Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial

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Summary

Background All recent treatment guidelines recommend integrase strand transfer inhibitors (INSTIs) as components of initial HIV therapy. Bictegravir, a novel, once-daily, unboosted INSTI, showed potent activity in a 10 day monotherapy study and has a high in-vitro resistance barrier. On the basis of these results, we did a phase 2 trial comparing bictegravir with dolutegravir.

Methods In this randomised, double-blind, phase 2 trial, we recruited previously untreated adults (aged ≥18 years) with HIV-1 infections from 22 outpatient centres in the USA. Eligible patients had HIV-1 RNA concentrations of at least 1000 copies per mL, CD4 counts of at least 200 cells per μL, estimated glomerular filtration rates of at least 70 mL per min, and HIV-1 genotypes showing sensitivity to emtricitabine and tenofovir. We excluded patients if they were hepatitis B-co-infected or hepatitis C-co-infected, had new AIDS-defining conditions within 30 days of screening, or were pregnant. We randomly allocated participants (2:1) to receive oral once-daily 75 mg bictegravir or 50 mg dolutegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide for 48 weeks. We randomly allocated participants via an interactive web system, stratified by HIV-1 RNA concentration. Investigators, patients, study staff giving treatment, collecting data, and assessing outcomes, and the funder were masked to treatment group. The primary outcome was the proportion of participants with plasma HIV-1 RNA concentrations of less than 50 copies per mL at week 24 according to the US Food and Drug Administration-defined snapshot algorithm. We included all participants receiving one dose of study drug in analyses. This trial is registered with ClinicalTrials.gov, number NCT02397694.

Findings Between March 23, 2015, and May 21, 2015, we screened 125 patients, randomly allocating and giving study drug to 98 (65 received bictegravir plus emtricitabine and tenofovir alafenamide and 33 received dolutegravir plus emtricitabine and tenofovir alafenamide). At week 24, 63 (96·9%) of 65 in the bictegravir group had HIV-1 RNA loads of less than 50 copies per mL compared with 31 (93·9%) of 33 in the dolutegravir group (weighted difference 2·9%, 95% CI −8·5 to 14·2; p=0·50). Treatment-emergent adverse events were reported by 55 (85%) of 65 participants in the bictegravir plus emtricitabine and tenofovir alafenamide group versus 22 (67%) of 33 in the dolutegravir plus emtricitabine and tenofovir alafenamide group. The most common adverse events were diarrhoea (eight [12%] of 65 *vs* four [12%] of 33) and nausea (five [8%] of 65 *vs* four [12%] of 33). One participant taking bictegravir plus emtricitabine and tenofovir alafenamide discontinued because of a drug-related adverse event (urticaria) after week 24. No treatment-related serious adverse events or deaths occurred.

Interpretation Bictegravir plus emtricitabine and tenofovir alafenamide and dolutegravir plus emtricitabine and tenofovir alafenamide both showed high efficacy up to 24 weeks. Both treatments were well tolerated. Administration of bictegravir, a novel, potent, once-daily INSTI designed to improve on existing INSTI options with the backbone of emtricitabine and tenofovir alafenamide, might provide an advantage to patients.

Funding Gilead Sciences.

Lancet HIV 2017

Published Online
February 14, 2017
http://dx.doi.org/10.1016/S2352-3018(17)30016-4

See Online/Comment
http://dx.doi.org/10.1016/S2352-3018(17)30017-6

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Introduction

Integrase strand transfer inhibitors (INSTIs) are included as part of initial HIV-1 therapy in most treatment guidelines.[1–3] Favourable characteristics of INSTIs include high antiviral potency and, compared with protease inhibitors and some non-nucleoside reverse transcriptase inhibitors, an improved safety and tolerability profile. Several clinical trials comparing INSTIs with non-INSTIs have shown better outcomes for INSTIs than for other classes, with high virological suppression and infrequent discontinuation because of adverse events.[4–8]

Bictegravir (formerly GS-9883) is a novel, potent, once-daily integrase inhibitor that does not require pharmacokinetic boosting. In vitro, bictegravir maintains improved activity against most patient-derived isolates with resistance to the INSTIs raltegravir, elvitegravir, and dolutegravir.[9] In a phase 1 dose-ranging study,[10] 10 days of bictegravir monotherapy led to a more than 2 log HIV-1 RNA concentration decrease for doses of 25 mg daily or

Research in context

Evidence before this study

We searched PubMed for randomised clinical trials of dolutegravir and bictegravir in patients with HIV-1 infections, with the search terms ("dolutegravir" OR "abacavir") AND "lamivudine" AND "HIV" AND ("randomised" OR "randomized"). We limited the search to articles published in English between Jan 1, 1997, and Aug 15, 2016. No articles about bictegravir had been published at this time. The search yielded 33 articles for the other search terms; we removed 22 because they were short-term monotherapy or pharmacokinetic studies or systemic reviews or meta-analyses and selected the 11 remaining articles for further review. Findings from these studies showed non-inferiority of regimens containing dolutegravir to those containing raltegravir, superiority of regimens containing dolutegravir to those containing darunavir plus ritonavir, atazanavir plus ritonavir, or efavirenz, with regard to the proportion with suppression of HIV-1 RNA load to less than 50 copies per mL, as well as antiviral activity of dolutegravir in integrase strand transfer inhibitors (INSTI)-resistant populations. Treatment with dolutegravir was well tolerated.

Added value of this study

Bictegravir is a novel, unboosted INSTI that has potent activity and has in-vitro activity against most INSTI-resistant viruses. This study is, to our knowledge, the first clinical trial that compares bictegravir with dolutegravir, both given with the fixed-dose combination of emtricitabine and tenofovir alafenamide, and is the first study of bictegravir as part of a complete antiretroviral regimen in patients with HIV-1. This nucleoside reverse transcriptase inhibitor combination is recognised for its potency and safety advantages, particularly related to bone and renal measures; it does not require pretreatment HLA-B*5701 testing, trigger hypersensitivity reactions, or have any known association with cardiovascular events.

Implications of all the available evidence

Results from this study show rapid virological response and high efficacy of both regimens containing bictegravir or dolutegravir, supporting further studies of bictegravir with emtricitabine and tenofovir alafenamide, which is being coformulated into a single tablet. This regimen might provide a potent, novel, unboosted INSTI with a favourable in-vitro resistance profile, which can be administered once daily.

higher, with no serious adverse events or development of INSTI resistance. Viral rebound after the 10 day treatment period was delayed to day 14 in the 50 mg dose group and to day 17 in the 100 mg group. On the basis of these promising results, we did a phase 2 trial comparing bictegravir with dolutegravir, both given with a fixed-dose combination of emtricitabine and tenofovir alafenamide. This nucleoside reverse transcriptase inhibitor (NRTI) backbone is included as part of initial therapy in many treatment guidelines.[1–3] We chose dolutegravir as the most appropriate comparator in this trial of bictegravir because both are unboosted INSTIs with resistance profiles improved over raltegravir and elvitegravir.

Methods

Study design and participants

In this randomised, double-blind, phase 2 trial, we recruited patients from 22 outpatient centres in the USA. Study investigators enrolled adults (aged ≥18 years) if they had HIV-1 infections, were previously untreated with antiretroviral therapy, had HIV-1 RNA loads of at least 1000 copies per mL, had CD4 counts of at least 200 cells per μL, and had estimated glomerular filtration rates (creatinine clearance estimated with the Cockcroft-Gault method[11]) of at least 70 mL per min at their screening visit. Eligible patients had screening HIV-1 genotypes showing sensitivity to emtricitabine and tenofovir. We did not ascertain integrase genotype for screening and eligibility. We excluded patients if they were hepatitis B-co-infected or hepatitis C-co-infected, had new AIDS-defining conditions within 30 days of screening, or were pregnant. We did this study in accordance with the Declaration of Helsinki and it was approved by the US Food and Drug Administration. Institutional review boards at all sites gave ethical approval. All patients gave written informed consent.

Randomisation and masking

We randomly allocated eligible patients (2:1) to receive treatment with either bictegravir or dolutegravir (each given with a fixed-dose combination of emtricitabine and tenofovir alafenamide); this was done centrally with a third-party interactive web response system, stratified by screening HIV-1 RNA concentration (≤100 000 copies per mL, >100 000 to ≤400 000 copies per mL, or >400 000 copies per mL). Patients also received placebo tablets matching either bictegravir or dolutegravir; thus, investigators, patients, study staff giving treatment, assessing outcomes, and collecting data, and the funder were masked to treatment group. We gave emtricitabine and tenofovir alafenamide open-label.

Procedures

Patients received 75 mg bictegravir or 50 mg dolutegravir, as well as a fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide, each without regard to food, for 48 weeks. We did postbaseline study visits at week 4, week 8, week 12, week 24, week 36, and week 48, after which patients continued masked treatment with visits every 12 weeks

until treatment assignments were unmasked, which occurred after the last patient had reached the week 48 visit. We did laboratory analyses (haematology, serum chemistries, CD4 cell count, and urinalysis; Covance Laboratories, Indianapolis, IN, USA), HIV-1 RNA viral load ascertainment (TaqMan 2.0; Roche Diagnostics, Indianapolis, IN, USA), and physical examinations at all visits. We tested HIV-1 genotype (reverse transcriptase and protease) at screening (GenoSure MG; Monogram Biosciences, South San Francisco, CA, USA). Any patient with confirmed virological failure (two consecutive viral load samples of >50 copies per mL) and an HIV RNA concentration of more than 400 copies per mL at week 8 or later had a second, confirmatory sample sent for resistance analysis with PhenoSense GT, GeneSeq Integrase, and PhenoSense Integrase (Monogram Biosciences).

Outcomes

The primary outcome was the proportion of patients who had plasma HIV-1 RNA of less than 50 copies per mL at week 24, as defined by the US FDA snapshot algorithm (the proportion of patients with HIV-1 RNA less than 50 copies per mL).[12] The primary outcome was centrally assessed. Secondary outcomes were the proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at week 12 and week 48 by snapshot, the proportion with HIV-1 RNA less than 20 copies per mL at week 48 by snapshot, the proportion with plasma HIV-1 RNA less than 50 copies per mL when missing data were classified as treatment non-response, and change in $\log_{10}$ HIV-1 RNA and CD4 count from baseline, as well as safety and tolerability up to 48 weeks and pharmacokinetics (pharmacokinetic data will be reported separately).

We summarised all safety data with descriptive statistics on all data collected after the date that the study drug was first given and up to 30 days after the last dose of study drug, if the participant discontinued treatment. We coded treatment-emergent adverse events (ie, events reported after the start of dosing up to 30 days after the last dose) with the Medical Dictionary for Regulatory Activities (version 19.0).

Statistical analysis

We chose a total sample size of 75 participants (50 in the bictegravir group and 25 in the dolutegravir group). This phase 2 trial was not powered for non-inferiority, and the proposed sample size provided only a 32% power to assess non-inferiority, assuming a response of 88% for both groups and a non-inferiority margin of 0·12. Actual enrolment was 98 participants, which increased the power to assess non-inferiority to 40%. In the snapshot analysis using the full analysis set that included all participants randomly assigned and receiving at least one dose of study drug, we analysed the proportion of participants with an HIV-1 RNA concentration of less than 50 copies per mL between day 127 and day 210 (week 24 window). We also calculated the proportion of participants with an HIV-1 RNA concentration of 50 copies per mL or higher between day 127 and day 210, for those who had missing HIV-1 RNA concentration data for the week 24 analysis window, who discontinued study drug, or who changed treatment before week 24. We did the week 48 snapshot analysis in a similar manner to the week 24 analysis, but used an analysis window between day 295 and day 378.

We summarised change from baseline in CD4 cell count at week 48 by treatment group with descriptive statistics based on recorded, on-treatment data in the full analysis set. We constructed the differences in changes from baseline in CD4 cell count between treatment group and the 95% CI with an analysis of variance model, including treatment group and baseline HIV-1 RNA concentration as fixed covariates in the model. The safety population included all randomly assigned patients who received at least one dose of study drug, which was assessed by pill counts. We computed adherence to the investigational antiretroviral regimens as the number of pills taken divided by the number dispensed. We did all statistical analyses in SAS version 9.4. An independent data and safety monitoring committee reviewed the progress of the study. This trial is registered with ClinicalTrials.gov, number NCT02397694.

Role of the funding source

The funder of the study had the lead role in study design, data collection, data analysis, data interpretation, and, along with the first author, writing of the manuscript. All authors had access to the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

For the **Medical Dictionary for Regulatory Activities** see http://www.meddra.org

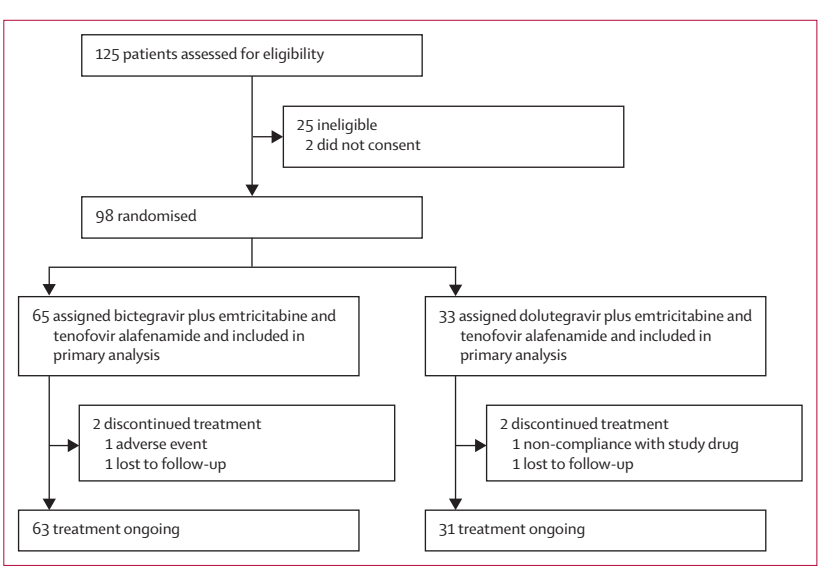

Figure 1: **Trial profile**

Results

Between March 23, 2015, and May 21, 2015, we screened 125 patients, randomly allocating and giving at least one dose of study drug to 98 (65 received bictegravir plus emtricitabine and tenofovir alafenamide and 33 received dolutegravir plus emtricitabine and tenofovir alafenamide; figure 1). Baseline characteristics were balanced between treatment groups (table 1).

	Bictegravir group (n=65)	Dolutegravir group (n=33)	Total (n=98)
Age (years)	30 (25–41)	36 (26–51)	31 (25–45)
Women	1 (2%)	3 (9%)	4 (4%)
Race			
White	38 (58%)	18 (55%)	56 (57%)
Black	24 (37%)	12 (36%)	36 (37%)
Asian	1 (2%)	2 (6%)	3 (3%)
Other	2 (3%)	1 (3%)	3 (3%)
HIV disease status			
Asymptomatic	61 (94%)	31 (94%)	92 (94%)
Symptomatic	4 (6%)	2 (6%)	6 (6%)
AIDS	0	0	0
HIV-1 RNA (log_{10} copies per mL)	4·41 4·01–4·78)	4·48 (3·94–4·82)	4·45 (3·96–4·79)
HIV-1 RNA category (copies per mL)			
≤100 000	55 (85%)	26 (79%)	81 (83%)
>100 000 to ≤400 000	6 (9%)	6 (18%)	12 (12%)
>400 000	4 (6%)	1 (3%)	5 (5%)
CD4 count (cells per μL)	441 (316–574)	455 (273–677)	444 (316–595)
CD4 count category (cells per μL)			
<200	3 (5%)	3 (9%)	6 (6%)
≥200 to <350	17 (26%)	8 (24%)	25 (26%)
≥350 to <500	20 (31%)	6 (18%)	26 (27%)
≥500	25 (38%)	16 (48%)	41 (42%)
eGFR (Cockcroft-Gault [mL/min])	130·1 (111·4–148·2)	122·2 (97·0–144·6)	125·3 (105·7–147·0)
BMI (kg/m²)	25·1 (22·5–27·8)	25·8 (23·5–27·4)	25·3 (22·7–27·8)

Data are median (IQR) or n (%). Both drugs given with emtricitabine and tenofovir alafenamide. eGFR=estimated glomerular filtration rate. BMI=body-mass index.

Table 1: **Baseline characteristics**

At week 24, according to the US FDA-defined snapshot algorithm, 97% in the bictegravir group had HIV-1 RNA less than 50 copies per mL versus 94% in the dolutegravir group (weighted difference 2·9%, 95% CI –8·5 to 14·2; p=0·50; table 2). At week 48, 97% versus 91% had HIV less than 50 copies per mL (weighted difference 6·4%, –6·0 to 18·8; p=0·17). At week 12, 61 (93·8%) of 65 versus 31 (93·9%) of 33 had HIV less than 50 copies per mL (weighted difference –1·3%, –12·9 to 10·2; p=0·79). In the analysis of virological response at week 48 with missing data classified as treatment non-response, 63 (96·9%) of 65 in the bictegravir group and 31 (93·9%) of 33 in the dolutegravir group had HIV-1 RNA less than 50 copies per mL (p=0·43). With the low-level viraemia threshold (HIV-1 RNA concentration of <20 copies per mL) according to the US FDA-defined snapshot algorithm, 59 (90·8%) of 65 in the bictegravir group and 29 (87·9%) of 33 in the dolutegravir group had viral response (weighted difference 2·8%, –11·9 to 17·5%; p=0·67).

Viral response was rapid, with a more than 2·5 log_{10} copies per mL decrease in HIV-1 RNA in both groups by week 4 (figure 2). Responses were maintained up to week 48, with no significant difference between groups at any timepoint. Up to week 48, median adherence to study treatment was 97% (IQR 94–99) in the bictegravir group and 96% (90–99) in the dolutegravir group. No participants discontinued treatment because of loss of efficacy. One participant in the dolutegravir group had HIV-1 RNA of more than 50 copies per mL at week 48 and discontinued because of non-compliance. The mean increase from baseline in CD4 count was 258 cells per mL (SD 221·7) in the bictegravir group and 192 cells per mL (242·0) in the dolutegravir group up to week 48 (difference in least squares mean 72 cells per mL, 95% CI –30 to 174; p=0·16).

Three participants met the protocol-defined criteria for HIV resistance testing: one in the bictegravir group and two in the dolutegravir group. Two of these individuals (one in

	Week 24		Week 48	
	Bictegravir (n=65)	Dolutegravir (n=33)	Bictegravir (n=65)	Dolutegravir (n=33)
HIV-1 RNA <50 copies per mL	63 (97%)	31 (94%)	63 (97%)	30 (91%)
HIV-1 RNA ≥50 copies per mL	2 (3%)	2 (6%)	1 (2%)	2 (6%)
HIV-1 RNA ≥50 copies per mL	1 (2%)	1 (3%)	0	1 (3%)
Discontinued for other reason and last HIV-1 RNA ≥50 copies per mL	1 (2%)	1 (3%)	1 (2%)	1 (3%)
Discontinued because of absence of efficacy	0	0	0	0
No virological data in time window	0	0	1 (2%)	1 (3%)
Discontinued because of adverse event or death	0	0	1 (2%)	0
Discontinued for other reason and last HIV-1 RNA <50 copies per mL	0	0	0	1 (3%)
Missing data in time window but on drug	0	0	0	0

Data are n (%). Both drugs given with emtricitabine and tenofovir alafenamide.

Table 2: **Virological outcomes at week 24 and week 48**

each treatment group) had confirmed virological rebound at week 12, with adherence of less than 90% and no drug resistance mutations. These two participants continued assigned study medication and had HIV-1 RNA less than 50 copies per mL at week 24 and week 48. The remaining participant in the dolutegravir group had virological rebound ranging from 107 copies per mL to 8010 copies per mL from week 24 to week 48, with 70% adherence. Genotypic resistance analysis revealed evolution of integrase mutation T97A at week 48 (which was not detected at baseline or a subsequent timepoint after week 48) and no resistance to emtricitabine or tenofovir; phenotypic resistance testing was not reportable because of assay failure. The participant discontinued the study at week 48 because of non-compliance.

Up to week 48, treatment-emergent adverse events were reported by 55 (85%) of 65 participants in the bictegravir group versus 22 (67%) of 33 in the dolutegravir group (table 3). The most common treatment-related adverse event was diarrhoea. Up to week 48, one patient in the bictegravir group with a medical history of atopic dermatitis discontinued assigned study medication after the week 24 visit because of urticaria, which was considered related to study drug. After discontinuing study treatment, the patient was given abacavir, lamivudine, and dolutegravir. The patient continues to have waxing and waning skin rashes requiring intermittent antihistamine and topical corticosteroid therapy. No patients in the dolutegravir group discontinued because of an adverse event. No treatment-related serious adverse events or deaths occurred.

Median changes from baseline in creatinine clearance at week 48 were decreases of 7·0 mL per min for the bictegravir group and 11·3 mL per min for the dolutegravir group. Overall incidence of postbaseline grade 2–4 laboratory abnormalities was similar in both groups (table 4). All of the creatine kinase elevations occurred in young men (age range 23–37 years) and resolved or improved without treatment interruption. None of the laboratory abnormalities were associated with adverse events or urine findings suggestive of rhabdomyolysis. Of the six participants in the bictegravir group who had grade 2–4 aspartate aminotransferase (AST) concentration increases, four had transient creatine kinase concentration elevations that resolved, one had an isolated, transient AST concentration increase, and one had incident hepatitis C infection and ongoing alcohol abuse with concurrent alanine aminotransferase concentration (ALT) elevations. One participant in the dolutegravir group had a transient grade 2–4 AST concentration elevation that subsequently normalised. Among the four participants in the bictegravir group who had grade 2–4 ALT concentration elevations, one was the individual with acute hepatitis C infection and alcohol abuse mentioned above, one had a transient elevation along with transient AST and creatine kinase concentration elevations, and two had isolated ALT concentration elevations that normalised while on therapy.

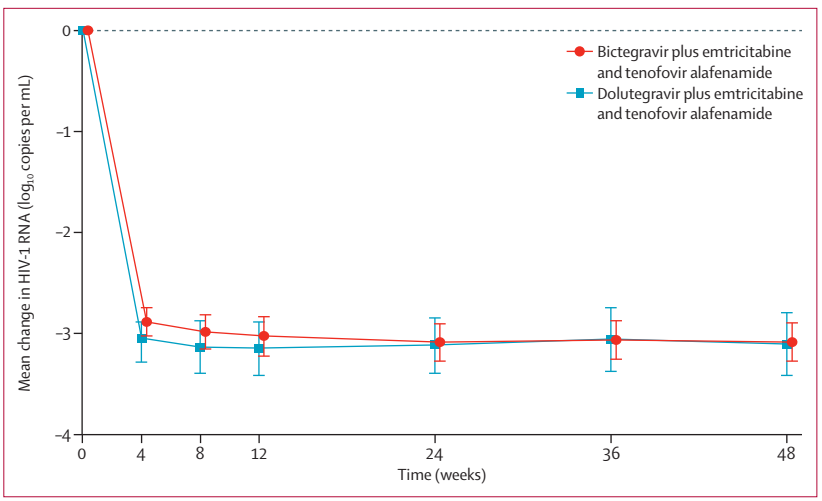

Figure 2: **Mean change from baseline in HIV-1 RNA load**
Error bars are 95% CIs.

	Bictegravir group (n=65)	Dolutegravir group (n=33)
Any adverse event	55 (85%)	22 (67%)
Diarrhoea	8 (12%)	4 (12%)
Nausea	5 (8%)	4 (12%)
Arthralgia	4 (6%)	2 (6%)
Fatigue	4 (6%)	2 (6%)
Headache	5 (8%)	1 (3%)
Chlamydial infection	4 (6%)	1 (3%)
Furuncle	3 (5%)	2 (6%)
Upper respiratory tract infection	5 (8%)	0
Back pain	4 (6%)	0
Flatulence	1 (2%)	2 (6%)
Gastroenteritis	1 (2%)	2 (6%)
Costochondritis	0	2 (6%)
Haemorrhoids	0	2 (6%)
Pruritus	0	2 (6%)

Data are n (%). Both drugs given with emtricitabine and tenofovir alafenamide.

Table 3: **Adverse events in at least 5% of patients in either group**

Discussion

Both bictegravir and dolutegravir led to high levels of viral suppression at both week 24 and week 48 when given in combination with emtricitabine and tenofovir alafenamide. Virological failure was rare, with no study discontinuations due to absence of efficacy. No INSTI or NRTI resistance occurred in the bictegravir group. A transient T97A INSTI mutation was seen in one participant in the dolutegravir group who had virological failure due to poor adherence. Although phenotypic testing on this isolate was not successful, virus with

	Bictegravir (n=64)	Dolutegravir (n=32)
Any laboratory abnormality	28 (44%)	15 (47%)
Creatine kinase concentration elevation	8 (13%)	3 (9%)
AST concentration elevation	6 (9%)	1 (3%)
Serum glucose concentration elevation (fasting hyperglycaemia)	5 (8%)	4 (13%)
ALT concentration elevation	4 (6%)	0
LDL concentration elevation	4 (6%)	3 (9%)
Amylase concentration elevation	3 (5%)	2 (6%)
Haematuria	2 (3%)	2 (6%)
Glycosuria	1 (2%)	2 (6%)

Data are n (%). Both drugs given with emtricitabine and tenofovir alafenamide. The denominators are the numbers of patients who were randomly allocated and received treatment who had at least one postbaseline laboratory assessment, excluding assessments not specified for all patients at any given visit and assessments for serum glucose concentration obtained in the non-fasted state. AST=aspartate aminotransferase. ALT=alanine aminotransferase.

Table 4: **Grade 2–4 laboratory abnormalities in at least 5% of patients in either group**

T97A mutations alone would be expected to remain phenotypically susceptible to dolutegravir.[9]

Both bictegravir and dolutegravir treatment regimens were well tolerated. A single participant in the bictegravir group discontinued therapy because of urticaria that occurred after the week 24 visit. We observed grade 2–4 creatine kinase elevations in 11 young men (eight in the bictegravir group and three in the dolutegravir group). All of these laboratory abnormalities were transient and resolved or improved without treatment interruption, and none were associated with adverse events or urine findings suggestive of rhabdomyolysis. Grade 2–4 AST and ALT concentration elevations were seen more commonly in the bictegravir plus emtricitabine and tenofovir alafenamide group than in the dolutegravir plus emtricitabine and tenofovir alafenamide group. However, with the exception of one participant with acute hepatitis C infection and ongoing alcohol abuse in the bictegravir plus emtricitabine and tenofovir alafenamide group, all elevations were transient and resolved or improved while on treatment. As the grade 2–4 laboratory abnormalities were noted in a small proportion of participants in our study with a small sample size, findings might have been attributed to chance and their clinical significance is unknown. Full demonstration of the safety of bictegravir compared with dolutegravir awaits results of fully powered phase 3 studies. No serious treatment-related adverse events and no deaths were reported in either group. Participants with low CD4 cell counts and chronic hepatitis B or C viral infection were excluded from this phase 2 study; therefore, safety and efficacy of these treatment regimens in these populations cannot be assessed.

Most HIV treatment guidelines recommend initial therapy with an INSTI plus two NRTIs.[1–3] However, individual INSTIs have different characteristics that can influence treatment choice, and available INSTIs might be less appropriate for some patients than might drugs from other antiretroviral classes. Raltegravir was approved in 2007 by the FDA and hence has the longest safety record; additionally, it has the fewest drug interactions among the INSTIs. Raltegravir must be dosed twice daily as currently formulated and is not coformulated with other antiretrovirals as a complete regimen. Elvitegravir is dosed once daily when given with a pharmacokinetic booster and is available as a complete regimen coformulated with cobicistat, emtricitabine, and either tenofovir disoproxil fumarate or tenofovir alafenamide. Since it requires boosting for once-daily dosing, it has additional drug interactions. Dolutegravir is dosed once-daily in most circumstances, is available coformulated with abacavir and lamivudine as a single tablet, and has fewer drug interactions than do elvitegravir and cobicistat regimens. However, abacavir is not appropriate in patients positive for HLAB*5701 and has been linked to risk of cardiovascular events in some epidemiological studies.[13–19]

The resistance profile of the approved INSTIs is an additional distinguishing factor. Resistance to raltegravir and elvitegravir occurs rarely in previously untreated patients; however, up to 50% of those with virological failure will develop resistance to these INSTIs, usually in conjunction with some degree of NRTI resistance, most commonly the Met184Val mutation conferring resistance to lamivudine and emtricitabine.[20–24] Viral isolates resistant to raltegravir are typically also resistant to elvitegravir. By contrast, no previously untreated patient in a trial of dolutegravir has developed resistance to this INSTI thus far, suggesting a higher barrier to resistance for dolutegravir than for raltegravir or elvitegravir. Dolutegravir also retains activity against many (but not all) raltegravir-resistant and elvitegravir-resistant isolates.

The antiviral potency, high resistance barrier, and safety and tolerability of bictegravir plus emtricitabine and tenofovir alafenamide in this phase 2 trial are being assessed in fully powered phase 3 trials. Coformulation of bictegravir, an unboosted, once-daily INSTI with an optimised genetic barrier to resistance, with emtricitabine and tenofovir alafenamide, would provide an advantage to patients. Two double-blind phase 3 studies are ongoing assessing bictegravir plus emtricitabine and tenofovir alafenamide as initial HIV therapy, one comparing a single-pill coformulation of bictegravir plus emtricitabine and tenofovir alafenamide versus dolutegrair plus emtricitabine and tenofovir alafenamide (NCT02607956) and the second comparing bictegravir plus emtricitabine and tenofovir alafenamide versus dolutegravir plus abacavir and lamivudine, each administered as a single-pill coformulation (NCT02607930). These phase 3 trials, with guideline-recommended INSTI comparators, will seek to susbstantiate the potency, safety, and tolerability of bictegravir plus emtricitabine and tenofovir

alafenamide. The results from these studies will help to establish if bictegravir plus emtricitabine and tenofovir alafenamide will emerge as an optimal initial strategy for HIV therapy.

Contributors

All authors were involved in development of the report, interpretation of data, and have read and approved the final version. PES, ED, GC, DW, PB, RD, AM, and CB enrolled participants, analysed data, independently interpreted results, and edited and approved the report. JP, XW, KW, and HM designed the study. XW analysed data, which were reviewed and interpreted by AC, EQ, and HM. The first draft was written by PES and HM. All authors contributed to edits of the final report.

Declaration of interests

PES has received research support from Bristol-Myers Squibb (BMS), Gilead, GlaxoSmithKline (GSK), and Merck and consulting fees from AbbVie, BMS, Gilead, GSK, Merck, and Janssen. ED has received research grant support from Abbott Laboratories, Achillion Pharmaceuticals, Avexa, BMS, Gilead, GSK, Idenix, Janssen, Merck, Sangamo, Taimed, and Tobira and consulting fees as a member of advisory boards for Gilead and Janssen. GC reports grants and personal fees from Gilead, GSK, Pfizer, Jansse, Sangamo, and Merck. DW reports research support from Gilead, ViiV, Tobira, and Kowa and honoraria for advisory or speaker services from BMS, ViiV, Gilead, Janssen, and Merck. PB reports grants from Gilead. JP, XW, KW, AC, HM, and EQ are employees of Gilead and hold stock interest in the company. RD has received payment for research studies as principal investigator from Gilead during the conduct of the study, has received medical group practice research study payments from Gilead outside the submitted work, and owns Gilead stock. CB has received reimbursement for travel to an Investigator Meeting from Gilead, has received grants from Gilead during the conduct of the study, and has received personal fees from Gilead, Theratech, Braintree, Novo Nordisk, GSK, ViiV, Colucid, Sliagen, Shionogi, Sanofi, Daiichi Sankyo, and Theratech, all outside the submitted work. AM reports grants and personal fees from Gilead during the conduct of the study, grants and personal fees from Viiv, grants and personal fees from Merck, and grants from BMS, all outside the submitted work.

Acknowledgments

This study was funded by Gilead Sciences. We thank the patients who participated in this trial and their families, the principal investigators and their staff, the Gilead study staff, and Anna Kido (Gilead employee) for providing editorial assistance. Parts of this study have been presented at the 24th Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; Feb 13–16, 2017.

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