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EDITORIAL COMMENTARY

High Baseline Viremia: An Achilles Heel for Integrase Inhibitor–Based Antiretroviral Therapy?

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(See the Major Article by Pyngottu et al on pages e2134-41.)

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Integrase strand transfer inhibitors (INSTIs) are considered a key advancement in our efforts to achieve global human immunodeficiency virus (HIV) viral suppression targets. Rates of pretreatment and acquired drug resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) have risen dramatically over the past decade [1]. In fact, in 2019, the World Health Organization reported that two-thirds of surveyed countries had >10% prevalence of pretreatment drug resistance to NNRTIs, calling into question their use in first-line antiretroviral therapy (ART) [2]. In contrast, the late-generation INSTIs dolutegravir (DTG) and bictegravir (BIC) have a high genetic barrier to resistance, and as such, are now included as part of preferred first-line ART regimens worldwide [3, 4]. In addition, a fixed-dose combination of tenofovir disoproxil fumarate, lamuvidine, and dolutegravir (TLD) was introduced in 2018 as first-line therapy for both ART-naive and ART-experienced patients. As millions of people with HIV are now receiving INSTI-containing ART, it is critical to understand the factors that may predict virologic failure on these regimens, even if it is a rare event.

In this issue of *Clinical Infectious Diseases*, Pyngottu et al present an insightful retrospective analysis of the Swiss HIV Cohort Study, which provided a comprehensive assessment of the virologic outcomes for 1472 ART-naive adults who initiated ART with INSTI-containing regimens over a 12-year period from 2006 to 2018, prior to the introduction of BIC. This represents the first large observational study to describe the incidence and evaluate predictors of virologic failure on INSTI-based first-line regimens in a routine clinical setting. The majority of patients in the study (65%) were on DTG-containing ART. The authors evaluated predictors of both time to virologic failure and time to viral suppression. They importantly concluded that a pretreatment HIV-1 RNA viral load >100 000 copies/mL was associated with an increased risk of both virologic failure and longer time to viral suppression. In addition, imperfect adherence (missing at least 1 dose within the past month) and AIDS-defining events were associated with virologic failure, whereas a CD4 count >200 cells/μL was found to be protective. Time to viral suppression was similarly influenced by pretreatment CD4, choice of INSTI (DTG being favorable), and financial independence. Notably, pretreatment minor integrase mutations and polymorphisms (present in 16% of the cohort) did not influence virologic outcomes.

We offer the following insights to consider when interpreting the study findings. First, data regarding single-tablet vs multiple-tablet regimens were not available to the investigators, which could also influence regimen efficacy due to differences in adherence and barrier to resistance. Currently, single-tablet regimens containing either DTG or BIC are more available globally than during the study period. In addition, the study defines virologic failure as either (1) confirmed viremia >50 copies/mL after at least 6 months on treatment; (2) a single episode of viremia >50 copies/mL after at least 6 months of treatment and followed by a regimen change off INSTIs; or (3) failure to achieve viral suppression within 6 months. Among 121 episodes of virologic failure in the study (<10%), only 23 occurred with HIV-1 RNA viral loads >1000 copies/mL. The majority of virologic failure events in the study would be classified as low-level viremia, which is reassuring. Although not specifically described in this study,

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viral resuppression rates, emergence of resistance, and long-term outcomes for individuals with low-level viremia while on INSTI-containing regimens could provide further insight into the impact of initial virologic failure. Regarding the study's third virologic failure criterion, it is important to recognize that 27% of the cohort was classified in the highest HIV-1 RNA viral load category (>100 000 copies/mL). However, the prevalence of extremely high viremia >1 000 000 copies/mL was not available. Individuals with a HIV-1 RNA viral load magnitude >1 000 000 copies/mL could require a longer time to viral suppression due to the limitations of exponential decay for most ART regimens and may not achieve viral suppression within 6 months. Despite this caveat, only 9 individuals out of 121 virologic failure episodes did not achieve initial viral suppression, potentially reflecting the greater potency of DTG-based ART [5]. The study also evaluated the impact of pretreatment integrase mutations on virologic outcomes. As the ART backbone consisted of nucleoside reverse transcriptase inhibitors, baseline resistance to this class could impact the effectiveness of INSTI-containing combination therapy. Finally, ART adherence was based on self-report response to whether >1 dose of ART had been missed within the past 1 month. A deeper exploration into the reasons for imperfect adherence or the impact of side effects (eg, weight gain) and drug toxicities could provide critical insights into where these regimens may have fallen short of the goal.

In considering possible mechanisms of action for the study findings, higher pretreatment HIV-1 RNA viral loads could feasibly contribute to virologic failure risk due to correlation with either a larger reservoir size or high replication capacity. In addition, immune factors including low CD4 count and AIDS-defining illnesses may impact virologic failure risk indirectly and may be mediated by poor adherence to ART in the setting of severe illness, increased pill burden due to concurrent medical therapy, or drug–drug interactions. Financial independence was associated with shorter time to virologic suppression, which may indicate lifestyle stability and higher rates of adherence and retention in care.

Regarding generalizability of the study findings, the Swiss cohort is comprised predominantly of white adult males. Still, many findings are consistent with predictors of virologic failure on INSTI-containing regimens that have been identified in other populations as well. Notably, the NAMSAL study, a clinical trial evaluating DTG-containing first-line ART in Cameroon, found that pretreatment HIV-1 RNA >100 000 copies/mL and AIDS-defining events were associated with virologic failure on DTG-containing regimens [6]. The ADVANCE study in South Africa identified employment as a significant factor associated with viral suppression [7], thus supporting the author's findings regarding the impact of financial independence.

In light of the study findings, additional key questions regarding virologic failure on first-line regimens containing INSTIs are brought to the forefront. While the Swiss cohort provides insight into an ART-naive population initiating INSTIs, the majority of people globally on INSTI-containing first-line regimens will be ART-experienced patients who are switched from NNRTI-based ART to TLD. Additional studies will be needed to determine if risk factors for virologic failure are similar in ART-experienced patients, compared to what has been seen in studies with ART-naive participants. In addition, as weight gain is more frequently described as a side effect of INSTI-containing regimens, data will be needed regarding the impact of this side effect on patient preferences and ART adherence. Finally, the findings also open the door for additional study regarding viral resuppression rates, long-term virologic outcomes, and prevalence of treatment-emergent drug resistance among individuals who experience virologic failure on INSTI-containing regimens. These data will be needed to determine how best to manage both low-level viremia and virologic failure on these high genetic barrier regimens.

In conclusion, virologic failure in this cohort was rare, occurring in only 121 of 1472 patients during >18 000 person-years of follow-up. However, these data provide a warning signal from a routine clinical setting that virologic failures on late-generation INSTI-based regimens do occur. The authors raise a humbling and insightful point that virologic, immunologic, and socioeconomic factors continue to have a critical role in the effectiveness of ART, irrespective of regimen potency and setting. Furthermore, as millions of ART-naive and ART-experienced people are prescribed TLD (with current estimates of >6 million in low- and middle-income countries now on this regimen and projected to increase [8]), these insights into virologic failure risk may prove even more valuable as we continue to learn that DTG and BIC are not impervious to treatment failure.

Notes

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Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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