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Adherence, resistance, and viral suppression on dolutegravir in sub-Saharan Africa: implications for the TLD era

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Dolutegravir (DTG) is now a component of preferred first-line antiretroviral therapy (ART) worldwide. ADVANCE and NAMSAL were two landmark clinical trials conducted exclusively in sub-Saharan Africa, which studied the effectiveness of DTG-based first-line regimens for ART-naive individuals. In this review, we examine the data from these studies to consider the contributions of adherence and HIV drug resistance to treatment failure on DTG-based ART, as compared with efavirenz (EFV)-based ART, which has a lower genetic barrier to resistance. We also discuss the implications of virologic failure on DTG and consolidate currently available data to conclude with recommendations for virologic monitoring on DTG-based ART.

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Introduction

As of 2019, approximately 18 million people with HIV (PWH) in sub-Saharan Africa (SSA) were receiving antiretroviral therapy (ART) [1]. With increasing access to ART, drug resistance to ART is also rising. The prevalence of drug resistance prior to treatment initiation (PDR) now exceeds 10% in much of SSA, and reaches 60–90% among those failing nonnucleoside reverse transcriptase inhibitor (NNRTI)-based ART [2–7]. Due to their recent inclusion in public health programs and relatively high genetic barrier [8,9], circulating resistance to dolutegravir (DTG) and other second generation integrase strand transfer inhibitors (INSTIs) has remained low [10,11]. In 2018, a low-cost fixed-dose combination of lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and DTG, known as tenofovir-lamivudine-dolutegravir (TLD), was endorsed by the WHO as the preferred first-line ART regimen for most adults and adolescents [12]. On the basis of its favorable resistance profile, as well as lower costs of TLD and better persistence, most national health systems in SSA have adopted TLD as first-line therapy for both ART-naive and for some ART-experienced individuals [13].

With widespread introduction of TLD in first-line therapy across SSA, it will be critical to develop updated treatment-monitoring guidelines. In the era of NNRTI-based first-line regimens, it has been difficult to ascertain whether virologic failure events occur because of poor adherence alone, existence of pretreatment drug resistance, acquired drug resistance, or a combination of these factors, given limited availability of genotypic resistance testing in resource-limited settings. Guidelines have emphasized utilization of viral load monitoring as the primary mechanism for determining when a switch to second-line therapy is required. NNRTIs have a low genetic barrier to resistance. Thus, when virologic failure is confirmed after a period of enhanced adherence

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Table 1. Summary of results from ADVANCE and NAMSAL.

	ADVANCE		NAMSAL	
	DTG arms	EFV arm	DTG arm	EFV arm
Number of participants	702	351	310	303
Viral suppression at 48 weeks (ITT)	84% (592/702)	79% (276/351)	75% (231/310)	69% (209/303)
Adherence <95%	16% (91/557)	13% (35/269)	31% (87/281)	30% (80/267)
Incident obesity	7% (17/250)[a]	6% (13/220)	12% (36/293)	5% (15/278)
Treatment emergent resistance to DTG	0	NA	0	NA
Pretreatment NRTI resistance	2% (20/873)		1% (8/611)	
Pretreatment NNRTI resistance	14% (122/873)		6% (37/611)	

DTG, dolutegravir; NNRTI, nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.
[a]Data only for study arm receiving emtricitabine, tenofovir disoproxil fumarate, and dolutegravir.

support, the mechanism of virologic failure is presumed to be HIV drug resistance. Dolutegravir has a much higher genetic barrier to resistance than NNRTIs, and it is expected that failure with resistance will occur less frequently. With minimal data on the use of TLD in practice to date, most guidelines have relied on expert opinion to formulate plans for disease monitoring on TLD and subsequent regimen changes. Two large, randomized controlled trials conducted wholly within SSA and with 96 weeks of observation offer a unique opportunity to use local data to empirically determine optimal programmatic use of TLD as first-line therapy [14–17]. Although the chief correlates of viral suppression on TLD are similar to other regimens (i.e. sociodemographic factors, regimen tolerability, adherence, and drug resistance), data from these studies appear to suggest that the relative contributions of each differ significantly from NNRTI-based first-line regimens. In this review, we examine the data from the NAMSAL and ADVANCE studies to consider the contributions of adherence and resistance to treatment failure on TLD-based ART, discuss implications of virologic failure and correlates of re-suppression, consolidate currently available data to conclude with recommendations for virologic monitoring on TLD, and highlight the most pressing gaps where data are still needed to improve treatment guidelines.

Overview of ADVANCE and NAMSAL studies

ADVANCE and NAMSAL were the first randomized controlled trials to evaluate the use of DTG-containing first-line regimens for ART-naive individuals, exclusively in African settings [15,16]. ADVANCE is a phase 3 noninferiority trial conducted in South Africa that randomized 1053 PWH aged 12 years and above to receive one of three regimens ($n = 351$ in each arm): emtricitabine (FTC) co-formulated with TDF with DTG, FTC co-formulated with tenofovir alafenamide (TAF) plus DTG, or FTC co-formulated with TDF with EFV 600 mg, with the latter considered as standard of care at the time the study commenced [15]. NAMSAL is a phase 3 noninferiority trial conducted in Cameroon that randomized 613 PWH aged 18 years and above to receive 3TC co-formulated with TDF with either DTG ($n = 310$) or low-dose (400 mg) EFV ($n = 303$), with EFV considered as standard of care [16]. Both ADVANCE and NAMSAL have completed 96 weeks of follow-up [14,17]. Single tablet combination of TLD was not used in either clinical trial. In this review, we extrapolate data from the DTG arms to be representative of TLD. We recognize that these data are not wholly generalizable to implementation of TLD in national ART programmes because of issues, such as coformulation of therapies, as well as medication stock-outs, challenges with viral load monitoring, and other barriers to treatment adherence outside a clinical trial setting. An overview of the results of these studies is summarized in Table 1.

Contributions of adherence to virologic failure in ADVANCE and NAMSAL

Antiretroviral therapy adherence in ADVANCE and NAMSAL

Despite concerns about reduced tolerability of EFV-based versus DTG-based ART [18,19], neither the ADVANCE nor NAMSAL studies demonstrated significantly different adherence patterns between the EFV and DTG arms. Both studies assessed adherence using self-report and pill count data [20,21]. In ADVANCE, a short-term measure of adherence was assessed by self-report of missed doses in the 4 days prior to each visit. Approximately 40% of participants in all three arms reported imperfect short-term adherence at least once during 96 weeks of observation, which was not significantly different between groups (113 of 269 in the EFV arm, 252 of 557 in the DTG arms) [22]. ADVANCE also reported no differences in average adherence based on pill counts across 96 weeks, with less than 95% adherence in only 13% (35 of 269) of participants in the EFV arm and 16% (91 of 557) in the DTG arms, respectively [22]. In NAMSAL, adherence levels were less than 95% in 30% (167/548) of study participants at 48 weeks with no significant difference

between arms. Over the 48-week follow-up period, 67% (365 of 548) of participants reported at least one lapse in adherence to 95% or less, also similar between arms [16]. As with much adherence data, these results come with caveats. Whereas both pill count and self-report correlate with viral suppression, both are susceptible to systematic over-reporting of adherence [23], as opposed to more objective measures, such as medication pick-up data and drug level monitoring that may provide more accurate adherence information. On the other hand, both ADVANCE and NAMSAL used two-pill formulations of DTG-based ART, which might also result in poorer adherence than the TLD fixed-dose combination single pill regimen used in much of SSA [24].

Tolerability and side effects

Tolerability is one of the predicted benefits of INSTI-based regimens, as compared with EFV. However, data from the SSA region have suggested that EFV might be associated with relatively less severe neuropsychiatric side effects than reported elsewhere [25]. Similarly, pharmacovigilance studies of the rollout of DTG in SSA should be implemented to assess tolerability of these regimens in the regional population. Early data from ADVANCE and NAMSAL showed both high tolerance for the DTG-based regimens but unexpectedly high reports of weight gain [15,16]. In ADVANCE, only one participant in the DTG arms had an adverse event leading to trial regimen discontinuation at 48 weeks, as compared with 10 participants in the EFV arm [15]. Overall, tolerability was similarly high in NAMSAL with no treatment discontinuations related to drug safety reported at 48 weeks in either arm [16]. Interestingly, although EFV has been known to cause neuropsychiatric side effects and sleep disturbances, insomnia was also identified in the DTG arms in both ADVANCE [1% (8/602) in DTG arms; 0.3% (1/351) in EFV arm] and NAMSAL [2% (7/310) in DTG arm; 3% (10/303) in EFV arm] [15,16], a finding reported in other clinical trials and observational cohorts [26]. Still, in ADVANCE, there was no difference in the duration or amount of sleep reported by participants across arms [15]. Perhaps more concerningly, weight gain was highlighted as a key association with DTG in both ADVANCE, especially in combination with TAF, and NAMSAL. Weight gain on DTG (and other INSTI)-containing regimens has been previously described in other settings [27,28], and NAMSAL and ADVANCE confirm this finding among a large cohort of patients in SSA [15,16]. Although mechanisms for DTG-related weight gain are under investigation (including that older drugs like EFV have side effects that may mitigate normal population weight gain), these studies importantly report higher rates of incident obesity among patients on 3(F)TC/TDF with DTG [7% (17 of 250) in ADVANCE; 12% (36 of 293) in NAMSAL], compared with EFV [6% (13 of 220) in ADVANCE; 5% (15 of 278) in NAMSAL]. Mean weight gain was greater in women in both studies across all arms. Importantly, the impact of this weight gain and metabolic repercussions did not appear to meaningfully impact cardiovascular disease risk [29].

Factors associated with poor adherence to dolutegravir

Although DTG-containing regimens were highly tolerated, demographic and social determinants strongly impacted adherence. In ADVANCE, younger age and unemployment predicted reduced adherence in the DTG arms (Fig. 1). Unemployment was also found to be negatively associated with viral suppression at 96 weeks [22]. The combination of unemployment among adolescents predicted the lowest level of adherence, with only 63% (39/62) of this sub-group having more than 95% average adherence over 96 weeks. These data continue to support targeted adherence interventions to optimize viral suppression among key at-risk groups, even in the setting of well tolerated and highly potent ART.

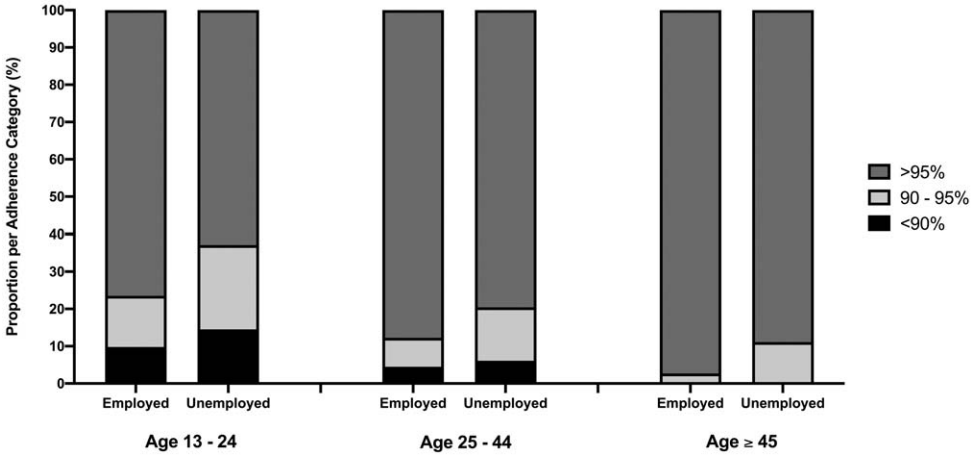

Fig. 1. Younger age and unemployment predicted poorer adherence in ADVANCE.

Consequences of suboptimal adherence to dolutegravir

In ADVANCE, both self-reported adherence (AOR 0.41; 95% CI 0.27–0.63) and average pill-count adherence for more than 95% adherence as compared with less than 90% adherence (AOR 3.51, 95% CI 1.70–7.24) were strong predictors of viral suppression at 96 weeks in adjusted models [22]. Conversely, adherence, measured by medication possession ratio and questionnaire, was not found to be a predictor of viral suppression (<50 copies/ml) at 48 weeks in either arm of NAMSAL, but did predict WHO-defined virologic failure in the EFV arm [16].

Contributions of drug resistance to virologic failure in ADVANCE and NAMSAL

Antiretroviral therapy-naive patients

ADVANCE and NAMSAL enrolled participants reporting to be ART-naive, and thus, PDR could be assessed in both studies. ADVANCE identified mutations conferring resistance to NNRTIs from the 2009 WHO list of transmitted drug resistance mutations [30] in 14% (122 of 873) of participants with successful pretreatment genotypic resistance testing and only 2% (20 of 873) of participants with resistance to NRTIs [22]. Pretreatment integrase sequencing has not yet been performed. A similar pattern was seen in NAMSAL, though rates of PDR were lower with 6% (37 of 611) of participants having NNRTI resistance and 1% (8 of 611) having NRTI resistance [16]. NAMSAL also provided data from pretreatment integrase sequences. No major integrase mutations were identified [16], as defined by the Stanford database [31,32]. The integrase polymorphisms T97A and E157Q were most frequently identified [16], which alone do not affect susceptibility to DTG [33,34]. Of note, one patient was found to have S153F, which has been found to cause low-level resistance to DTG [16,35]. Other studies from SSA have found pretreatment primary resistance mutations to late generation INSTIs to be rare, with prevalence less than 1% [10,11,36]. More recent data from studies of long-acting rilpivirine with cabotegravir showed that three virologic failures with subtype A1 all had L74I and a major known INSTI mutation at virologic failure [37]. L74I is found in up to 40% of West African isolates [38], and more work is needed on novel determinants of INSTI resistance.

Given low prevalence of PDR to the components of the DTG-containing regimens used in these studies, the impact of PDR on viral suppression was expected to be minimal. However, in ADVANCE, PDR was found to be a strong negative predictor of viral suppression at 48 and 96 weeks for both the EFV and DTG arms in models adjusted for demographic factors, pretreatment $CD4^+$ count, pretreatment viral load, and adherence [22]. With very low prevalence of PDR to NRTIs, this effect was primarily driven by resistance to NNRTIs. In fact, no participants who suffered virologic failure in the DTG arms had baseline resistance to NRTIs. Of note, in ADVANCE minority variant PDR did not predict virologic outcomes. Possible mechanisms for the unexpected impact of PDR to NNRTIs on viral suppression with DTG include an as of yet unexplained impact of NNRTI resistance mutations on viral fitness or that NNRTI resistance might serve as a proxy for undisclosed prior ART use and previous adherence challenges. Undisclosed prior ART use occurs frequently in SSA, for which the reasons are likely multifactorial because of stigma, fear of health worker disapproval, and other beliefs regarding treatment status [39–42]. In ADVANCE and NAMSAL, participants were thought to be ART-naive; however, because of limitations of medical record systems and lack of availability of routine drug-level testing, prior undisclosed ART use may have occurred. In contrast, NAMSAL reported no statistically significant association between PDR and viral suppression at 48 weeks, albeit with much lower rates of PDR detected in the study. However, NAMSAL did report a significant association between PDR and the outcome of WHO-defined virologic failure in the EFV arm.

Neither ADVANCE nor NAMSAL reported any instances of treatment-emergent resistance to DTG by 96 weeks [14,17]. These findings are consistent with other studies involving DTG-containing regimens in ART-naive populations [19,43–45]. However, treatment-emergent resistance to NRTIs and NNRTIs occurred in the EFV arms of both studies [15–17,46]. Although NAMSAL did not report emergence of any NRTI resistance mutations in the DTG arm, ADVANCE reported two such cases [15,46]. The lack of DTG resistance in clinical trials in ART-naive patients is reassuring; however, the long-term effects of emergent NRTI resistance in this population have yet to be determined.

Antiretroviral therapy-experienced patients

Although data on the use of DTG in ART-naive populations have been quite reassuring, the majority of PWH to receive DTG globally will be ART-experienced because of the programmatic switching from EFV-based first-line ART currently recommended in the region [47,48]. Data regarding the effectiveness of TLD in ART-experienced patients in resource-limited settings remain limited because of the recent introduction of this regimen in 2018 (or later in many countries). Rates of HIV drug resistance to both TDF and 3TC at the time of virologic failure on NNRTI-based regimens exceed 50% in much of

SSA [7]. Thus, if treatment-experienced patients are transitioned to TLD without recent viral load monitoring, there is a much greater risk of occult NRTI resistance than in an ART-naive population. Data from an ongoing prospective cohort study in Malawi reported that 101 of 1892 (5%) participants transitioned from NNRTI-based regimens to TLD were found to have detectable viral loads at least 50 copies/ml at the time of transition. Of those, three participants (3%) had confirmed virologic failure (≥500 copies/ml) at 6 months. Genotypic resistance testing from the time of transition to TLD revialed NRTI resistance in all three participants. Only one participant had preexisting resistance to both 3TC and TDF (M184V and K70E). Two of these individuals developed treatment-emergent resistance to DTG (R263K, G118R) after only 6 months on TLD [49]. Ongoing surveillance of DTG resistance among ART-experienced individuals who fail TLD is warranted, to identify whether these mutations were a function of prior poor adherence, existing resistance, or newly evolved on a DTG-containing regimen that was not suppressive. Longitudinal data from ongoing observational studies in SSA are expected in 2021 to provide additional clarity on this issue.

Interactions between adherence and resistance

Data from NAMSAL and ADVANCE reemphasize the impact of both adherence and resistance on virologic outcomes on DTG-based therapy in the region. Particularly in the ADVANCE study, both treatment adherence and preexisting drug resistance mutations to the NNRTI class strongly predicted virologic outcomes, even in non-NNRTI-containing regimens. Consequently, interaction between the two is equally important to consider. Data from ADVANCE demonstrate an additive effect of both factors, such that those with both PDR and poor adherence do worse than either risk factor alone (Fig. 2). We did not detect a significant multiplicative interaction between the two ($P = 0.11$).

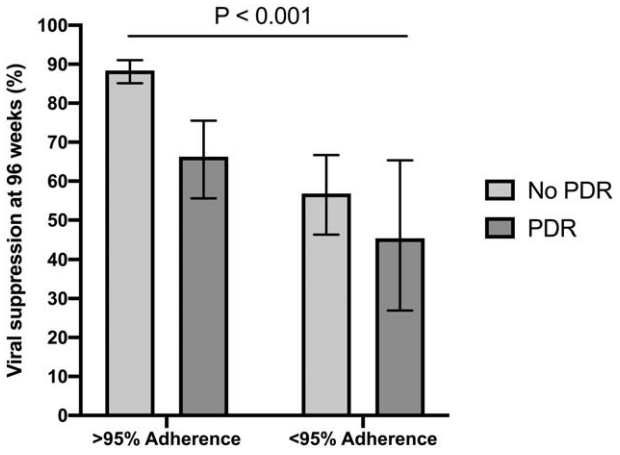

Fig. 2. Effect of pretreatment drug resistance and average adherence on viral suppression at 96 weeks for participants on dolutegravir in ADVANCE. DTG, dolutegravir, PDR, pretreatment drug resistance.

Re-suppression after failure on TLD

Viral re-suppression after a single elevated viral load occurs in less than half of individuals with virologic failure on NNRTI-based first-line ART [50], likely because of high prevalence of HIVDR in the setting of a low resistance barrier regimen or inability to address the underlying adherence challenges [5,6,51]. Thus, WHO guidelines recommended a switch to second-line if virologic failure is confirmed on NNRTI-based regimens following a repeat viral load measurement after a period of adherence counseling. ADVANCE reports re-suppression rates for both EFV and DTG-based regimens and provides insight into whether management of virologic failure should be similar or different for these two groups. We conducted a sub-analysis of viral re-suppression data, shown in Table 2. A total of 188 participants in the ADVANCE study had an episode of detectable viremia on treatment. Participants were considered to have viremia if the HIV-1 viral load was at least 1000 copies/ml HIV RNA at week 12 or later, at least 200 copies/ml at week 24 or later, or at least

Table 2. Viral re-suppression in ADVANCE.

Study arm	Total re-suppressed	Re-suppressed after viral load less than 1000 copies/ml	Re-suppressed after viral load greater than 1000 copies/ml	*P* value*
Pooled DTG arms	100/118 (85)	40/46 (87)	60/72 (83)	0.794
TAF/FTC + DTG	49/59 (83)	24/27 (89)	25/32 (78)	0.319
TDF/FTC + DTG	51/59 (86)	16/19 (84)	35/40 (88)	0.704
TDF/FTC/EFV	21/40 (53)	11/16 (69)	10/24 (42)	0.117
Total	122/158 (77)	52/62 (84)	70/96 (73)	0.124

Data are recorded as count (percentage). DTG, dolutegravir; FTC, emtricitabine; TAF, tenofovir alafenamide.
*Calculated using Fisher's exact test.

Table 3. Implications for treatment guidelines for first-line tenofovir-lamivudine-dolutegravir use in sub-Saharan Africa.

Considerations for ART programs	Key supporting findings from ADVANCE and NAMSAL	Data gaps and future research
1. ART programs should anticipate and prepare for significant virologic failure rates on TLD in both ART-naive and ART-experienced populations	Rates of long-term viral suppression were similar between the EFV and DTG arms in both studies. Thus, up to 10–30% of people on TLD are likely to suffer treatment discontinuation or virologic failure during the first 2 years of treatment. In addition, PDR to NNRTIs strongly predicted virologic failure in ADVANCE, which has implications for both ART-naive and ART-experienced individuals	Research is needed to determine the factors associated with virologic failure on TLD
2. A patient-centered approach should be taken to understand and respond to adherence challenges and drug intolerance. Regimen switches should be considered if adherence challenges occur because of drug side effects	Although DTG-based regimens were well tolerated with less than 1% of participants discontinuing therapy because of adverse events after 48 weeks, greater weight gain and higher prevalence of incident obesity occurred in the DTG vs. EFV arms in both studies.	Research is needed to determine the impact of weight gain on adherence to TLD
3. Targeted adherence interventions should still be highly considered for key populations traditionally at risk of virologic failure, including adolescents and individuals facing unemployment	Younger age and unemployment were strong predictors of reduced adherence in ADVANCE	Studies are needed to evaluate the optimal adherence interventions for key populations
4. Adherence interventions should be considered for individuals with any level of detectable viremia, not only for those with viral loads more than 1000 copies/ml	VL magnitude at the time of detection did not predict the probability of re-suppression in ADVANCE	Research is needed to determine the feasibility and acceptability of offering adherence interventions for all individuals with any level of detectable viremia.
5. Low cost, objective adherence assays may be incorporated into management strategies to better identify poor adherence as a cause of virologic failure on TLD	Adherence strongly predicted viral suppression in the DTG arm of ADVANCE with 85% achieving viral suppression if adherence was more than 95% over the study observation period	Clinical trials and implementation studies are needed to determine the optimal use of objective adherence assays into routine care
6. Guidelines should provide a longer window of opportunity for viral re-suppression on TLD before switch to second-line ART, as compared with EFV-based regimens	Participants on DTG with episodes of viremia re-suppressed at higher rates than those on EFV in ADVANCE	Clinical trials are needed to determine the most clinically effective and cost-effective switch strategies for patients with virologic failure on TLD
7. National programs should consider surveillance strategies to monitor for emergence of resistance to DTG in the population	Treatment-emergent resistance to DTG was rare for treatment-naive patients in ADVANCE and NAMSAL but has been seen in those who switch to DTG from EFV with NRTI mutations	Surveillance studies are needed to monitor the frequency of treatment emergent resistance to DTG at the population level

ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; NNRTI, nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TLD, fixed-dose combination of tenofovir disoproxil fumarate, lamivudine, and dolutegravir.

50 copies/ml anytime between week 48 and week 96. Of these 188 participants with detectable viremia, 30 were lost to follow-up, leaving 118 participants for analysis on DTG-containing regimens and 40 on EFV. Eighty-five percent (100 of 118) of participants with detectable viremia on DTG re-suppressed to less than 50 copies/ml within the next three viral load measurements, as compared with 53% (21 of 40) in the EFV arm (Table 2). Notably, rates of viral re-suppression in ADVANCE were not statistically different between those with initial elevated viral loads less than 1000 versus at least 1000 copies/ml (Table 2). Such data suggest that any detectable viral load on DTG-based ART might be indicative of a need for intervention and closer monitoring, as opposed to the 1000 copies/ml threshold that has been historically adopted in the NNRTI era.

Data gaps and future research

Key data gaps remain regarding the management PWH on TLD in SSA. Drug-specific factors associated with virologic failure on TLD require further study. Additional studies at the population level are also needed to understand the frequency of treatment emergent resistance to DTG, the impact of both NRTI and NNRTI resistance on TLD effectiveness, and virologic mechanisms leading to DTG resistance, including resistance that may occur outside of the integrase gene [9]. It will also be important to clarify the effects of significant weight gain on long-term adherence on DTG-containing regimens. Short-term weight gain may be welcome, but data are required if accelerated weight gain should persist over several years. Finally, the optimal management of

virologic failure for individuals on TLD, as well as optimal switch strategies to DTG-containing regimens, should be a priority of future studies, as the field seeks to understand the circumstances, which should prompt a change from TLD to alternative ART.

Implications for treatment guidelines

Data from these trials provide key insights for treatment guidelines, which we have summarized in Table 3. Both studies provide evidence that virologic failures do occur on DTG-based ART, a finding, which has implications for ART programs worldwide. Adherence was highly predictive of viral suppression in ADVANCE, which suggests a potential role for objective adherence monitoring in management guidelines. Adherence remains a challenge for high-risk groups, including adolescents and individuals facing unemployment, and while DTG-based regimens were overall well tolerated, weight gain emerged as a significant side effect, which will require a patient-centered approach. Data also indicate that magnitude of viremia less than 1000 copies/ml versus more than 1000 copies/ml was not predictive of viral re-suppression, and thus, adherence interventions should be considered even for those with lower level viremia, though feasibility and viral blips may also need to be taken into account. Finally, treatment-emergent resistance to DTG remains a rare event in ART-naive individuals, and viral re-suppression is much more common on DTG-based as compared with EFV-based ART, supporting a longer window of opportunity for viral re-suppression before switch to second-line ART from TLD.

Conclusion

The introduction of TLD in SSA represents a major advancement in global HIV care. ADVANCE and NAMSAL are two historic trials performed solely in SSA, which pragmatically evaluated the effectiveness of DTG-containing first-line regimens in ART-naive individuals. They not only clarified both the strengths of DTG-based therapy but also many new considerations about deleterious impacts of imperfect adherence and PDR on virologic control, which should be considered in treatment guidelines in the region. To continue progress toward achieving greater epidemic control, we must continue to evaluate the durability of TLD-based therapy, find subpopulations at risk for failure or substantial side-effects that challenge adherence, and develop clear and data-driven guidelines for transition to alternate ART in the region.

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Conflicts of interest

There are no conflicts of interest.

References

1. Joint United Nations Programme on HIV/AIDS. Fact Sheet: Global HIV Statistics. 2020.
2. World Health Organization. HIV drug resistance report. Geneva; 2017.
3. Gupta RK, Gregson J, Parkin N, Haile-Selassie H, Tanuri A, Andrade Forero L, *et al*. **HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis.** *Lancet Infect Dis* 2018; **18**:346–355.
4. World Health Organization. HIV Drug Resistance Report. Geneva; 2019.
5. Ssemwanga D, Asio J, Watera C, Nannyonjo M, Nassolo F, Lunkuse S, *et al*. **Prevalence of viral load suppression, predictors of virological failure and patterns of HIV drug resistance after 12 and 48 months on first-line antiretroviral therapy: a national cross-sectional survey in Uganda.** *J Antimicrob Chemother* 2020; **75**:1280–1289.

6. Steegen K, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D, Variava E, *et al*. **HIV-1 antiretroviral drug resistance patterns in patients failing NNRTI-based treatment: results from a national survey in South Africa.** *J Antimicrob Chemother* 2017; **72**:210–219.
7. TenoRes Study Group. **Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study.** *Lancet Infect Dis* 2016; **16**:565–575.
8. Clutter DS, Jordan MR, Bertagnolio S, Shafer RW. **HIV-1 drug resistance and resistance testing.** *Infect Genet Evol* 2016; **46**:292–307.
9. Collier DA, Monit C, Gupta RK. **The impact of HIV-1 drug escape on the global treatment landscape.** *Cell Host Microbe* 2019; **26**:48–60.
10. Inzaule SC, Hamers RL, Noguera-Julian M, Casadella M, Parera M, Rinke de Wit TF, Paredes R. **Primary resistance to integrase strand transfer inhibitors in patients infected with diverse HIV-1 subtypes in sub-Saharan Africa.** *J Antimicrob Chemother* 2018; **73**:1167–1172.
11. Ndashimye E, Avino M, Kyeyune F, Nankya I, Gibson RM, Nabulime E, *et al*. **Absence of HIV-1 drug resistance mutations supports the use of dolutegravir in Uganda.** *AIDS Res Hum Retroviruses* 2018; **34**:404–414.
12. World Health Organization. *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendation on early infant diagnosis of HIV*. Geneva: WHO; 2018.
13. USAID Global Health Supply Chain Program. The Dolutegravir Opportunity. 2017.
14. Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, Mashabane N, *et al*. **Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial.** *Lancet HIV* 2020; **7**:e666–e676.
15. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, *et al*. **Dolutegravir plus two different prodrugs of tenofovir to treat HIV.** *N Engl J Med* 2019; **381**:803–815.
16. NAMSAL Study Group. Kouanfack C, Mpoudi-Etame M, Omgba Bassega P, Eymard-Duvernay S, Leroy S, *et al*. **Dolutegravir-based or low-dose efavirenz-based regimen for the treatment of HIV-1.** *N Engl J Med* 2019; **381**:816–826.
17. Calmy A, Tovar Sanchez T, Kouanfack C, Mpoudi-Etame M, Leroy S, Perrineau S, *et al*. **New Antiretroviral and Monitoring Strategies in HIV-infected Adults in Low-Income Countries (NAMSAL) ANRS 12313 Study Group. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon.** *Lancet HIV* 2020; **7**:e677–e687.
18. Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, *et al*. **Brief report: dolutegravir plus abacavir/lamivudine for the treatment of hiv-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial.** *J Acquired Immune Defic Syndr* 2015; **70**:515–519.
19. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, *et al*., SINGLE Investigators. **Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection.** *N Engl J Med* 2013; **369**:1807–1818.
20. Mudhune V, Gvetadze R, Girde S, Ndivo R, Angira F, Zeh C, *et al*. **Correlation of adherence by pill count, self-report, MEMS and plasma drug levels to treatment response among women receiving ARV therapy for PMTCT in Kenya.** *AIDS Behav* 2018; **22**:918–928.
21. Wu P, Johnson BA, Nachega JB, Wu B, Ordonez CE, Hare AQ, *et al*. **The combination of pill count and self-reported adherence is a strong predictor of first-line ART failure for adults in South Africa.** *Curr HIV Res* 2014; **12**:366–375.
22. Siedner MJ, Moorhouse M, Simmons B, de Oliveira T, Lessells R, Giandhari J, *et al*. **Reduced efficacy of HIV-1 integrase inhibitors in patients with drug resistance mutations in reverse transcriptase.** *Nat Commun* 2020; **11**:5922.
23. Castillo-Mancilla JR, Haberer JE. **Adherence measurements in HIV: new advancements in pharmacologic methods and real-time monitoring.** *Curr HIV/AIDS Rep* 2018; **15**:49–59.
24. Gandhi M, Gandhi RT. **Single-pill combination regimens for treatment of HIV-1 infection.** *N Engl J Med* 2014; **371**:248–259.
25. Chang JL, Tsai AC, Musinguzi N, Haberer JE, Boum Y, Muzoora C, *et al*. **Depression and suicidal ideation among HIV-infected adults receiving efavirenz versus nevirapine in Uganda: a prospective cohort study.** *Ann Intern Med* 2018; **169**:146–155.
26. Fettiplace A, Stainsby C, Winston A, Givens N, Puccini S, Vannappagari V, *et al*. **Psychiatric symptoms in patients receiving dolutegravir.** *J Acquir Immune Defic Syndr* 2017; **74**:423–431.
27. Norwood J, Turner M, Bofill C, Rebeiro P, Shepherd B, Bebawy S, *et al*. **Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens.** *J Acquir Immune Defic Syndr* 2017; **76**:527–531.
28. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgan T, Raffanti SP, *et al*. **Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy.** *Clin Infect Dis* 2020; **70**:1267–1274.
29. Hill A, McCann K, Pilkington V, Moorhouse M, Sokhela S, Serenata C, *et al*. Risks of metabolic syndrome, diabetes, and cardiovascular disease in ADVANCE Trial. *Conference on Retroviruses and Opportunistic Infections*. Boston, MA, 2020.
30. Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, *et al*. **Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update.** *PLoS One* 2009; **4**:e4724.
31. Rhee SY, Gonzales MJ, Kantor R, Betts BJ, Ravela J, Shafer RW. **Human immunodeficiency virus reverse transcriptase and protease sequence database.** *Nucleic Acids Res* 2003; **31**:298–303.
32. Shafer RW. **Rationale and uses of a public HIV drug-resistance database.** *J Infect Dis* 2006; **194 (Suppl 1)**:S51–S58.
33. Abram ME, Ram RR, Margot NA, Barnes TL, White KL, Callebaut C, *et al*. **Lack of impact of preexisting T97A HIV-1 integrase mutation on integrase strand transfer inhibitor resistance and treatment outcome.** *PLoS One* 2017; **12**:e0172206.
34. Charpentier C, Malet I, Andre-Garnier E, Storto A, Bocket L, Amiel C, *et al*. **Phenotypic analysis of HIV-1 E157Q integrase polymorphism and impact on virological outcome in patients initiating an integrase inhibitor-based regimen.** *J Antimicrob Chemother* 2018; **73**:1039–1044.
35. Oliveira M, Ibanescu RI, Anstett K, Mesplede T, Routy JP, Robbins MA, *et al*. **Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir.** *Retrovirology* 2018; **15**:56.
36. Derache A, Iwuji CC, Danaviah S, Giandhari J, Marcelin AG, Calvez V, *et al*. **Predicted antiviral activity of tenofovir versus abacavir in combination with a cytosine analogue and the integrase inhibitor dolutegravir in HIV-1-infected South African patients initiating or failing first-line ART.** *J Antimicrob Chemother* 2019; **74**:473–479.
37. Jeffrey J, St. Clair M, Wang P, Wang C, Li Z, Fridell R, *et al*. HIV A1 or B do not differentially impact cabotegravir in vitro potency or durability. In: *Conference on Retroviruses and Opportunistic Infections*. Boston, MA; 2020.
38. El Bouzidi K, Kemp SA, Datir RP, Murtala-Ibrahim F, Aliyu A, Kwaghe V, *et al*. **High prevalence of integrase mutation L74I in West African HIV-1 subtypes prior to integrase inhibitor treatment.** *J Antimicrob Chemother* 2020; **75**:1575–1579.
39. Gregson J, Kaleebu P, Marconi VC, van Vuuren C, Ndembi N, Hamers RL, *et al*. **Occult HIV-1 drug resistance to thymidine analogues following failure of first-line tenofovir combined with a cytosine analogue and nevirapine or efavirenz in sub Saharan Africa: a retrospective multicentre cohort study.** *Lancet Infect Dis* 2017; **17**:296–304.
40. Fogel JM, Wang L, Parsons TL, Ou SS, Piwowar-Manning E, Chen Y, *et al*. **Undisclosed antiretroviral drug use in a multinational clinical trial (HIV Prevention Trials Network 052).** *J Infect Dis* 2013; **208**:1624–1628.

41. Moyo S, Gaseitsiwe S, Powis KM, Pretorius Holme M, Mohammed T, Zahralban-Steele M, *et al*. **Undisclosed antiretroviral drug use in Botswana: implication for national estimates.** *Aids* 2018; **32**:1543–1546.
42. Grabowski MK, Reynolds SJ, Kagaayi J, Gray RH, Clarke W, Chang LW, *et al*. **The validity of self-reported antiretroviral use in persons living with HIV: a population-based study.** *AIDS* 2018; **32**:363–369.
43. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, *et al*. **Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, noninferiority SPRING-2 study.** *Lancet* 2013; **381**:735–743.
44. Orrell C, Hagins DP, Belonosova E, Porteiro N, Walmsley S, Falco V, *et al*. **Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, noninferiority, phase 3b study.** *Lancet HIV* 2017; **4**:e536–e546.
45. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, *et al*. **Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study.** *Lancet* 2014; **383**:2222–2231.
46. Venter WDF, Moorehouse MA, Sokhela S, Serenata C, Pepperrell T, Simmons B, *et al*. ADVANCE Trial: higher risk of treatment-emergent resistance on first-line TDF/FTC/EFV. In: *Conference on Retroviruses and Opportunistic Infections*. Boston, Massachusetts, 2020.
47. World Health Organization. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, 2019.
48. The U.S. President's Emergency Plan for AIDS Relief. Country Operational Plan Guidance for Standard Process Countries. 2018.
49. Temfack E, Jahn A, Kalua T, Bitilinyu-Bangoh J, Nyirenda R, Marcelin AG, *et al*. Prospective enhanced monitoring of dolutegravir-based first line in Malawi. Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts, USA, 2020.
50. Ford N, Orrell C, Shubber Z, Apollo T, Vojnov L. **HIV viral resuppression following an elevated viral load: a systematic review and meta-analysis.** *J Int AIDS Soc* 2019; **22**:e25415.
51. Gupta RK, Goodall RL, Ranopa M, Kityo C, Munderi P, Lyagoba F, *et al.*, DART Virology Group and Trial Team. **High rate of HIV resuppression after viral failure on first-line antiretroviral therapy in the absence of switch to second-line therapy.** *Clin Infect Dis* 2014; **58**:1023–1026.