

The Clinical Implications of Pretreatment Drug Resistance—A Moving Target

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Drug-resistance testing is not routinely available in the low- and middle-income countries with the highest human immunodeficiency virus (HIV) prevalence. The choice of first-line antiretroviral therapy (ART) regimens in these areas is thus informed by HIV drug resistance surveillance studies in people who initiate therapy. World Health Organization (WHO)-prescribed studies initially quantified transmitted drug resistance (TDR) in recently infected individuals, but these studies were subsequently expanded to assess pretreatment drug resistance (PDR) by including people who present for initial therapy, those in whom ART was interrupted, and those who received ART to prevent mother-to-child transmission. This surveillance strategy reflects the programmatic reality of the WHO's public health approach that initiates HIV treatment in all people without a documented history of virological failure (VF) on the same first-line regimen [1]. Not surprisingly, PDR rates are usually higher than those of TDR, although there has been a worrisome gradual upward trend in both. Nonnucleoside reverse transcriptase

inhibitor (NNRTI)-associated PDR rates approach 10% in Latin America and many parts of Southern and Eastern Africa, with lower rates in Asia and West and Central Africa [2]. NNRTI-associated PDR causes great concern, as any one of several mutations is often sufficient to markedly reduce NNRTI susceptibility. Conversely, some nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)-associated drug-resistance mutations (DRMs), particularly several of the thymidine analog mutations selected by zidovudine (AZT) and stavudine (d4T), are less likely to compromise an NRTI backbone that contains tenofovir (TDF).

The study by Derache and colleagues is the largest to assess the effect of baseline NNRTI resistance on the virological response to the fixed-dose combination of TDF/emtricitabine (FTC)/efavirenz (EFV), one of the WHO-recommended first-line ART regimens [3]. It is also one of the largest studies to quantify PDR prevalence using a next-generation sequencing technology, Illumina MiSeq, in place of the more common dideoxynucleoside Sanger sequencing technology. The authors defined PDR at frequencies of $\geq 20\%$ and $\geq 5\%$ to detect 1 or more mutations from a list of WHO-defined surveillance DRMs [4] within a person's virus population. The 20% threshold approximates the sensitivity of Sanger sequencing, which usually detects mutations in $\geq 20\%$ of a person's plasma viruses. The more sensitive 5% threshold is often

used to identify lower abundance mutations not typically detected by Sanger sequencing.

The prevalence of NNRTI-associated PDR in the cohort of 1148 people undergoing successful resistance testing was 8.8% and 11.1% using the 20% and 5% thresholds, respectively. Both prevalences are similar to recently reported PDR rates from Southern and Eastern Africa [2]. Additional analysis was performed on the 837 people in the cohort who began therapy and had at least 1 follow-up virus load test. Of these, 67 (8.0%) and 82 (9.8%), respectively, had NNRTI-associated PDR using the 20% and 5% thresholds. Five (0.6%) and 7 (0.8%) people had combined NRTI plus NNRTI PDR using these thresholds. Sequencing detected just 1 NNRTI-associated DRM, K103N, in approximately 75% of persons with NNRTI-associated PDR, whereas K103N was detected in combination with a second NNRTI-associated DRM in about 10% of persons.

In the few people with combined NRTI plus NNRTI PDR, there was a strong, albeit nonstatistically significant, trend toward a reduced likelihood of achieving virological suppression using both the 20% and 5% detection thresholds. However, at both thresholds and in both unadjusted and adjusted regression models, NNRTI-associated PDR was not associated with a reduced likelihood of virological suppression. In contrast, a high baseline virus load and reduced

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adherence were strongly associated with reduced virological suppression. The finding that NNRTI PDR did not result in reduced virological suppression on a first-line TDF/FTC/EFV-containing regimen is an important contrast with past studies and makes this study worthy of editorial comment.

The impact of PDR on the response to a first-line regimen has been difficult to quantify as resistance testing prior to initiating ART is used to guide therapy in high-resource regions. However, there have been at least 13 studies in which a first-line NNRTI-based ART regimen was initiated either according to public health guidelines [5–15] or a clinical trial protocol [16, 17] and for which stored samples were available to assess the impact of pretreatment DRMs on virological success. These studies included about 340 persons with PDR. Nine studies consisted entirely or largely of persons from Africa. The majority of the persons received an AZT- or d4T-containing regimen; a minority received a TDF-containing regimen. About one-half received nevirapine (NVP) and one-half received EFV.

In 11 of these studies, NNRTI-associated PDR was significantly associated with an increased risk of VF; conversely, a nonstatistically significant increased risk of VF was reported in 2 studies [5, 13]. Several of these studies noted a significantly increased risk of VF with AZT or d4T compared with TDF and with NVP compared with EFV. The combination of TDF/FTC/EFV was used in only 2 studies and as a fixed-dose combination in just 1 study [8, 16]. Study heterogeneity has therefore impeded efforts to develop point estimates of VF risk in persons with NNRTI-associated PDR who receive an NNRTI-containing regimen. Nonetheless, a rough estimate of a 2–3 times increased risk of VF has often been cited and used in modeling studies [1, 18].

Judged within the context of previous studies, including the 2 studies in which TDF/FTC/EFV was used for initial therapy [8, 16], the study by Derache

and colleagues suggests that the point estimate of the risk of VF with NNRTI-associated PDR in persons receiving this regimen is lower than estimates based on other regimens. Indeed, several lines of evidence suggest that the TDF/FTC/EFV combination is more efficacious than other first-line WHO-recommended NRTI/NNRTI combinations, particularly when administered as a fixed-dose combination [19–23]. A specific advantage of this combination is the similar half-lives of its components, making it less likely for resistance to emerge when doses are missed.

However, it is premature to argue that TDF/FTC/EFV is equally efficacious at treating persons with and without NNRTI-associated PDR. The 2 previous studies in which TDF/FTC/EFV was used showed a reduced virological response in persons with NNRTI-associated PDR [8, 16]. While Derache and colleagues had a larger initial cohort, one-third were lost to follow-up by 1 year. Moreover, the dominant form of PDR detected by Derache and colleagues, K103N, reduces EFV susceptibility by approximately 20-fold in subtype B viruses [24], which considering the potency of EFV may not compromise its activity as much as once believed. There is no evidence that its effect differs in the subtype C viruses that predominate in South Africa [25].

The integrase strand transfer inhibitor dolutegravir (DTG) has an improved safety profile, a higher genetic barrier to resistance, and a lower cost than EFV and therefore is preferred in countries with and without high levels of NNRTI-associated PDR [18, 26]. As the adoption of first-line DTG-containing regimens is expected to be gradual, the study by Derache and colleagues is a timely addition to the literature on the clinical impact of NNRTI-associated PDR. While the conclusions of this study should not be generalized beyond the regimen studied, the demonstration that NNRTI PDR did not reduce virological suppression on a first-line TDF/FTC/EFV-containing regimen underscores the effectiveness of

this combination, even in patients with the most common forms of NNRTI-associated PDR.

Note

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