

# Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials



Pedro Cahn, Juan Sierra Madero, José Ramón Arribas, Andrea Antinori, Roberto Ortiz, Amanda E Clarke, Chien-Ching Hung, Jürgen K Rockstroh, Pierre-Marie Girard, Jörg Sievers, Choy Man, Alexander Currie, Mark Underwood, Allan R Tenorio, Keith Pappa, Brian Wynne, Anna Fettiplace, Martin Gartland, Michael Aboud, Kimberly Smith, and the GEMINI Study Team

## Summary

**Background** Effective two-drug regimens could decrease long-term drug exposure and toxicity with HIV-1 antiretroviral therapy (ART). We therefore aimed to evaluate the efficacy and safety of a two-drug regimen compared with a three-drug regimen for the treatment of HIV-1 infection in ART-naive adults

**Methods** We conducted two identically designed, multicentre, double-blind, randomised, non-inferiority, phase 3 trials: GEMINI-1 and GEMINI-2. Both studies were done at 192 centres in 21 countries. We included participants ( $\geq 18$  years) with HIV-1 infection and a screening HIV-1 RNA of 500 000 copies per mL or less, and who were naive to ART. We randomly assigned participants (1:1) to receive a once-daily two-drug regimen of dolutegravir (50 mg) plus lamivudine (300 mg) or a once-daily three-drug regimen of dolutegravir (50 mg) plus tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg). Both regimen drugs were administered orally. We masked participants and investigators to treatment assignment: dolutegravir was administered as single-entity tablets (similar to its commercial formulation, except with a different film colour), and lamivudine tablets and tenofovir disoproxil fumarate and emtricitabine tablets were over-encapsulated to visually match each other. Primary endpoint was the proportion of participants with HIV-1 RNA of less than 50 copies per mL at week 48 in the intention-to-treat-exposed population, using the Snapshot algorithm and a non-inferiority margin of  $-10\%$ . Safety analyses were done on the safety population. GEMINI-1 and GEMINI-2 are registered with ClinicalTrials.gov, numbers NCT02831673 and NCT02831764, respectively.

**Findings** Between July 18, 2016, and March 31, 2017, 1441 participants across both studies were randomly assigned to receive either the two-drug regimen ( $n=719$ ) or three-drug regimen ( $n=722$ ). At week 48 in the GEMINI-1 intention-to-treat-exposed population, 320 (90%) of 356 participants receiving the two-drug regimen and 332 (93%) of 358 receiving the three-drug regimen achieved plasma HIV-1 RNA of less than 50 copies per mL (adjusted treatment difference  $-2.6\%$ , 95% CI  $-6.7$  to  $1.5$ ); in GEMINI-2, 335 (93%) of 360 in the two-drug regimen and 337 (94%) of 359 in the three-drug regimen achieved HIV-1 RNA of less than 50 copies per mL (adjusted treatment difference  $-0.7\%$ , 95% CI  $-4.3$  to  $2.9$ ), showing non-inferiority at a  $-10\%$  margin in both studies (pooled analysis: 655 [91%] of 716 in the two-drug regimen vs 669 [93%] of 717 in the three-drug regimen; adjusted treatment difference  $-1.7\%$ , 95% CI  $-4.4$  to  $1.1$ ). Numerically, more drug-related adverse events occurred with the three-drug regimen than with the two-drug regimen (169 [24%] of 717 vs 126 [18%] of 716); few participants discontinued because of adverse events (16 [2%] in the three-drug regimen and 15 [2%] in the two-drug regimen). Two deaths were reported in the two-drug regimen group of GEMINI-2, but neither was considered to be related to the study medication.

**Interpretation** The non-inferior efficacy and similar tolerability profile of dolutegravir plus lamivudine to a guideline-recommended three-drug regimen at 48 weeks in ART-naive adults supports its use as initial therapy for patients with HIV-1 infection.

**Funding** ViiV Healthcare.

**Copyright** © 2018 Elsevier Ltd. All rights reserved.

## Introduction

Standard-of-care first-line therapy for HIV-1 infection in adults naive to antiretroviral therapy (ART) is a regimen of three antiretroviral agents that includes two nucleoside

reverse transcriptase inhibitors and one other drug from either the boosted protease inhibitor, integrase strand transfer inhibitor, or non-nucleoside reverse transcriptase inhibitor classes.<sup>1</sup> However, concerns exist regarding the

Published Online  
November 9, 2018  
[http://dx.doi.org/10.1016/S0140-6736\(18\)32462-0](http://dx.doi.org/10.1016/S0140-6736(18)32462-0)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(18\)32783-1](http://dx.doi.org/10.1016/S0140-6736(18)32783-1)

Department of Infectious Diseases, Buenos Aires University, Buenos Aires, Argentina (Prof P Cahn MD); Fundación Huésped, Buenos Aires, Argentina (Prof P Cahn); Infectious Diseases, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico (Prof J S Madero MD); Hospital Universitario La Paz, Instituto de Investigación Hospital La Paz, Madrid, Spain (J R Arribas MD); UOC Immunodeficienze virali, Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani-IRCCS, Rome, Italy (A Antinori MD); Bliss Healthcare Services, Orlando, FL, USA (R Ortiz MD); Sexual Health and Clinical Trials, Royal Sussex County Hospital, Brighton, UK (A E Clarke BM); Division of Infectious Diseases, National Taiwan University Hospital, Taipei, Taiwan (Prof C-C Hung MD); Department of Medicine, University Hospital Bonn, Bonn, Germany (Prof J K Rockstroh MD); Service des Maladies Infectieuses et Tropicales, Hôpital Saint Antoine, Paris, France (Prof P-M Girard MD); Clinical Development (J Sievers DPhil) and Global Medical Affairs (M Aboud MD), ViiV Healthcare, Brentford, UK; Clinical Development (C Man BSc, A R Tenorio MD, B Wynne MD, K Pappa PharmD), Clinical

**Virology** (M Underwood PhD),  
**Medicine Development**  
 (M Gartland PhD), **Global  
 Research and Medical Strategy**  
 (K Smith MD), **ViiV Healthcare,**  
**Research Triangle Park, NC,**  
**USA; and Statistics**  
 (A Currie MSc), **Global Clinical  
 Safety and Pharmacovigilance**  
 (A Fettiplace PhD),  
**GlaxoSmithKline, Stockley  
 Park, UK**

Correspondence to:  
 Dr Jörg Sievers, Clinical  
 Development, ViiV Healthcare,  
 Brentford TW8 9GS, UK  
[jorg.x.sievers@viivhealthcare.com](mailto:jorg.x.sievers@viivhealthcare.com)

## Research in context

### Evidence before this study

We searched PubMed for publications of clinical trials, cohort studies, and review articles using combinations, abbreviations, and variations of the search terms “HIV”, “antiretroviral therapy”, “dolutegravir”, “integrase strand transfer inhibitor”, “lamivudine”, “nucleoside reverse transcriptase inhibitor”, “dual therapy”, “two-drug regimens”, “treatment-naive”, and “treatment simplification”. We also used other public search engines to identify and retrieve relevant practice guidelines, regulatory documents, and package inserts from governments, non-governmental organisations, and companies. We did the searches from May 17, 2018, to May 30, 2018, and included materials published from Jan 1, 1995, to May 30, 2018. We observed from this search an increasing concern regarding the potential consequences of exposing people living with HIV-1 infection to combinations of three or more antiretroviral drugs for the duration of their lives, which have been lengthened because of the success of combination antiretroviral therapy (ART). All ART agents are associated with specific adverse events or other challenges to tolerability and adherence to therapy. Two-drug regimens are being developed to simplify ART and reduce lifelong drug exposure and toxicity compared with current standard of care, which requires a combination of three or more drugs.

### Added value of this study

The GEMINI studies provide evidence from two fully powered, phase 3 studies that a two-drug regimen of dolutegravir plus lamivudine is non-inferior at a –10% non-inferiority margin compared with a recommended standard-of-care three-drug regimen (ie, dolutegravir plus tenofovir disoproxil fumarate and emtricitabine) for the treatment of ART-naive, HIV-1-infected participants through 48 weeks. In particular, these studies show

that the antiviral activity of dolutegravir plus lamivudine is similar to a dolutegravir-based three-drug regimen in participants with screening HIV-1 RNA of 1000–500 000 copies per mL. There were fewer participants with advanced disease (ie, CD4+ count <200 cells per  $\mu$ L) in the two-drug regimen group who achieved virological response, although this finding was confounded by low sample size and was not associated with a substantially higher frequency of treatment-related discontinuations. Importantly, dolutegravir plus lamivudine was not associated with treatment-emergent mutations, suggesting a high barrier to resistance.

### Implications of all the available evidence

These studies are the first to demonstrate the non-inferiority of a two-drug regimen containing dolutegravir in ART-naive individuals. Furthermore, these data are the first to show similar efficacy of any two-drug regimen with a standard integrase strand transfer inhibitor-based three-drug regimen, regardless of baseline viral load. These study results support dolutegravir as an optimal core agent for use in two-drug regimens. The GARDEL study showed non-inferiority of the two-drug regimen of lopinavir plus ritonavir and the ANDES study showed non-inferiority of darunavir plus ritonavir both in combination with lamivudine, suggesting lamivudine is a suitable agent for a two-drug regimen for treatment-naive individuals. The present results show that a two-drug regimen of dolutegravir plus lamivudine can be used for the treatment of HIV-1-infected adults naive to ART with a screening viral load of 500 000 copies per mL or less. As cumulative drug exposure becomes a more important treatment consideration with patients living longer, initial treatment strategies composed of two-drug regimens such as dolutegravir plus lamivudine might become an essential factor in treatment decisions.

toxicities accruing from cumulative exposure to drugs that need to be taken for life.<sup>2</sup> Thus, two-drug regimens capable of inducing or maintaining virological suppression, or both, while decreasing lifetime cumulative drug exposure and potential long-term toxicities would represent another treatment option for people living with HIV-1 infection.

Early trials between 2000 and 2014 evaluating two-drug regimens in treatment-naive populations yielded inconclusive results, perhaps partly because of small sample sizes, short treatment durations, and limitations of available treatments.<sup>3</sup> The phase 3 MODERN trial (n=797) reported inferior viral suppression with maraviroc plus ritonavir-boosted darunavir compared with a three-drug regimen.<sup>4</sup> The AIDS Clinical Trials Group Study A5142 team found that the virological efficacy of a two-drug regimen comprising efavirenz plus ritonavir-boosted lopinavir (n=250) was similar to that of efavirenz plus two nucleoside reverse transcriptase inhibitors (n=250) through 96 weeks of treatment in ART-naive participants but was associated with increased emergence of drug resistance.<sup>5</sup> In the phase 3 NEAT001/ANRS143

trial (n=805), raltegravir plus ritonavir-boosted darunavir was non-inferior to a three-drug regimen in the overall population of treatment-naive participants.<sup>6</sup> However, the two-drug regimen was inferior to the three-drug regimen in the subgroup of participants with CD4+ counts of less than 200 cells per  $\mu$ L and did not show non-inferiority with the subgroup of participants with baseline HIV-1 RNA of more than 100 000 copies per mL. The results of these studies highlight the need for two-drug regimens to contain agents with potent antiviral activity and high barrier to resistance.

The reported efficacy, safety, and tolerability of lamivudine over the past two decades of use make it a good candidate as a two-drug regimen partner.<sup>7</sup> Week 48 results from the ANDES trial (n=145) showed that lamivudine plus ritonavir-boosted darunavir is non-inferior to a ritonavir-boosted darunavir-based three-drug regimen for achieving HIV-1 RNA of less than 50 copies per mL in treatment-naive HIV-1-infected patients.<sup>8</sup> The GARDEL study showed the non-inferior virological efficacy of open-label ritonavir-boosted lopinavir plus lamivudine

(n=214) compared with ritonavir-boosted lopinavir plus two nucleoside reverse transcriptase inhibitors (n=202) in ART-naive participants after 48 weeks, although it should be noted that 54% of participants in the three-drug regimen group were taking zidovudine.<sup>9</sup> Results from these two studies suggest that lamivudine is an effective two-drug regimen partner with an antiretroviral agent with a high barrier to resistance. However, these two-drug regimens included ritonavir-boosted protease inhibitors, which are associated with a variety of metabolic adverse reactions and drug–drug interactions, and might negate any anticipated benefit from decreased cumulative toxicity due to reduced drug exposure.<sup>10</sup>

The phase 3 clinical development of dolutegravir as a component of a three-drug regimen has provided extensive evidence that dolutegravir is a good candidate as a core agent in two-drug regimens, with up to 144 weeks of follow-up data supporting the virological efficacy, favourable tolerability profile, and high barrier to resistance.<sup>11–14</sup>

The two-drug regimen of dolutegravir plus lamivudine was evaluated in the 48-week pilot study PADDLE for the treatment of ART-naive participants.<sup>15</sup> By week 8, all 20 participants, including four with baseline HIV-1 RNA of 100 000 copies per mL or more, had achieved a viral load of less than 50 copies per mL; 18 participants maintained virological suppression at week 48,<sup>15</sup> and all 18 participants remained suppressed at week 96.<sup>16</sup> Additionally, the phase 2, single-arm ACTG A5353 study in 120 treatment-naive participants with HIV-1 RNA of less than 500 000 copies per mL treated with dolutegravir plus lamivudine showed that 90% (n=108) achieved HIV-1 RNA of less than 50 copies per mL at week 24, regardless of baseline HIV-1 RNA.<sup>17</sup> Thus, dolutegravir plus lamivudine might constitute a viable combination as a novel two-drug regimen for treatment of HIV-1 infection in ART-naive patients.

The primary objective of the GEMINI-1 and GEMINI-2 studies was to therefore evaluate the efficacy and safety of the two-drug regimen comprising dolutegravir plus lamivudine compared with the three-drug regimen of dolutegravir plus tenofovir disoproxil fumarate and emtricitabine for treatment of HIV-1 infection in ART-naive adults.

## Methods

### Study design and participants

We did two identically designed, multicentre, double-blind, randomised, non-inferiority, phase 3 trials: GEMINI-1 and GEMINI-2. Both studies were done at 192 centres in 21 countries (appendix). Study protocols were approved by national, regional, or investigational centre ethics committees and institutional review boards in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice. The study protocols for GEMINI-1 and GEMINI-2 are available online.

We recruited participants who were 18 years or older with HIV-1 infection and naive to ART (defined as  $\leq 10$  days of previous therapy with any ART). Entry criteria at study start specified screening viral loads of 1000–100 000 copies per mL but, as permitted per protocol, the upper limit was increased to 500 000 copies per mL during the study after an independent review of data from independently sponsored studies evaluating the two-drug regimen of dolutegravir plus lamivudine. We included women of reproductive potential if they were not pregnant or lactating, and were using approved contraception. We excluded individuals with pre-existing major viral resistance mutations to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, or protease inhibitors;<sup>18</sup> and active US Centers for Disease Control and Prevention stage 3 HIV disease,<sup>19</sup> except for cutaneous Kaposi's sarcoma and CD4+ cell counts of less than 200 cells per  $\mu\text{L}$ . The appendix provides further information about the exclusion criteria. We obtained written informed consent from each participant before initiation of study procedures.

### Randomisation and masking

We randomly assigned participants (1:1) to receive a two-drug regimen of dolutegravir plus lamivudine or a three-drug regimen of dolutegravir plus tenofovir disoproxil fumarate and emtricitabine. We screened and stratified participants by HIV-1 RNA ( $\leq 100\,000$  or  $>100\,000$  copies per mL) and CD4+ cell count ( $\leq 200$  or  $>200$  cells per  $\mu\text{L}$ ). Treatment assignment was done in accordance with a central randomisation schedule generated with SAS (version 9.2). We masked both participants and investigators to treatment assignment until week 96. Some sponsor personnel were unmasked at week 24 to facilitate analysis of interim results for submission to regulatory authorities. Dolutegravir was administered as single-entity tablets similar to its commercial formulation, except with a different film colour. Lamivudine tablets and tenofovir disoproxil fumarate and emtricitabine fixed-dose combination tablets were over-encapsulated to visually match each other.

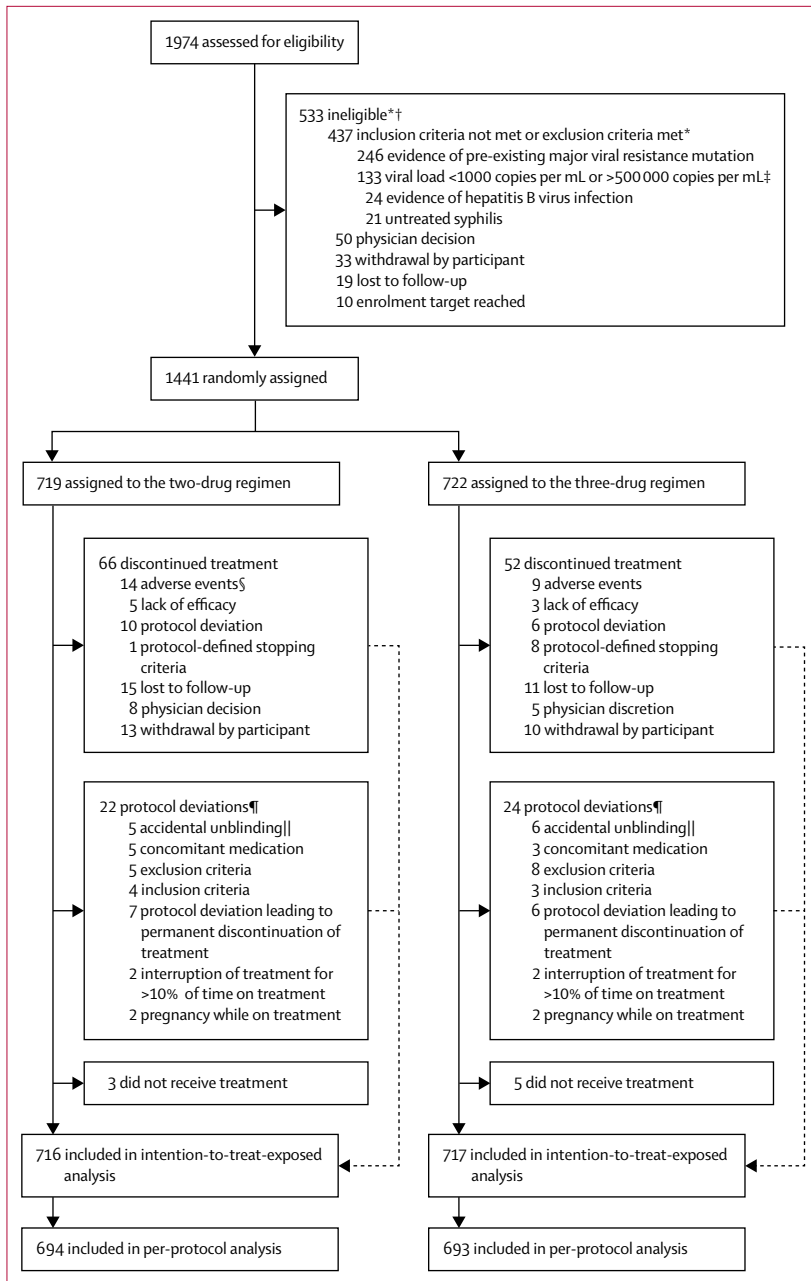
### Procedures

Participants received either a once-daily two-drug regimen of dolutegravir (50 mg) plus lamivudine (300 mg) or a once-daily three-drug regimen of dolutegravir (50 mg) plus tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg). Both drug regimens were administered orally. The study comprises a screening period of up to 35 days, a double-blind randomised phase from day 1 to week 96, and an open-label randomised phase from weeks 96 to 148. Study visits for all participants were planned at baseline and at weeks 4, 8, 12, 16, 24, 36, and 48, with additional retest visits at weeks 28 and 52 to confirm viral test results for participants with HIV-1 RNA of 50 copies per mL or

See Online for appendix

For the GEMINI-1 protocol see <https://www.viiv-clinicalstudyregister.com/study/204861#ps>

For the GEMINI-2 protocol see <https://www.viiv-clinicalstudyregister.com/study/205543#ps>



**Figure 1: Trial profile**

\*Participants could have multiple reasons for ineligibility. †Most common reasons for not meeting inclusion criteria or meeting exclusion criteria listed. All other reasons occurred in less than 1% of participants. ‡Viral load criterion was revised to allow enrolment of participants with plasma HIV-1 RNA of 1000–500 000 copies per mL on or after Nov 5, 2016. §Includes two fatal outcomes in the GEMINI-2 study. All other adverse event-related withdrawals were non-fatal. ¶Protocol deviations leading to exclusion from the per-protocol population; participants could have had more than one reason. ||Accidental unblinding resulted from broken or altered capsules (n=10) and one pharmacist who inadvertently received an unblinded drug report. The study sponsor remained blinded throughout the study.

more at weeks 24 or 48, respectively. Subsequent study visits every 12 weeks are planned through week 148. This report describes results of the primary analysis at week 48 that was done after the last participant had their week 48 viral load assessment, including a week 52 retest as

appropriate, in accordance with the US Food and Drug Administration (FDA) Snapshot algorithm.<sup>20</sup>

Participants met confirmed virological withdrawal criteria if a second and consecutive HIV-1 RNA value met any of the following definitions: decrease from baseline in HIV-1 RNA of less than one log<sub>10</sub> copies per mL, unless HIV-1 RNA of less than 200 copies per mL, by week 12; confirmed plasma HIV-1 RNA of 200 copies per mL or more at or after week 24; or confirmed rebound (HIV-1 RNA ≥200 copies per mL after confirmed consecutive HIV-1 RNA <200 copies per mL). These participants were discontinued from the study, and a plasma sample from the initial suspected viral load sample was used for genotypic and phenotypic resistance tests. The following prespecified resistance mutations of integrase strand transfer inhibitor were included for determining the emergence of resistance mutations: His51Tyr, Thr66Ala/Ile/Lys, Leu74Met, Glu92Gln/Val/Gly, Gln95Lys, Thr97Ala, Gly118Arg, Phe121Tyr, Glu138Ala/Lys/Asp, Gly140Ala/Cys/Ser, Tyr143Cys/His/Arg/Lys/Ser/Gly/Ala, Pro145Ser, Gln146Pro, Ser147Gly, Gln148His/Lys/Arg, Val151Ile/Leu/Ala, Ser153Phe/Tyr, Asn155His/Ser/Thr, Glu157Gln, Gly163Arg/Lys, Ser230Arg, Arg263Lys, Leu68Val/Ile, Leu74Ile, Glu138Thr, and Gly193Glu. We used the most recent International Antiviral Society–USA guidelines available at the time of the database lock to determine major resistance mutations to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.<sup>18</sup>

In addition to virological efficacy, we assessed adverse events, concomitant medications, and symptom-directed physical examinations at all study visits. We collected plasma for quantitative HIV-1 RNA analysis and storage at all visits, and we used the Abbott RealTime HIV-1 assay (lower limit of quantitation, 40 copies per mL; Abbott Molecular, Des Plaines, IL, USA) for the quantitative analysis. We coded adverse events using MedDRA (version 21.0), and graded the maximum toxicity of adverse events using guidelines from the Division of AIDS (version 2.0).<sup>21</sup> Clinical chemistry values, haematology values, and lymphocyte subsets were assessed at all routine study visits. Testing for fasting lipids and glucose, urinalysis, and assessments of renal and bone biomarkers were done at baseline and weeks 24 and 48. Renal biomarkers assessed were serum and urine creatinine; ratios of urine albumin and protein, retinol-binding protein, and β-2 microglobulin to urine creatinine; serum cystatin C; and estimated glomerular filtration rate, which was calculated using creatinine or cystatin C parameters with the Chronic Kidney Disease Epidemiology Collaboration equation. Bone biomarkers assessed were bone-specific alkaline phosphatase, osteocalcin, procollagen type 1 N-terminal propeptide, and type 1 collagen cross-linked C-telopeptide. Pregnancy tests were done for women of reproductive potential at all study visits. We used the Columbia Suicide-Severity Rating Scale to monitor

suicidal ideation and behaviour at all routine study visits starting from day 1.

Changes in health-related quality of life were assessed using the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire<sup>22</sup> at baseline; weeks 4, 24, and 48; or upon study withdrawal. The EQ-5D-5L consists of two distinct scoring components: the health state utility score (potential range of -0.281 to 1) and the visual analogue scale (VAS; potential range of 0–100). Higher scores on the EQ-5D-5L indicate better health.

### Outcomes

The primary objective of each GEMINI study was to show the non-inferior virological efficacy of the two-drug regimen compared with the three-drug regimen, with the primary endpoint being the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 using the FDA Snapshot algorithm<sup>20</sup> in the intention-to-treat-exposed population. Secondary endpoints included proportion of participants with HIV-1 RNA of less than 50 copies per mL at week 24, time to achieve HIV-1 RNA of less than 50 copies per mL, absolute values and change from baseline to week 48 in CD4+ cell count, disease progression (ie, HIV-associated conditions, AIDS, or death), and incidence of emergence of mutations conferring genotypic and phenotypic resistance to dolutegravir plus lamivudine or tenofovir disoproxil fumarate and emtricitabine in participants meeting criteria for confirmed virological withdrawal. Virological efficacy was also assessed in participant subgroups defined by demographic and baseline disease characteristics, including plasma viral load, CD4+ cell count, hepatitis C virus infection, HIV-1 infection subtype, age, sex, race, and ethnicity. Safety endpoints included incidence and severity of adverse events and proportion of participants who discontinued treatment because of adverse events. Renal and bone biomarkers as well as lipids were monitored by assessing changes from baseline to weeks 24 and 48. A complete list of secondary endpoints is provided in the appendix.

### Statistical analysis

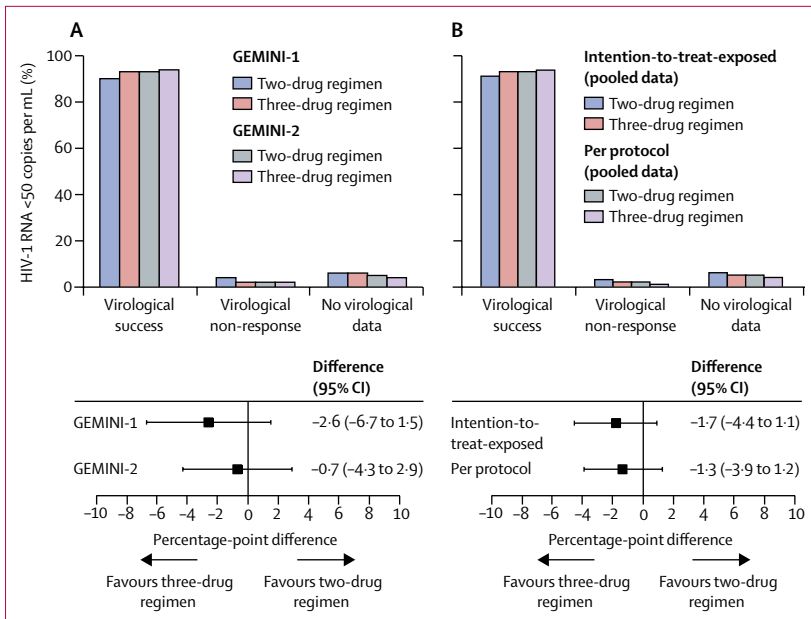
Two studies were done to comply with regulatory guidance and to show reproducibility in the efficacy and safety analyses across two fully powered studies. For each study, the targeted sample size of 347 participants per treatment group was based on 90% power, a 2.5% one-sided  $\alpha$  level, a non-inferiority margin of -10% for virological efficacy (non-inferiority concluded if the lower boundary of the two-sided 95% CI for the difference in response is greater than -10% between the two groups), and assumed true response of 87% for the two-drug regimen and 89% for the three-drug regimen. There was no predefined non-inferiority margin for the pooled analysis. All participants who received one or more doses of study medication were included in the

	Two-drug regimen group (n=716)	Three-drug regimen group (n=717)
Age (years)	32.0 (26–40)	33.0 (26–42)
<35	420 (59%)	408 (57%)
35 to <50	231 (32%)	229 (32%)
≥50	65 (9%)	80 (11%)
Sex		
Female	113 (16%)	98 (14%)
Male	603 (84%)	619 (86%)
Ethnicity		
Hispanic or Latino	215 (30%)	232 (32%)
Not Hispanic or Latino	501 (70%)	485 (68%)
Race		
White	480 (67%)	497 (69%)
African	99 (14%)	76 (11%)
Asian	71 (10%)	72 (10%)
American Indian or Alaskan Native	49 (7%)	52 (7%)
Multiracial	15 (2%)	15 (2%)
Native Hawaiian or Pacific Islander	2 (<1%)	5 (<1%)
HIV-1 RNA (log <sub>10</sub> copies per mL)	4.42 (0.66)	4.45 (0.65)
≤100 000 copies per mL	576 (80%)	564 (79%)
>100 000 copies per mL	140 (20%)	153 (21%)
CD4+ cell count (cells per $\mu$ L)	462.0 (219.2)	461.3 (213.1)
≤200 cells per $\mu$ L	63 (9%)	55 (8%)
>200 cells per $\mu$ L	653 (91%)	662 (92%)
Serum or plasma GFR from creatinine adjusted, using CKD-EPI (mL/min per 1.73 m <sup>2</sup> )	111.7 (16.6)	111.1 (16.1)
HIV infection category		
Stage 0	1 (<1%)	1 (<1%)
Stage 1	257 (36%)	263 (37%)
Stage 2	392 (55%)	393 (55%)
Stage 3	66 (9%)	60 (8%)
HIV subtype		
A	86 (12%)	78 (11%)
B	467 (65%)	488 (68%)
Other	163 (23%)	151 (21%)
Hepatitis C virus infection*	39 (5%)	49 (7%)

Data are median (IQR), n (%), or mean (SD). Analyses are pooled from the GEMINI-1 and GEMINI-2 studies. CKD-GFR=glomerular filtration rate. EPI=Chronic Kidney Disease Epidemiology Collaboration equation. \*No participants had positive test results for hepatitis B virus infection.

**Table 1: Demographics and clinical baseline characteristics in the intention-to-treat-exposed populations**

intention-to-treat-exposed population, which was used for the primary efficacy analysis. The safety population included all participants who received one or more doses of study medication and was analysed according to actual treatment received. The per-protocol population comprised all participants in the intention-to-treat-exposed population, except for those with a protocol violation that could affect assessment of antiviral activity; this population was used for sensitivity analyses.



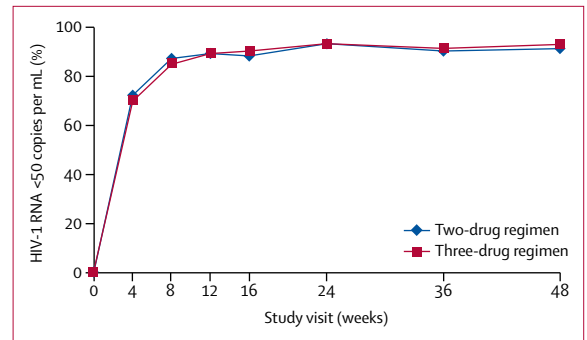
**Figure 2: Snapshot analysis of participants with HIV-1 RNA of less than 50 copies per mL at week 48** (A) Intention-to-treat-exposed populations of the separate GEMINI-1 and GEMINI-2 studies (ie, the primary endpoints). (B) Pooled analysis of the intention-to-treat-exposed and per-protocol populations. Treatment differences (bottom of panel) were adjusted on the basis of the Cochran–Mantel–Haenszel stratified analysis, adjusting for baseline plasma HIV-1 RNA ( $\leq 100\,000$  vs  $>100\,000$  copies per mL) and CD4+ cell count ( $\leq 200$  vs  $>200$  cells per  $\mu\text{L}$ ). Non-inferiority margin was  $-10\%$ . Error bars are 95% CIs.

	Two-drug regimen group (n=716)	Three-drug regimen group (n=717)
Virological response	655 (91%)	669 (93%)
Virological non-response	20 (3%)	13 (2%)
Data in window and HIV-1 RNA $\geq 50$ copies per mL	8 (1%)	5 (1%)
Discontinued for lack of efficacy	5 (1%)	2 (<1%)
Discontinued for other reason and HIV-1 RNA $\geq 50$ copies per mL	5 (1%)	5 (1%)
Change in ART	2 (<1%)	1 (<1%)
No virological data	41 (6%)	35 (5%)
Discontinued study because of adverse event or death	10 (1%)	13 (2%)
Discontinued study for other reasons	29 (4%)	22 (3%)
On study but missing data in window	2 (<1%)	0

Data are n (%). ART=antiretroviral therapy.

**Table 2: Snapshot analysis of participants with HIV-1 RNA of less than 50 copies per mL at week 48 in the pooled analysis of the intention-to-treat-exposed populations**

For the primary efficacy endpoint, the proportion of responders at week 48 was analysed using a Cochran–Mantel–Haenszel test stratified by plasma HIV-1 RNA ( $\leq 100\,000$  vs  $>100\,000$  copies per mL) and CD4+ cell count ( $\leq 200$  vs  $>200$  cells per  $\mu\text{L}$ ) at baseline. Baseline characteristics, proportion of participants who achieved



**Figure 3: Snapshot analysis of the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL by visit in the pooled analysis of the intention-to-treat-exposed populations**

a response by study visit or participant subgroup (using Snapshot algorithm), and adverse events were summarised with descriptive statistics. Protocol-defined serious adverse events included those that resulted in death, disability, incapacity, congenital anomaly, or birth defect; are life-threatening; require hospitalisation or prolongation of existing hospitalisation; are associated with liver injury and impaired liver function (ie, alanine aminotransferase  $\geq$ three times the upper limit of normal [ULN] and either total bilirubin  $\geq$ two times the ULN or international normalised ratio  $>1.5$ ); or require a medical or surgical intervention to prevent a serious adverse event. Participants who had not met confirmed virological withdrawal criteria and were ongoing in the study, or who had discontinued for reasons other than those related to treatment or lack of efficacy, were censored. Change from baseline to week 48 in CD4+ cell counts was analysed with ANCOVA on the basis of a dataset in which multiple imputations have been drawn from a multivariate normal model with a Markov chain Monte Carlo approach to impute missing observations. The statistical model was adjusted for treatment, baseline CD4+ cell count as a covariate, randomisation strata term baseline plasma HIV-1 RNA ( $\leq 100\,000$  vs  $>100\,000$  copies per mL), and baseline CD4+ cell count ( $\leq 200$  vs  $>200$  cells per  $\mu\text{L}$ ). Time-to-viral suppression was based on time of first viral load of less than 50 copies per mL estimated with non-parametric Kaplan–Meier method. We used SAS version 9.4 within a LINUX environment for all statistical analyses.

An independent data monitoring committee provided external review of efficacy and safety data, including a futility analysis when approximately half of participants in each study had completed the week 24 study visit. GEMINI-1 and GEMINI-2 are registered with ClinicalTrials.gov, numbers NCT02831673 and NCT02831764, respectively.

**Role of the funding source**

The funder of the study had a role in the study design, data collection, data analysis, data interpretation, and writing the report. All authors had full access to the data

Week	Treatment group	Gender	Baseline CD4 count (cells per $\mu$ L)	Time between SVW and CVW (day)	Viral loads at baseline, SVW, CVW, and withdrawal (copies per mL)	Resistance mutations		Fold change at baseline and CVW
						Baseline	Suspected virological withdrawal	
Week 16	Two-drug regimen	Female	212	7	124 492, 6648, 56 435, 95	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.67, 0.72; 3TC 1.13, 1.12
Week 24	Two-drug regimen	Male	284	28	50 263, 348, 206, 96	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.76, 0.7; 3TC 0.98, 0.69
Week 24	Two-drug regimen	Male	19	23	368 439, 212, 376, 362	NRTI: none; INSTI: Gly193Gly/Glu	NRTI: none; INSTI: none	DTG 0.88, 0.86; 3TC 1.02, 1.43
Week 48	Two-drug regimen	Male	414	22	37 701, 43 908, 38 457*	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.8, 0.79; 3TC 0.9, 1.74
Week 24	Three-drug regimen	Male	226	27	10 930, 1136, 809, 264	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.72, NR; TDF 1, 0.81; FTC 0.92, 0.95
Week 48	Three-drug regimen	Male	602	83	1568, 8384, 3653, 3011	NRTI: Leu70Lys/Glu; INSTI: Gly193Glu	NRTI: none; INSTI: Gly193Gly/Glu	DTG 1.05, 1.05; TDF 0.76, 0.77; FTC 1.14, 1.28
Week 24	Two-drug regimen	Male	213	27	96 277, 451, 9602, 67	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.92, 0.8; 3TC 1.16, 1.16
Week 24	Two-drug regimen	Female	529	34	17 232, 461, 251, 59	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.81, 0.87; 3TC 1.17, 1.09
Week 24	Three-drug regimen	Male	251	30	76 325, 569, 362, <50	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.68, 1.38; TDF 0.95, 0.61; FTC 1.13, 0.67
Week 24	Three-drug regimen	Male	201	28	156 701, 213, 1559, 97	NRTI: none; INSTI: none	NRTI: none; INSTI: none	DTG 0.9, NR; TDF 1.04, 1.07; FTC 0.97, 1.01

Data that were NR was because of assay failure. SVW=suspected virological withdrawal. CVW=confirmed virological withdrawal. NRTI=nucleoside reverse transcriptase inhibitor. INSTI=integrase strand transfer inhibitor. DTG=dolutegravir. 3TC=lamivudine. NR=not reported. TDF=tenofovir disoproxil fumarate. FTC=emtricitabine. \*Participant met confirmed virological withdrawal at the withdrawal visit; no subsequent visit occurred.

**Table 3: Confirmed virological withdrawal through week 48**

and are responsible for the accuracy and completeness of this report. The corresponding author had final responsibility for the decision to submit for publication.

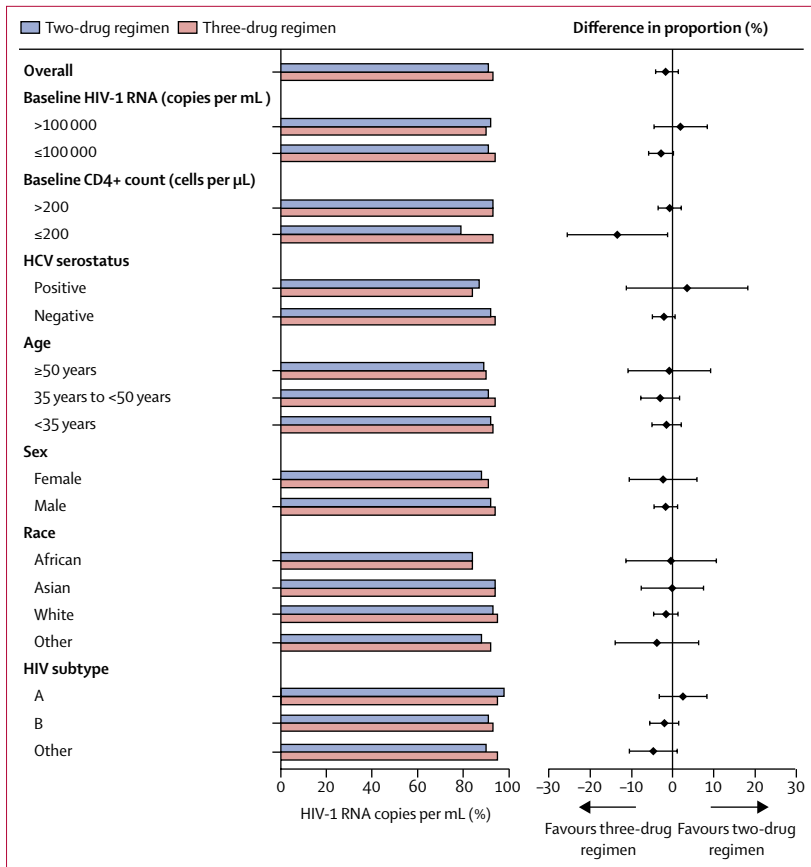
## Results

Participant screening commenced on July 21, 2016, for GEMINI-1, and July 18, 2016, for GEMINI-2. Screening ended on March 28, 2017, for GEMINI-1 and March 31, 2017, for GEMINI-2. The data cutoff date used for the week 48 database freeze was May 22, 2018. Of the 1974 participants screened across both studies, 1441 met eligibility criteria and were randomly assigned to receive either the two-drug regimen (n=719) or three-drug regimen (n=722); 533 were not eligible (figure 1). Eight participants randomly assigned to the two-drug regimen (n=3) or three-drug regimen (n=5) groups did not receive study treatment, leading to 716 participants in the two-drug regimen group and 717 in the three-drug regimen group being included in the primary efficacy and safety analysis (GEMINI-1: 356 participants for the two-drug regimen and 358 for the three-drug regimen; GEMINI-2: 360 for the two drug-regimen and 359 for the three-drug regimen). Key demographic and baseline clinical characteristics were well balanced between the treatment groups in the intention-to-treat-exposed population pooled across both trials (n=1433; table 1; appendix p 4). Participants had a median age of 33 years (range 18–72), with most participants being younger than 50 years (1288 [90%] of 1433), men (1222 [85%]), and white (977 [68%]). Baseline HIV-1 RNA of more than 100 000 copies per mL occurred in 293 (20%) and

CD4+ cell count of 200 cells per  $\mu$ L or less occurred in 118 (8%) participants.

In the pooled study population, the numbers of participants who discontinued treatment at the time of the database lock at week 48 were similar between the two-drug regimen (66 [9%] of 719) and three-drug regimen (52 [7%] of 722) groups (figure 1). The most common reasons for study withdrawal were participant lost to follow-up (26 [2%] of 1433), discontinuation due to adverse events (23 [2%]), and withdrawn consent (23 [2%]). Withdrawals due to protocol deviations occurred for ten (1%) participants in the two-drug regimen group compared with six (<1%) in the three-drug regimen group; the most common reasons were due to non-compliance with protocol procedures (eight [<1%] of 1433). Four participants (two in each treatment group) became pregnant during the study.

In the GEMINI-1 intention-to-treat-exposed population, 320 (90%) of 356 participants in the two-drug regimen group and 332 (93%) of 358 in the three-drug regimen group achieved HIV-1 RNA of less than 50 copies per mL at week 48 (adjusted treatment difference  $-2.6\%$ , 95% CI  $-6.7$  to  $1.5$ ; figure 2A); the corresponding number of participants in GEMINI-2 were 335 (93%) of 360 in the two-drug regimen group and 337 (94%) of 359 in the three-drug regimen group (adjusted treatment difference  $-0.7\%$ , 95% CI  $-4.3$  to  $2.9$ ; figure 2A). Each study met its primary efficacy endpoint of non-inferior virological efficacy at week 48, as the lower boundary of the two-sided 95% CI for the difference was greater than  $-10\%$ . In the pooled analysis, 655 (91%) of 716 participants in the



**Figure 4:** Snapshot analysis of the proportion of participants with HIV-1 RNA of less than 50 copies per mL in subgroups of the pooled analysis of the intention-to-treat-exposed populations at week 48. Data are unadjusted for treatment group differences, except for the overall data that show the adjusted treatment difference. Error bars are 95% CIs. HCV=hepatitis C virus.

	Two-drug regimen (n=63)	Three-drug regimen (n=55)
HIV-1 RNA ≥50 copies per mL*	3 (5%)	1 (2%)
Discontinued because of non-treatment-related adverse event	2 (3%)	0
Protocol violations	2 (3%)	0
Lost to follow-up	2 (3%)	1 (2%)
Confirmed virological withdrawal	1 (2%)	0
Withdrew consent	1 (2%)	1 (2%)
Withdrew to start HCV treatment	1 (2%)	0
Unplanned change in ART	1 (2%)	0
Investigator discretion	0	1 (2%)

Data are n (%). HCV=hepatitis C virus. ART=antiretroviral therapy. \*Two of three participants in the two-drug regimen group and one participant in the three-drug regimen group resuppressed.

**Table 4: Reasons for Snapshot non-response in the subgroup of participants with baseline CD4+ cell count of 200 cells per μL or less**

two-drug regimen group and 669 (93%) of 717 in the three-drug regimen group had HIV-1 RNA of less than 50 copies per mL at week 48 (adjusted treatment

difference -1.7%, 95% CI -4.4 to 1.1; figure 2B). Virological non-response (defined by Snapshot analysis as ≥50 copies per mL at week 48) was observed in 20 (3%) of 716 participants in the two-drug regimen group versus 13 (2%) of 717 in the three-drug regimen group (table 2).

In the GEMINI-1 per-protocol population, 317 (92%) of 345 participants in the two-drug regimen group and 325 (94%) of 346 in the three-drug regimen group achieved HIV-1 RNA of less than 50 copies per mL at week 48 (adjusted treatment difference -1.9%, 95% CI -5.7 to 1.9); the corresponding number of participants in GEMINI-2 was 328 (94%) of 349 in the two-drug regimen group and 329 (95%) of 347 in the three-drug regimen group (adjusted treatment difference -0.7%, 95% CI -4.1 to 2.7). In the pooled per-protocol population, 645 (93%) of 694 participants in the two-drug regimen group versus 654 (94%) of 693 in the three-drug regimen group achieved HIV-1 RNA of less than 50 copies per mL (adjusted treatment difference -1.3%, 95% CI -3.9 to 1.2; figure 2B). The proportion of participants who achieved a response was high and similar between both treatment groups at all visits, and most participants achieved a plasma HIV-1 RNA of less than 50 copies per mL by week 4 (figure 3). A rapid decline of viral load was observed (appendix p 6), with a median time to viral suppression of 29.0 days in both treatment groups (IQR 29.0–55.0 for the two-drug regimen group and 29.0–57.0 days for the three-drug regimen group).

Ten (<1%) participants overall (six in the two-drug regimen group and four in the three-drug regimen group) met prespecified criteria for confirmed virological withdrawal through week 48. Genotypic testing of the HIV-1 reverse transcriptase, protease-reverse transcriptase, and integrase (*IN*) genes was successful for baseline and virological withdrawal samples from all ten participants, except for one *IN* genotype assay failure for one participant in the three-drug regimen group. For those with successfully amplified and sequenced samples, none had emergence of mutations conferring resistance to integrase strand transfer inhibitors or nucleoside reverse transcriptase inhibitors (table 3). All ten participants meeting confirmed virological withdrawal criteria were classified as virological rebounds.

Response rates analysed by demographic and baseline characteristics were generally consistent with the overall response (figure 4). In the pooled analysis of the intention-to-treat-exposed population, 129 (92%) of 140 participants in the two-drug regimen group with baseline HIV-1 RNA of more than 100 000 copies per mL achieved virological success compared with 138 (90%) of 153 in the three-drug regimen group; 2% of participants in both groups had baseline viral loads of 500 000 copies per mL or more (after screening viral load <500 000 copies per mL). Efficacy outcomes in these participants were similar in the two-drug regimen group (11 [85%] of 13) and three-drug regimen group (12 [80%] of 15). In participants with baseline HIV-1 RNA of 100 000 copies



per mL or less, 526 [91%] of 576 in the two-drug regimen and 531 [94%] of 564 in the three-drug regimen achieved virological success. In participants with CD4+ counts of more than 200 cells per  $\mu\text{L}$ , 605 (93%) of 653 in the two-drug regimen and 618 (93%) of 662 in the three-drug regimen achieved virological success. In participants with CD4+ counts of 200 cells per  $\mu\text{L}$  or less, 50 (79%) of 63 participants in the two-drug regimen group achieved HIV-1 RNA values of less than 50 copies per mL compared with 51 (93%) of 55 in the three-drug regimen group. Most reasons for Snapshot failures (ie, participants who did not achieve HIV-1 RNA <50 copies per mL at week 48) for this subgroup were unrelated to efficacy or treatment failure (table 4).

The most commonly reported adverse events across both treatment groups were headache, diarrhoea, nasopharyngitis, upper respiratory tract infection, nausea, and insomnia (table 5). Numerically, fewer participants reported drug-related adverse events in the two-drug regimen group than in the three-drug regimen group (126 [18%] of 716 vs 169 [24%] of 717). Differences in drug-related adverse events were primarily explained by lower frequencies of drug-related grade 1 nausea in the two-drug regimen group than in the three-drug regimen group (12 [2%] vs 33 [5%]). In the safety analysis, similar numbers of participants in the two-drug regimen group (15 [2%]) and three-drug regimen group (16 [2%]) had adverse events that led to permanent discontinuation of study drug. Similar proportions of serious adverse events were observed in the two-drug regimen group (50 [7%]) and three-drug regimen group (55 [8%]), with no single disorder reported as a serious adverse event in more than 1% of participants in either group. Two deaths were reported, both in the two-drug regimen group of GEMINI-2: one due to Burkitt's lymphoma and the other due to acute myocardial infarction with possible association with drug abuse. Neither death was considered by the investigators to be related to the study medication. The adverse event profile was similar between studies (appendix p 5).

Overall adverse events related to suicidal ideation and behaviour occurred in 29 participants: 17 (2%) in the two-drug regimen group (nine had suicidal ideation, three had suicidal behaviour, and five attempted suicide) and 12 (2%) in the three-drug regimen group (nine had suicidal ideation, one had suicidal behaviour, one attempted suicide, and one had intentional drug overdose). 13 (76%) of 17 in the two-drug regimen group and seven (58%) of 12 in the three-drug regimen group had a previous history of depression or suicidal behaviour or other psychiatric events.

Two pregnancies resulted in spontaneous abortions at 7 weeks and 4–5 weeks of gestation, and two resulted in elective abortions both at 6 weeks of gestation. No apparent congenital abnormalities were detected.

Changes in renal biomarkers were generally favourable in the two-drug regimen group compared

	Two-drug regimen (n=716)	Three-drug regimen (n=717)
Any adverse event	543 (76%)	579 (81%)
Adverse events occurring in $\geq 4\%$ of participants in either group		
Headache	71 (10%)	75 (10%)
Diarrhoea	68 (9%)	77 (11%)
Nasopharyngitis	55 (8%)	78 (11%)
Upper respiratory tract infection	56 (8%)	44 (6%)
Pharyngitis	36 (5%)	32 (4%)
Back pain	35 (5%)	31 (4%)
Nausea	27 (4%)	53 (7%)
Insomnia	27 (4%)	45 (6%)
Syphilis	27 (4%)	27 (4%)
Bronchitis	28 (4%)	21 (3%)
Influenza	22 (3%)	28 (4%)
Arthralgia	15 (2%)	26 (4%)
Fatal adverse events (grade 5)	2 (<1%)*	0
Drug-related adverse events	126 (18%)	169 (24%)
Grade 2–5†	42 (6%)	47 (7%)
Serious adverse events	50 (7%)	55 (8%)
Drug-related‡	4 (1%)	4 (1%)
Adverse events leading to permanent discontinuation of treatment or withdrawal from study§	15 (2%)	16 (2%)
Drug-related	6 (1%)	9 (1%)

Data are n (%). \*Includes one event due to Burkitt's lymphoma and the other due to acute myocardial infarction with possible association with drug abuse; neither was considered by the investigators to be related to study medication; both participants had HIV-1 RNA of less than 40 copies per mL at last study visit. †The only grades 2–5 drug-related adverse event occurring in 1% or more in either group was headache (n=8 [1%] in each group). ‡Serious adverse events were cholelithiasis, hepatotoxicity, psychotic disorder, rhabdomyolysis, substance-induced psychotic disorder, suicide attempt (n=1 for each), and suicidal ideation (n=2). §Two-drug regimen group (more than one reason can be listed per patient): acute hepatitis C virus infection (n=1), hepatitis A virus infection (n=2), tuberculosis (n=2), psychotic disorder (n=2), sleep disorder or insomnia (n=2), suicide attempt or suicidal ideation (n=2), Burkitt's lymphoma (n=1), acute myocardial infarction (n=1), anxiety (n=1), depression (n=1), hepatitis from alcohol abuse (n=1), hepatotoxicity (n=1), and renal impairment (n=1); three-drug regimen group (more than one reason can be listed per patient): creatinine renal clearance or glomerular filtration rate decreased (n=2), hepatitis C virus infection (n=1), hepatitis A virus infection (n=1), renal impairment (n=2), suicide attempt or suicidal ideation (n=2), alcoholic psychosis (n=1), anxiety (n=1), B-cell lymphoma (n=1), depression (n=1), drug-induced liver injury (n=1), illicit drug overdose (n=1), hepatitis from alcohol abuse (n=1), non-Hodgkin lymphoma (n=1), osteoporosis (n=1), and rhabdomyolysis (n=1).

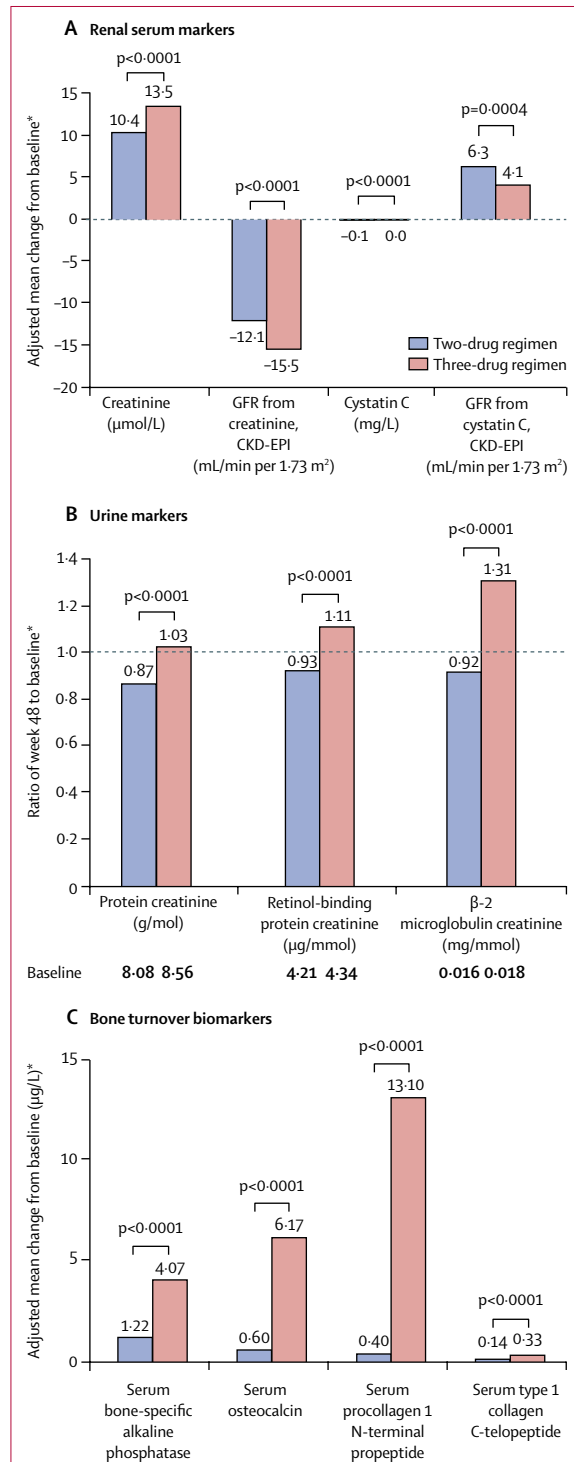
**Table 5: Reported adverse events (pooled GEMINI-1 and GEMINI-2 analysis)**

with the three-drug regimen group (figures 5A, 5B). Increases in bone turnover biomarkers were observed in both treatment groups at week 48 (figure 5C); the magnitudes of the increases were smaller in the two-drug regimen group than in the three-drug regimen group. Changes in lipid parameters at week 48 varied between parameters and treatment groups (figure 6). Total cholesterol, LDL cholesterol, and total triglycerides increased from baseline to week 48 in the two-drug regimen group and decreased in the three-drug regimen

group, with the differences between groups being significant for each. A significantly greater increase was observed in HDL cholesterol in the two-drug regimen group than in the three-drug regimen group. Small decreases in total cholesterol-to-HDL cholesterol ratio were observed, but the decrease in the three-drug

regimen group was significantly greater than in the two-drug regimen group.

Mean baseline scores were high in both treatment groups on the EQ-5D-5L health state utility scale (0.950 [SD 0.076] for 716 participants in the two-drug regimen group; 0.940 [0.105] for 716 in the three-drug regimen group) and VAS (86.5 SD [12.1] for 715 in the two-drug regimen group; 85.1 [13.4] for 714 in the three-drug regimen group). At week 48, mean scores remained high for the health state utility scale (0.963 [SD 0.078] for 712 participants in the two-drug regimen group; 0.961 [0.076] for 710 in the three-drug regimen group) and VAS (90.2 [SD 10.0] for 712 in the two-drug regimen group; 89.3 [10.5] for 710 in the three-drug regimen group). For both scales, the between-group differences in the adjusted mean change from baseline to week 48 were not significant (health state utility score  $-0.0008$  [95% CI  $-0.0078$  to  $0.0063$ ];  $p=0.834$ ; and VAS score  $0.4$  [95% CI  $-0.6$  to  $1.3$ ];  $p=0.432$ ).



## Discussion

The GEMINI studies showed non-inferior virological efficacy of a two-drug regimen versus a recommended three-drug regimen in the first fully powered, randomised, controlled studies of dolutegravir plus lamivudine in an ART-naive study population. Both regimens were associated with low numbers of confirmed virological withdrawal through week 48; and in participants who met this criterion, neither regimen was associated with emergence of any mutations conferring resistance to integrase strand transfer inhibitors or nucleoside reverse transcriptase inhibitors. Virological suppression rates at week 48 as shown in the GEMINI studies are similar to those observed in other dolutegravir combination studies in ART-naive participants at the week 48 timepoint.<sup>11,12,14</sup> The rapid reduction in viral load, as supported by the percentage of participants who achieved viral suppression at week 4 (72% in the two-drug regimen and 70% in the three-drug regimen) and the rapid median time to viral suppression (29 days), demonstrated that the initial antiviral potency of dolutegravir plus lamivudine is similar to that of the three-drug regimen and consistent with previous reports of dolutegravir plus abacavir and lamivudine from the SINGLE study.<sup>23</sup>

**Figure 5: Profiles of renal and bone biomarkers**

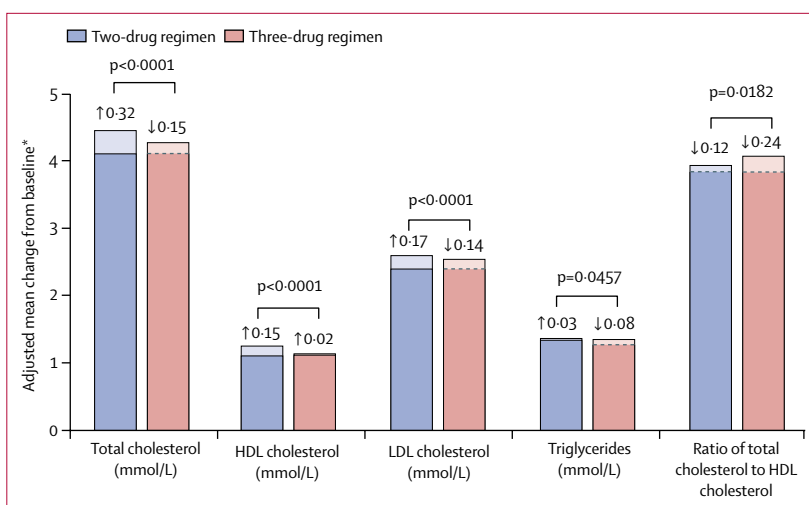
(A) Adjusted mean change from baseline in serum or plasma renal biomarkers at week 48. (B) Week 48 to baseline ratios of urine renal biomarkers. (C) Adjusted mean change from baseline in bone turnover biomarkers at week 48. All values are calculated from multiple imputation data (missing at random). CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation. GFR=glomerular filtration rate. \*Mean change from baseline adjusted for study, treatment, baseline viral load, baseline CD4+ cell count, age, sex, race, and baseline biomarker value. For renal biomarkers, mean change from baseline was also adjusted for presence of diabetes and presence of hypertension. For bone biomarkers, mean change was also adjusted for body-mass index, smoking status, and current vitamin D use.

The GEMINI studies confirm key virological findings of the ACTG A5353 and PADDLE studies.<sup>15,17</sup> Additionally, the A5353 study showed no difference between the low ( $\leq 100\,000$  copies per mL) and high ( $> 100\,000$  copies per mL) baseline viral load strata in participants with plasma HIV-1 RNA of less than 50 copies per mL using the US FDA Snapshot algorithm at week 24 (90% for the low viral load strata and 89% for the high viral load strata).<sup>17</sup> Similarly, comparable virological efficacy was observed in subgroups stratified by baseline viral load ( $\leq 100\,000$  or  $> 100\,000$  copies per mL) in the present studies. These results indicate that the two-drug regimen can suppress even high viral loads in ART-naïve patients. Although the study aimed to enrol individuals with HIV-1 RNA of less than 500 000 copies per mL, 28 (2%) of 1433 participants had a baseline viral load of 500 000 or more copies per mL (after screening viral load  $< 500\,000$  copies per mL).

A lower Snapshot response in the two-drug regimen group than in the three-drug regimen group was observed in the subgroup of participants with baseline CD4+ count of 200 cells per  $\mu\text{L}$  or less. Most reasons for Snapshot failures (participants who did not have HIV-1 RNA  $< 50$  copies per mL at week 48) for this subgroup were unrelated to efficacy or treatment failure, and, as such, the lower response in the participants with lower baseline CD4+ cell counts in the two-drug regimen group should be interpreted with caution.

One perceived risk of treatment with a two-drug regimen compared with a three-drug regimen is greater frequency of drug resistance development in the case of virological failure. In the ACTG A5353 study, three (2%) of 120 participants treated with dolutegravir plus lamivudine had virological failure, and emergence of mutations conferring resistance to treatment was detected in two of the participants (Val106Ile in one patient and Met184Val and Arg263Arg/Leu in the other).<sup>17</sup> However, in the GEMINI studies, ten (1%) of 1433 participants had confirmed virological withdrawal criteria and underwent resistance testing. No emergence of mutations conferring resistance to integrase strand transfer inhibitors or nucleoside reverse transcriptase inhibitors was detected for any participants meeting confirmed virological withdrawal criteria, suggesting there is no increased risk of resistance after virological failure on dolutegravir plus lamivudine compared with a three-drug regimen containing dolutegravir.

Overall safety and tolerability profiles at week 48 were similar between the two regimens, which was expected as dolutegravir was used as the core agent in both regimens. Moreover, the adverse event profile of the two-drug regimen was similar to the recognised profiles of dolutegravir and lamivudine, components of standard-of-care regimens,<sup>24,25</sup> with no unexpected tolerability or safety findings. Numerically, fewer drug-related adverse events were observed in the two-drug regimen group than in the three-drug regimen group, which was primarily explained by lower frequencies of grade 1 nausea. Changes in renal



**Figure 6:** Mean change from baseline in serum or plasma lipids (last observation carried forward) at week 48

\*The adjusted mean is the estimated mean change from baseline in each fasting lipid at week 48 in each group calculated from an ANCOVA model, adjusting for the following covariates or factors: study treatment, baseline plasma HIV-1 RNA, baseline CD4+ cell count, age, and baseline fasting lipids. Multiple imputed data set (missing at random). Absolute values are based on summaries. Baseline values are represented by the non-shaded opaque colours, with changes at week 48 represented by shaded areas. Increases are denoted by an up arrow and decreases by a down arrow.

and bone biomarkers favoured the two-drug regimen and might be attributed to the inclusion of tenofovir disoproxil fumarate in the three-drug regimen group, which is associated with impaired renal function and bone health.<sup>26,27</sup> Observed lipid changes in the three-drug regimen group, particularly triglycerides and total cholesterol-to-HDL cholesterol ratio, were also consistent with the known effect of tenofovir disoproxil fumarate on cholesterol<sup>28</sup> and were significantly reduced compared with the two-drug regimen group.

This study has several limitations. Enrolment of predominantly men younger than 50 years as participants in a global study suggests that the study demographics do not fully represent the worldwide population living with HIV-1 infection. The analysis of female participants was limited to those using contraceptives and who were not pregnant when initiating treatment. The exclusion criterion of HIV-1 RNA of more than 500 000 copies per mL did not allow any consideration for clinical use of dolutegravir plus lamivudine in treatment-naïve individuals with very high viral loads. The study excluded individuals with evidence of hepatitis B virus infection and resistance mutations. It should be noted that 533 (27%) of those screened were not eligible for the study, and the most common reasons for ineligibility were evidence of pre-existing major viral resistance mutations and baseline viral load of less than 1000 copies per mL or more than 500 000 copies per mL. Use of dolutegravir as the core agent in both regimens might constitute another limitation, because dolutegravir could limit the extent to which these safety conclusions can be extrapolated to comparisons with other regimens. Lastly, follow-up

beyond 48 weeks will be required to show the durability of dolutegravir plus lamivudine; for this reason, the study is currently ongoing with planned 96-week and 144-week analyses forthcoming.

Of note, our study shows that, as in the GARDEL<sup>9</sup> and ANDES<sup>8</sup> studies, inclusion of a nucleoside reverse transcriptase inhibitor in a two-drug regimen supported by a potent drug with high genetic barrier seems to be crucial for a successful outcome.

Combined with earlier evidence, including comparisons with other agents evaluated in two-drug regimens, these data suggest that the two-drug regimen of dolutegravir plus lamivudine provides high antiviral potency with a high barrier to resistance and favourable safety and tolerability profiles. The GEMINI studies provide strong data supporting dolutegravir plus lamivudine as an effective, well tolerated option for treatment of patients with HIV-1 infection.

#### Contributors

PC, JS, ART, KP, BW, MG, MA, and KS participated in the conceptualisation of the studies. JS, CM, AC, MU, and ART curated data. JS, CM, AC, MU, ART, KP, BW, AF, MG, MA, and KS were involved with formal data analysis, methodology, project administration, and supervision. MG and KS were responsible for funding acquisition. PC, JSM, JRA, AA, RO, AEC, C-CH, JKR, and P-MG were study investigators and participated in the conduct of the study, including the recruitment and follow-up of participants. KP, MG, and KS were responsible for study resources. AC and MU handled software and program development and validation. All authors participated in the drafting and review of the manuscript.

#### Declaration of interests

PC has served on advisory boards for GlaxoSmithKline, ViiV Healthcare, and Merck; served as an investigator for Abbott, Avexa, Boehringer Ingelheim, Gilead Sciences, ViiV Healthcare, GlaxoSmithKline, Merck, Pfizer, Pharmasset, Richmond, Roche Laboratories, and Tibotec Therapeutics; and has received honoraria for his speaking or chairing engagements from Abbott Laboratories, Bristol-Myers Squibb, GlaxoSmithKline, Merck, and ViiV Healthcare. JSM has received lecture fees, sponsorship, and honoraria from Gilead, Stendhal, AbbVie, ViiV Healthcare, Janssen, and Merck Sharp & Dohme. JRA has received advisory fees, speaker fees, and grant support from ViiV Healthcare, Janssen, Gilead, Merck Sharp & Dohme, and Alexa. AA has served as a paid consultant to AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare; and has received research funding from Bristol-Myers Squibb, Gilead Sciences, Janssen, and ViiV Healthcare. AEC has received advisory fees from GlaxoSmithKline, ViiV Healthcare, and Gilead; conference sponsorship from Gilead and Janssen; and speaker travel fees from GlaxoSmithKline. C-CH has received honoraria for speaking at educational events or consulting for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and ViiV Healthcare; and has received research funding from Bristol-Myers Squibb, Janssen, Gilead Sciences, Merck, and ViiV Healthcare. JKR has received grant or research support from Gilead Sciences; served as a consultant or advisor to Abbott, AbbVie, Bionor, Gilead Sciences, Hexal, Janssen, Merck, and ViiV Healthcare; and was a speaker at educational events for AbbVie, Gilead Sciences, Janssen, and Merck. P-MG has received grants from Bristol-Myers Squibb and Janssen; and has received honoraria and consulting fees from Gilead Sciences, ViiV Healthcare, and AbbVie. JS, CM, MU, ART, KP, BW, MG, MA, and KS are employees of ViiV Healthcare and own stock in GlaxoSmithKline. AC and AF are employees and stockholders of GlaxoSmithKline. RO declares no competing interests.

#### Data sharing

Anonymised individual participant data and study documents can be requested for further research.

#### Acknowledgments

This study was funded by ViiV Healthcare. The authors thank the study participants; their families and caregivers; investigators and site staff who participated in the study; and the ViiV Healthcare, GlaxoSmithKline, Pharmaceutical Product Development, and Parexel study team members for participation in the study. Editorial assistance was provided under direction of the authors by Jeffrey Stumpf, Jennifer Rossi, and Sherri Damlo of MedThink SciCom and was funded by ViiV Healthcare.

#### References

- 1 US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf> (accessed Aug 16, 2018).
- 2 Pau AK, George JM. Antiretroviral therapy: current drugs. *Infect Dis Clin North Am* 2014; **28**: 371–402.
- 3 Baril JG, Angel JB, Gill MJ, et al. Dual therapy treatment strategies for the management of patients infected with HIV: a systematic review of current evidence in ARV-naive or ARV-experienced, virologically suppressed patients. *PLoS One* 2016; **11**: e0148231.
- 4 Stellbrink H-J, Le Febvre E, Carr A, et al. Once-daily maraviroc versus tenofovir/emtricitabine each combined with darunavir/ritonavir for initial HIV-1 treatment. *AIDS* 2016; **30**: 1229–38.
- 5 Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; **358**: 2095–106.
- 6 Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet* 2014; **384**: 1942–51.
- 7 Staszewski S, Loveday C, Picazo JJ, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in zidovudine-experienced patients. A randomized controlled comparison with zidovudine monotherapy. Lamivudine European HIV Working Group. *JAMA* 1996; **276**: 111–17.
- 8 Figueroa MJ, Sued OG, Gun AM, et al. DRV/R/3TC FDC for HIV-1 treatment naive patients: week 48 results of the ANDES study. Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 4–7, 2018. 489.
- 9 Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis* 2014; **14**: 572–80.
- 10 Lv Z, Chu Y, Wang Y. HIV protease inhibitors: a review of molecular selectivity and toxicity. *HIV AIDS* 2015; **7**: 95–104.
- 11 Walmsley SL, Baumgarten A, Berenguer J, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr* 2015; **70**: 515–19.
- 12 Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet* 2014; **383**: 2222–31.
- 13 Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. *Lancet HIV* 2017; **4**: e536–46.
- 14 Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2013; **13**: 927–35.
- 15 Cahn P, Rólón MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir Lamivudine) study. *J Int AIDS Soc* 2017; **20**: 21678.

- 16 Figueroa MI, Rólon MJ, Patterson P, Gun A, Cahn P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naïve patients: 96 week results of the PADDLE trial. The 9th International AIDS Society Conference on HIV Science; Paris, France; July 23–26, 2017. MOPEB0287.
- 17 Taiwo BO, Zheng L, Stefanescu A, et al. ACTG A5353: a pilot study of dolutegravir plus lamivudine for initial treatment of human immunodeficiency virus-1 (HIV-1)-infected participants with HIV-1 RNA <500000 copies/mL. *Clin Infect Dis* 2018; **66**: 1689–97.
- 18 Wensing AM, Calvez V, Günthard HF, et al. 2017 update of the drug resistance mutations in HIV-1. *Top Antivir Med* 2017; **24**: 132–33.
- 19 US Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Recomm Rep* 2014; **63**: 1–10.
- 20 US Food and Drug Administration. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. Guidance for industry. 2015. <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf> (accessed Oct 8, 2017).
- 21 US National Institute of Allergy and Infectious Diseases. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, version 2.0. 2014. [http://rsc.tech-res.com/docs/default-source/safety/daids\\_ae\\_grading\\_table\\_v2\\_nov2014.pdf?sfvrsn=8](http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8) (accessed Jan 9, 2017).
- 22 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**: 1727–36.
- 23 Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369**: 1807–18.
- 24 Tivicay (package insert). Research Triangle Park, NC: ViiV Healthcare, 2018.
- 25 Epivir (package insert). Research Triangle Park, NC: ViiV Healthcare, 2018.
- 26 Mulligan K, Glidden DV, Anderson PL, et al. Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2015; **61**: 572–80.
- 27 Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010; **51**: 496–505.
- 28 Santos JR, Saumoy M, Curran A, et al. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. *Clin Infect Dis* 2015; **61**: 403–08.