Virological and drug-resistance outcomes for people living with HIV initiating or switching to tenofovir, lamivudine, and dolutegravir in six PEPFAR-supported countries: a prospective cohort study

Jean Bernard Marc, Caitlyn McCarthy*, Carole L Wallis*, Cissy Kityo, Michael D Hughes, Catherine Godfrey, N Sarita Shah, Urvi M Parikh, Gary Maartens, Francis Kanyike, Marije Van Schalkwyk, Raymond Bernard Kihumuro, Philip Asiimwe, Isaac Tsikhutsu, Cornelius Munyanga, Fatma F Some, Yvetot Joseph, Tracy Flowers, Lerato Mohapi, Wadzanai P Samaneka, Kelvin Mponda, Mohammed S Rassool, Samuel Pierre, Elizabeth Woolley, Yukari C Manabe, John W Mellors, Charles Flexner, Serena P Koenig†, Rosie Mngqibisa†, and the ACTG A5381–Hakim Study Team‡*

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*Contributed equally

†Contributed equally

‡Members listed at the end of the Article

Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO-INLR), Port-au-Prince, Haiti (J B Marc MD, S P Koenig MD); **Center for Biostatistics in AIDS Research, Department of Biostatistics, Harvard T H Chan School of Public Health, Boston, MA, USA** (C McCarthy MA, Prof M D Hughes PhD); **Innovative Clinical Laboratories, Johannesburg, South Africa** (C L Wallis PhD); **Joint Clinical Research Centre, Kampala Clinical Research Site Research and Clinical Services, Kampala, Uganda** (C Kityo MBChB, F Kanyike MBChB, R B Kihumuro MBChB, P Asiimwe B Pharm); **Walter Reed Army Institute of Research, Department of Defense, Kampala, Uganda** (C Godfrey MD); **Department of Epidemiology, Emory Rollins School of Public Health, Atlanta, GA, USA** (Prof N S Shah MD); **Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA** (U M Parikh PhD, Prof J W Mellors MD); **Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa** (Prof G Maartens MMed); **Family Centre for Research with Ubuntu, Division of Adult Infectious Diseases, Department of Medicine, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa**

Summary

Background A combined regimen of tenofovir disoproxil fumarate, lamivudine, and dolutegravir is widely prescribed for people living with HIV in programmes supported by the US President's Emergency Plan for AIDS Relief (PEPFAR). This study aimed to assess long-term virological and drug-resistance outcomes in response to initiation of or switching to the tenofovir–lamivudine–dolutegravir combination among individuals receiving care through such programmes.

Methods The Advancing Clinical Therapeutics Globally (ACTG) A5381–Hakim Study was a prospective cohort study of participants aged 10 years or older initiating or switching to tenofovir–lamivudine–dolutegravir therapy at 13 PEPFAR-supported sites in Haiti, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. Group 1 switched from non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy (ART), group 2 switched from protease inhibitor-based ART, and group 3 was ART-naive; before switching, group 1A and group 2A had HIV-1 RNA of more than 1000 copies per mL and group 1B and group 2B had 1000 copies per mL or less. Viral suppression (HIV-1 RNA ≤1000 copies per mL), emergence of dolutegravir-resistance mutations, and adverse events were assessed up to 36 months. Adherence, based on tenofovir diphosphate concentrations in dried blood spots, was evaluated in a nested case–control study.

Findings Between Oct 28, 2019, and Sept 27, 2022, 1241 participants were enrolled in the study, four of whom were excluded (two in group 2B who started tenofovir–lamivudine–dolutegravir before enrolment and two in group 3 who did not start tenofovir–lamivudine–dolutegravir). Therefore, 1237 participants were included in the full analysis population: 44 in group 1A, 425 in group 1B, 173 in group 2A, 416 in group 2B, and 179 in group 3. 65% were female, 35% were male. 12 (1%) participants discontinued tenofovir–lamivudine–dolutegravir therapy because of adverse events. Among participants for whom viral load data were available and who did not discontinue tenofovir–lamivudine–dolutegravir before viral load measurement, HIV-1 RNA of 1000 copies per mL or less was recorded in 88% (37 of 42 participants) at 6 months and 76% (16 of 21 participants) at 24 months in group 1A; 99% (380 of 384 participants) and 98% (368 of 375 participants) in group 1B; 72% (118 of 165 participants) and 70% (45 of 64 participants) in group 2A; 95% (376 of 395 participants) and 93% (190 of 204 participants) in group 2B; and 90% (136 of 151 participants) and 90% (128 of 143 participants) in group 3. Mutations associated with decreased dolutegravir susceptibility were detected in three participants in group 2A (G118R, R263K) and in no participants in the other groups. Of 87 case–control pairs analysed at 6 months, tenofovir diphosphate concentrations were lower among participants with HIV-1 RNA of more than 1000 copies per mL than among those with 1000 copies per mL or less (p<0·0001).

Interpretation High rates of viral suppression in response to tenofovir–lamivudine–dolutegravir therapy in individuals who had suppression before switching support international treatment guidelines for this population. Findings on resistance mutations and tenofovir diphosphate concentrations suggest that incomplete adherence was a key factor in the suboptimal outcomes of people with virological failure at the time of switching treatment.

Funding National Institutes of Health and PEPFAR.

Introduction

Since 2018, WHO has recommended the use of dolutegravir as first-line and second-line antiretroviral therapy (ART) for people living with HIV.[1] Concurrently, the US President's Emergency Plan for AIDS Relief (PEPFAR) programme began supporting the

Research in context

Evidence before this study

Most people living with HIV in low-income and middle-income countries (LMICs) who receive US President's Emergency Plan for AIDS Relief (PEPFAR)-supported services are prescribed the fixed-dose antiretroviral therapy (ART) combination of tenofovir disoproxil fumarate, lamivudine, and dolutegravir. We searched PubMed for papers published from database inception to April 1, 2025, with no language restrictions, using the terms ["HIV"], ["dolutegravir"], ["resistance"], ["non-nucleoside reverse transcriptase inhibitor"], ["protease inhibitor"], ["low and middle-income countries"], and ["virologic outcomes"] in different combinations. Although several cohort studies have reported virological outcomes and emergent resistance with tenofovir–lamivudine–dolutegravir for both treatment-naive individuals and individuals switching from non-nucleoside reverse transcriptase inhibitor-based regimens, no prospective studies have also included individuals switching from protease inhibitor-based regimens. There was also a paucity of data on long-term virological outcomes and emergence of dolutegravir resistance with tenofovir–lamivudine–dolutegravir when scaled up in programmatic settings, where HIV-1 RNA and drug-resistance testing are often limited by resource availability. Furthermore, objective data on adherence have rarely been included.

Added value of this study

This prospective cohort study was designed to assess therapeutic efficacy and emergence of HIV-1 drug resistance following initiation of tenofovir–lamivudine–dolutegravir for first-line or second-line ART in a longitudinal cohort receiving care at 13 sites in six PEPFAR-supported countries. This study fills important knowledge gaps for policy makers and clinicians in LMICs by providing long-term outcome data—virological outcomes for up to 3 years and emergence of drug resistance in those with virological failure—from ART-naive individuals and individuals who switched from other treatment regimens to tenofovir–lamivudine–dolutegravir. We also conducted a case–control study in which we measured tenofovir diphosphate concentrations in dried blood spots to assess the association between virological failure and adherence.

Implications of all the available evidence

This study shows that tenofovir–lamivudine–dolutegravir is well tolerated and associated with high rates of long-term viral suppression among previously treated individuals with suppression before switching, supporting international treatment guidelines for this population. By contrast, individuals with viraemia before switching had suboptimal outcomes, which might be explained by adherence challenges. Future studies are needed to assess novel strategies to improve adherence in this population, such as long-acting ART.

transition of individuals to the single-tablet formulation of tenofovir disoproxil fumarate, lamivudine, and dolutegravir.[2] Most people living with HIV in low-income and middle-income countries (LMICs) are now prescribed fixed-dose tenofovir–lamivudine–dolutegravir therapy. Dolutegravir-based regimens are preferred over previously recommended regimens owing to better tolerability and potency, a high genetic barrier to resistance, and fewer drug–drug interactions.[3] Previous regimens recommended by WHO included non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens for first-line ART and ritonavir-boosted protease inhibitor-based regimens for second-line ART; these were generally prescribed in combination with tenofovir, abacavir, or zidovudine plus lamivudine or emtricitabine.[1]

Multiple cohort studies have shown that individuals who initiate tenofovir–lamivudine–dolutegravir or switch to this combination from suppressive NNRTI-based regimens maintain high levels of viral suppression and that emergence of dolutegravir-resistance mutations is unlikely.[4–7] However, robust prospective data have been scarce for individuals switching from suppressive second-line protease inhibitor-based regimens.[8,9] Furthermore, the effectiveness of tenofovir–lamivudine–dolutegravir for people with HIV with viraemia before switching from NNRTI-based or boosted protease inhibitor-based regimens is less certain.[10,11] This is of particular concern in the setting of concurrent resistance to nucleoside reverse transcriptase inhibitors (NRTIs), which might increase the risk of acquired dolutegravir resistance.[4,12] Until recently, WHO guidelines recommended optimising the NRTI backbone in the dolutegravir-based regimen; for individuals with previous virological failure on a tenofovir-based regimen, this often included switching to zidovudine in the subsequent regimen.[1] WHO guidelines were recently updated, based on evolving data suggesting that viral suppression can be achieved with recycled tenofovir, even in the presence of extensive NRTI resistance.[13–15] Importantly, a single regimen for all people with HIV-1 is preferred at the programmatic level, because it is easier to manage and reduces the complexity of the supply chain, therefore improving access to ART.

The Advancing Clinical Therapeutics Globally (ACTG) network protocol A5381 (the Hakim Study) was designed to assess therapeutic efficacy and emergence of HIV-1 drug resistance in ART-naive individuals initiating tenofovir–lamivudine–dolutegravir or in those previously on NNRTI-based or protease inhibitor-based regimens switching to this combination in a longitudinal cohort receiving care through PEPFAR-supported programmes.[16]

(M Van Schalkwyk MD); **Kenya Medical Research Institute–Walter Reed Project Clinical Research Center, Kericho, Kenya** (I Tsikhutsu MBChB); **University of North Carolina at Chapel Hill Project, Lilongwe, Malawi** (C Munyanga MBChB); **Moi University Clinical Research Centre, Eldoret, Kenya** (F F Some MBChB); **GHESKIO Institute of Infectious Diseases and Reproductive Health (GHESKIO-IMIS), Port-au-Prince, Haiti** (Y Joseph MD); **University of Cape Town Lung Institute Clinical Research Site, Cape Town, South Africa** (T Flowers MBChB); **Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa** (L Mohapi MBBCh); **Milton Park Clinical Research Site, University of Zimbabwe Clinical Trials Research Centre, Harare, Zimbabwe** (W P Samaneka MBChB); **Blantyre Clinical Research Site, Blantyre, Malawi** (K Mponda MBChB); **Clinical HIV Research Unit, Wits Health Consortium, Health Science Research Office, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (M S Rassool MBChB); **Epidemiology Department, Vanderbilt University, Nashville, TN, USA** (S Pierre MD); **DLH Corporation, Bethesda, MD, USA** (E Woolley MPH); **Division of Infectious Diseases, Johns Hopkins University, Baltimore, MD, USA** (Prof Y C Manabe MD); **Division of Clinical Pharmacology, Johns Hopkins University, Baltimore, MD, USA** (Prof C Flexner MD); **Division of Global Health Equity, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA** (S P Koenig); **Durban International Clinical Research Site, Enhancing Care Foundation, Wentworth Hospital, Durban, South Africa** (R Mngqibisa MBChB)

Correspondence to:
Dr Serena Koenig, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
skoenig@bwh.harvard.edu

Methods

Study design

The ACTG A5381–Hakim Study was a prospective cohort study conducted at 13 PEPFAR-supported sites that are affiliated with ACTG sites in Haiti, Kenya, Malawi, South Africa, Uganda, and Zimbabwe.[16] Enrolment occurred between Oct 28, 2019, and Sept 27, 2022, with a pause from March to July, 2020, due to the COVID-19 pandemic. The trial was approved by the following local ethics committees and national regulatory agencies in the respective countries: Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO; 00005515, 00000093), Joint Clinical Research Centre, Kampala Clinical Research Site (CRS; JC1019), Kenya Medical Research Institute–Walter Reed Project Clinical Research Center CRS (SERU 3912, WRAIR 2693), University of the Witwatersrand Clinical HIV Research Unit, Wits Helen Joseph Hospital CRS (190901), Moi University Clinical Research Centre (IREC/2019/000082), Durban International CRS, Enhancing Care Foundation (M19/07/017), University of Cape Town Lung Institute CRS (532/2019), Milton Park CRS (MRCZ/A/2508), Perinatal HIV Research Unit, University of the Witwatersrand–Soweto CRS (190901), Blantyre CRS (P.11/19/2873, 00009752/CR349), University of North Carolina at Chapel Hill Project–Malawi CRS (NHSRC 19/05/2330, UNC 19-1443), and Family Centre for Research with Ubuntu CRS (M19/07/017). See the appendix (pp 24–114) for the study protocol.

See Online for appendix

Participants

Participants were aged 10 years or older and had documented HIV-1. To the extent that it was practically possible, the study site investigators attempted to approach all individuals who were on NNRTI-based or boosted protease inhibitor-based ART or who were starting tenofovir–lamivudine–dolutegravir for screening and enrolment in the study. ART history and an HIV-1 RNA measurement obtained at the start of or switch to tenofovir–lamivudine–dolutegravir therapy (study entry) were used to group participants into five cohorts: individuals in group 1A had switched from NNRTI-containing ART with HIV-1 RNA of more than 1000 copies per mL; those in group 1B had switched from NNRTI-containing ART with HIV-1 RNA of 1000 copies per mL or less; those in group 2A had switched from protease inhibitor-containing ART with HIV-1 RNA of more than 1000 copies per mL; those in group 2B had switched from protease inhibitor-containing ART with HIV-1 RNA of 1000 copies per mL or less; and individuals in group 3 had initiated ART with tenofovir–lamivudine–dolutegravir. Detailed inclusion and exclusion criteria are provided in the appendix (p 2).

All participants aged 18 years or older provided written informed consent; participants aged younger than 18 years provided assent and their parents or guardians provided written informed consent. This study is registered with ClinicalTrials.gov, NCT04050449.

Procedures

Participants were managed according to local standards of care and WHO guidelines, and initiation of or switching to tenofovir–lamivudine–dolutegravir provided by a PEPFAR-supported programme took place within 7 days of enrolment.[1] Each tablet was taken once daily and contained tenofovir disoproxil fumarate 300 mg, lamivudine 300 mg, and dolutegravir 50 mg. All study evaluations were conducted by each site's research staff. Participants were seen at screening, study entry, 3 months, 6 months, and every 6 months thereafter up to 36 months. At each visit, participants were assessed for adverse events; only those related to treatment discontinuation were reported on case report forms and graded according to Division of AIDS criteria.[17] Targeted clinical events, which included AIDS-defining conditions, fractures, coronary heart disease, cancer, death, depression, diabetes, immune reconstitution inflammatory syndrome, suicidal ideation, suicide attempt, tuberculosis, and HIV-associated nephropathy, were also reported.

Plasma HIV-1 RNA concentrations were measured in near real time at study entry and at 6 months, 12 months, 24 months, and 36 months; samples were stored for retrospective testing at 18 months and 30 months. For participants with HIV-1 RNA of more than 1000 copies per mL at 6 months, HIV-1 drug-resistance testing using population-based sequencing was performed to identify dolutegravir-resistance mutations (located on the integrase gene) and NRTI mutations (located on the reverse transcriptase gene), and to determine their associated levels of resistance. Participants with HIV-1 RNA of more than 1000 copies per mL at the 6-month, 12-month, or 24-month visits received adherence counselling and repeat viral load evaluation for confirmation of virological failure (defined as two consecutive HIV-1 RNA measurements of >1000 copies per mL); repeat assessments took place within 6 months of the initial test at which viraemia was identified (at next scheduled visit if possible), consistent with country-level guidelines for confirmation of virological failure. For participants with confirmed virological failure, HIV-1 drug-resistance testing was performed on a plasma sample obtained at the time of the repeat test. For participants with HIV-1 drug-resistance testing at either 6 months or at the time of confirmation of virological failure, samples obtained before initiation of the tenofovir–lamivudine–dolutegravir regimen were tested using population-based sequencing if the sample had HIV-1 RNA of more than 1000 copies per mL. Population-based HIV-1 drug-resistance testing was performed in South African National Accreditation System (SANAS, ISO15189) and College of American Pathologists-accredited specialty laboratories (Lancet Molecular Laboratory and Pittsburgh Virology Specialty Laboratory,

respectively). HIV-1 drug-resistance mutations were identified and predicted levels of resistance were determined using the Stanford Algorithm (version 8.8).[18]

Dried blood spots were collected at 6 months, 12 months, 24 months, and 36 months to assess intracellular tenofovir diphosphate concentrations as a marker of tenofovir–lamivudine–dolutegravir adherence. Tenofovir diphosphate concentrations were measured by liquid chromatography using 3 mm punch sizes at the University of Cape Town Pharmacokinetic Research Laboratory. The lower limit of quantification was 16·6 fmol/3mm punch.

BMI was measured at screening and at 6 months, 12 months, 24 months, and 36 months. CD4 cell count was measured at study entry and at the final study visit. Sex was self-reported as male or female at birth. Pregnancies occurring during the study and pregnancy outcomes were recorded on case report forms from diagnosis until the end of the pregnancy.

During the COVID-19 pandemic, remote data collection was allowed when necessary for participants who were unable to attend scheduled visits and at locations that were unable to conduct on-site visits. The study planned to follow up all participants for 36 months. However, because of funding limitations, follow-up of all participants was terminated on March 31, 2023.

Outcomes

The primary outcomes were the proportion of participants with HIV-1 RNA of 1000 copies per mL or less and the proportion of participants with HIV-1 RNA of more than 1000 copies per mL with new dolutegravir-resistance mutations 6 months after starting tenofovir–lamivudine–dolutegravir, within participant groups. New dolutegravir-resistance mutations were defined as those detected in participants with HIV-1 RNA of more than 1000 copies per mL at 6 months that had not been detected at the time of tenofovir–lamivudine–dolutegravir initiation; for participants with study entry HIV-1 RNA of 1000 copies per mL or less, any mutations identified during follow-up were considered to be new.

Secondary outcomes, assessed within participant groups, included the proportion of participants with HIV-1 RNA of less than 50 copies per mL at 6 months; the proportion of participants with HIV-1 RNA concentrations at each threshold (≤1000 copies per mL and <50 copies per mL) at 12 months, 24 months, and 36 months; cumulative incidence of confirmed virological failure; and emergence of drug-resistance mutations associated with confirmed virological failure. Additional outcomes included tenofovir diphosphate concentrations at 6 months and at the time of confirmed virological failure, change in mean CD4 cell counts from study entry to last study visit, change in mean BMI from baseline to 24 months in adults aged 18 years or older, and pregnancies and pregnancy outcomes within participant groups.

Findings for primary outcomes and secondary outcomes up to 6 months of follow-up have been reported elsewhere for group 1B and group 3.[16]

Statistical analysis

The target sample sizes were 180 participants in each of group 1A, group 2A, and group 3, and 360 participants in each of group 1B and group 2B. These were chosen to estimate with reasonable precision the 6-month virological success rate in each group after starting tenofovir–lamivudine–dolutegravir treatment. For group 1A, group 2A, and group 3, the 95% CI would be approximately 79·8–90·2% at the hypothesised success rate of 85%. For group 1B and group 2B, the 95% CI would be approximately 86·9–93·1% at the hypothesised success rate of 90%. The larger target sample size of 360 participants in group 1B and group 2B (with HIV-1 RNA ≤1000 copies per mL at the start of tenofovir–lamivudine–dolutegravir) was based on the overall goal of enrolling 180 participants in each of group 1A and group 2A (with HIV-1 RNA >1000 copies per mL at the start of tenofovir–lamivudine–dolutegravir) and the assumption of an enrolment ratio of 2:1 in the B subgroups versus the A subgroups, recognising that testing of samples to determine HIV-1 RNA concentrations at the start of tenofovir–lamivudine–dolutegravir therapy would be done after enrolment. This sample size, however, was not achieved for group 1A before funding for the study ended.

Analyses of the primary outcomes and secondary treatment-related outcomes excluded participants who discontinued tenofovir–lamivudine–dolutegravir before the HIV-1 RNA evaluation. Within each group, the proportion of participants with the observed outcome was estimated with an exact 95% CI using the Clopper–Pearson method. Analyses of confirmed virological failure included all participants who were enrolled and started tenofovir–lamivudine–dolutegravir (ie, the full analysis population). Cumulative incidence of confirmed virological failure over time was estimated using Kaplan–Meier methods; follow-up was censored at the last available HIV-1 RNA measurement at 6 months, 12 months, or 24 months. 95% CIs for these outcomes are presented in the figures.

The relationship between tenofovir diphosphate concentrations and HIV-1 RNA measurements was evaluated using a nested case–control design, in which cases were participants with either HIV-1 RNA of more than 1000 copies per mL at 6 months or confirmed virological failure at any of 6 months, 12 months, or 24 months. Controls were participants with HIV-1 RNA of 1000 copies per mL or less throughout study follow-up, matched to cases (1:1) by study group, sex at birth, geographical location, and duration of tenofovir–lamivudine–dolutegravir treatment (±2 months). Differences in tenofovir diphosphate concentrations between cases and matched controls, with lower

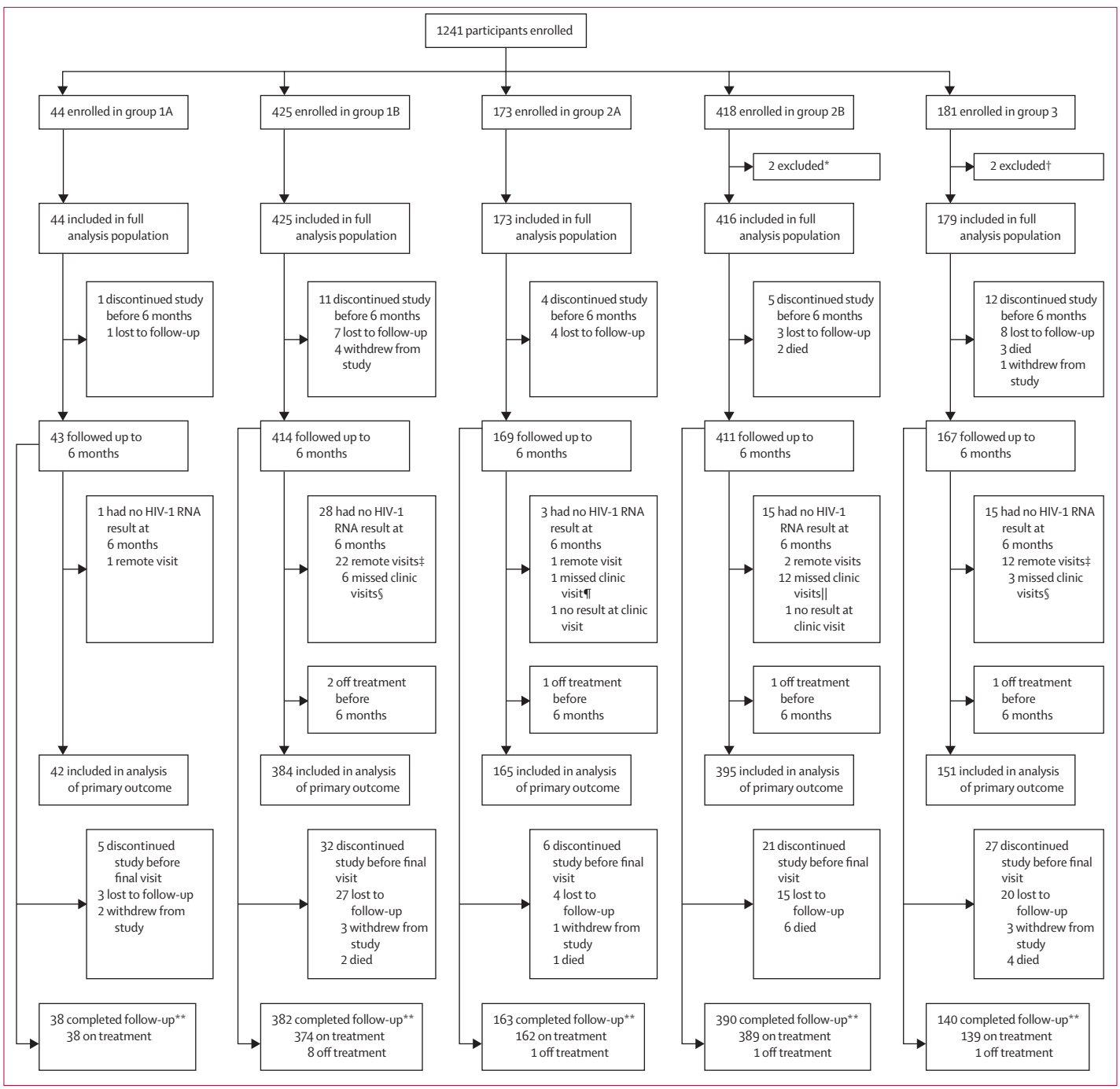

Figure 1: **Study profile**
Group 1A had HIV-1 RNA >1000 copies per mL on an NNRTI-based regimen; group 1B had HIV-1 RNA ≤1000 copies per mL on an NNRTI-based regimen; group 2A had HIV-1 RNA >1000 copies per mL on a protease inhibitor-based regimen; group 2B had HIV-1 RNA ≤1000 copies per mL on a protease inhibitor-based regimen; and group 3 was ART-naive. Availability of HIV-1 RNA data at each study visit is presented by cohort in the appendix (pp 4–8). Reasons for discontinuation of treatment, including adverse events, are detailed in the main text. ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor. *Two participants had started tenofovir–lamivudine–dolutegravir before enrolment and had no history of protease inhibitor-based regimen. †Two participants did not start tenofovir–lamivudine–dolutegravir (one withdrew from the study, one reported that they were not sick). ‡22 remote visits in group 1B and ten in group 3 were due to the COVID-19 pandemic. §All with HIV-1 RNA results at the subsequent visit. ¶Without HIV-1 RNA result at the subsequent visit. ||Ten with and two without HIV-1 RNA results at the subsequent visit. **To at least 6 months and up to 36 months before the study was terminated.

concentrations interpreted to reflect adherence challenges, were assessed by use of a sign test across all groups combined.

Predictors of viral suppression at 6 months were analysed using logistic regression, with the following prespecified variables in univariable models: sex at birth, age at start of tenofovir–lamivudine–dolutegravir treatment, baseline CD4 cell count, and baseline $\log_{10}$ HIV-1 RNA copies per mL. A supplementary analysis of viral suppression including all participants who started tenofovir–lamivudine–dolutegravir was done with treatment discontinuations and missing viral load results (due to death, loss to follow-up, and missing measurements) classified as HIV-1 RNA of more than 1000 copies per mL. For the primary outcome, post-hoc sensitivity analyses excluding all participants who had remote follow-up visits owing to the COVID-19 pandemic were done. All analyses were done with SAS version 9.4.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 1241 participants enrolled into the study, two in group 2B who started tenofovir–lamivudine–dolutegravir therapy before enrolment and two in group 3 who did not start tenofovir–lamivudine–dolutegravir were excluded. Therefore, 1237 participants were included in the full analysis population: 44 in group 1A, 425 in group 1B, 173 in group 2A, 416 in group 2B, and 179 in group 3 (figure 1). Median follow-up (time from tenofovir–lamivudine–dolutegravir initiation to last contact) was shortest in group 2A and group 2B because of proportionately slower initial enrolment rates than in the other groups (table).

During the study period, six (1%) participants in group 1B, three (2%) in group 2A, eight (2%) in group 2B, and 14 (8%) in group 3 had a targeted clinical event (including death in 18 patients). Causes of death were tuberculosis (n=3), pneumonia (n=3), major cardiac event (n=2), sepsis (n=1), cervical cancer (n=1), acute renal failure (n=1), homicide (n=1), and unspecified (n=6). Other targeted clinical events are shown in the appendix (p 3). No participants in group 1A had targeted clinical events.

14 (1%) of 1237 participants discontinued tenofovir–lamivudine–dolutegravir, 11 of whom completed study follow-up. Of the 14 participants who discontinued treatment, reasons included adverse events (12 participants), incarceration (one participant), and participant decision (one participant). Of the 12 participants who discontinued owing to adverse events, seven were in group 1B, one was in group 2A, two were in group 2B, and two were in group 3. Renal insufficiency (grade 2–4) was the most common adverse event resulting in tenofovir–lamivudine–dolutegravir discontinuation (five in group 1B; two in group 2B; and two in group 3); in these cases, tenofovir was switched to abacavir except in one participant who died of acute renal failure 1 week after tenofovir–lamivudine–dolutegravir discontinuation. The remaining three adverse events were nausea and vomiting, weight gain, and drug-induced liver injury. No participant discontinued tenofovir–lamivudine–dolutegravir because of virological failure.

Among participants on tenofovir–lamivudine–dolutegravir for 6 months with an HIV-1 RNA result, 37 (88%) of 42 participants in group 1A, 380 (99%) of 384 in group 1B, 118 (72%) of 165 in group 2A, 376 (95%) of 395 in group 2B, and 136 (90%) of 151 in group 3 had HIV-1 RNA of 1000 copies per mL or less (figure 2). 22 (5%) of 425 participants in group 1B and ten (6%) of 179 in group 3 did not have results at 6 months because they had remote follow-up visits owing to the COVID-19 pandemic (appendix pp 4–8); all were enrolled at a single site (figure 1). Post-hoc sensitivity analyses in these groups that excluded all participants at the affected site showed similar results: 99% (346 of 349 participants) in group 1B and 91% (124 of 137 participants) in group 3.

HIV-1 RNA results of more than 1000 copies per mL at 6 months were measured in five participants in group 1A, four in group 1B, 19 in group 2B, and 15 in group 3 (appendix pp 9–14). None of these participants had dolutegravir-resistance mutations detected at study entry or at 6 months that led to reduced susceptibility to dolutegravir. In group 1A, three of five participants had high-level lamivudine resistance, two of whom also had low-level tenofovir resistance; in group 1B, no NRTI-resistance mutations were detected; in group 2B, three of 19 participants had high-level lamivudine resistance, two of whom also had low-level tenofovir resistance; and in group 3, one of 15 participants had low-level tenofovir resistance and potential low-level lamivudine resistance. In group 2A, 47 participants had HIV-1 RNA of more than 1000 copies per mL at 6 months, 45 of whom had results available from genotypic testing. 12 of 45 participants had NRTI-resistance mutations. Two participants in group 2A had possible new dolutegravir-resistance mutations (G118R, R263K; 1·2% of 163 participants [95% CI 0·0–4·4]); both also had NRTI-resistance mutations (conferring reduced susceptibility to tenofovir and lamivudine) at study entry that were unchanged at 6 months (appendix pp 9–14).

In all study groups, tenofovir diphosphate concentrations were lower among participants with HIV-1 RNA of more than 1000 copies per mL at 6 months than in matched controls with HIV-1 RNA of 1000 copies per mL or less ($p<0·0001$ for 87 case–control pairs across all groups combined; figure 3).

Analyses of predictors of viral suppression (HIV-1 RNA ≤1000 copies per mL) at 6 months after starting tenofovir–lamivudine–dolutegravir were not done in

	Group 1A (n=44)	Group 1B (n=425)	Group 2A (n=173)	Group 2B (n=416)	Group 3 (n=179)
Sex					
Female	34 (77%)	339 (80%)	98 (57%)	255 (61%)	75 (42%)
Male	10 (23%)	86 (20%)	75 (43%)	161 (39%)	104 (58%)
Gender identity					
Cisgender	43 (98%)	425 (100%)	163 (94%)	408 (98%)	178 (99%)
Transgender spectrum	0	0	0	4 (1%)	1 (1%)
Not reported	1 (2%)	0	10 (6%)	4 (1%)	0
Age (years)					
Median (IQR)	33 (24–41)	41 (33–47)	41 (27–49)	44 (32–51)	35 (28–42)
Range	15–67	10–74	11–68	11–78	18–61
Country					
Haiti	2 (5%)	7 (2%)	80 (46%)	145 (35%)	47 (26%)
Kenya	19 (43%)	123 (29%)	27 (16%)	108 (26%)	29 (16%)
Malawi	2 (5%)	40 (9%)	13 (8%)	57 (14%)	71 (40%)
South Africa	3 (7%)	140 (33%)	9 (5%)	45 (11%)	4 (2%)
Uganda	15 (34%)	57 (13%)	44 (25%)	60 (14%)	25 (14%)
Zimbabwe	3 (7%)	58 (14%)	0	1 (<1%)	3 (2%)
BMI (kg/m²)*					
Median (IQR)	22·5 (20·0–25·2)	24·9 (21·3–29·3)	22·1 (19·8–25·8)	23·3 (20·6–28·4)	21·6 (19·6–24·4)
Duration of ART at entry (years)					
Median (IQR)	5·5 (3·1–9·2)	6·6 (3·4–10·3)	5·4 (2·8–8·9)	6·2 (3·3–11·5)	NA
NRTI-based regimen					
Tenofovir	39 (89%)	385 (91%)	124 (72%)	295 (71%)	NA
Zidovudine	5 (11%)	36 (8%)	42 (24%)	88 (21%)	NA
Abacavir	0	4 (1%)	5 (3%)	27 (6%)	NA
Lamivudine	40 (91%)	295 (69%)	173 (100%)	392 (94%)	NA
Emtricitabine	3 (7%)	130 (31%)	0	17 (4%)	NA
Missing	0	0	0	6 (1%)	NA
NNRTI-based regimen					
Efavirenz	38 (86%)	389 (92%)	NA	NA	NA
Nevirapine	6 (14%)	35 (8%)	NA	NA	NA
Rilpivirine	0	1 (<1%)	NA	NA	NA
Protease inhibitor-based regimen					
Ritonavir-boosted atazanavir	NA	NA	101 (58%)	263 (63%)†	NA
Ritonavir-boosted lopinavir	NA	NA	72 (42%)	147 (35%)	NA
Missing	NA	NA	0	6 (1%)	NA
HIV-1 RNA					
Median (IQR; log_{10} copies per mL)‡	4·0 (3·7–4·6)	..	4·2 (3·6–4·6)	..	4·4 (3·5–5·1)
<50 copies per mL	0	402 (95%)	0	295 (71%)	25 (14%)
50–200 copies per mL	0	13 (3%)	0	52 (13%)	1 (1%)
201–1000 copies per mL	0	10 (2%)	0	69 (17%)	10 (6%)
>1000 copies per mL	44 (100%)	0	173 (100%)	0	143 (80%)
CD4 cell count					
Median (IQR; cells per μL)	306 (173–419)	676 (477–893)	262 (134–370)	527 (336–723)	302 (165–517)
Missing	2 (5%)	10 (2%)	5 (3%)	14 (3%)	10 (6%)
Follow-up time (weeks)					
Median (IQR)	116 (49–126)	122 (120–135)	75 (47–96)	92 (69–108)	127 (119–144)

Group 1A had HIV-1 RNA >1000 copies per mL on an NNRTI-based regimen; group 1B had HIV-1 RNA ≤1000 copies per mL on an NNRTI-based regimen; group 2A had HIV-1 RNA >1000 copies per mL on a protease inhibitor-based regimen; group 2B had HIV-1 RNA ≤1000 copies per mL on a protease inhibitor-based regimen; and group 3 was ART-naive. Not all percentages add up to 100% owing to rounding. ART=antiretroviral therapy. NA=not applicable. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. *BMI is presented for adults aged ≥18 years. †Two participants received unboosted atazanavir. ‡Median HIV-1 RNA data are presented only for groups that included participants with HIV-1 RNA >1000 copies per mL.

Table: **Baseline characteristics and follow-up duration**

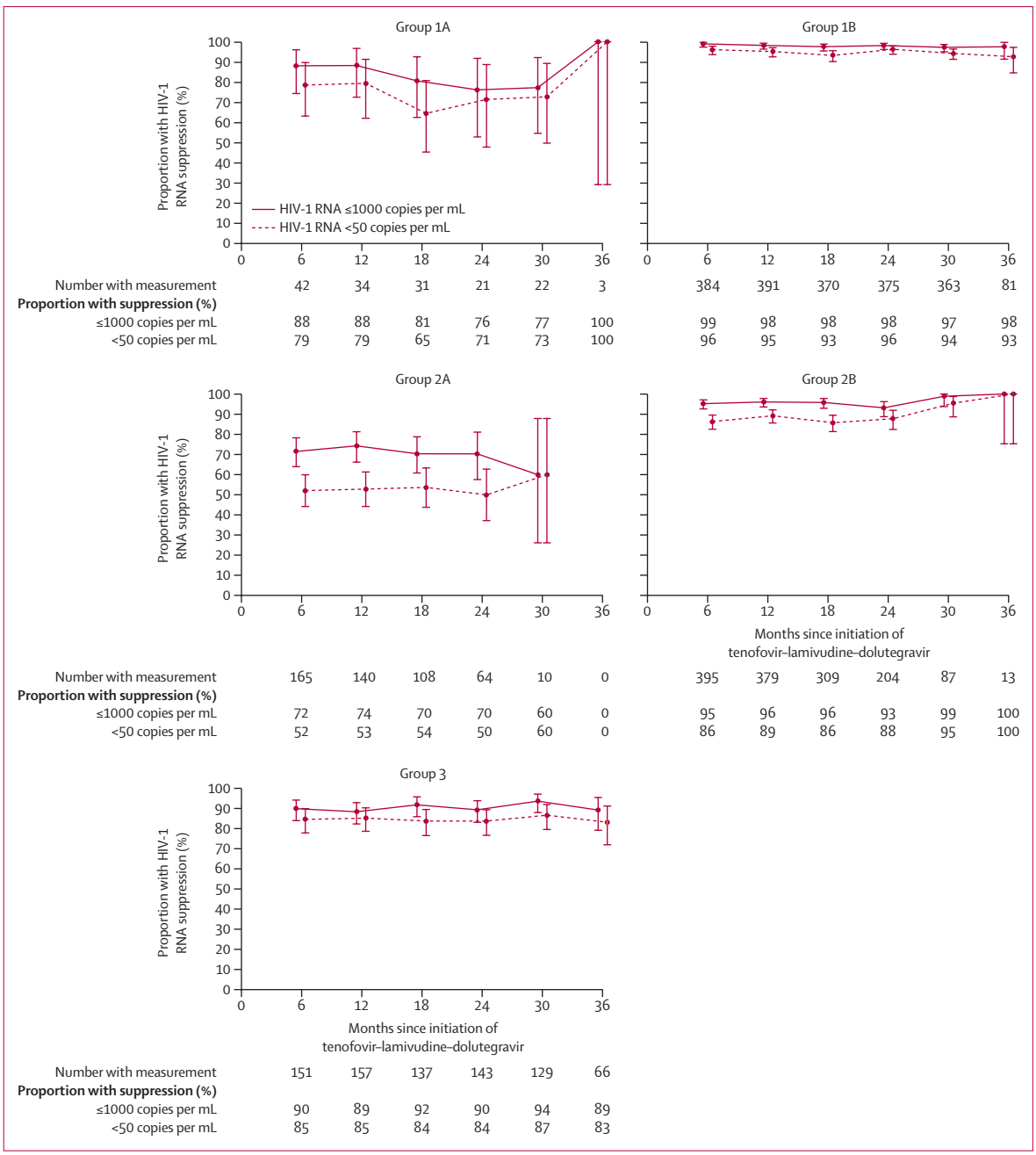

Figure 2: **Proportion of participants with HIV-1 RNA suppression up to 36 months**
Proportions of participants with viral suppression at thresholds of HIV-1 RNA ≤1000 copies per mL (solid lines) and <50 copies per mL (dashed lines) among those on tenofovir–lamivudine–dolutegravir with HIV-1 RNA results are shown over time. Group 1A had HIV-1 RNA >1000 copies per mL on an NNRTI-based regimen; group 1B had HIV-1 RNA ≤1000 copies per mL on an NNRTI-based regimen; group 2A had HIV-1 RNA >1000 copies per mL on a protease inhibitor-based regimen; group 2B had HIV-1 RNA ≤1000 copies per mL on a protease inhibitor-based regimen; and group 3 was ART-naive. Vertical bars represent exact 95% CIs. ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor.

group 1A owing to the insufficient sample size or in group 1B because of the very high suppression rate. In group 2A, higher quantitative HIV-1 RNA measurements at study entry were associated with lower odds of viral suppression at 6 months (odds ratio [OR] 0·62 per 1 $\log_{10}$ increase in copies per mL; 95% CI 0·39–1·00). In group 2B, higher baseline CD4 counts were associated with higher odds of viral suppression at 6 months (OR 1·46 per 100 cells per µL; 95% CI 1·16–1·84), as was baseline HIV-1 RNA of less than 50 copies per mL versus 50–1000 copies per mL (OR 4·73; 95% CI 1·81–12·4). In group 3, older age at tenofovir–lamivudine–dolutegravir

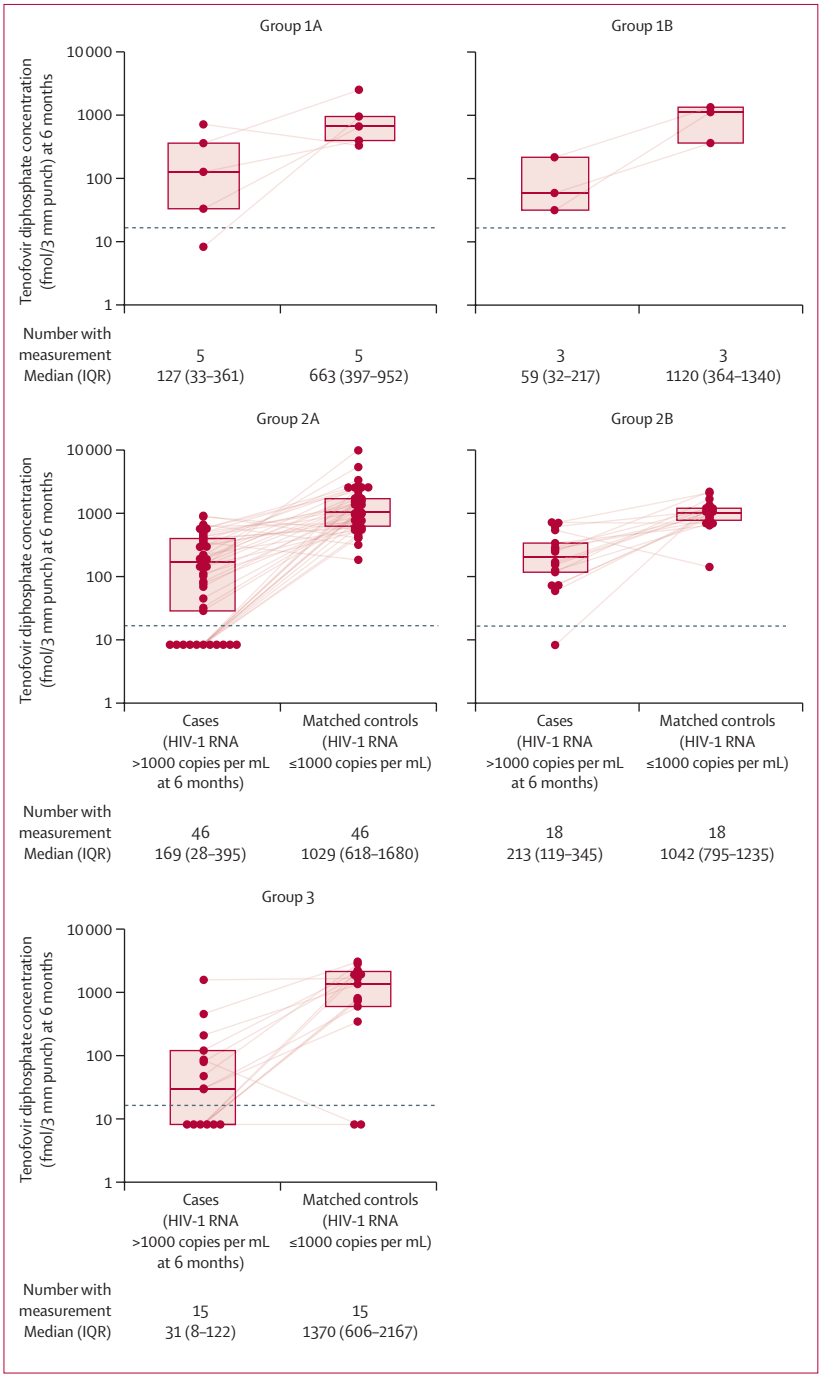

Figure 3: **Tenofovir diphosphate concentrations in dried blood spots at 6 months**
Median concentrations in participants on tenofovir–lamivudine–dolutegravir with HIV-1 RNA of >1000 copies per mL at 6 months (cases) versus those with ≤1000 copies per mL throughout study follow-up (matched controls) are shown. Group 1A had HIV-1 RNA >1000 copies per mL on an NNRTI-based regimen; group 1B had HIV-1 RNA ≤1000 copies per mL on an NNRTI-based regimen; group 2A had HIV-1 RNA >1000 copies per mL on a protease inhibitor-based regimen; group 2B had HIV-1 RNA ≤1000 copies per mL on a protease inhibitor-based regimen; and group 3 was ART-naive. The boxes show the lower and upper quartiles, and the line within the boxes shows the median. Joining lines indicate matched cases and controls. Tenofovir diphosphate concentrations below the lower limit of quantification of the assay (dashed lines; 16·6 fmol/3 mm punch) were imputed as half of the lower limit of quantification (8·3 fmol/3 mm punch). For the two cases in group 2A with new dolutegravir-resistance mutations at 6 months conferring reduced susceptibility to dolutegravir, tenofovir diphosphate concentrations at that timepoint were 611 fmol/3 mm punch and 655 fmol/3 mm punch. ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor.

initiation was associated with greater odds (OR 4·59 per 10 years; 95% CI 1·98–10·7) and higher quantitative baseline HIV-1 RNA was associated with lower odds (OR 0·56 per 1 $\log_{10}$ increase in copies per mL; 95% CI 0·32–1·00) of viral suppression at 6 months. Sex at birth was not significantly associated with higher odds of viral suppression in any study group.

The numbers of participants with a measurement at 36 months when the study closed was small (figure 2; appendix pp 4–8). Among those on tenofovir–lamivudine–dolutegravir with HIV-1 RNA results available, the proportion with HIV-1 RNA of 1000 copies per mL or less showed a modest decline over 24 months in group 1A (figure 2), but remained more stable in the other groups. The proportion of participants with HIV-1 RNA of less than 50 copies per mL was lower than that for 1000 copies per mL or less (figure 2). Rates of viral suppression were lower when tenofovir–lamivudine–dolutegravir discontinuations and missing viral load results (due to death, loss to follow-up, and missing measurements) were classified as HIV-1 RNA of more than 1000 copies per mL (appendix p 15).

At 24 months, the estimated cumulative incidence of confirmed virological failure (two consecutive HIV-1 RNA measurements of >1000 copies per mL) was 18·2% in group 1A, 1·3% in group 1B, 47·5% in group 2A, 1·1% in group 2B, and 6·8% in group 3 (figure 4). Virological failure was confirmed in four participants in group 1A, five in group 1B, four in group 2B, and 11 in group 3. None of these participants had dolutegravir-resistance mutations detected at study entry or during follow-up that led to reduced susceptibility to dolutegravir (appendix pp 16–22). NRTI mutations occurred in three of four participants in group 1A and one of four in group 2B; in group 1B, no NRTI resistance was detected; and in group 3, no NRTI-resistance mutations were detected after the study entry visit. In group 2A, 34 participants had confirmed virological failure, 32 of whom had HIV-1 drug-resistance results available. 11 participants had NRTI-resistance mutations. Three of 32 participants (9%) had possible new dolutegravir-resistance mutations that led to reduced susceptibility to dolutegravir: two participants had the G118R mutation and one had the R263K mutation; all three were from samples drawn at 12 months when confirmatory testing for virological failure was done. For two of the three participants, the dolutegravir-resistance mutations were also identified when HIV-1 drug-resistance testing was done on the sample from the 6-month timepoint. All three of these participants had concurrent NRTI resistance (conferring reduced susceptibility to tenofovir and lamivudine).

In all study groups, tenofovir diphosphate concentrations were lower among participants with confirmed virological failure than in matched controls ($p<0·0001$ for 56 case–control pairs across all groups combined; figure 5).

Mean changes in CD4 count from study entry to end of follow-up were +130 cells per µL (95% CI 87 to 174; p<0·0001) in group 1A, +26 cells per µL (0 to 51; p=0·053) in group 1B, +110 cells per µL (73 to 147; p<0·0001) in group 2A, –13 cells per µL (–38 to 11; p=0·29) in group 2B, and +171 cells per µL (126 to 215; p<0·0001) in group 3.

Mean changes in BMI from baseline to 24 months were –0·1 kg/m² (95% CI –1·3 to 1·1) in group 1A, +0·8 kg/m² (0·6 to 1·1) in group 1B, +0·2 kg/m² (–0·2 to 0·7) in group 2A, and +0·7 kg/m² (0·5 to 1·0) in group 2B (appendix p 23). In group 3, BMI increased substantially by 6 months (mean change 1·3 kg/m² [1·0–1·7]) and continued to show an increasing trajectory thereafter, with a mean increase of 1·8 kg/m² by 24 months (1·3–2·3).

55 participants were pregnant at study entry or became pregnant during the study period (four in group 1A; 25 in group 1B; five in group 2A; 12 in group 2B; and nine in group 3); of these, two (one each in group 2B and group 3) had two pregnancies and one (in group 2A) had a twin pregnancy. Of 14 pregnancies that began before study entry, ten resulted in livebirths, three in stillbirths, and one in spontaneous abortion. Of 43 pregnancies that began after study entry, 36 (84%) resulted in livebirths (including twins), three in stillbirths, three in spontaneous abortion, and one in induced abortion. Among HIV-1 RNA measurements obtained during 57 pregnancies, 50 (88%) were below 1000 copies per mL before delivery (46 [81%] were <50 copies per mL). Of the remaining seven pregnancies, four resulted in livebirths (three in group 2A, one in group 3) and three in stillbirths (one in group 1A, two in group 3); the participants in these three cases delivered before the first study measurement of HIV-1 RNA after tenofovir–lamivudine–dolutegravir initiation.

Discussion

In this prospective cohort study, we found that among subgroups of people with HIV who had viral suppression before switching from NNRTI-based or protease inhibitor-based regimens to tenofovir–lamivudine–dolutegravir, there was near-universal maintenance of viral suppression at 6 months, which was sustained during follow-up to at least 24 months. Viral suppression rates were slightly lower among participants who were ART-naive at treatment initiation. By contrast, long-term virological outcomes were suboptimal for participants who had virological failure on a previous regimen at the time of switching to tenofovir–lamivudine–dolutegravir, particularly in the subgroup that switched from second-line protease inhibitor-based ART. Emergent drug-resistance mutations leading to reduced susceptibility to dolutegravir were rare (occurring only in the subgroup that had virological failure on protease inhibitor-based regimens before switching), and individuals with HIV-1 RNA of more than 1000 copies per mL had lower intracellular tenofovir diphosphate concentrations in dried blood spots than did matched

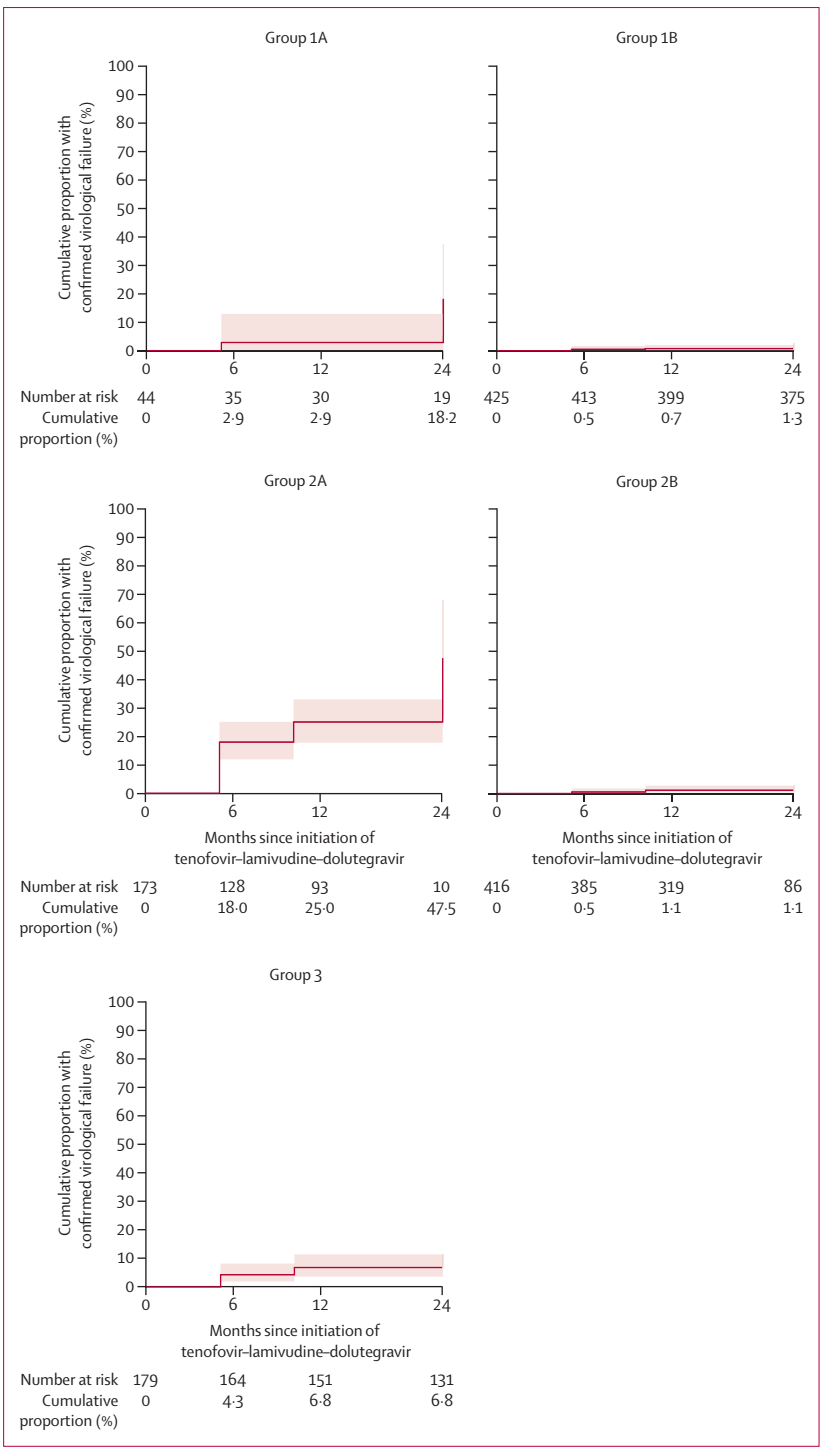

Figure 4: **Cumulative proportion of participants with confirmed virological failure**
Estimated cumulative proportion of participants with confirmed virological failure, defined as two consecutive HIV-1 RNA measurements of >1000 copies per mL, restricted to real-time measurements at 6 months, 12 months, and 24 months of follow-up. Analysis was in the full analysis population. Follow-up was censored at the last available HIV-1 RNA measurement at 6 months, 12 months, or 24 months. Group 1A had HIV-1 RNA >1000 copies per mL on an NNRTI-based regimen; group 1B had HIV-1 RNA ≤1000 copies per mL on an NNRTI-based regimen; group 2A had HIV-1 RNA >1000 copies per mL on a protease inhibitor-based regimen; group 2B had HIV-1 RNA ≤1000 copies per mL on a protease inhibitor-based regimen; and group 3 was ART-naive. Shaded areas indicate 95% CIs. ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor.

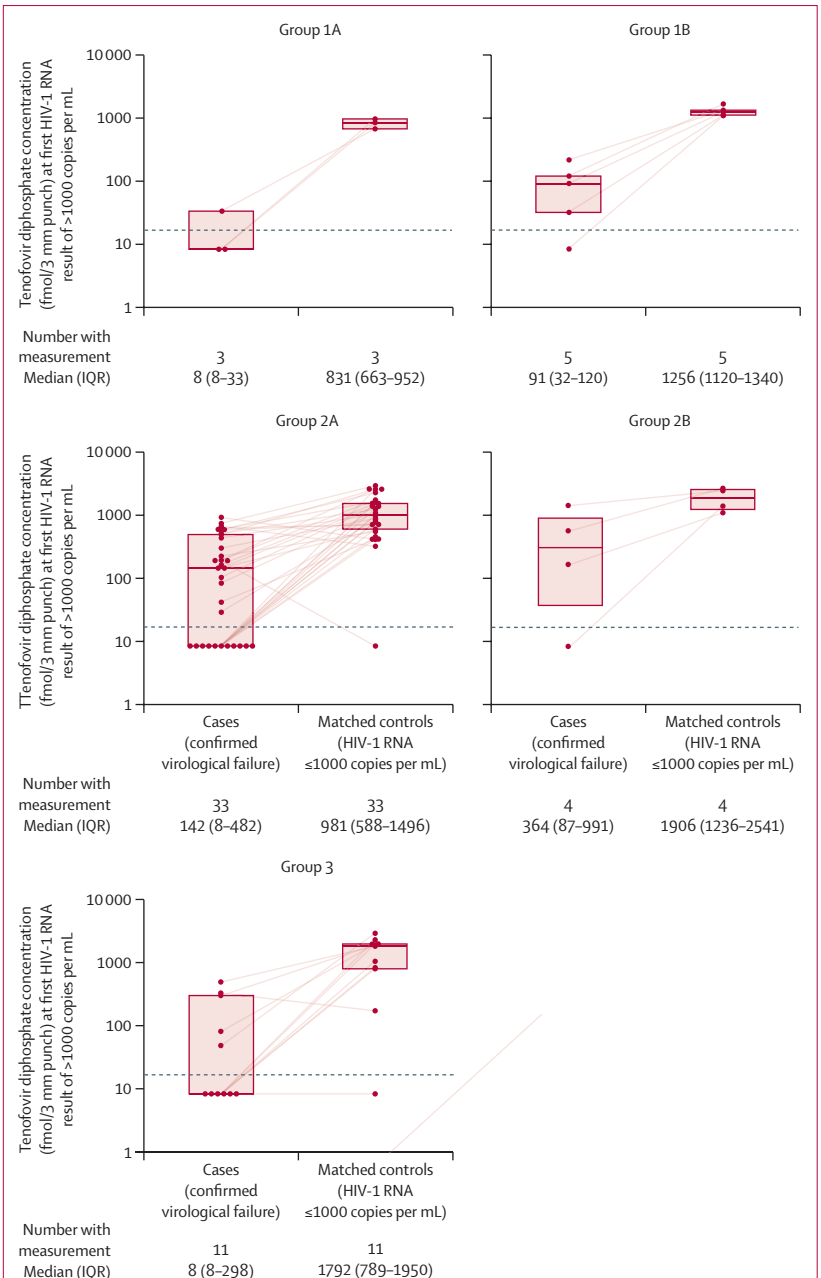

Figure 5: **Tenofovir diphosphate concentrations in dried blood spots associated with confirmed virological failure**

Median concentrations in participants with confirmed virological failure at 6 months, 12 months, or 24 months (cases) versus those with HIV-1 RNA ≤1000 copies per mL throughout study follow-up (matched controls). Group 1A had HIV-1 RNA >1000 copies per mL on an NNRTI-based regimen; group 1B had HIV-1 RNA ≤1000 copies per mL on an NNRTI-based regimen; group 2A had HIV-1 RNA >1000 copies per mL on a protease inhibitor-based regimen; group 2B had HIV-1 RNA ≤1000 copies per mL on a protease inhibitor-based regimen; and group 3 was ART-naive. The boxes show the lower and upper quartiles, and the line within the boxes shows the median. Joining lines indicate matched cases and controls. Tenofovir diphosphate concentrations below the lower limit of quantification of the assay (dashed lines; 16·6 fmol/3 mm punch) were imputed as half of the lower limit of quantification (8·3 fmol/3 mm punch). For the three cases in group 2A with new dolutegravir-resistance mutations, the tenofovir diphosphate concentrations at the time of confirmatory evaluation for virological failure (12 months for all three) were 723 fmol/3 mm punch, 329 fmol/3 mm punch, and 693 fmol/3 mm punch. ART=antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor.

controls with viral suppression, suggesting inadequate adherence as the primary reason for virological failure.

Clinical trials in LMICs have also reported excellent outcomes for people with HIV and viral suppression at the time of switching to tenofovir–lamivudine–dolutegravir. In the VISEND trial, 99% of participants who switched from NNRTI-based ART with HIV-1 RNA of less than 1000 copies per mL maintained suppression at 144 weeks.[15] In the 2SD trial, 95% of participants with viral load data in the group that switched from a suppressive ritonavir-boosted second-line protease inhibitor-based regimen to a dolutegravir-based regimen had 48-week HIV-1 RNA of less than 50 copies per mL.[8] In a study with a similar design in Haiti (with bictegravir instead of dolutegravir), more than 99% of participants in the bictegravir group had HIV-1 RNA of less than 200 copies per mL.[9] None of these trials reported emergent dolutegravir-resistance mutations in participants with virological failure.[8,9,15]

Similar results were reported in African cohort studies, with high levels of viral suppression after switching from suppressive NNRTI-based regimens to tenofovir–lamivudine–dolutegravir.[5–7,10,11,19] In a study from Malawi, no cases of emergent dolutegravir resistance were detected among participants who switched from suppressive first-line NNRTI-based regimens, and, in Lesotho, mutations were detected in only 0·01% of such participants.[4,6] We are not aware of any other prospective cohort studies that have assessed virological outcomes and resistance mutations in individuals switching to tenofovir–lamivudine–dolutegravir from a suppressive second-line ritonavir-boosted protease inhibitor-based regimen in a programmatic setting. Individuals on second-line ritonavir-boosted protease inhibitor-based regimens generally have a history of virological failure on first-line NNRTI-based regimens, and previous studies have indicated high rates of NRTI resistance in such participants.[12–15,20] Nevertheless, our study showed high rates of viral suppression in this population and no emergent dolutegravir-resistance mutations.

The results that we report for ART-naive participants are similar to those of clinical trials and cohort studies of people with HIV initiating dolutegravir-based regimens in LMICs. The NAMSAL trial reported that 83% of ART-naive participants who started tenofovir–lamivudine–dolutegravir and received testing had viral suppression at 96 weeks.[21] In the ADVANCE trial, suppression rates were higher: 96% of participants with viral load data had HIV-1 RNA of less than 50 copies per mL at 96 weeks after initiating dolutegravir.[22] A retrospective cohort study of ART-naive participants from 59 sites in South Africa found that among those with HIV-1 RNA measurements at approximately 1 year after dolutegravir initiation, 83% had less than 50 copies per mL.[23] A small study from Cameroon reported even higher rates of viral suppression among participants initiating and those switching to a dolutegravir-based

regimen and no dolutegravir-resistance mutations among those with virological failure.[7] Phase 3 clinical trials in high-income settings have also reported high rates of viral suppression without emergent dolutegravir resistance among ART-naive participants.[24–26]

In this study, participants with virological failure on second-line boosted protease inhibitor-based regimens at the time of switching to tenofovir–lamivudine–dolutegravir (group 2A) had lower rates of viral suppression (70% at 24 months) than did the other groups, although most had HIV-1 RNA of 1000 copies per mL or less. Group 2A also had the lowest proportion of participants with HIV-1 RNA of less than 50 copies per mL (50% at 24 months). This finding is expected, given that this high-risk group had been exposed to multiple regimens, had virological failure more than once, and had more NRTI-resistance mutations than other groups. These results are consistent with those of studies of previously recommended ART agents in this population, including the large, international A5288 clinical trial.[27] Although the emergence of dolutegravir resistance was rare in group 2A, it developed in about 9% of participants with confirmed virological failure in this group, which is consistent with findings from cohort studies of people with HIV in Africa who switched from failing NNRTI-based regimens to dolutegravir-based regimens.[4,6,11] Participants in group 1A, who were viraemic when switching from NNRTI-based regimens, had higher rates of viral suppression during follow-up than did those in group 2A, although results were still suboptimal. Viral suppression rates did not improve over time in either group 1A or group 2A, and declined in group 1A over the course of the study; although this group had frequent NRTI-resistance mutations, no emergent dolutegravir-resistance mutations were detected. Studies are underway to determine whether there are mutations outside the integrase region that could emerge on treatment and result in reduced dolutegravir susceptibility.

Our case–control study results of intracellular tenofovir diphosphate concentrations in dried blood spots suggest that incomplete adherence was the major cause of HIV-1 RNA measurements of more than 1000 copies per mL at 6 months of follow-up and at the time of confirmed virological failure across all groups. Adherence challenges might also explain why there was a higher rate of confirmed virological failure in group 1A, group 2A, and group 3 than in group 1B and group 2B. Participants in group 1B and group 2B were virologically suppressed when starting tenofovir–lamivudine–dolutegravir therapy and so were achieving high adherence to daily oral therapy, but that was not the case for the treatment-naive participants enrolled into group 3 or for those in the A subgroups who switched from failing regimens. Our findings contribute to existing knowledge on therapeutic management for populations that are challenging to treat and highlight the importance of developing person-centred interventions and alternative treatment options, such as expanded access to long-acting ART for people with HIV with chronic adherence challenges in LMICs.[28,29]

This study was conducted at PEPFAR sites that are affiliated with ACTG sites, which might limit the generalisability of our findings. However, all sites followed standard PEPFAR and WHO-recommended procedures, which follow a public health approach and are similar across most LMICs.[1,2] In addition, some countries enrolled only a small number of participants in some groups because most eligible patients had already switched to tenofovir–lamivudine–dolutegravir or because there were delays in country-level guidelines for switching from NNTRI-based or boosted protease inhibitor-based regimens in individuals with virological failure; this is also the reason that the target sample size was not reached for group 1A, limiting interpretation of results from that group. Furthermore, genotypic testing was triggered by HIV-1 RNA measurements of more than 1000 copies per mL, which probably led to an underestimation of resistance given that resistance is possible in people with HIV-1 RNA of less than 1000 copies per mL. Resistance mutations could also have been missed owing to insufficient drug pressure on the virus due to non-adherence to ART, with potential reversion to wild-type virus at the time of resistance testing.

In conclusion, this study shows that tenofovir–lamivudine–dolutegravir is associated with high rates of tolerability and long-term viral suppression among individuals with viral suppression at the time of switching to this treatment. By contrast, virological outcomes were suboptimal for people with HIV with viraemia at the time of switching to tenofovir–lamivudine–dolutegravir and did not improve over time. The low rate of emergent dolutegravir-resistance mutations and the low tenofovir diphosphate concentrations among participants with confirmed virological failure suggest that incomplete adherence was the leading cause of virological failure. However, the development of dolutegravir-resistance mutations among some individuals with virological failure in group 2A (ie, those who had been viraemic when switching from protease inhibitor-based regimens) highlights the importance of dolutegravir resistance as an emerging threat. Alternative approaches, such as long-acting injectable ART, present an opportunity to overcome adherence challenges in some people with HIV.

ACTG A5381–Hakim Study Team members
Marie Jude Jean Louis, Daphie Jean François, Vanessa Rouzier, and Damocles Patrice Severe (Les Centres GHESKIO, Port-au-Prince, Haiti); Mina C Hosseinipour (University of North Carolina at Chapel Hill Project–Malawi Clinical Research Site [CRS], Lilongwe, Malawi); Peter Ehrenkranz (Gates Foundation, Seattle, USA); Elliot Raizes (US Centers for Disease Control and Prevention, Atlanta, USA); Deborah Langat (Kenya Medical Research Institute–Walter Reed Project Clinical Research Center CRS, Kericho, Kenya); Vuyokazi S Jezile and Noluthando Mwelase (University of the Witwatersrand Clinical HIV Research Unit, Wits Helen Joseph Hospital CRS, Johannesburg, South Africa); Abraham Siika and Viola Kirui (Moi University Clinical

Research Centre, Eldoret, Kenya); Penelope Madlala and Sundrapragassen Pillay (Durban International CRS, Durban, South Africa); Yeukai Musodza (Milton Park CRS, Harare, Zimbabwe); Nadia Marengo and Suri Moonsamy (Soweto CRS, Soweto, South Africa); Mulinda Nyirenda (Blantyre CRS, Blantyre, Malawi); and Lynne Cornelissen and Lindee Ganger (Family Centre for Research with Ubuntu CRS, Cape Town, South Africa).

Contributors

CM, CLW, CK, MDH, CG, NSS, UMP, GM, YCM, JWM, CF, SPK, and RM were responsible for study conceptualisation and methodology. CK, EW, JWM, and CF coordinated the study. JBM, CK, FK, MVS, RBK, PA, IT, CM, FFS, YJ, TF, LM, WPS, KM, MSR, and SP curated the data. CM and MDH did the formal analysis and validation. CM and MDH accessed and verified the data. JBM, SPK, and RM wrote the original draft. All authors reviewed and edited the manuscript and had final approval of the version to be submitted. All authors had full access to all the data in the study and to the statistical analysis reports, and had final responsibility for the decision to submit for publication.

Declaration of interests

UMP has received consultation fees from Merck and travel reimbursement from ThermoFisher, outside the submitted work. JWM has received consultation fees from Gilead Sciences, support for travel to the Conference on Retroviruses and Opportunistic Infections (CROI), is a previous member of the CROI Scientific Program Committee, is past President of the Foundation of Control of HIV Drug Resistance, and has share options in Galapagos NV, Infectious Disease Connect, and MingMed Biotechnology, outside the submitted work. CF has been a paid consultant in the past 3 years for American Gene Technologies, Johnson & Johnson, Gilead Sciences, Theratechnologies, Merck, and ViiV Healthcare, and has stock options in Navigen, outside the submitted work. All other authors declare no competing interests.

Data sharing

De-identified participant data will be available upon request to the ACTG (https://actgnetwork.org/submit-a-proposal-2/) with the written agreement of the ACTG. The study protocol and consent and assent forms are included in the appendix (pp 24–114).

Acknowledgments

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