Viral suppression and HIV-1 drug resistance 1 year after pragmatic transitioning to dolutegravir first-line therapy in Malawi: a prospective cohort study

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See Comment page e523

For the French translation of the abstract see Online for appendix 1

For the Portuguese translation of the abstract see Online for appendix 2

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Summary

Background Many countries are now replacing non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line antiretroviral therapy (ART) with a regimen containing tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD). Recognising laboratory limitations, Malawi opted to transition those on NNRTI-based first-line ART to TLD without viral load testing. We aimed to assess viral load and HIV drug resistance during 1 year following transition to TLD without previous viral load testing.

Methods In this prospective cohort study, we monitored 1892 adults transitioning from NNRTI-based first-line ART to the TLD regimen in the Médecins Sans Frontières-supported decentralised HIV programme in Chiradzulu District, Malawi. Eligible adults were enrolled between Jan 17 and May 11, 2019, at Ndunde and Milepa health centres, and between March 8 and May 11, 2019, at the Boma clinic. Viral load at the start of the TLD regimen was assessed retrospectively and measured at month 3, 6, and 12, and additionally at month 18 for those ever viraemic (viral load ≥50 copies per mL). Dolutegravir minimal plasma concentrations (C_{min}) were determined for individuals with viraemia. Drug-resistance testing was done at the start of TLD regimen and at viral failure (viral load ≥50 copies per mL, followed by viral load ≥500 copies per mL; resistance defined as Stanford score ≥15).

Findings Of 1892 participants who transitioned to the TLD regimen, 101 (5·3%) were viraemic at TLD start. 89 of 101 had drug-resistance testing with 31 participants (34·8%) with Lys65Arg mutation, 48 (53·9%) with Met184Val/Ile, and 42 (40·4%) with lamivudine and tenofovir disoproxil fumerate dual resistance. At month 12 (in the per-protocol population), 1725 (97·9% [95% CI 97·1–98·5]) of 1762 had viral loads of less than 50 copies per mL, including 83 (88·3% [80·0–94·0]) of 94 of those who were viraemic at baseline. At month 18, 35 (97·2% [85·5–99·9]) of 36 who were viraemic at TLD start with lamivudine and tenofovir disoproxil fumarate resistance and 27 (81·8% [64·5–93·0]) of 33 of those viraemic at baseline without resistance had viral load suppression. 14 of 1838 with at least two viral load tests upon transitioning had viral failure (all with at least one dolutegravir C_{min} value <640 ng/mL; active threshold), suggesting suboptimal adherence. High baseline viral load was associated with viral failure (adjusted odds ratio [aOR] 14·1 [2·3–87·4] for 1000 to <10 000 copies per mL; aOR 64·4 [19·3–215·4] for ≥10 000 copies per mL). Two people with viral failure had dolutegravir resistance at 6 months (Arg263Lys or Gly118Arg mutation), both were viraemic with lamivudine and tenofovir disoproxil fumarate resistance at baseline.

Interpretation High viral load suppression 1 year after introduction of the TLD regimen supports the unconditional transition strategy in Malawi. However, high pre-transition viral load, ongoing adherence challenges, and possibly existing nucleoside reverse transcriptase inhibitor resistance can lead to rapid development of dolutegravir resistance in a few individuals. This finding highlights the importance of viral load monitoring and dolutegravir-resistance surveillance after mass transitioning to the TLD regimen.

Funding Médecins Sans Frontières.

Introduction

Over the past two decades, global antiretroviral therapy (ART) has averted an estimated 16·5 million AIDS-related deaths; however, long-term gains are threatened by HIV drug resistance.[1–4] Widely used non-nucleoside reverse transcriptase inhibitors (NNRTIs; mainly nevirapine and efavirenz) are particularly vulnerable due to their low resistance barrier, with reports showing alarming levels of drug resistance.[5] Consequently, WHO changed first-line treatment recommendations in 2018 by replacing NNRTIs with dolutegravir.[6] Dolutegravir is a second-generation HIV integrase strand transfer inhibitor (INSTI) with considerable public health benefits due to its excellent tolerability

Research in context

Evidence before this study

We searched MEDLINE for publications using the terms "HIV", "dolutegravir", "resistance", and "tenofovir" or "reverse transcriptase inhibitor", published between Jan 1, 2016, and Dec 15, 2021. Before the start of this study, clinical evidence was scarce that would support the mass transitioning of people with (unknown) viraemia and possibly pre-existing resistance from non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART) to the newer, WHO-recommended, first-line combined regimen of tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD). Only one prospective descriptive study has since reported transitioning outcomes in a clinical prescription setting in sub-Saharan Africa, while providing information on viral load at the start of TLD regimen. However, the reported follow-up was only 16 weeks and no information on baseline drug resistance was given. Data on the impact of nucleoside reverse transcriptase inhibitor (NRTI) backbone resistance on dolutegravir-based regimen performance have become available from clinical trials of second-line treatments: a three-arm trial (NADIA) reported excellent viral load suppression at 48 weeks in participants switched to a dolutegravir-based second-line regimen despite extensive NRTI resistance. A prospective interventional study (ARTIST) reported good viral suppression after switching people to TLD as a second-line regimen after failing an NNRTI-based first-line regimen, including those with lamivudine and tenofovir disoproxil fumarate resistance. The latter report was also at a relatively early timepoint (24 weeks).

Added value of this study

This study fills crucial knowledge gaps for HIV clinicians and policy makers in resource-limited settings, where viral load testing during mass transitioning to the newly recommended TLD first-line regimen is mostly unfeasible. We assessed 1-year outcomes of participants who transitioned without known viral loads to a TLD regimen. We also examined the relevance of pre-existing lamivudine and tenofovir disoproxil fumarate resistance for viral load suppression on the TLD regimen and measured the rate of dolutegravir resistance in this real-world prescription context. Furthermore, therapeutic drug monitoring with assessment of dolutegravir plasma concentrations shed light on the potential mechanisms of viral failure. These are the first longer-term outcome data on TLD use in an African setting outside of a clinical trial context.

Implications of all the available evidence

Many countries in sub-Saharan Africa are currently adopting Malawi's approach to the introduction of a TLD regimen, with similarly insufficient viral load and drug-resistance monitoring capacities. Careful evaluation of this transition strategy will be of great importance for millions of people in resource-constrained ART programmes. Our results add to a growing body of evidence supporting the mass transition of people with HIV from NNRTI-based first-line regimens to TLD ART, showing that viral load suppression rates can be achieved even in those who are genotypically predicted to be resistant to the NRTI regimen backbone of lamivudine and tenofovir disoproxil fumarate. This finding has important implications for the use of TLD as an effective first-line regimen in low-resource settings, where high levels of NRTI resistance are frequent in viraemic people. The finding that viral suppression might be more difficult to achieve for those who transitioned with an unknown high viral load, as well as infrequent reports of early dolutegravir resistance, emphasise the continued importance of viral load monitoring and need for resistance surveillance.

and efficacy in clinical trials, availability as a low-cost single-tablet generic formulation in a combined regimen of tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD), and a high genetic barrier to resistance.[2,7–10] Many low-income and middle-income countries (LMICs) have since endorsed TLD as a new first-line regimen. Malawi changed its national first-line policy in 2018,[11] transitioning over 750 000 ART recipients to TLD without a viral load test. This pragmatic approach was chosen because of limited viral load monitoring capacity, similar to many LMICs.[12]

Yet, concerns were raised about rolling out a new drug regimen in a context without sufficient viral load monitoring and with almost no resistance testing available.[13,14] Specifically, there was no clinical evidence in support of switching large cohorts of people to TLD who might have unsuppressed viral load and possibly genotypic resistance to lamivudine and tenofovir disoproxil fumarate.[13–15] Lamivudine and tenofovir disoproxil fumarate resistance are frequent in people failing NNRTI-first-line regimens in sub-Saharan Africa.[16] The transition approach risked a considerable number of people taking an ineffective dolutegravir-functional monotherapy, and could thus develop dolutegravir resistance.[13–18] Dolutegravir-resistance data from routine health-care settings (especially in a non-subtype B HIV-1 epidemic context) were similarly unavailable for sub-Saharan Africa.[8,14,19]

To assess Malawi's national TLD-transitioning programme, we conducted a prospective observational study to assess viral load and HIV drug resistance for 1 year following transition to TLD without previous viral load testing. Therapeutic monitoring of antiretroviral plasma concentrations was used to better understand viral failure, and retrospective assessment of viral load and HIV drug resistance at the start of the TLD regimen mimicked the transition without viral load testing approach, adding to the extremely scarce evidence base in this area.

Methods

Study site and design

A prospective observational study was carried out in the Médecins Sans Frontières (MSF)-supported decentralised HIV programme in Chiradzulu District, Malawi, where about 35 000 people access ART in ten health centres and the district hospital. At the time of study inclusion, national guidelines recommended routine viral load monitoring at 6 months and 2 years following ART initiation, and every 2 years thereafter. In preparation for the mass regimen transition, Malawi Ministry of Health (MoH) implemented a catch-up viral load campaign aiming to cover all people without a viral load result in the preceding 12 months; however, this was only partially implemented.[11] In Chiradzulu, about 63% of people on ART had received a viral load test within 2 years before TLD roll-out (unpublished data, MSF). Study inclusion was in two health centres (Milepa and Ndunde) and the district hospital's outpatient clinic (Boma). Men older than 20 years and women aged 45 years or older on standard NNRTI-based first-line ART who weighed 30 kg or more were eligible. Women younger than 45 years and older women who were pregnant or intended to become pregnant were excluded. Initially, Malawian guidelines restricted TLD prescription to women aged 45 years or older (and younger women if consistent contraception could be assured) due to a reported increased risk of congenital anomalies (neural tube defects) after periconceptional dolutegravir exposure.[11,13] Individuals who met WHO-defined suspected clinical or virological failure (viral load result of ≥1000 copies per mL in the past 6 months),[20] or people with known contraindications to tenofovir disoproxil fumarate were also excluded. The study was approved by the Malawi National Health Sciences Research Committee, and the ethical review board of MSF. Participants provided written informed consent.

The main outcome was viral load suppression (<50 copies per mL) at 12 months post-transitioning and additionally at 18 months for those viraemic at the start of the TLD regimen. Secondary outcomes were (1) the proportion of participants with at least one detectable viral load (≥50 copies per mL) on TLD or with viral failure, (2) factors associated with detectable viral load or viral failure, (3) the proportion of viral failure with dolutegravir resistance, and (4) time to viral load suppression (among baseline viraemic) and time to viral failure.

The target sample size was 2300 assuming 10% (230 participants) were viraemic at baseline and 40% (90) of those would be lamivudine and tenofovir disoproxil fumarate-resistant, allowing a 50% viral load suppression estimate (requiring maximum sample size for desired precision) with a two-sided 95% CI and SD 10% precision in the lamivudine and tenofovir disoproxil fumarate-resistant subgroup. We invited eligible individuals to participate at their routine clinic visits between Jan 17 and May 11, 2019. Enrolment started in Ndunde and Milepa health centres. Since parallel TLD-transitioning in routine care proceeded quickly, Boma clinic was added as a third study site (from March 8, 2019, onward) to increase daily inclusion rates (protocol amendment approved). Inclusion was stopped on May 11, 2019, after enrolment of 1893 participants, once most of those eligible had been transitioned to TLD in all three sites.

Plasma viral load and HIV drug resistance were assessed from baseline blood specimens. Study clinicians and participants were masked to the results and received these at months 9 or 12 to mimic the MoH approach of unknown viraemia at the time of transitioning. TLD fixed-dose combination (tenofovir disoproxil fumarate 300 mg, lamivudine 300 mg, and dolutegravir 50 mg) was prescribed quarterly following the MoH routine, recommended to be taken in the morning. Viral load tests were conducted at month 3, 6, and 12. Participants with a detectable viral load at baseline or during follow-up through to month 12 (ever viraemic) had one additional viral load test at month 18.

Detectable viral load (viraemia) was defined as 50 or more copies per mL using the US Food and Drug Administration snapshot definition.[21] In addition, viraemia was reported using the WHO threshold (viral load ≥1000 copies per mL).[20] Suspected viral failure was defined as viral load of 50 or more copies per mL at or after month 3. Following suspected viral failure, enhanced adherence counselling was provided, and a confirmatory viral load test was done 3 months later. Viral failure was defined as viral load of 500 or more copies per mL at confirmatory viral load test.

Laboratory methods

Plasma HIV-1 RNA viral load was quantified at the regional reference laboratory at Queen Elizabeth Central Hospital in Blantyre using an Abbott RealTime HIV-1 assay (Abbott Molecular, Des Plaines, IL, USA) with a quantification threshold of less than 40 copies per mL. Drug-resistance testing was performed by Sanger sequencing at the virology laboratories at Pitié-Salpêtrière and Bichat-Claude Bernard hospitals in Paris, France, on plasma specimens at baseline (if viral load ≥100 copies per mL, technical threshold), and on dried blood spots (DBS) at viral failure (if confirmatory viral load test result ≥500 copies per mL, technical threshold for drug-resistance testing on DBS). For DBS testing, nucleic acids were recovered from filter papers, as previously described.[22] The sequences of reverse transcriptase, protease, and integrate genes of the HIV-1 *pol* gene were determined using the Agence Nationale de Recherche sur le SIDA consensus in-house Sanger sequencing technique. Drug resistance was defined as a resistance penalty score of 15 or greater (Stanford algorithm, version 9.0), which includes low-level, intermediate-level, and high-level resistance, but excludes potential low-level resistance. For all viraemic cases on TLD, dolutegravir plasma concentration (a snapshot indicator of recent

For the **Sanger sequencing technique** see https://hivfrenchresistance.org/wp-content/uploads/2021/10/ANRS-procedures.pdf

	N=1892
Sex	
Female	947 (50·1%)
Male	945 (49·9%)
Age, years	
Male	46 (40–54)
Female	53 (48–59)
Time on ART, years	
All patients with available data	8·0 (4·5–11·4)
Missing time on ART	10 (0·5%)
Known exposure to antiretroviral drugs	
Stavudine	1129 (59·7%)
Didanosine	0
Abacavir	13 (0·7%)
Zidovudine	169 (8·9%)
Tenofovir disoproxil fumarate	1849 (97·7%)
Nevirapine	1197 (63·3%)
Efavirenz	1842 (97·4%)
Any protease inhibitor	5 (0·3%)
Any integrase inhibitor	0
ART regimen at inclusion	
Lamivudine, tenofovir disoproxil fumarate, efavirenz	1802 (95·2%)
Lamivudine, tenofovir disoproxil fumarate, nevirapine	55 (2·9%)
Lamivudine, zidovudine, nevirapine	29 (1·5%)
Lamivudine, abacavir, nevirapine	3 (0·2%)
Lamivudine, zidovudine, efavirenz	2 (0·1%)
Missing regimen information	1 (0·1%)
Plasma HIV-1 RNA copies per mL	
Target not detected	1592 (84·1%)
<50	199 (10·5%)
50 to <100	9 (0·5%)
100 to <1000	30 (1·6%)
1000 to <10 000	29 (1·5%)
10 000 to <100 000	26 (1·4%)
≥100 000	7 (0·4%)
Resistance to NRTIs	
Drug resistance test results successful in eligible*	89/92 (96·7%)
Lamivudine and tenofovir disoproxil fumarate-susceptible	36/89 (40·4%)
Lamivudine and tenofovir disoproxil fumarate drug resistance	42/89 (47·2%)
Lamivudine drug resistance (tenofovir disoproxil fumarate-susceptible)	11/89 (12·4%)
(Table 1 continues in next column)	

	N=1892
(Continued from previous column)	
Drug resistance mutation pattern	
≥1 thymidine analogue	24/89 (27·0%)
≥3 thymidine analogue	9/89 (10·1%)
Lys65Arg (no Met184Val/Ile, no thymidine analogue drug resistance)	5/89 (5·6%)
Lys65Arg plus Met184Val/Ile	26/89 (29·2%)
≥1 TAM plus Met184Val/Ile with any NNRTI drug resistance	24/89 (27·0%)
Lys65Arg plus Met184Val/Ile with any NNRTI drug resistance	26/89 (29·2%)

Data are n (%), n/N (%), or median (IQR). Information on ART start date (time on ART at inclusion) was missing for ten participants, and information on exact first-line regimen at inclusion was missing for one participant (recently transferred in from South Africa on NNRTI-based first-line, one tablet regimen, evening dose, individual drugs not specified). ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *92 participants had viral load of ≥100 copies per mL (technical threshold for drug resistance testing on plasma), three drug resistance testing reactions failed. Lamivudine or tenofovir disoproxil fumarate drug resistance was defined as score of 15 or greater and susceptible if score of less than 15 (Stanford HIV database).

Table 1: **Baseline characteristics**

suboptimal dolutegravir exposure due to non-adherence or malabsorption) was assessed from dried plasma spots by ultra performance liquid chromatography coupled with tandem mass spectrometry at the Laboratoire de Pharmacologie, hospital Bichat-Claude Bernard, Paris, France. The global estimated time between an individual's last antiretroviral dose and blood collection was 3–6 h. Nearly all participants reported TLD intake in the early morning hours (6–7 am). Based on the usual mean dolutegravir half-life (12 h), concentrations were extrapolated to calculate minimum plasma concentration values (dolutegravir C_{min}, 24 h after the last drug intake). Dolutegravir C_{min} values were interpreted in reference to the active threshold (640 ng/mL, 10-fold protein-adjusted 90% inhibitory concentration).[23]

Statistical analysis

Descriptive analyses included medians with IQR, counts with proportions, and 95% CI using the exact method. Proportions were compared using Pearson χ^2 testing or Fisher's exact test. Reported outcomes at follow-up milestones were within SD 1·5 months of predefined timepoints (ie, 3, 6, 12, or 18 months from the start of TLD regimen), unless otherwise specified. Viral load suppression at month 12 and at month 18 was assessed using two populations: (1) per-protocol group—all participants included and analysed who were assessed at their month 12 or month 18 milestone visit—and (2) the modified intention-to-treat (mITT) group—all included and analysed, with viral load of 50 or more copies per mL or any premature end of follow-up (lost to follow-up to the study [still in routine care], withdrew consent to the study, transfer out of routine care, lost to follow-up to routine care, discontinuation of TLD due to failure or adverse event, and deaths) or those with a missing viral load test at month 12 or at month 18, were classified as viraemic at month 12 or viraemic at month 18. Univariate and multivariate logistic regressions (using the Firth method to account for rare outcomes, sparse data, and quasi-complete separation) were conducted to identify factors associated with viraemia (≥50 copies per mL), or

See Online for appendix 3

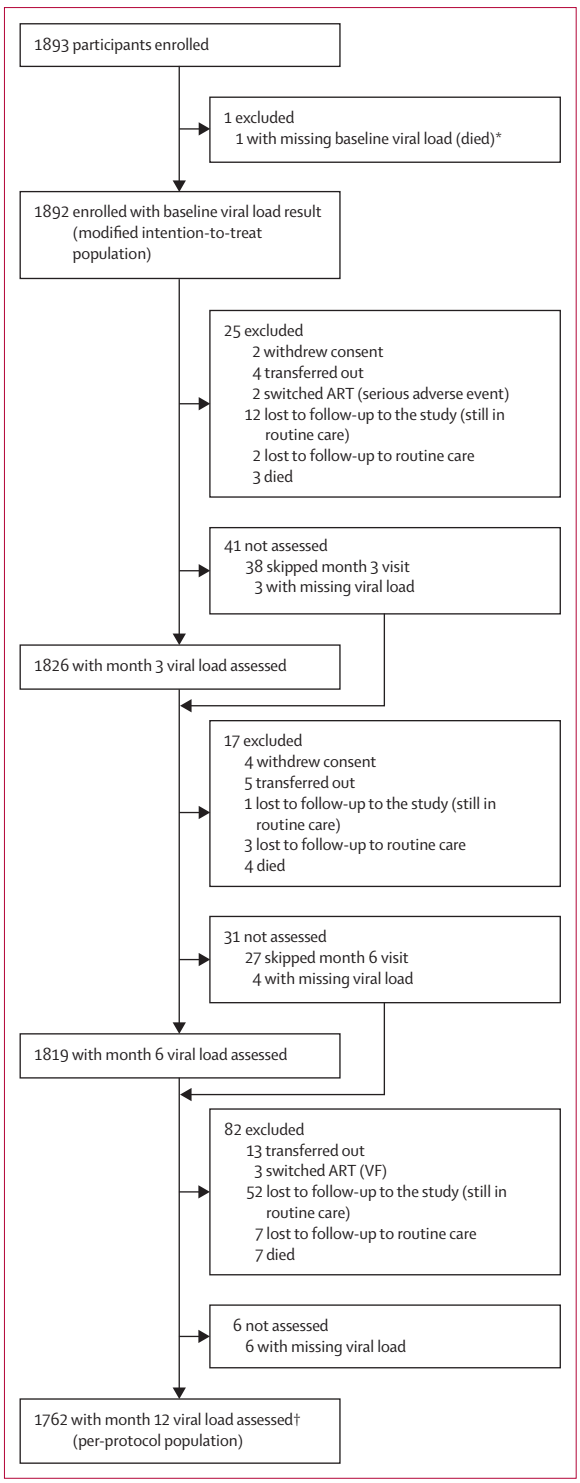

Figure 1: **Study profile for enrolled participants**
ART=antiretroviral therapy. VF=viral failure. *One was excluded from analysis (participant did not come to laboratory for baseline viral load sample collection and did not return to the study study; tracing revealed participant died 2 weeks later, of unknown cause at home). †229 participants had a delayed month 12 visit and 1710 attended all month 3, month 6, and month 12 visits.

viral failure, respectively, during follow-up.[24] Age and sex (combined), years on ART, baseline viral load, and lamivudine or tenofovir disoproxil fumarate, or both, resistance status were considered. Crude odds ratios (ORs) and adjusted ORs (aORs) are presented with 95% CIs. Analyses were performed using STATA (version 16.1).

Role of the funding source

Authors affiliated with MSF and the Department of HIV AIDS, Ministry of Health, Malawi, were involved in study conceptualisation, interpretation of data, in the writing of the manuscript and the decision to submit the manuscript for publication.

Results

A total of 1893 participants were included, representing approximately 59·8% of those eligible in Ndunde health centre, 48·2% in Milepa health centre, and 11·8% in Boma clinic, respectively (table 1, appendix 3 p 2). One was excluded from analysis because baseline viral load and follow-up data were missing (figure 1). The total follow-up until month 12 was 1913·4 person-years (median 11·9 months [IQR 11·7–12·2]; n=1892). Of 1892 participants, 1710 (90·4%) attended their milestone visits (month 3, month 6, and month 12), 1838 (97·1%) had two or more viral load tests, and 1730 (91·4%) had three or more viral load tests while on TLD. Baseline viraemic participants had 103·6 person-years of follow-up at month 18 (median 18·2 months [IQR 17·7–18·9]; appendix 3 p 8). Prevention measures during the first wave of COVID-19 in Malawi (April–August, 2020) limited investigators' visits to study sites to once per week, thus 229 (12·1%) of 1762 month 12 assessments were delayed (occurring at a median of 17·9 months [IQR 15·8–18·6]), and 29 (19·7%) of 147 month 18-eligible participants had a delayed month 18 assessment (occurring at a median of 19·9 months [IQR 19·8–20·8]).

Overall, of 1892 participants only 101 (5·3%) had a viral load of 50 or more copies per mL (median 1745 copies per mL [IQR 305–20479]), and 62 (3·3%) had a viral load of 1000 or more copies per mL at baseline (table 1). 92 were eligible for plasma drug-resistance testing (viral load ≥100 copies per mL). Among 89 successfully genotyped (figure 2), 100% were HIV-1 subtype C, 42 (47·2%) had lamivudine and tenofovir disoproxil fumarate dual resistance, 11 (12·4%) had lamivudine resistance and 36 (40·5%) were both lamivudine and tenofovir disoproxil fumarate-susceptible. 48 (90·6%) of 53 participants with lamivudine resistance had the mutation Met184Val/Ile. Of 42 with tenofovir disoproxil fumarate resistance, 31 (73·8%) had Lys65Arg, three (7·1%) had Lys70Glu, and 18 (42·9%) had at least one thymidine analogue mutation. Of 42 with lamivudine and tenofovir disoproxil fumarate dual resistance, 26 (61·9%) had Met184Val/Ile with Lys65Arg mutation. Overall, nine (10·1%) of 89 participants had tenofovir disoproxil fumarate and

zidovudine dual drug resistance. None of the participants had integrase inhibitor (INSTI) or protease inhibitor resistance at baseline.

Viral load suppression rates were very high throughout the 12 month follow-up, with few viraemic events at clinical milestones (figure 3A). Most participants with viraemia at baseline (85 [87·6%] of 97) were virally suppressed (<50 copies per mL) by month 3 (figure 3A), irrespective of lamivudine and tenofovir disoproxil fumarate resistance (figure 3B), and only three had continuously detectable viral load until month 18 (two were baseline lamivudine and tenofovir disoproxil fumarate-susceptible, one without baseline drug-resistance testing). In the per-protocol population (n=1762) at month 12, overall 1725 (97·9% [95% CI 97·1–98·5]) were fully suppressed (viral load <50 copies per mL). Month 12 viral load suppression in the subgroup with baseline viraemia was 88·3% (95% CI 80·0–94·0; 83 of 94 participants) and 98·4% (95% CI 97·7–99·0; 1642 of 1668) among those who were viral load suppressed at baseline (p<0·0001, per-protocol population; figure 3A, table 2). Viral load suppression at month 18 was 81·8% (95% CI 64·5–93·0; 27 of 33) among those who were viraemic at baseline without lamivudine and tenofovir disoproxil fumarate resistance and 97·2% (95% CI 85·5–99·9; 35 of 36) among those with lamivudine and tenofovir disoproxil fumarate resistance (p=0·049, per-protocol population; table 2). Participants with only lamivudine resistance (tenofovir disoproxil fumarate-susceptible) were virally suppressed at all clinical milestones (figure 3B, table 2). Analysis of the mITT population also showed significantly lower month 12 viral suppression among the viraemic-at-baseline group compared with the suppressed-at-baseline group, and lower month 12 or month 18 viral suppression among lamivudine and tenofovir disoproxil fumarate-susceptible individuals than lamivudine and tenofovir disoproxil fumarate-resistant ones (table 2).

Few participants (83 [4·5%] of 1863) had one or more detectable viral load while on TLD (appendix 3 p 3). The cumulative proportion of participants with one or more detectable viral load was significantly higher among the group with viraemia at baseline than the participants virally suppressed at baseline (22·0% *vs* 3·5%, p<0·0001; appendix 3 p 3). Logistic regression identified high baseline viral load (≥1000 copies per mL; aOR 11·4 [95% CI 6·3–20·7]) as a risk factor for having at least one subsequent detectable viral load result within a year of taking TLD (appendix 3 p 5). 14 (0·8%) of 1838 with at least two viral load tests on TLD met the definition for viral failure after a median of 11·3 months (minimum 5·3, maximum 21·1; appendix 3 p 4). Seven of 14 people with viral failure (50%) had low-level viral load (≥50 to <1000 copies per mL, median 2037 copies per mL, IQR 81–25 894) at suspected failure, all 14 had viral load of 1000 or more copies per mL at viral failure (median 35 378 copies per mL, IQR 2977–103 936).

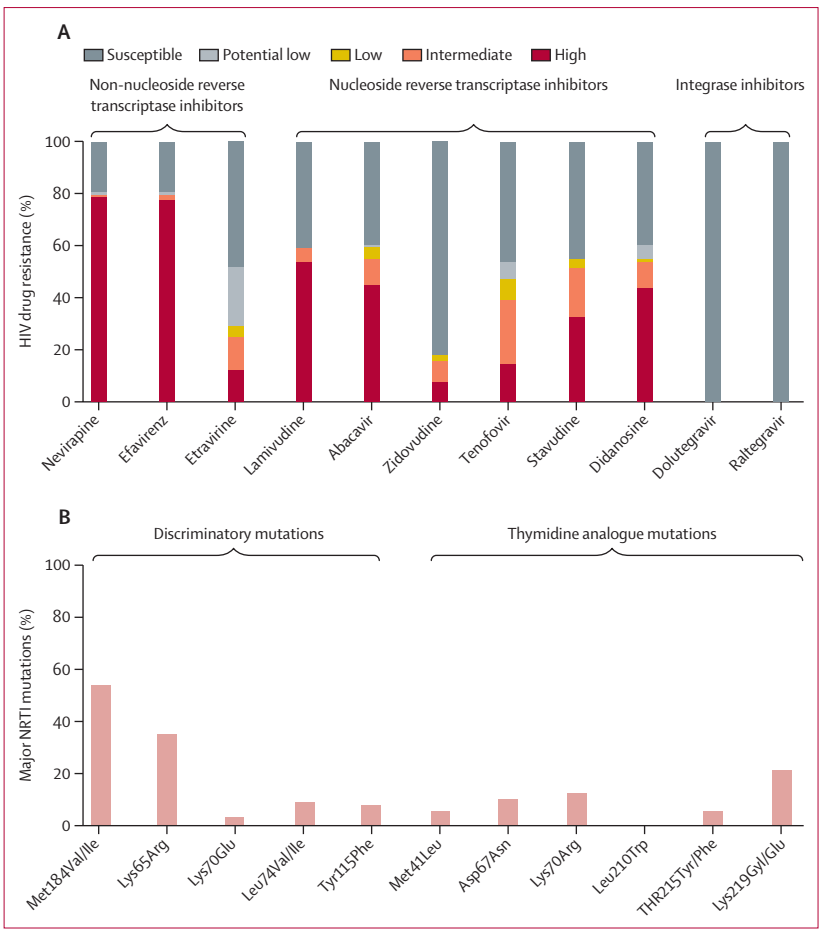

Figure 2: **HIV-1 drug-resistance pattern at baseline**
Frequency of HIV drug resistance at baseline among 89 participants with viral load of 100 or more copies per mL and with a successful drug-resistance test result. (A) HIV drug resistance by individual antiretroviral drug with resistance levels according to Stanford HIV database. Levels low, intermediate, or high (score ≥15) are considered resistant; levels susceptible or potential low are considered susceptible. (B) Frequency of major NRTI HIV drug-resistance mutations, discriminatory mutations (left), thymidine analogue mutations (right; Stanford HIV database). NRTI=nucleoside reverse transcriptase inhibitor.

A high baseline viral load (1000 to <10 000 copies per mL, aOR 14·1 [95% CI 2·3–87·4]; ≥10 000 copies per mL, aOR 64·4 [95% CI 19·3–215·4]) was associated with viral failure (appendix 3 p 6). Four cases of viral failure were detected in individuals with baseline lamivudine and tenofovir disoproxil fumarate resistance, four among individuals who were baseline lamivudine and tenofovir disoproxil fumarate-susceptible, and none among those with only lamivudine resistance (p=0·77). There was no evidence for increased risk of viraemia or viral failure during 18 months on TLD for participants with baseline lamivudine and tenofovir disoproxil fumarate resistance compared with those without (aOR 0·4 [95% CI 0·1–1·2]; aOR 0·9 [95% CI 0·2–4·3]; appendix 3 p 6).

Two participants with viral failure had dolutegravir resistance at month 6 (INSTI-resistant mutations Arg263Lys or Gly118Arg), both had been viraemic and lamivudine and tenofovir disoproxil fumarate-resistant

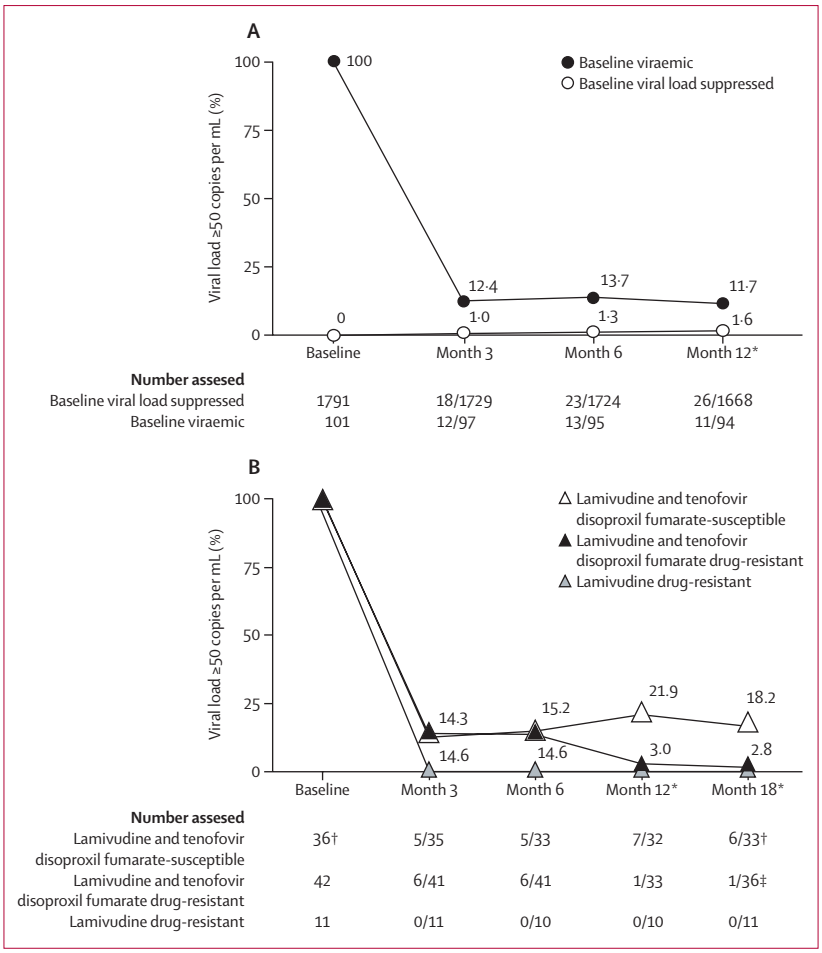

Figure 3: **Proportion with detectable viral load at milestone visits**
(A) Detectable viral load (≥50 copies per mL) at milestone visits at month 3, month 6 and month 12, by baseline viral load status. (B) Detectable viral load (≥50 copies per mL) at milestone visits at month 3, month 6, month 12, and month 18 among 89 with baseline viral load detectable and drug susceptibility test result, by lamivudine and tenofovir disoproxil fumarate resistance status. *Delayed visit results are included. †Of 36 included, 33 were assessed at last visit (month 18), one was transferred out, one lost to follow-up to the study (still in routine care), one died. ‡Of 42 included, 36 were assessed at month 18, two were transferred out, three switched antiretroviral therapy following failure (two with dolutegravir drug resistance), and one lost to follow-up to the study (still in routine care).

at baseline (mutations Met184Val with Lys70Glu or Met184Val with three thymidine analogue mutations). The cumulative proportion of viral failure with dolutegravir resistance was 0·1% (two of 1836) among all participants with at least two viral load tests on TLD, 4·9% (two of 41) among those with baseline lamivudine and tenofovir disoproxil fumarate resistance and 14·3% (two of 14) among those with viral failure. Both cases of dolutegravir resistance were switched to a protease inhibitor-regimen, and two without dolutegravir resistance but major adherence difficulties and tenofovir disoproxil fumarate resistance also switched regimens. Three of 14 samples from participants with viral failure failed reverse transcriptase genotyping reaction, but none of the integrase sequencing reactions failed. Among those with viral failure with available nucleoside reverse transcriptase inhibitor (NRTI) resistance data, one shifted from low-level tenofovir drug resistance (three thymidine analogue mutations) at baseline to intermediate drug resistance at failure (detection of the Asp67 deletion, in addition to the dolutegravir resistance mutation Gly118Arg indicated above), and one had lamivudine and tenofovir disoproxil fumarate dual resistance at baseline and was lamivudine or tenofovir disoproxil fumarate-susceptible at viral failure. Both cases with dolutegravir resistance were monitored following regimen switch. One had again viral failure 18 months later (without detection of any resistance), indicating continued adherence challenges. The second remained virally suppressed after switching.

We identified a total of 150 detectable viral load results for participants on TLD over 18 months, with dolutegravir plasma concentrations available for 149. For 116 (77·9%) of these events, dolutegravir C_{min} values were below the active threshold (<640 ng/mL), and 60 (40·3%) were below the limit of quantification. Only 33 (22·1%) had dolutegravir C_{min} values of 640 or more ng/mL (appendix 3 p 7). All 14 participants with viral failure had dolutegravir C_{min} values below the active threshold when they were first identified as suspected viral failure; all but one were below the active threshold when viral failure was confirmed, including two with dolutegravir resistance. Absence of comedication with rifampicin or other enzymatic inducers or kaolin intake and TLD was verified for all those with viral failure.

Discussion

We report 12 months of follow-up outcomes in a large cohort of treatment-experienced, INSTI-naive participants who transitioned to TLD first-line therapy in the context of national roll-out in Malawi. This is the first report of long-term TLD outcomes from a real-world programme setting, as well as the first assessment of the impact of a strategy to switch to TLD without viral load testing, a common scenario in many resource-constrained settings with insufficient access to viral load testing. We found that in an already well suppressed cohort on NNRTI-based first-line ART, viral load suppression was maintained, and even increased, after transitioning to a TLD regimen. Detectable viral load results and confirmed viral failure were rare, and genotypically predicted lamivudine and tenofovir disoproxil fumarate resistance did not compromise overall TLD viral suppression. However, having a high viral load before transitioning to TLD was a risk factor for viral failure, and the two cases of dolutegravir resistance seen in this cohort emphasise the importance of viral load monitoring and resistance surveillance.

Encouragingly, most participants with viraemia at baseline became virally suppressed within 3 months, and nearly all were suppressed after 1 year (88·3%) and 18 months (89·4%). However, the few participants who were viraemic at baseline (especially those whose viral

load was high) were more likely to have another detectable viral load or to experience viral failure while on TLD. In contrast, a considerable amount of the viraemia seen in those on TLD was low-level viral load (≥50 to <1000 copies per mL), and only 14 participants overall had viral failure. Botswana, one of the first countries to roll out dolutegravir-based first-line ART, reported high viral suppression (>95%) 12 months after transitioning to a TLD regimen (although without information on baseline viraemia for the study's small cohort).[25] To date, only one sub-Saharan African cohort (DO-REAL study)[26] reported on TLD transitioning with baseline viral load information. Early outcomes (16 weeks) in this group were good (98% had viral load <100 copies per mL), with high suppression also among the few with viraemia at TLD initiation (95%).[26] It is highly encouraging that our results uphold and expand upon these earlier findings.

Another concern surrounding large-scale TLD regimen roll-out was whether genotypically predicted lamivudine and tenofovir disoproxil fumarate resistance would compromise TLD efficacy for people with unidentified viraemia. This question also applies to the selection of an NRTI backbone for second-line regimens. In our cohort, nearly half of the group viraemic at baseline (42 [47·2%] of 89) were lamivudine and tenofovir disoproxil fumarate-dual resistant and thus at risk of potentially taking a functional dolutegravir monotherapy. The high levels of lamivudine and tenofovir disoproxil fumarate resistance and mutations seen (mainly driven by Met184Val/Ile and Lys65Arg) match with other reports from sub-Saharan Africa.[16] Reassuringly, although high viral load at baseline was a risk factor for viral failure, this seemed independent of lamivudine and tenofovir disoproxil fumarate resistance. The lower viral load suppression that we found in baseline viraemic participants susceptible to lamivudine and tenofovir disoproxil fumarate, compared with those with lamivudine and tenofovir disoproxil fumarate resistance, corroborates reports from clinical trials that showed worse outcomes for dolutegravir-based or protease inhibitor-based regimens in participants with a fully susceptible NRTI backbone, compared with those with NRTI resistance, further underlining the importance of adherence.[27,28] The mechanism that supports viral load suppression despite (genotypically predicted) resistance to the NRTI backbone regimen is not yet understood. Potentially fitness-reducing effects of certain resistance mutations might play a role, as proposed for Met184Val and Lys65Arg.[31] Indeed, although the Lys65Arg mutation was frequent in our study, the two participants with viral failures who developed dolutegravir resistance had baseline tenofovir disoproxil fumarate resistance and did not carry Lys65Arg (but instead thymidine analogue mutations or Lys70Glu). Combined with research into second-line options for people with treatment failure in sub-Saharan Africa,[28,29] our findings show that TLD might be efficacious despite the presence of genotypically predicted lamivudine and tenofovir disoproxil fumarate resistance, which also supports the idea of recycling the preferred lamivudine and tenofovir disoproxil fumarate backbone in dolutegravir-based second-line treatments (similar to what has been reported for protease inhibitor-based regimens).[27,28]

Additionally, although TLD is well tolerated and conveniently formulated as a one-tablet-per-day regimen, suboptimal adherence seemed to accompany most cases of viraemia in our study. Both viral failure

	Per-protocol analysis		Modified intention-to-treat analysis	
	n/N	% (95% CI)	n/N	% (95% CI)
Month 12 milestone				
Total				
<50 copies per mL	1725/1762	97·9% (97·1–98·5)	1725/1892	91·2% (89·8–92·4)
<1000 copies per mL	1751/1762	99·4% (98·9–99·7)	1751/1892	92·6% (91·2–93·7)
Baseline viral load suppressed				
<50 copies per mL	1642/1668	98·4% (97·7–99·0)	1642/1791	91·7% (90·3–92·9)
<1000 copies per mL	1662/1668	99·6% (99·2–99·9)	1662/1791	92·8% (91·5–93·9)
Baseline viraemic†				
<50 copies per mL	83/94	88·3% (80·0–94·0)	83/101	82·2% (73·3–89·0)
<1000 copies per mL	89/94	94·7% (88·0–98·3)	89/101	88·1% (80·2–93·7)
Baseline lamivudine and tenofovir disoproxil fumarate-susceptible				
<50 copies per mL	25/32	78·1% (60·0–90·7)	25/34	73·5% (55·6–87·1)
<1000 copies per mL	29/32	90·6% (74·9–98·0)	29/34	85·3% (68·9–95·0)
Baseline lamivudine and tenofovir disoproxil fumarate drug-resistant				
<50 copies per mL	32/33	97·0% (84·2–99·9)	32/37	86·5% (71·2–95·4)
<1000 copies per mL	32/33	97·0% (84·2–99·9)	32/37	86·5% (71·2–95·4)
Baseline lamivudine drug resistant				
<50 copies per mL	10/10	100	10/10	100
<1000 copies per mL	10/10	100	10/10	100
Month 18 milestone				
Baseline viraemic†				
<50 copies per mL	76/85	89·4% (80·8–95·0)	83/101	82·2% (73·3–89·1)
<1000 copies per mL	81/85	95·3% (88·4–98·7)	89/101	88·1% (80·2–93·7)
Baseline lamivudine and tenofovir disoproxil fumarate-susceptible				
<50 copies per mL	27/33	81·8% (64·5–93·0)	27/36	75·0% (57·8–87·9)
<1000 copies per mL	31/33	93·9% (79·8–99·3)	31/36	86·1% (70·5–95·3)
Baseline lamivudine and tenofovir disoproxil fumarate drug-resistant				
<50 copies per mL	35/36	97·2% (85·5–99·9)	35/42	83·3% (68·6–93·0)
<1000 copies per mL	35/36	97·2% (85·5–99·9)	35/42	83·3% (68·6–93·0)
Baseline lamivudine drug-resistant				
<50 copies per mL	11/11	100	11/11	100
<1000 copies per mL	11/11	100	11/11	100

Data are n/N and % (95% CI). ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. TLD=tenofovir disoproxil fumarate, lamivudine, and dolutegravir. *Month 12 and month 18 viral load suppression data are presented using two definitions of detectable viral load on TLD: (1) the US Food and Drug Administration snapshot definition (<50 copies per mL) is more conservative, whereas (2) the WHO failure threshold (<1000 copies per mL) is more frequently applied in clinical follow-up. Analysis was done with per-protocol and modified intention-to-treat population, respectively. For eight participants with a delayed month 12 visit, the month 12 visit date overlapped with the prescheduled month 18 milestone visit, and their respective viral load results are here exclusively included in month 18 outcomes. NRTI resistance subgroups (lamivudine and tenofovir disoproxil fumarate) refer to participants who were viraemic at baseline and had a baseline drug resistance test result available. †Includes all baseline viraemic, with or without available drug susceptibility test result.

Table 2: **Viral load suppression at month 12 and month 18 clinical milestones*, by participant subgroup**

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cases with early (month 6) dolutegravir resistance had high baseline viraemia and lamivudine and tenofovir disoproxil fumarate resistance. Their respective INSTI-resistant mutations (Arg263Lys or Gly118Arg) predict intermediate level dolutegravir resistance and have been reported before in previously INSTI-naive people.[8] Neither of the two cases had the most frequently reported tenofovir disoproxil fumarate mutation—Lys65Arg. Notably, dolutegravir plasma C_{min} values indicated inadequate antiretroviral exposure at the time of suspected and confirmed viral failure for both cases, matching with previous case reports on non-adherence as risk factor for treatment failure with dolutegravir resistance.[30] Whether extensive NRTI resistance can further augment the risk of dolutegravir resistance developing in such cases needs further research.

Although dolutegravir resistance might be infrequent, our data indicate that it might occur rapidly in unsuppressed people. Similarly, in the recent second-line trial (NADIA), four of 14 of those with confirmed viral failure had intermediate or high-level dolutegravir resistance detected before week 48.[28] Infrequent but possible dolutegravir resistance and the restricted resistance genotyping capacities in LMICs challenge identification and clinical management of those with viral failure on a TLD regimen in routine care. Antiretroviral drug level monitoring (in blood or urine) might help to distinguish resistance from simple non-adherence and triage for drug-resistance testing,[32] although in our study both participants who were dolutegravir-resistant also had low or undetectable dolutegravir plasma levels. Development of simplified point-mutation assays could support urgently needed access to resistance testing.[32] In Malawi, by the end of December, 2021, 889 665 (99%) of 897 880 people on first-line and second-line ART were receiving a TLD regimen, and most transitioned without viral load testing (unpublished data, MoH, Department of HIV and AIDS, Malawi). Average viral load suppression rates (<1000 copies per mL) before the policy change were 93%,[32] implying that a proportion of people with an increased risk of treatment failure are present in the national treatment programme, underlining the importance of further scale-up in viral load testing and implementation of surveillance for dolutegravir resistance. Malawi hopes to provide drug-resistance testing for all people for whom the TLD regimen is failing; however, capacity and cost remain a challenge, as in most LMICs. Of more than 6000 people with viral failure using a dolutegravir regimen, identified in routine care in Malawi, only 33 could undergo resistance testing (in South Africa), and of 30 successful reactions eight had dolutegravir resistance[33]

Our study took place in a real-world, routine programme setting, so investigators were only able to recruit a convenience sample. Viral load suppression on NNRTI-based first-line ART was already high when the TLD regimen was introduced, the study focused on adults, and women younger than 45 years were excluded (per MoH guidelines at the time; policy was updated in 2019). As a result, people with higher risk of treatment failure might have been under-represented. Yet, demographic and clinical characteristics of the adult population receiving ART in Chiradzulu closely matched the study cohort (unpublished data, MSF). The envisioned sample size was not fully met, but viral load suppression in the main subgroup of interest (participants viraemic with lamivudine and tenofovir disoproxil fumarate resistance) could be reported with satisfactory precision. The enhanced monitoring provided during the transition period to the TLD regimen also allowed for more frequent viral load tests than under usual conditions, which might have contributed to better 1-year outcomes. Data from less well monitored cohorts with higher viral failure rates will also be important.

In conclusion, we observed high viral load suppression and infrequent viral failure in our cohort, which is in support of Malawi's pragmatic national strategy of transitioning from NNRTI-based first-line ART to TLD regimen without demanding a preceding viral load test (likely reflecting the reality in most LMICs). Importantly, our findings support the concept that genotypically predicted lamivudine and tenofovir disoproxil fumarate resistance might not compromise viral suppression on TLD, which was one of the main concerns surrounding a pragmatic roll-out of the TLD regimen. Nonetheless, caution is required since those who transitioned to the TLD regimen with (unknown) viraemia had a higher risk of unsuppressed viral load. In these cases, adherence challenges might have provoked infrequent but rapid dolutegravir resistance. Longer-term follow-up of treatment-experienced, INSTI-naive people transitioned to the TLD regimen (with or without NRTI resistance) is recommended. Further scale-up of routine viral load monitoring and INSTI resistance surveillance remain crucial.

Contributors

BS, AJ, ES, DD, VC, A-GM, SN, ET, GP, and TK contributed to study conception and design, ET supervised field data collection, DD, A-GM, GP, JEB-B, AS, MPL, and BA conducted laboratory analyses. BS, ET, ES, AJ, DD, A-GM, GP, JEB-B, SN, AS, MPL, BA, JO, and VC interpreted the data. BS, ET, and SN verified the data underlying this report. BS and SN conducted the statistical analysis. BS wrote the first draft; AJ, ET, JO, ES, DD, A-GM, and GP substantially reviewed and edited the manuscript. All authors critically reviewed the manuscript for important intellectual content and decided to publish the final version.

Declaration of interests

DD reports honoraria for attending symposia, research grants, and support for attending meetings or travel from Gilead Sciences, MSD, Janssen-Cilag, and Merck Sharp and Dohme. A-GM reports funds for attending symposia, speaking, and research grants from ViiVHealthcare, Gilead Sciences, Theratechnologies, and Merck Sharp & Dohme. GP reports consulting fees from Gilead Sciences, ViiVHealthcare, Merck, Takeda, Pfizer, and TheraTechnologies; and honoraria from Gilead Sciences, ViiVHealthcare, and Merck. VC reports consulting fees and payment or honoraria from Gilead Sciences, ViiVHealthcare, and MSD; he is founder and member of the board of SkinDermic. All other authors declare no competing interests.

Data sharing

Individual pseudonymised participant data that underlie the results reported in this Article (text, tables, figures, and appendices, with data dictionary) will be made available to others upon submission of a proposal. Requests will be reviewed and sharing of the data will follow the conditions required by all applicable laws and the possible prior signature of any necessary agreement, in accordance with the legal framework set forth by Médecins Sans Frontières (MSF) data sharing policy, which ensures that all security, legal, and ethical concerns are addressed. For data access and additional related documents, such as the study protocol, readers can contact the corresponding author directly or through the Epicentre contact form on the Epicentre website.

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