Comparative Efficacy of Lamivudine and Emtricitabine: Comparing the Results of Randomized Trials and Cohorts

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(See the HIV/AIDS Major Article by Rokx et al on pages 143–53.)

Over the last decade, World Health Organization (WHO) guidelines for human immunodeficiency virus (HIV)/AIDS treatment and care have evolved toward simplifying recommendations for first-line antiretroviral therapy (ART) to promote a public health approach to treatment scale-up [1]. Whereas in 2002, WHO recommended 5 different treatment options for first-line ART, the latest guidelines released in 2013 recommend a single first-line regimen comprising tenofovir, efavirenz, and either lamivudine or emtricitabine, preferably as fixed-dose combinations [2]. These last 2 nucleoside analogues were recommended as interchangeable based on the results of a systematic review and meta-analysis of randomized trials showing no difference in rates of virological suppression, virological failure, or the development of resistance mutations [3]. Lamivudine is available from multiple generic sources and is cheaper than emtricitabine [4].

In this issue of Clinical Infectious Diseases, an analysis from Rokx et al and the AIDS Therapy Evaluation in the Netherlands nationwide HIV cohort (ATHENA) HIV treatment cohort in the Netherlands suggests better virological responses to emtricitabine compared with lamivudine as part of first-line ART. The authors of this nonrandomized cohort study conclude that using lamivudine instead of emtricitabine may result in additional morbidity and costs associated with virological failure and the development of drug resistance [5].

To date, 3 randomized clinical trials (n = 1242) have directly compared lamivudine and emtricitabine; the pooled results of these trials found no difference in terms of virological suppression (relative risk [RR], 1.03; 95% confidence interval [CI], .96–1.10) or virological failure (RR, 0.93; 95% CI, .74–1.18). In comparison, the risk of virological failure in the ATHENA cohort was three times higher for patients receiving lamivudine compared with efavirenz (RR, 2.99; 95% CI, 2.08–4.30).

How should clinical guidelines respond to this seemingly contradictory evidence from 3 randomized trials vs a nonrandomized cohort study? The development of clinical guidelines by WHO and an increasing number of national guidelines follows the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, which rates the quality of evidence supporting a recommendation according to 5 criteria: risk of bias, imprecision, inconsistency, indirectness, and publication bias [6]. Randomized trials are generally rated as high-quality evidence but can be downgraded if key methodological issues arise. According to the GRADE approach, observational studies are usually rated as low-quality evidence but can be upgraded based on the quality of evidence under certain exceptional conditions [7]. Adequately powered randomized clinical trials are also required for the marketing approval of new antiretrovirals by the US Food and Drug Administration and other regulatory authorities; cohort studies in which different treatments are compared are not acceptable for such approvals [8].

Observational studies have made invaluable contributions in the field of HIV/AIDS, providing evidence of the feasibility of delivering ART at scale, giving insights into innovations in service delivery that could help efforts to support further ART scale-up, and generating datasets on adverse drug reactions that may not be apparent in trial settings. However, randomized trials remain the gold standard...
for assessing comparative drug efficacy for the simple reason that cohort studies can never ensure that observed differences in treatment efficacy are not in fact due to measured or unmeasured differences between patient populations.

The ATHENA cohort study provided an adjusted analysis using propensity scoring. Although such analyses are preferable to unadjusted analyses, selection bias will remain if imbalances in unobserved confounding variables exist. The comparison groups in the ATHENA cohort study by Rokx et al are greatly unbalanced both geographically, between Western and sub-Saharan settings, and temporally, with the median ART initiation year at 2004 for lamivudine and 2009 for emtricitabine. Patients receiving lamivudine also had a higher baseline viral load and lower baseline CD4 cell counts, were more likely to be injection drug users (which could influence adherence), coinfected with hepatitis B virus, and managed within a large treatment programme (>2000 patients). These differences could be associated with important differences such as culture and clinical practice that can never be fully corrected for statistically through methods like propensity scores [9].

Thus, in light of these methodological limitations and the large discrepancy between the results reported by Rokx et al and those provided by prospective randomized controlled trials (Figure 1), it is reasonable to believe that the observed treatment differences are the result of study design rather than actual differences in efficacy between lamivudine and emtricitabine. Although many cohort studies and randomized trials result in similar effect estimates, it is not possible to know whether a cohort study is robustly valid until a randomized trial is conducted [10].

The authors of the ATHENA cohort suggest that additional randomized trials are needed to evaluate the comparative efficacy of lamivudine and emtricitabine. We agree that such evidence would be valuable; if future trials find important differences between these 2 drugs, then this evidence should be interpreted in light of the 3 completed randomized trials, and may have implications for future guidelines. In the meantime, on the basis of the currently available randomized evidence, we conclude that lamivudine and emtricitabine can be considered to be interchangeable.

**Note**

**Potential conflicts of interest.** All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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