Editorial

Second-line antiretroviral therapy in resource-limited settings: what we know and the challenges of ever-changing antiretroviral therapy

Diganth Ningappa[1,2], **Ann C. Collier**[3]

[1]Department of Medicine, University of Washington, AIDS Clinical Trials Unit, Seattle, WA, USA; [2]Harborview Medical Center, Seattle, WA, USA; [3]University of Washington School of Medicine, Seattle, WA, USA

Correspondence to: Ann C. Collier. Harborview Medical Center, Box 359929, 325 9th Avenue, Seattle, WA 98104, USA.
Email: acollier@u.washington.edu.

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Almost 22 million persons with human immunodeficiency virus (HIV) are receiving antiretroviral therapy (ART) with the majority living in resource-limited settings (RLS) (1). This remarkable achievement owes much of its success to the public health approach adopted by the World Health Organization (WHO) (2). The public health approach relies upon simplified tools and approaches to clinical decision-making, in contrast to the individualized approach to ART that is utilized in high-income settings. As data have emerged about the personal and public health benefits of sustained viral suppression, ART has been recommended for a greater proportion of persons with HIV. Persons with sustained plasma viral suppression are no longer at risk to transmit HIV sexually, underscoring the concept of "treatment as prevention" (3). WHO and multiple other relevant organizations now recommend treatment for all persons with HIV (4-6).

Past definitions of treatment success in RLS relied primarily upon clinical and immunologic criteria, while modern definitions focus on virologic criteria. WHO has preferred plasma HIV RNA (viral load) criteria to denote treatment failure since 2013 although cut-offs for virologic success (or failure) vary in different countries and settings (4,5,7). Even though modern antiretroviral drugs have less toxicity than earlier agents, unfortunately not all persons prescribed ART are able to achieve sustained virologic suppression. Approximately 5–15% of recommended initial regimens in RLS will be unsuccessful during the first year of ART (8-10). As more persons gain access to first-line ART in RLS, the greater the number of HIV-infected persons who will need second-line ART. The recent publication by Hakim and his colleagues of the EARNEST study provides novel long-term data directly relevant to treatment of the growing population of first-line ART failures in RLS (11).

The EARNEST study is one of three large prospective international randomized clinical trials that compared one or more novel regimens to a standard second-line ART regimen of a boosted protease inhibitor (PI) plus nucleoside reverse transcriptase inhibitors (NRTIs) (12-14). With the recently reported 144-week data, the EARNEST study provides the longest follow-up information of these three studies (11). However, the efficacy data from 144 weeks are not fully consistent with the earlier results from the same study or the results from these other two randomized studies. Additionally, many advances in ART since the EARNEST study was planned also create applicability challenges for these data.

Until late July 2018, WHO ART guidelines recommended first-line regimens consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two NRTIs (4). In the event of treatment failure, a switch to a second-line ART regimen consisting of a boosted PI plus 2 NRTIs was recommended. Without ready availability of resistance testing, this switch strategy raised several concerns which

led to the development of clinical trials investigating other second-line strategies. Questions of interest in RLS included whether NRTI mutations arising during first-line ART would compromise the efficacy of the NRTIs likely to be part of second-line regimens, and would a second-line regimen with two new drug classes increase efficacy—and by avoiding NRTI-associated side effects—also decrease toxicity? The new drug class known as integrase strand transfer inhibitors (INSTI) was emerging at the time these questions were first being asked. INSTI-containing regimens are associated with potent anti-HIV activity and rapid virologic suppression (15). Raltegravir was the first member of the INSTI class that was approved for use to treat HIV (15).

The EARNEST study was designed to answer an additional question not addressed by the other two studies; whether PI monotherapy (after an initial 12 weeks of raltegravir that was designed to rapidly decrease plasma HIV RNA) would be non-inferior to a standard second-line regimen (11). The arm was likely included since this strategy, if successful, might have been associated with lower costs and toxicities.

All three of these randomized studies compared a novel oral regimen of a boosted PI (ritonavir-boosted lopinavir) plus an INSTI, raltegravir, to a standard of care oral regimen consisting of ritonavir-boosted lopinavir plus 2 or 3 NRTIs. In addition, the EARNEST study included a third arm of oral ritonavir-boosted lopinavir monotherapy after an initial 12 weeks of raltegravir.

Each of these studies enrolled HIV-infected persons with confirmed virologic failure after at least six months of an initial standard regimen with a NNRTI plus NRTIs regimen. They all had open-label treatment and non-inferiority designs with 10% non-inferiority margins. The SELECT trial had a virologic endpoint of HIV RNA <400 copies/mL at 48 weeks (14). The SECOND-LINE trial's primary endpoint was HIV RNA <200 copies at 48 weeks but they also reported 96 weeks data for this same metric (13). The primary endpoint for EARNEST at 96 weeks was a composite endpoint of clinical and laboratory information (12). Specifically, this endpoint included "good disease control" (survival with no new WHO grade 4 events), CD4 count more than 250 cells/mm^3, and HIV RNA <10,000 copies/mL with no protease resistance mutations. For the recent 144 weeks timepoint, the EARNEST primary endpoint was virological (HIV RNA <400 copies/mL) (11). Other differences among these studies included the location of study sites and the participants' immunologic status at baseline, which are relevant characteristics that impact the generalizability of the results. The EARNEST study enrolled participants in five sub-Saharan African countries. The SELECT study enrolled participants in nine countries on three continents that were a mix of low- and middle-income countries. The SECOND-LINE study enrolled participants in 15 middle- and upper-income countries. The median baseline CD4 count (cells/mm^3) in participants in the EARNEST, SELECT, and SECOND-LINE studies were 71, 180 and 189, respectively.

Despite their differences, the 48- and 96-week results from these studies were remarkably consistent. In each study, the novel ritonavir-boosted lopinavir plus raltegravir regimen was non-inferior to the standard regimen. However, the novel regimen was not shown to be superior. The overall toxicity and adverse events rates and types were not significantly different between the study arms except for some small differences in lipids in the two studies that assessed these (SELECT and SECOND-LINE); these favored the NRTI-containing arm. The likely explanation for these observations is that tenofovir disoproxil fumarate (TDF), one of the commonly used NRTIs, has an anti-lipid effect (16).

Interestingly, in all three studies, the probability of virologic failure was inversely proportional to the extent of NRTI resistance at study entry regardless of treatment assignment (12-14). These data have several implications. They suggest that ritonavir-boosted lopinavir played an important role in the virologic activity of these second-line regimens, given the 96–98% prevalence rates of baseline NRTI or NNRTI resistance in the SELECT and SECOND-LINE trials. Whether the NRTI resistance mutations that arose during the use of first-line NRTIs impacted viral replicative capacity favorably was not addressed in these studies (17). A likely alternative explanation is that development of NRTI resistance was a marker of non-adherence during first-line ART and this behavior pattern continued with second-line therapy (18).

In addition to the standard of care and boosted PI plus INSTI regimens, the EARNEST trial also included a PI monotherapy arm (after a 12-week "induction" treatment with raltegravir). At the end of 96 weeks, the monotherapy group in this study was discontinued due to inferiority and all participants in this group were continued on ritonavir-boosted lopinavir with the addition of 2–3 NRTIs (11). The study staff had access to HIV viral load tests and resistance testing for this group's participants in order to choose the NRTIs that were added to the boosted PI. However, even after an additional 48 weeks of a standard of care regimen chosen with these modern tools; at 144 weeks,

the participants assigned to the PI monotherapy group had significantly inferior virological outcomes compared to the original standard of care group. These data are consistent with results of several other studies of PI monotherapy that have demonstrated PI monotherapy, even with an induction regimen, is not as effective virologically as standard triple ART with NRTIs and a 3rd drug of a different drug class (19). Of note, PI monotherapy has continued to be of interest for selected patients in settings where frequent viral load monitoring is available, since this type of regimen can be "rescued" with the addition of dual NRTIs when persons develop virologic failure while taking PI monotherapy. Addition of NRTIs to failing PI monotherapy treatment usually results in suppression of HIV RNA without apparent negative consequences. However, this strategy is not in widespread use.

Unlike the consistent inferiority of ritonavir-boosted lopinavir monotherapy arm compared with the standard of care arm at all reported timepoints in EARNEST, the results comparing the novel ritonavir-boosted lopinavir plus raltegravir regimen to the standard of care arm were not the same at the earlier timepoints and at the recently reported 144-week timepoint. At 144 weeks, the non-inferiority criteria of the novel regimen were not met in either the complete-case (primary) and the per-protocol analyses of viral load suppression, meaning that the novel regimen could not be described as non-inferior (11). However, at 144 weeks, in other analyses (time to loss of virological response and the FDA snapshot analysis), the novel regimen did meet the pre-specified non-inferior criterion. These inconsistencies complicate interpretation of these data. In total, the 144-week results suggest that the ritonavir-boosted lopinavir plus raltegravir regimen should not displace boosted PI plus NRTIs regimens in RLS for second-line ART, given the consistent lack of virologic superiority without clear advantages in toxicity or other clinical or immunologic outcomes.

The EARNEST trial had multiple strengths, including large size (N=1,277); longer follow-up than many ART studies, making the results more relevant for a condition treated life-long; a low loss to follow-up rate; and sparse laboratory monitoring for toxicities and predominantly nurse-led care, making the study results generalizable to RLS that have a public health approach to HIV care.

This study also has limitations, including its open-label design, the possibility that public availability of the week 96 interim results could have impacted the 144-week results, and the fact that the NRTIs commonly used in the (failing) first-line regimens (zidovudine and stavudine) have been supplanted in many settings by TDF (4-6).

One of the strengths of EARNEST is also its "Achilles heel". In the 8 years between enrollment of the first participants and the report of the 144-week data, substantial changes in ART have occurred. There are new and better drugs; NRTIs including tenofovir alafenamide (TAF), PIs such as darunavir, and INSTIs, including dolutegravir (5). Like TDF, TAF is a prodrug of tenofovir. TAF achieves substantially higher intracellular concentrations of the active metabolite in peripheral blood mononuclear cells and markedly lower plasma tenofovir exposures than TDF. Available data suggests that it has less potential renal and bone toxicity than TDF. In the US clinical practice, TAF has begun to replace TDF as part of most triple ART regimens. Dolutegravir has a higher genetic barrier to resistance and a longer half-life than the original formulation of raltegravir, which was to be taken twice a day (20). Numerous clinical trials have demonstrated the superiority of dolutegravir-based regimens compared with a variety of standard of care combination antiretroviral regimens (5,20). For second-line therapy in middle-income countries, dolutegravir with 2 NRTIs was superior to ritonavir-boosted lopinavir plus 2 NRTIs at a 24 weeks interim analysis that resulted in a recommendation to discontinue the lopinavir-containing arm (21). Long-acting injectable antiretroviral agents are on the horizon and may provide an opportunity to improve adherence and decrease virologic failure and thus decrease the need for second-line ART (22). ART guidelines and practice patterns in resource-rich and resource-constrained settings have also changed in the interim (5,6,23,24).

Current WHO ART guidelines (as of July 2018) prefer dolutegravir-containing regimens over NNRTI-containing regimens for first-line therapy and for second-line therapy in individuals who have failure of a first-line non-dolutegravir (e.g., NNRTI-containing) regimen (23). TDF (with lamivudine or emtricitabine) is the preferred first-line NRTI combination, so the current NRTI cross-resistance profile in first-line failures is likely very different than in the participants in the EARNEST study (and the other two second-line studies described above). Point of care viral load tests and possibly point of care resistance tests are also on the horizon in RLS, which may also favorably impact adherence and alter viral resistance patterns. Implementation of the new global ART recommendations and increasing access to dolutegravir in the form of an inexpensive generic TDF/lamivudine/dolutegravir (TLD) will take time. However, as well done

as the EARNEST trial was, these ART advances mean that its results are applicable to a shrinking proportion of persons with HIV.

It is also impossible to know if the results might have differed if a different PI (e.g., darunavir) or INSTI (e.g., dolutegravir) had been included in the regimens used.

The 144-week results of EARNEST remind us that high quality, long-term, randomized clinical trials can and should be done in RLS in order to inform the standard of care for ART.

Prospective data about outcomes with the widespread global adoption of dolutegravir-containing regimens, especially the switch from current second-line regimens in the absence of viral load testing to detect individuals with virologic failure, is urgently needed. If ineffective NRTIs are paired with dolutegravir, such a combination regimen may be functional monotherapy. Despite its high efficacy and excellent tolerability when combined with two NRTIs, dolutegravir has been reported to be suboptimal as monotherapy (25) and the issue of NRTI cross-resistance with current NRTI use patterns (e.g., TDF as first-line therapy) has not been well studied. Despite these challenges and the lack of relevant long-term clinical trial results of dolutegravir-containing regimens in RLS, it is likely that increased access to such regimens, including TLD, and to modern monitoring tools, including viral load testing and resistance testing, when appropriate, will benefit millions of persons with HIV around the globe. Until then, the data from the EARNEST study suggests that a boosted PI plus 2–3 NRTIs should remain the standard of care for second-line ART in RLS.

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Footnote

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References

1. UNAIDS. Global HIV & AIDS statistics — 2018 fact sheet. Available online: http://www.unaids.org/en/resources/fact-sheet
2. Gilks CF, Crowley S, Ekpini R, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet 2006;368:505-10.
3. The Lancet HIV. Editorial: U=U taking off in 2017. Lancet 2017;4:e475.
4. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach - second edition. Available online: http://www.who.int/hiv/pub/arv/arv-2016/en/
5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Available online: https://aidsinfo.nih.gov/guidelines
6. European AIDS Clinical Society. EACS Guidelines. Available online: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html
7. UNAIDS. The need for routine viral load testing. Questions and answers. Available online: http://www.unaids.org/sites/default/files/media_asset/JC2845_en.pdf
8. Shet A, Neogi U, Kumarasamy N, et al. Virological efficacy with first-line antiretroviral treatment in India: predictors of viral failure and evidence of viral

resuppression. Trop Med Int Health 2015;20:1462-72.
9. Rohr JK, Ive P, Horsburgh CR, et al. Developing a predictive risk model for first-line antiretroviral therapy failure in South Africa. J Int AIDS Soc 2016;19:20987.
10. Mekuria LA, Prins JM, Yalew AW, et al. Which adherence measure - self-report, clinician recorded or pharmacy refill - is best able to predict detectable viral load in a public ART programme without routine plasma viral load monitoring? Trop Med Int Health 2016;21:856-69.
11. Hakim J, Thompson J, Kityo C, et al. Lopinavir plus nucleoside reverse-transcriptase inhibitors, lopinavir plus raltegravir, or lopinavir monotherapy for second-line treatment of HIV (EARNEST): 144-week follow-up results from a randomized controlled trial. Lancet Infect Dis 2018;18:47-57.
12. Paton N, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. N Engl J Med 2014;371:234-47.
13. Boyd MA, Kumarasamy N, Moore CL, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. Lancet 2013;381:2091-9.
14. La Rosa A, Harrison L, Taiwo B, et al. Raltegravir in second-line antiretroviral therapy in resource-limited settings (SELECT): a randomised, phase 3, non-inferiority study. Lancet HIV 2016;3:e247-58.
15. Blanco JL, Whitlock W, Milinkovic A, et al. HIV integrase inhibitors: a new era in the treatment of HIV. Expert Opin Pharmacother 2015;16:1313-24.
16. Souza SF, Suzia LA, Santos SS, et al. Lipid profile of HIV-infected patients in relation to antiretroviral therapy: a review. Rev Assoc Med Bras 2013:59:186-98.
17. Ross L, Parkin N, Lanier R. Short communication: the number of HIV major NRTI mutations correlates directly with other antiretroviral-associated mutations and indirectly with replicative capacity and reduced drug susceptibility. AIDS Res Hum Retroviruses 2008;24:617-20.
18. von Wyl V, Klimkait T, Yerly S, et al. Adherence as a predictor of the development of class-specific resistance mutations: the Swiss HIV Cohort Study. PLOS One 2013;8:e77691.
19. Arribas JR, Girard PM, Paton N, et al. Efficacy of protease inhibitor monotherapy vs. triple therapy: meta-analysis of data from 2303 patients in 13 randomized trials. HIV Med 2016;17:358-67.
20. Singh H, Kaur M, Kakkar A, et al. The promise of dolutegravir: a novel second generation integrase strand transfer inhibitor. Curr Clin Pharmacol 2016;11:88-94.
21. Aboud M, Kaplan R, Lombard J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir plus ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. Available online: http://programme.ias2017.org/Abstract/Abstract/5613
22. Boffito M, Jackson A, Owen A, et al. New approaches to antiretroviral drug delivery: challenges and opportunities associated with the use of long-acting injectable agents. Drugs 2014;74:7-13.
23. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance. Available online: http://www.who.int/hiv/pub/guidelines/ARV2018update/en
24. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. JAMA 2018;320:379-96.
25. Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. Lancet HIV 2017;4:e547-54.

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