Evidence Gathered From Randomized Clinical Trials and Observational Studies on the Equivalence of Emtricitabine and Lamivudine

To the Editor—We read the commentary by Ford et al on our study regarding the comparability of results from trials and cohorts regarding the efficacy of lamivudine (3TC) and emtricitabine (FTC) in combination antiretroviral therapy (ART) [1, 2]. Of course, we can only agree with the statement that evidence from randomized clinical trials (RCTs) is of higher quality than observational studies. But we absolutely cannot agree with the conclusion that the results of the RCTs in the 3 studies Ford et al refer to provide sufficient proof of clinical equivalence of 3TC and FTC in first-line human immunodeficiency virus type 1 (HIV-1) treatment. Actually, 3 RCTs do not even address the main question of our study, which concerned the risk of virological failure in treatment-naive patients starting FTC or 3TC, combined with tenofovir (TDF) specifically in a nucleoside reverse transcriptase inhibitor (NRTI) backbone plus a nonnucleoside reverse transcriptase inhibitor (NNRTI). We specifically focused on patients on TDF plus an NNRTI and FTC or 3TC because these are the most frequently used regimens worldwide.
To be concrete about these 3 RCTs, the first study by Sanne et al (FTC-302) randomized 468 ART-naive HIV-1–infected patients to initiate stavudine with FTC or 3TC and nevirapine or efavirenz [3]. Nevirapine was only administered to patients with baseline HIV-1 RNA ≤ 100 000 copies/mL. The second study by Sanne et al (FTC-303) enrolled 440 already virologically suppressed HIV-1–infected patients at the time of randomization to FTC and 3TC between 1998 and 2000 [3]. The 289 patients in the open-label study by Benson et al (FTC-350) were enrolled from FTC-303 and had chosen to be included in FTC-350 [4]. These virologically suppressed patients continued their initial combination ART from FTC-303, which consisted of FTC (n = 215) or 3TC (n = 74) combined with predominantly stavudine (the second NRTI never included TDF), and 79% had protease inhibitor backbones consisting of indinavir or nelfinavir.

The only RCT that we are aware of that specifically focused on the FTC vs 3TC issue in ART-naive patients treated with TDF and an NNRTI is the unpublished open-label study by Mulenga et al [5]. However, as discussed in our article, this study was not powered to reject clinically significant differences in virological failure between FTC and 3TC, as the lower bound of the 97.5% confidence interval of proportional difference was −28.1%. This means that a 28% higher week 48 virological failure rate cannot be excluded. Also, the study population consisted of predominantly female (58.4%) sub-Saharan patients. We do, however, agree that FTC and 3TC are probably interchangeable once patients are virologically suppressed, as was seen in the RCTs described above and in our own observations.

In conclusion, extrapolating the data from the studies mentioned above by Ford et al to ART-naive patients initiating currently recommended TDF/NNRTI-based regimens could be a bridge too far. We agree that guidelines should not be changed based on a single observational study as ours, but these should also not be based on a single underpowered study.

Note

Potential conflict of interest. Both authors: No reported conflicts.
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