experience in resource-rich countries, where monitoring is routinely provided thrice yearly, may be instructive [23]. With modern once-daily, full-dose drug combinations, virologic failure rates in clinical trial settings in the United States using stringent intention-to-treat analysis have arrived at virologic failure rates (including missing = failure rates) of approximately 14% (A5202). In an analysis of 49 studies in resource-limited settings, including 30,016 individuals gathered by McMahon and colleagues, 16% of the pooled on-treatment population and 30% of the intention-to-treat population had virologic failure [24]. In assessments of population-based ART in the United States, where viral load monitoring is routinely required, current rates of virologic failure after 1 year considerably exceed 20% [25–27]. Thus, it is difficult to ascribe rates of virologic failure in resource-limited settings to a lack of viral load monitoring. Even the program surveyed by the ANRS 12168 study, in Cote d’Ivoire, which was in the midst of civil strife and economic collapse, performed better than many of the public health ART programs in the United States where viral load monitoring is required.

What about the acquisition of resistance in the absence of viral load monitoring? The capacity of national laboratories in Africa and Asia to identify drug resistance continues to improve [28], and the laboratories in the ANRS studies were able to sequence virus from >90% of samples. In a recent, large US clinical trial in which viral load was measured every 3 months, the frequency of resistance among study subjects receiving optimal first-line regimens was 62% at virologic failure [29]. This is not dissimilar to the 70% with drug resistance in the PharmAccess African Studies to Evaluate Resistance (PASER) study where RNA was measured after 12 months of a first-line regimen [30]. In the ANRS 1268 study, as illustrated in Table 3 of the Aghokeng et al article [9], the overall prevalence of major drug resistance mutations without any RNA monitoring was 71% and 86% among those assessed after >12 and >24 months, respectively, consistent with evidence of a modest increase in resistance without monitoring among recipients of first-line treatment in Africa [31–33].

The cost of genotyping could be reduced and accessibility increased by adoption of homebrew assays and dried blood spot testing [34–36], and the quality of genotyping in laboratories in resource-limited settings is improving [28, 37]. The cost-effectiveness of genotyping in South Africa, as estimated by Levison et al, was sensitive to prevalence of wild-type virus and test cost, with genotyping at <$100, becoming cost-saving [38]. However, consensgenotyping as in the ANRS 12186 study distinguishes only those with and without major drug resistance mutations, and there are ample demonstrations of low levels of drug resistance mutations that are detectable only by specialized tests that mitigate against the initiation or resumption of an NNRTI-based regimen [39–41].

To integrate public health ART into primary healthcare, to strengthen health services, and to sustain affordable treatment, the WHO has promulgated an approach that is a compromise between the practices recommended in resource-rich settings and those that are practical and possible in resource-constrained settings. Debate will continue about balancing the costs of drugs, performing monitoring, and strengthening health systems as investments to promote equitable economic development for countries struggling against poverty and the high burdens of HIV [42, 43].

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