A Phase 2b randomised, controlled, partially blinded trial of the HIV Nucleoside Reverse Transcriptase Inhibitor BMS-986001 (AI467003): Weeks 24 and 48 Efficacy, Safety, Bone and Metabolic Results

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I. SUMMARY

Background

BMS-986001 is a thymidine analogue nucleoside reverse transcriptase inhibitor (NRTI) designed to maintain the *in vitro* antiviral activity demonstrated by other NRTIs, whilst minimising off-target effects. This study assessed efficacy and safety of BMS-986001 versus tenofovir disoproxil fumarate (TDF) in treatment-naïve, HIV-1-infected subjects.

Methods

AI467003 was a Phase 2b, randomised, active-controlled, blinded-to-BMS-986001 dose trial. HIV-1-infected adults with plasma HIV-1 RNA greater than 5000 copies per mL and CD4+ T-cell counts greater than 200 cells/mm^3 were randomised 2:2:2:3 to three BMS-986001 arms (100, 200 or 400 mg once daily), or reference arm (TDF 300 mg once daily), each with efavirenz (600 mg once daily) and lamivudine (300 mg once daily). Both subjects and investigators remained blinded to BMS-986001 dose, but not allocation, through Week 48. Proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL and safety (serious adverse events [SAEs] and AEs leading to discontinuation) through Week 24 were primary endpoints. Resistance analysis was a secondary endpoint, and additional safety parameters were exploratory endpoints. AI467003 is registered with ClinicalTrials.gov (NCT01489046).

Findings

A total of 757 subjects were assessed for eligibility and 301 randomised. Randomised subjects were assigned to receive either BMS-986001 (n=67 for the 100 mg once-daily group, n=67 for the 200 mg once-daily group, n=66 for the 400 mg once-daily group) or TDF (n=101). 297 subjects received at least one dose of study drug. At Week 24, 57 (88%) of out 65 subjects in the 100 mg once-daily group, 54 (81%) of 67 subjects in the 200 mg once-daily group, 62 (94%) of 66 subjects in the 400 mg once-daily group achieved HIV-1 RNA less than 50 copies per mL, compared with 88 (89%) out of 99 subjects in the TDF group (modified intent-to-treat

population). BMS-986001 was generally well tolerated through Week 48. Two subjects had BMS-986001-related SAEs (atypical drug eruption and thrombocytopenia) and two subjects in the TDF arm had study drug-related SAEs (potential drug-induced liver injury and depression/lipodystrophy) that led to discontinuation. NRTI and non-NRTI resistance-associated mutations were reported in 4/198 (2·0%) and 17/198 (8·6%) subjects, respectively, receiving BMS-986001, versus 0/99 and 1/99 subjects receiving TDF. BMS-986001 arms showed an apparent smaller decrease in lumbar spine and hip bone mineral density but greater accumulation of limb and trunk fat, subcutaneous and visceral adipose tissue, and increased total cholesterol compared with TDF.

Interpretation

BMS-986001 demonstrated similar efficacy to TDF; however, more subjects developed resistance to study drug(s) in BMS-986001 arms. A smaller bone mineral density decline was seen for BMS-986001 versus TDF. However, gains in both peripheral and central fat accumulation were observed for BMS-986001. Bristol-Myers Squibb has discontinued its involvement in the development of BMS-986001, and future decisions on the development of BMS-986001 will be made by Oncolys BioPharma, Inc.

Funding

Bristol-Myers Squibb.

INTRODUCTION

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are the backbone agents upon which most combination antiretroviral therapy (cART) for HIV is built. Current treatment guidelines recommend that cART regimens for treatment-naïve patients incorporate two NRTIs and one other active class of agent, such as an integrase inhibitor (INSTI) or a protease inhibitor (PI) with a pharmacokinetic enhancer (cobicistat or ritonavir).[1,2]

Despite the widespread use of NRTIs in first-line treatment regimens, they are associated with toxicities, which can lead to long-term complications. These can include decreased bone mineral density (BMD),[3] lipoatrophy,[4,5] anaemia, pancreatitis,[6,7] and hypersensitivity reaction.[8] Several NRTIs, including didanosine, stavudine (d4T), and zidovudine, are not used routinely due to toxicities associated with mitochondrial (mt) dysfunction, namely peripheral neuropathy,[9,10] lipoatrophy,[4,5] hepatic steatosis[11], and metabolic acidosis[12,13]. Thus, there is a need for an NRTI with potent anti-HIV-1 activity, a tolerability profile better than currently available NRTI agents, a long-term safety profile that is favourable in terms of BMD and renal function, and limited cross-resistance to existing NRTIs.

BMS-986001 (also known as OBP-60) is a thymidine analogue NRTI (an analogue of d4T) specifically designed to maintain the in vitro antiviral activity demonstrated by other NRTIs and minimise off-target effects that cause toxicities.[14,15] In vitro experiments have shown that BMS-986001 has potent antiviral activity and reduced mitochondrial toxicity compared with d4T.[15,16] BMS-986001 also shows reduced inhibition of host DNA polymerases[14,15] and, in preclinical studies, has shown no evidence of bone or renal toxicity.[17] Furthermore, BMS-986001 has demonstrable activity against most HIV-1 subtypes (Bristol-Myers Squibb, unpublished data, 2011) and against HIV-1 isolates with certain NRTI resistance-associated mutations (RAMs), including K65R, L74V, and the Q151M constellation (without M184V).[18] M184V induced a low-level decrease (2- to 3-fold) in viral susceptibility to BMS-986001.[18]

In a Phase 2a, dose-escalating, monotherapy study conducted for 10 days in treatment-experienced, HIV-1-infected, subjects who were not exposed to any antiretroviral treatment in the previous 3 months, BMS-986001 demonstrated a median decrease in HIV-1 RNA from baseline of at least 1 $\log_{10}$ copies per mL for all doses.[19] These findings were used to support the design of this dose-finding Phase 2b study, which assessed the efficacy and safety of three doses of BMS-986001 (100, 200, and 400 mg once daily) versus tenofovir disoproxil fumarate (TDF 300 mg once daily), when co-administered with efavirenz (EFV 600 mg once daily) and lamivudine (3TC 300 mg once daily) in treatment-naïve, HIV-1-infected subjects. A detailed assessment of bone, renal, metabolic and mitochondrial parameters was performed to assess the safety of BMS-986001.

METHODS

Study design

AI467003 was a Phase 2b, randomised, active-controlled, blinded-to-BMS-986001 dose trial carried out at 47 sites across South America, North America, South Africa, Australia, Asia, and Europe.

This study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study was conducted in compliance with the protocol. The protocol and any amendments, and the subject informed consent received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favourable opinion prior to initiation of the study.

Participants

Eligible subjects were treatment-naïve (defined as no current or previous exposure to an antiretroviral drug for more than 1 week), HIV-1-infected adults aged at least 18 years with plasma HIV-1 RNA greater than 5,000 copies per mL and CD4+ T-cell counts greater than 200 cells/mm^3 at screening. Exclusion criteria included a history of phenotypic and/or genotypic drug resistance testing showing resistance to EFV, TDF, or 3TC, presence of hepatitis B surface antigen, hepatitis C virus antibody or RNA, history of abnormal liver transaminases (defined as greater than three times the upper limit of normal) at screening, and creatinine clearance less than 60 mL/min at screening. All subjects provided written informed consent in agreement with the Declaration of Helsinki principles.

Outcomes

Primary endpoints were the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL at Week 24 and the frequency of SAEs and AEs leading to discontinuation through Week 24. Secondary endpoints were proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL

at Week 48 and the frequency of SAEs and AEs leading to discontinuation through Week 48. Additional secondary endpoints were change from baseline in CD4+ T-cell counts and the number of subjects with virologic failure who had virus exhibiting genotypic drug RAMs through Weeks 24 and 48.

Exploratory endpoints were assessment of the effect of BMS-986001 and TDF on change from baseline in mtDNA copy number, BMD, body fat distribution, fasting lipid profile, and renal function at Weeks 24 and 48.

Procedures

Study visits were completed at screening and Weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 (or upon early termination) during the study. Plasma HIV-1 RNA levels were quantified by polymerase chain reaction using the Abbott m2000 RealTime System (Abbott Molecular, USA). Protocol-defined virologic failure was defined as confirmed plasma HIV-1 RNA at least 50 copies per mL at Week 24, or later (confirmed by second measurement within 4 weeks of the original sample), or virologic rebound (confirmed HIV-1 RNA at least 50 copies per mL at any time after prior confirmed suppression to less than 50 copies per mL, or confirmed increase in HIV-1 RNA greater than 1 $\log_{10}$ copies per mL above the nadir level at any time [where nadir is at least 50 copies per mL]).

Viral drug resistance testing was conducted at screening and in the event of confirmed PDVF, or at a minimum in the event of a confirmed plasma HIV-1 RNA measurement of at least 400 copies per mL at any time during the study (having previously achieved viral suppression [less than 50 copies per mL]) or discontinuation before achieving viral suppression after Week 8 with a last plasma HIV-1 RNA measurement of at least 400 copies per mL. Genotypic and phenotypic resistance testing were performed using the GenoSure® MG (screening) and the Phenosense® GT (failure) assays (both Monogram Biosciences, South San Francisco, CA).

Physical examinations, measurement of vital signs, and clinical laboratory evaluations were performed at selected times throughout the study, and subjects were closely monitored for adverse

events (AEs) and serious AEs (SAEs) throughout. AEs were coded according to MedDRA version 16·0. The severity and relationship to study drug was assessed by the corresponding local investigator. Dual-energy X-ray absorptiometry (DXA) scans for measurement of BMD (hip and lumbar spine) and limb/trunk fat (whole body DXA scans) were performed at baseline and Weeks 24 and 48, or upon early termination. Single slice computed tomography (CT) scans of the abdomen for measurement of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and total adipose tissue (TAT), were performed at baseline and Week 48, or upon early termination. For both DXA and CT scans, standardisation and blinded central reading were performed by BioClinica (Newtown, PA). Subcutaneous fat was obtained from a 3-mm skin punch biopsy from the lower abdomen or buttock area, from consenting subjects, for measurement of mtDNA content at baseline and Weeks 24 and 48, or upon early termination. The fat samples were separated from the overlying skin and stored in RNAlater® at -70ºC freezer until batch processing at the end of the study. Quantification of mtDNA content was performed as described previously[20] with an optimized DNA input of 1ng per 20uL reaction. Laboratory measurements, including CD4+ T-cell counts, and serum creatinine for estimation of creatinine clearance, were assessed.

Randomisation and masking

Eligible subjects were randomised 2:2:2:3 into four treatment arms: three treatment arms of BMS-986001 (100, 200 or 400 mg once daily), and a reference treatment arm of TDF (300 mg once daily), each with a common background therapy of EFV (600 mg once daily) and 3TC (300 mg once daily). EFV and 3TC were selected owing to their known safety profiles, which allowed for reasonable assessment of the specific safety profile of BMS-986001 when used as a component of cART, and also their common use globally as first-line therapies.

For subjects who met the protocol eligibility criteria, randomisation was performed using a computer-generated code and stratified according to baseline viral load (HIV-1 RNA less than 100,000 copies per mL versus HIV-1 RNA at least 100,000 copies per mL). Both subjects and investigators remained blinded to BMS-986001 dose, but not allocation, through Week 48. BMS-986001 dose masking was

performed using once-daily dosing for all BMS-986001 treatment arms and similar looking placebo tablets. Sponsors were unblinded to BMS-986001 doses after the last subject had reached Week 24 and subjects/investigators were unblinded after the last subject had reached Week 48.

Statistical analysis

This study was designed to estimate the effects of the randomised study medication. Thus, sample size considerations were based on the precision with which these effects can be estimated and not on the ability of the study to find statistically significant differences between treatment groups. Assuming a response rate of 80% , a target sample size of approximately 300 randomised subjects (67 per BMS-986001 dose group and 100 in the TDF dose group) would provide a 95% exact binomial confidence interval (CI) that extends from 69% to 89% for a BMS-986001 arm (n=67) or from 71% to 87% for the TDF arm (n=100).

The primary efficacy endpoint assessment used the FDA-defined snapshot algorithm that takes the last plasma HIV-1 RNA in the predefined Week 24 and 48 visit windows (+/- 6 weeks) to determine response. Thus, the modified intent-to-treat (mITT) population consisted of subjects who received at least one dose of BMS-986001 or TDF. The observed population consisted of subjects who received at least one dose of BMS-986001 or TDF, with plasma HIV-1 RNA measurements within the Week 24 and 48 windows.

The percent change from baseline in hip BMD was analysed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and baseline value as a covariate. The analyses were conducted with the data limited to baseline and the time point of interest (Week 24 or Week 48). This was intended to increase the precision of the estimates by removing variability attributable to baseline differences.

The trial is registered with ClinicalTrials.gov (NCT01489046) and the European Clinical Trials Database (EudraCT: 2011-003329-89).

Role of funding source

The sponsor of the study had a role in the study design, and data collection, analysis and interpretation, in conjunction with external study investigators. The first draft of the manuscript was prepared by a professional medical writer, paid for by the sponsor, and edited and revised by all authors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Recruitment into the study took place between January 25, 2012 and October 3, 2012. A total of 757 subjects were screened, of which 301 were randomised and 297 treated (**Figure 1**). The majority of screening failures were due to failure to meet entry criteria; while not mutually exclusive, the most common reasons were a screening plasma HIV-1 RNA less than 5,000 copies per mL (238/456 [52·2%]) and CD4+ T-cell count less than 200 cells/mm^3 (79/456 [17·3%]). Of those receiving treatment, 40/198 (20·2%) across the BMS-986001 arms and 16/99 (16·1%) in the TDF arm, had discontinued from the study by the Week 48 database lock. Reasons for discontinuation included AEs, loss-to-follow-up, no longer meeting study criteria and poor/non-compliance.

Baseline demographics and disease characteristics were similar across study arms (**Table 1**); median age was 31 years, two-thirds of subjects were male, and almost half were Black/African-American. Most subjects had HIV-1 subtypes C (38·4%), B (37·0%), or AE (20·2%). Median baseline HIV-1 RNA and CD4+ T-cell count was 4·39 $\log_{10}$ copies per mL (17·5% had at least 100,000 copies per mL) and 307·0 cells/mm^3 (8·4% had less than 200 cells/mm^3), respectively.

The FDA-defined snapshot algorithm (mITT population) and observed population criteria were used to determine the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL at Weeks 24 and 48 for all study arms (**Table 2**). At Week 24 in the mITT population, 88%, 81% and 94% of subjects receiving BMS-986001 100, 200 and 400 mg once daily, respectively, and 89% receiving TDF had achieved HIV-1 RNA less than 50 copies per mL. In the observed population, 92%, 95% and 97% of subjects receiving BMS-986001 100, 200 and 400 mg once daily, respectively, and 97% receiving TDF achieved HIV-1 RNA less than 50 copies per mL. By Week 48, 75%, 81% and 89% of subjects receiving BMS-986001 100, 200 and 400 mg once daily, respectively, and 82% receiving TDF in the mITT population, and 96%, 100% and 100% of subjects receiving BMS-986001 100, 200 and 400 mg once daily, respectively, and 96% of subjects receiving TDF in the observed population, had achieved HIV-1 RNA less than 50 copies per mL. CD4+ T-cell counts increased from baseline to Week 24 by a median of 157·0 (interquartile range [IQR] 104·0–236·0), 127·0 (IQR 67·0–192·0) and

139·0 (IQR 49·0–199·0) cells/mm^3 for the BMS-986001 100, 200 and 400 mg once-daily arms, respectively, and 119·0 cells/mm^3 (IQR 54·0–188·0) for the TDF arm. An increase in CD4+ T-cell count from baseline to Week 48 by a median of 171·0 (IQR 74·0–286·0), 139·5 (IQR 69·0–248·5) and 155·0 (IQR 97·0–225·0) cells/mm^3 for the BMS-986001 100, 200 and 400 mg once-daily arms, respectively, and 147·5 cells/mm^3 (IQR 79·0–281·0) for TDF was also observed.

Through the Week 48 database lock, 18/198 (9·1%) subjects in the BMS-986001 arms and 4/99 (4·0%) subjects in the TDF arm met on-study criteria for resistance testing. Of these, 16/18 and 1/4 subjects, in the BMS-986001 arms and TDF arm, respectively, were successfully tested. Data from five additional subjects was received shortly after the Week 48 database lock. Combining both sets of data, it was found that 4/198 (2·0%) subjects in the BMS-986001 arms and 0/99 in the TDF arm had developed NRTI RAMs. M184V was the only NRTI RAM observed (2·0%). Additionally, 17/198 (8·6%) subjects in the BMS-986001 arms and 1/99 (1·0%) in the TDF arm developed NNRTI RAMs. K103N was the most common NNRTI RAM observed (7·1%) (**Table 3)**. Overall, the BMS-986001 100 mg arm had the greatest numbers of NNRTI and NRTI RAMs compared with the BMS-986001 200 mg and 400 mg arms, and the TDF arm.

BMS-986001 was generally well tolerated through Week 48. Particular Grade 2–4-related AEs, such as skin/subcutaneous tissue disorders (BMS-986001, 6·1–12·3%; TDF, 4·0%), metabolic disorders (primarily high cholesterol) (BMS-986001, 1·5–7·6%; TDF, 1·0%) and gastrointestinal disorders (BMS-986001, 1·5–6·2%; TDF, 1·0%), were more frequently reported for BMS-986001 compared with TDF (**Supplementary Table 1**)**.** SAEs were reported in 19/198 (9·6%) subjects across the BMS-986001 and in 9/99 (9·1%) subjects for TDF (**Supplementary Table 2**). Two subjects had BMS-986001-related SAEs: atypical drug eruption and thrombocytopenia. A female aged 49 years developed genital ulcers and episcleritis 7 days after initiating treatment and oral ulcers 5 days later, leading to hospitalisation. Ulcer swabs were PCR-negative for cytomegalovirus and herpes simplex virus. The subject received acyclovir, xylocaine–epinephrine, and dexamethasone, and the SAE resolved. A male aged 25 years developed an asymptomatic decline in platelet count (without other haematological dyscrasias), which started 3 months and progressed during 1 year of treatment. The

SAE resolved without intervention after treatment completion. Two subjects in the TDF arm also had study drug-related SAEs (potential drug-induced liver injury and depression/lipodystrophy) that led to discontinuation. One non-study-related death occurred (pneumonia) in the BMS-986001 200 mg once-daily group. Grade 2–4 lab abnormalities were transient and mostly did not lead to discontinuation.

Average change from baseline in lumbar spine BMD (calculated using baseline-adjusted ANCOVA [data not shown]) for BMS-986001 was −0·9% (CI −1·3, −0·5) and −1·4% (CI −1·9, −0·8) at Weeks 24 and 48, respectively, compared with a roughly 2-fold lower result of −3·0% (CI −3·6, −2·4) and −3·2% (CI −4·1, −2·4) for TDF (**Figure 2a**). Similarly, average change from baseline in hip BMD for BMS-986001 was −0·5% (CI −0·8, −0·2) and −1·2% (CI −1·6, −0·75) at Weeks 24 and 48, respectively, compared with a roughly 3-fold lower result of −1·7% (CI −2·2, −1·2) and −3·0% (CI −3·7, −2·4) for TDF (**Figure 2b**). Concordant with the smaller declines in BMD for BMS-986001, the magnitudes of percentage changes from baseline for biomarkers of bone resorption, C-terminal telopeptide of type I collagen (CTx), and formation, serum type 1 procollagen N-terminal (P1NP), bone sialoprotein (B-SAP), osteocalcin, were lower in the BMS-986001 arms relative to TDF at Weeks 12, 24 and 48 (**Supplementary Figure 1**). Mean change in creatinine clearance at Week 48 was 4·0 (standard error [SE] 3·0), 1·1 (SE 1·8), −1·6 (SE 2·7) mL/min for the BMS-986001 100, 200 and 400 mg once-daily arms, respectively, and 0·048 (SE 1·9) mL/min for the TDF arm.

DXA measurements showed that mean percentage increase in limb fat at Week 24 across the BMS-986001 100, 200 and 400 mg arms was 4·5% (SE 2·9), 2·3% (SE 1·8) and 10·0% (SE 3·0), respectively, which was higher compared with the 1·2% (SE 1·7) increase for TDF. Similarly, at Week 48 the BMS-986001 100, 200 and 400 mg arms reported greater increases in limb fat of 12·0% (SE 5·0), 8·0% (SE 2·9) and 15·8% (SE 4·7), respectively, compared with 2·1% (SE 1·9) for TDF. Trunk fat increase was also observed at Week 24 across the BMS-986001 100, 200 and 400 mg arms by a mean percentage of 2·3% (SE 2·9), 1·3% (SE 1·6) and 12·7% (SE 4·1) respectively, compared with 2·5% (SE 2·5) for TDF. At Week 48, the BMS-986001 100, 200 and 400 mg arms reported

increases in trunk fat of 8·3% (SE 3·6), 7·0% (SE 2·6) and 18·4% (SE 6·2), respectively, compared with the lower 3·8% (SE 3·1) for TDF.

Loss in baseline limb fat of at least 10% at Week 24 was reported in 6/53 (11·3% [95% CI 4·3, 23·0]), 7/47 (14·9% [CI 6·2, 28·3]), and 6/53 (11·3% [CI 4·3, 23·0]) subjects in the 100, 200, and 400 mg BMS-986001 arms, respectively, compared with the slightly higher 13/69 (18·8% [CI 10·4, 30·1]) subjects in the TDF arm. At Week 48, this was reported in 4/45 (8·9% [CI 2·5, 21·2]), 6/45 (13·3% [CI 5·1, 26·8]), and 6/51 (11·8% [CI 4·4, 23·9]) subjects in the 100, 200, and 400 mg BMS-986001 arms, respectively, compared with the slightly higher 13/65 (20·0% [CI 11·1, 31·8]) subjects for TDF. Loss in baseline limb fat of at least 20% at Week 24 was reported in 4/53 (7·5% [CI 2·1, 18·2]), 1/47 (2·1% [CI 0·1, 11·3]), 2/53 (3·8% [CI 0·5, 13·0]) subjects on BMS-986001 100, 200 and 400 mg once-daily arms respectively, similar to the 4/69 (5·8% [CI 1·6, 14·2]) subjects receiving TDF. At Week 48, this was reported in 3/45 (6·7% [CI 1·4, 18·3]), 2/45 (4·4% [CI 0·5, 15·1]), 4/51 (7·8 % [CI 2·2, 18·9]) subjects receiving BMS-986001 100, 200 and 400 mg once-daily respectively, similar to the 5/65 (7·7% [CI 2·5, 17·0]) subjects receiving TDF.

CT scans showed greater gains in mean percentage SAT and VAT across the BMS-986001 arms (SAT, 11·1% [standard deviation, SD 37·5], 9·3% [SD 28·9] and 23·1% [SD 76·4] for the 100, 200 and 400 mg once-daily arms; VAT, 12·5% [SD 45·8], 16·5% [SD 41·6] and 33·3% [SD 90·9] for the 100, 200 and 400 mg once-daily arms), compared with TDF (SAT, –3·4% [SD 30·064]; VAT, 13·7% [SD 72·7]) at Week 48 (**Supplementary Figure 2)**. The greatest changes from baseline in SAT and VAT occurred in the BMS-986001 400 mg arm. Mean change in mtDNA copy number (extracted from subcutaneous fat biopsies) at Week 48 was 3·9% ([SE 5·9], n=47), −1·0% ([SE 6·8], n=50) and −3·7% ([SE 6·4], n=55) for the BMS-986001 100, 200 and 400 mg once-daily arms, respectively, and −2·5% ([SE 5·6], n=72) for TDF. A numerically greater increase in total cholesterol was observed across the BMS-986001 arms (mean change from baseline in total cholesterol at Week 24 was 23·3 [SE 3·5], 34·3 [3·5], 24·0 [3·8] mg/dL and at Week 48 was 33·7 [SE 5·2], 37·1 [SE 4·0] and 33·8 [SE 4·5] mg/dL for the BMS-986001 100, 200 and 400 mg once-daily arms, respectively), compared with the TDF arm (14·5 [2·9] mg/dL at Week 24 and 23.0 [SE 3·1] mg/dL at Week 48). At Week 48,

mean ratios of total cholesterol to high-density lipoprotein-cholesterol were similar between the BMS-986001 arms (3·5 [SD 1·0], 3·4 [SD 1·1], 3·3 [SD 0·9] for the BMS-986001 100, 200 and 400 mg once-daily arms, respectively) and TDF (3·6 [SD 1·3]) (baseline levels of cholesterol and triglycerides provided in **Supplementary Table 3**).

DISCUSSION

The continued use of NRTIs as backbone agents for cART, despite their associated toxicity concerns, highlights the need to develop new NRTI agents with potent antiviral activity, improved toxicity profiles and limited cross-resistance to existing NRTIs. BMS-986001 is a thymidine analog NRTI (a novel analog of d4T) that was developed to have similar in vitro activity to existing NRTIs but with an improved toxicity profile.[15,16] In this study, 24 weeks of treatment with BMS-986001 (100, 200, and 400 mg once daily) or TDF 300 mg once daily, each with a common background therapy of EFV 600 mg once daily and 3TC 300 mg once daily, resulted in a similar number of subjects achieving plasma HIV-1 RNA less than 50 copies per mL. However, within the BMS-986001 arms, antiviral activity for the 400 mg arm was higher when compared with the 100 mg and 200 mg arms. At Week 48, in the mITT population, BMS-986001 dose-dependent efficacy was observed, and the 400 mg arm showed the greatest efficacy across all treatment arms, including the TDF arm.

A higher percent of subjects developed emergent resistance to study drug(s) across all the BMS-986001 arms compared with the TDF arm; the BMS-986001 100 mg arm had the highest proportion of subjects who developed emergent resistance to study drug(s). We speculate that the lower intracellular half-life of the active triphosphate form of BMS-986001 (approximately 9·7 hours)[21] compared with the intracellular half-life of the active diphosphate form of TDF (>60 hours)[22] may have led to the resistance pattern observed. Also, subjects randomized to receive BMS-986001 took six pills a day whereas subjects in the TDF arm took three pills a day. This difference in pill burden may have affected adherence, however this effect was not formally assessed. Importantly, the emergent resistance observed was primarily to EFV and 3TC. This is in line with results from a previous randomised trial (ACTG 5202), which evaluated the efficacy, safety and resistance profile of four regimens (ritonavir-boosted atazanavir or EFV, both combined with abacavir [ABC] + 3TC or TDF + emtricitabine [FTC]) in treatment-naïve subjects. In this trial, both NRTI and NNRTI RAMs were more frequently observed in subjects who received EFV compared with those who received ATV + RTV.[23] In a separate randomised trial (SINGLE), which compared dolutegravir (DTG) + ABC + 3TC and EFV + FTC + TDF, no subjects in the DTG + ABC + 3TC group had detectable antiviral

resistance whereas one TDF–associated mutation and four EFV-associated mutations were detected in the EFV–TDF–FTC group.[24]

BMS-986001 was generally well tolerated through Week 48. Some Grade 2–4-related AEs were more frequently reported in the BMS-986001 arms compared with TDF, however no dose-related trends for the BMS-986001 arms were apparent.

Given the importance of toxicity issues associated with NRTIs, including decreased BMD,[3] renal dysfunction, lipoatrophy,[4,5] dyslipidaemia, and mitochondrial toxicity,[4,5] we evaluated each of these parameters during this study. Compared with the BMS-986001 arms, the decrease in lumbar spine and hip BMD in the TDF arm was ~2·5-fold greater. This observation is consistent with several other studies,[25,26] which have shown a greater decrease in BMD when using TDF-based therapies, compared with other regimens. Reassuringly, changes in BMD observed with BMS-986001 were comparable with those seen with ABC (combined with 3TC and EFV)[25] and recently with tenofovir alafenamide fumarate.[27] Consistent with the lower declines in lumbar spine and hip BMD, the changes from baseline for biomarkers of bone resorption and formation were also lower for the BMS-986001 arms compared with TDF, suggesting that BMS-986001 has less pronounced effects on the bone. No appreciable changes in creatinine clearance were seen across any treatment arm at Week 48, although longer-term studies would be required to determine if larger changes occur with more prolonged use.

Increases in limb and trunk fat were observed for all BMS-986001 and TDF arms, with the greatest gains observed in the BMS-986001 400 mg once-daily arm. Increases in SAT and VAT were seen mainly in the BMS-986001 arms, particularly the 400 mg once-daily arm, and not with TDF. The clinical significance of these gains in peripheral and central fat for BMS-986001, particularly for the 400 mg once-daily arm, will require further study and mechanistic understanding given that visceral fat accumulation has been generally associated with both insulin resistance and cardiovascular disease.[28] Furthermore, the fat accumulation observed after 48 weeks in this study is similar to that seen after 96 weeks in two other ART-initiation studies using either ABC/3TC or TDF/FTC.[29,30] The loss of baseline limb fat (of at least 10%) reported in a small subset of subjects in this study was

generally low for the BMS-986001 arms and the loss of baseline limb fat (of at least 20%) and was similar to TDF. These data for BMS-986001 are reminiscent of findings from other studies with ABC or TDF-containing regimens.[29,30] The clinical significance of the small differences in lipid levels between BMS-986001 and TDF is presently unclear and would require longer-term study.

As BMS-986001 is an analogue of d4T, and d4T has been associated with mitochondrial toxicity,[31] changes in mtDNA copy number were monitored during this study. No meaningful changes from baseline in mtDNA copy number were observed, consistent with the lack of lipoatrophy reported, for BMS-986001. Similar observations were also made for TDF.

There were several strengths in our study. The study was conducted across six continents and female subjects were well represented (34%). Resistance data, including those beyond the Week 48 database lock, was included within the analysis of the study. Additionally, thorough safety assessments (bone, metabolic, renal and mitochondrial safety) were performed as part of the study. However, there were also limitations in our study. Only 17·5% of subjects had baseline HIV-1 RNA of at least 100,000 copies per mL, making it difficult to draw conclusions about this subset of subjects. This was also a partially-blinded study, with both subjects and investigators blinded to BMS-986001 dose, but not allocation. Adherence was also not formally assessed; therefore any potential effect of pill burden on the observed resistance profile could not be determined. Finally, a greater study size would be required to convincingly demonstrate non-inferior efficacy and safety of any dose of BMS-986001 to TDF.

In conclusion, following 48 weeks of treatment, higher doses of BMS-986001 demonstrated similar efficacy to TDF (both combined with EFV + 3TC). BMS-986001 was generally well tolerated, with smaller declines in BMD noted across the BMS-986001 arms compared with TDF. No signals for mitochondrial toxicity or concerns about lipoatrophy were observed. However, more subjects developed resistance to study drugs in the BMS-986001 arms compared with TDF. Additionally, gains in both peripheral and central fat accumulation were seen in the BMS-986001 arms, especially with the 400 mg dose, which potentially raises concerns about insulin resistance and cardiovascular

disease. In light of these results in total, AI467-003 was terminated after the Week 48 secondary endpoint and Bristol-Myers Squibb has discontinued its involvement in the development of BMS-986001. Any future decisions on the development of BMS-986001 will be made by Oncolys BioPharma, Inc, which owns the rights to the compound.

RESEARCH IN CONTEXT

Evidence before this study

A PubMed search using the terms, “mitochondrial toxicity” or “renal toxicity” or “bone mineral density” and “NRTI” provides substantial evidence of the toxicity concerns that are associated with long-term NRTI use. BMS-986001 is a novel analogue of d4T, structurally engineered to address the toxicities commonly attributed to the NRTI class, without altering the potency of the agent. The present clinical study, designed based on findings from previous preclinical and clinical studies, investigated if BMS-986001 showed both potent antiviral activity and a superior safety profile as a component of cART when compared to a robust comparator arm. To select a relevant comparator arm, PubMed searches were performed with the terms, “A5202” or “GS-01-934” (an additional search for ““Study 934 group”” was also performed) or ““903 study group”” as these trials investigated robust and commonly used first-line regimens for treatment-naïve, HIV-1 infected subjects. Searches were restricted to articles published in English between 2003 and 2013. Of the 18 articles, the majority reported findings relating to the ACTG A5202 study (and sub studies, e.g. ACTG A5224) and two from the GS-01-934 trial and one from study GS-903. In all three trials, TDF was used as a component of cART. The ACTG A5202 study reported that virologic failure was significantly less likely and time to primary safety endpoint was shorter if subjects were assigned TDF-FTC compared to ABC-3TC. In study GS-01-934, EFV plus TDF-FTC was non-inferior to EFV plus zidovudine (ZDV)-3TC and superior with respect to virologic suppression, CD4 response and AEs leading to discontinuation. Finally, in study 903 TDF appeared to be associated with better lipid profiles and less lipodystrophy compared with d4T. Thus, these studies facilitated in selecting TDF as a cART component of the comparator arm in the present study.

Added value of this study

This Phase 2b study investigated the efficacy and safety profile of BMS-986001 as a component of cART. Higher doses of BMS-986001 showed greater efficacy (both combined with EFV and 3TC). BMS-986001 was generally well tolerated with no signals for mitochondrial toxicity or concerns

about lipoatrophy, and with smaller declines in BMD compared with TDF. However, more subjects developed resistance to study drugs in the BMS-986001 arms compared with TDF and some gains in both peripheral and central fat accumulation were seen.

Implications of all the available evidence

This study demonstrates that small structural changes can positively influence the safety profile of an antiretroviral therapy, but these structural alterations need optimisation so as not to alter other drug characteristics important to long-term cART use. Although further development of BMS-986001 is not being pursued at this time, the strategy of introducing structural changes to existing NRTIs may improve the overall clinical profile of such agents.

Contributors

The AI467003 investigators were responsible for enrolment of subjects and collection of clinical data. ML, GH, SRJ, NR and DAS performed the analyses, NR was responsible for planning, executing and analysing data relating to mtDNA, bone and renal safety, and DAS was responsible for the statistical outputs. All authors contributed to the interpretation of the results, including critique of key findings, and drafting of the final version of the report for submission.

Declaration of interests

SKG received a travel grant from Bristol-Myers Squibb during the conduct of the study and also consultancy fees from Bristol-Myers Squibb outside this submitted work; travel and unrestricted research grants from Gilead Sciences; unrestricted research grants from Janssen Pharmaceuticals; an unrestricted research grant and consultancy fees from Merck & Co; consultancy fees from ICON and Oncolys BioPharma. GAM received grants from Bristol-Myers Squibb, GlaxoSmithKline and Gilead Sciences; consultant fees from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline/ViiV and ICON; and speaker's fees from Bristol-Myers Squibb. JE received grants and personal fees from Hospital Nacional Cayetano Heredia during the conduct of the study. CO reports grants from Bristol-Myers Squibb during the conduct of the study to her organisation. OO reports grants from Gilead Sciences, speaker's fees from Gilead Sciences and Janssen Pharmaceuticals, and consultancy fees from Gilead Sciences, Bristol-Myers Squibb, Janssen Pharmaceuticals and AbbVie. NR, DAS, SRJ, GJH and ML are employees of Bristol-Myers Squibb and hold stock/stock options. The remaining authors declare that they have no competing interests.

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References

1 European AIDS Clinical Society. European AIDS Clinical Society Guidelines Version 7.1. European AIDS Clinical Society 2014 November; Available from: URL: http://www.eacsociety.org/files/guidelines_english_71_141204.pdf

2 Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo nih gov/ContentFiles/AdultandAdolescentGL pdf 2015 April; Available from: URL: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

3 Haskelberg H, Hoy JF, Amin J, et al. Changes in bone turnover and bone loss in HIV-infected patients changing treatment to tenofovir-emtricitabine or abacavir-lamivudine. *PLoS One* 2012; **7:** e38377.

4 Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS* 2009; **23:** 1109–18.

5 Hendrickson SL, Kingsley LA, Ruiz-Pesini E, et al. Mitochondrial DNA haplogroups influence lipoatrophy after highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2009; **51:** 111–6.

6 Moreno A, Quereda C, Moreno L, et al. High rate of didanosine-related mitochondrial toxicity in HIV/HCV-coinfected patients receiving ribavirin. *Antivir Ther* 2004; **9:** 133–8.

7 Reisler RB, Murphy RL, Redfield RR, Parker RA. Incidence of pancreatitis in HIV-1-infected individuals enrolled in 20 adult AIDS clinical trials group studies: lessons learned. *J Acquir Immune Defic Syndr* 2005; **39:** 159–66.

8 Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther* 2001; **23:** 1603–14.

9 Cherry CL, Skolasky RL, Lal L, et al. Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. *Neurology* 2006; **66:** 867-73.

10 Moore RD, Wong WM, Keruly JC, McArthur JC. Incidence of neuropathy in HIV-infected patients on monotherapy versus those on combination therapy with didanosine, stavudine and hydroxyurea. *AIDS* 2000; **14:** 273–8.

11 Stein DS, Helfert KS. A new syndrome of hepatomegaly with severe steatosis in HIV-seropositive patients. *AIDS Clin Care* 1994; **6:** 17–21.

12 Jolliet P, Widmann JJ. Reye's syndrome in adult with AIDS [letter]. *Lancet* 1989; **335:** 1457.

13 Chattha G, Arieff AI, Cummings C, Tierney LMJ. Lactic acidosis complicating the acquired immunodeficiency syndrome. *Ann Intern Med* 1993; **118:** 37–9.

14 Yang G, Dutschman GE, Wang CJ, et al. Highly selective action of triphosphate metabolite of 4'-ethynyl D4T: a novel anti-HIV compound against HIV-1 RT. *Antiviral Res* 2007; **73:** 185–91.

15 Dutschman GE, Grill SP, Gullen EA, et al. Novel 4'-substituted stavudine analog with improved anti-human immunodeficiency virus activity and decreased cytotoxicity. *Antimicrob Agents Chemother* 2004; **48:** 1640–6.

16 Wang F, Flint O. The NRTI BMS-986001 does not degrade mitochondrial DNA in long-term primary cultures of cells isolated from human kidney, muscle and subcutaneous fat. *AIDS* 2012, 19th International AIDS Conference, Washington, DC.

17 Guha M, Pilcher G, Moehlenkamp J, Wang F, Clark S, Simutis F et al. Absence of renal and bone toxicity in non-clinical studies of BMS-986001, a nucleoside reverse transcriptase inhibitor (NRTI) of human immunodeficiency virus (HIV). *AIDS* 2012, 19th International AIDS Conference, Washington, DC.

18 Li Z, Terry B, Olds W, et al. The *in vitro* cross-resistance profile of the nucleoside reverse transcriptase inhibitor (NRTI) BMS-986001 against known NRTI resistance mutations. *Antimicrob Agents Chemother* 2013; **57:** 5500–8.

19 Cotte L, Dellamonica P, Raffi F, et al. Randomized, placebo-controlled study of the safety, tolerability, antiviral activity and pharmacokinetics of 10-day monotherapy with BMS-986001, a novel HIV NRTI, in treatment-experienced HIV-1-infected subjects. *J Acquir Immune Defic Syndr* 2013; **63:** 346–54.

20 McComsey GA, Kang M, Ross AC,et al. Increased mtDNA levels without change in mitochondrial enzymes in peripheral blood mononuclear cells of infants born to HIV-infected mothers on antiretroviral therapy. *HIV Clin Trials* 2008; **9:** 126–36.

21 Wang X, Tanaka H, Baba M, Cheng YC. Retention of metabolites of 2',3'-didehydro-3'-deoxy-4'-ethynylthymidine, a novel anti-human immunodeficiency virus type 1 thymidine analog, in cells. *Antimicrob Agents Chemother* 2009; **53:** 3317–24.

22 Chapman T, McGavin J, Noble S. Tenofovir disoproxil fumarate. *Drugs* 2003; **63:** 1597–608.

23 Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. *Ann Intern Med* 2014.

24 Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* 2013; **369:** 1807–18.

25 McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. *J Infect Dis* 2011; **203:** 1791–801.

26 Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010; **51:** 963–72.

27 Sax PE, Zolopa AR, Brar I, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr* 2014; **67:** 52–8.

28 Kissebah AH, Krakower JR. Regional adiposity and morbidity. *Physiol Rev* 1994;**74:**761-811.

29 McComsey GA, Kitch D, Sax PE, Tebas P, Tierney C, Jahed NC et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. *Clin Infect Dis* 2011 July 15;**53:**185-96.

30 McComsey GA CMC, Ribaudo H, et al. Body composition changes after initiation of raltegravir or protease inhibitors. *22nd Conference on Retroviruses and Opportunistic Infections*, Seattle, WA, 23-26 February 2015.

31 Walker UA, Setzer B, Venhoff N. Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse-transcriptase inhibitors. *AIDS* 2002; **16:** 2165–73.

TABLES AND FIGURES

Table 1: Baseline demographics and disease characteristics

	BMS-986001 + EFV + 3TC			**TDF + EFV + 3TC**
	100 mg once daily N=65	200 mg once daily N=67	400 mg once daily N=66	300 mg once daily N=99
Median age, years (range)	31 (18–64)	32 (18–53)	34 (19–57)	29 (18–61)
Gender, n (%)				
Male	43 (66%)	42 (63%)	41 (62%)	70 (71%)
Female	22 (34%)	25 (37%)	25 (38%)	29 (29%)
Race, n (%)				
Black	31 (48%)	32 (48%)	35 (53%)	40 (40%)
Asian	15 (23%)	15 (22%)	14 (21%)	27 (27%)
White	11 (17%)	10 (15%)	7 (11%)	15 (15%)
Other*	8 (12%)	10 (15%)	10 (15%)	17 (17%)
Baseline body mass index, kg/m^2, median	23.9	23.8	22.3	23.3
Baseline adipose tissue, cm^2, median				
Subcutaneous adipose tissue	110.7	89.6	68.1	71.0
Total adipose tissue	181.0	141.9	100.3	107.5
Visceral adipose tissue	37.4	33.4	32.2	33.2
HIV-1 subtype, n (%)				
AE	14 (22%)	13 (19%)	8 (12%)	25 (25%)
B	28 (43%)	22 (33%)	24 (36%)	36 (36%)

C	22 (34%)	30 (45%)	29 (44%)	33 (33%)
Other	1 (2%)	2 (3%)	5 (8%)	5 (5%)
Baseline viral load (HIV-1 RNA)				
Median, log_{10} copies per mL	4·34	4·43	4·46	4·38
Proportion of subjects with ≥100,000 copies per mL, n (%)	11 (17%)	12 (18%)	12 (18%)	17 (17%)
Baseline CD4+ T-cell count				
Median, cells/mm^3	290	325	330	301
Proportion of subjects with <200 cells/mm^3, n (%)	6 (9%)	3 (5%)	4 (6%)	12 (12%)

3TC, lamivudine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate.

Table 2: Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Weeks 24 and 48: FDA-defined snapshot algorithm (mITT population) and observed population analysis

Parameter, n (%)		BMS-986001 + EFV + 3TC			TDF + EFV + 3TC
		100 mg once daily N=65	200 mg once daily N=67	400 mg once daily N=66	300 mg once daily N=99
mITT analysis (FDA Snapshot algorithm)					
Week 24	**HIV-1 RNA <50 cop/mL**	57 (88%)	54 (81%)	62 (94%)	88 (89%)
	HIV-1 RNA ≥50 c/mL*	8 (12%)	9 (13%)	4 (6%)	7 (7%)
	No virological data at Week 24				
	Discontinued due to AE or death	0	4 (6%)	0	2 (2%)
	Discontinued for other reason	0	0	0	2 (2%)
	Missing data during window but on-study	0	0	0	0
Week 48	**HIV-1 RNA <50 c/mL**	49 (75%)	54 (81%)	59 (89%)	81 (82%)
	HIV-1 RNA ≥50 c/mL*	12 (19%)	8 (12%)	3 (5%)	8 (8%)
	No virological data at Week 48				
	Discontinued due to AE or death	0	5 (7%)	2 (3%)	4 (4%)
	Discontinued for other reason	4 (6%)	0	1 (1·5%)	6 (6%)
	Missing data during window but on-study	0	0	1 (1·5%)	0
Observed analysis					
Week 24	**Observed population, N**	62	57	64	91
	HIV-1 RNA <50 copies/mL, n (%)	57 (92%)	54 (95%)	62 (97%)	88 (97%)
Week 48	**Observed population, N**	51	54	59	84
	HIV-1 RNA <50 copies/mL, n (%)	49 (96%)	54 (100%)	59 (100%)	81(96%)

*Virological failure

3TC, lamivudine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate.

Table 3: Treatment-emergent resistance profile

	BMS-986001 + EFV + 3TC			TDF + EFV + 3TC
	100 mg once daily N=65	**200 mg once daily N=67**	**400 mg once daily N=66**	**300 mg once daily N=99**
Met criteria for resistance testing, n*	10	6	2	4
Genotype determinable, n*	10	4	2	1
Emergent resistance/reduced susceptibility to study drugs (includes recent data post-DBL)				
NNRTI RAM, n (%)	9 (14%)	4 (6%)	4 (6%)[†]	1 (1%)[‡]
K103N, n	8	3	3	1
V106M, n	1	1	0	0
Y188C, n	1	0	0	0
G190A, n	1	0	1	0
NRTI RAM, n (%)	3 (5%)	0	1 (2%)	0
M184V, n	3	0	1	0

* Minimum criteria for resistance testing: (1) Confirmed HIV-1 RNA >400 copies/mL after achieving viral suppression (HIV-1 RNA <50 copies/mL) (2) Discontinuation from study prior to achieving viral suppression after Week 8, with last plasma HIV-1 RNA >400 copies/mL. Based on all data available through the Week 48 database lock (DBL). [†] Two patients developed EFV RAM (Week 40 and Week 12) and provided data after DBL. [‡] One patient developed EFV RAM (Week 32) and provided data after DBL. Additionally, one patient in the 100 mg (Week 56) and one patient in the 400 mg (Week 56) arms developed EFV RAM and provided data after DBL.

3TC, lamivudine; EFV, efavirenz; RAM, resistance associated mutation; TDF, tenofovir disoproxil fumarate.

Figure legends

Figure 1: Study enrolment and randomization
3TC, lamivudine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate.

Figure 2: Mean percent change in BMD by DXA from baseline to Week 24 and 48
BMD, bone mineral density; QD, once daily; SE, standard error of the mean.