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EDITORIAL COMMENTARY

HIV-1 Subtype C, Tenofovir, and the Relationship With Treatment Failure and Drug Resistance

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(See the major article by White et al on pages 1302–8.)

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Tenofovir disoproxil fumarate (TDF) has emerged as a cornerstone of initial antiretroviral therapy (ART) [1, 2]. However, human immunodeficiency virus type 1 (HIV) subtype C, the most prevalent worldwide subtype, accounting for >50% of all HIV infections, harbors polymorphisms in reverse transcriptase codons 64, 65, and 66, which lead to more-rapid in vitro selection of the K65R mutation [3], the signature mutation conferring resistance to TDF [4]. Subtype C viruses may only require a single point mutation at position 65 to select for K65R. Several clinical studies have suggested that this mechanism may contribute to higher treatment failure rates and higher rates of the emergence of the K65R mutations observed in HIV subtype C–infected, compared with subtype B–infected, individuals treated with TDF-containing regimens [5–9], although others could not confirm different response rates between subtype B and C [10–12].

In this issue of *The Journal of Infectious Diseases,* White et al report a comprehensive study on this issue [13]. They analyzed data from the UK Collaborative HIV Cohort (CHIC) Study (available at: http://www.ukchic.org.uk) and included 8746 patients who had initiated ART containing TDF, plus lamivudine or emtricitabine and either a nonnucleoside reverse transcriptase inhibitor (NNRTI; efavirenz or nevirapine) or a ritonavir-boosted protease inhibitor (lopinavir, atazanavir, or darunavir), and were followed for a median of 3.3 years. Unadjusted analyses indicated an approximately 2-fold higher virological failure rate for subtype C–infected individuals as compared to subtype B–infected individuals. However, when they adjusted for demographic and clinical factors, no differences in treatment response between subtype C– and subtype B–infected patients was seen. The analysis of emerging resistance showed that in patients who failed treatment, the K65R mutation occurred significantly more often in subtype C than in B or non B/C infected individuals. The authors concluded from their analysis that there is no intrinsic effect of viral subtype C on the efficacy of tenofovir-containing first-line regimens.

A strength of the UK CHIC study is that it only analyzed TDF-containing first-line regimens, that they had large absolute numbers of subtype B– and subtype C–infected patients obtaining these first-line regimens, and that the study was conducted in a single large national health system where all HIV-infected patients have similar access to ART and care. The clinical and demographic data available allowed them to adjust for potential confounding factors such as ethnicity, which may be associated with adherence to therapy, baseline viral load, baseline $CD4^+$ T-cell count, time of enrollment, and transmission groups.

Why is it that some previous studies demonstrated increased failure and resistance rates in subtype C– as compared to subtype B–infected patients treated with TDF [5–9]? The major factor explaining these discrepancies most likely is confounding by adherence or continuous access to treatment, which was more difficult to adjust for in other studies that were performed across various countries and healthcare systems. Within the same healthcare system, it has been shown that black ethnicity of sub-Saharan origin was associated with higher treatment failure rates, compared with white or Asian ethnicities [14, 15]. In addition, among patients treated in resource-limited settings, detection of viral failure is often delayed because of lack of viral monitoring [8, 16], and in some studies definition of viral load failure was set considerably higher (eg, >1000 HIV RNA copies/mL or 2 consecutive viral loads of >1000 HIV RNA copies/mL) [6, 7], when compared to those used by White et al (2 consecutive viral loads of >200 HIV RNA copies/mL). This means that in the previous studies, replicating viruses were exposed to the selection pressure exerted by TDF for longer periods and, thus, that the chance to acquire the K65R mutation was higher. Another potential factor explaining differences may be that White et al looked at relatively modern treatments: the median year of ART initiation was 2008 for subtype B–infected subjects and 2009 for subtype C–infected subjects, and 70.2%

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and 66.3% of the treatments, respectively, consisted of EFV + TDF + FTC or 3TC. Most likely, the majority of these regimens consisted of coformulated TDF and FTC (Truvada), although this was not specified in the article. It has previously been shown that NNRTI-containing regimens including TDF and 3TC showed higher rates of treatment failure and resistance when compared to TDF/FTC-containing regimens [17, 18], although if corrected for pill burden and ethnicity, the differences between the 2 nucleoside reverse transcriptase inhibitor backbones waned [14, 18]. Potentially, 3TC was more often used in resource-limited settings than in the UK-CHIC analysis. We can speculate that, in treatments consisting of drugs with a lower barrier to virological failure and resistance, subtype C infection can have an impact on treatment outcome. A paradox, however, persists: if patients infected with subtype C do not respond to treatment, the likelihood is higher to select for the K65R mutation, as also shown by White et al, even though no differences in failure rates were observed when compared to patients infected with subtype B. An explanation for this phenomenon could be that, in an optimal treatment setting, treatment response is not affected by the single point mutation. However, if adherence or the other factors mentioned above are suboptimal, then the mutation occurs much faster in subtype C than in subtype B. Further studies in well-controlled settings will be needed to elucidate this phenomenon.

The study by White et al provides reassurance that TDF-containing therapies also work well in subtype C–infected patients starting first-line NNRTI-based ART and that, currently, no change in recommendations regarding ART for HIV subtype C is warranted. This also should not change when the less toxic nucleotide reverse transcriptase inhibitor tenofovir alafenamide likely replaces TDF as part of initial regimens, because the mechanism of resistance of the 2 drugs is the same [19]. However, rates of transmitted drug resistance in all parts of the world need to be monitored closely, since recent reports suggest considerable increases of NNRTI-based transmitted drug resistance, such as in sub-Saharan Africa [20], where HIV prevalence is highest and availability of different drug classes still limited.

The major message from lower treatment responses that have been reported in some studies among subtype C–infected individuals is that, as White et al show, this is not primarily a result of a single nucleotide change leading to the K65R mutation, but rather because treatment conditions in studies conducted in resource-rich and resource-limited settings were different. For these reasons, it is of utmost importance to globally improve treatment conditions so that adherence problems and treatment failures can be identified early, most importantly through viral load monitoring, optimally every 3–6 months [1], or that strategies such as the recently proposed viral-load-informed differentiated care [21] are also adopted.

Notes

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