Table 1. All-Cause Mortality Stratified by Microorganism and Minimum Inhibitory Concentrations, Through Day 42

		MIC Values[a], µg/mL (%)							
Treatment	***Aspergillus* spp**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**> 16**
ISA	*Aspergillus* spp	1/9 (11.1)	1/8 (12.5)	1/10 (10.0)	2/5 (33.3)	0/6	0/1	0	1/1 (100)
	A flavus	1/2 (50.0)	0/1	0/3	0/2	0/1	0	0	0
	A fumigatus	1/8 (12.5)	0/7	1/6 (16.7)	0/2	0	0/1	0	1/1 (100.0)
	A niger	0	0	0	1/1 (100.0)	0/4	0	0	0
	A terreus	0/1	1/1 (100.0)	0/1	0/1	0/1	0	0	0
	A westerdijkiae	0	0	0	1/1 (100.0)	0	0	0	0
VRC	*Aspergillus* spp	2/2 (100)	3/5 (60)	0/12	3/5 (80)	0	0	0	0
	A flavus	0	0/1	0/4	1/2 (50.0)	0	0	0	0
	A fumigatus	2/2 (100.0)	3/4 (75.0)	0/7	2/3 (66.7)	0	0	0	0
	A terreus	0	0	0/1	0	0	0	0	0

ISA, isavuconazole; VRC, voriconazole; MIC, minimum inhibitory concentration.

[a]The denominator is the number of patients whose isolates had that MIC value: Some patients contributed multiple isolates with different MIC values or had multiple isolates with the same MIC values.

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BMS-986001 Is Effective Treatment for HIV-1-Infected Subjects

Written by Maria Vinall

BMS-986001 is a novel nucleoside analog reverse-transcriptase inhibitor (NRTI) that, in higher doses, demonstrated comparable efficacy to tenofovir (TDF) in treatment-naïve HIV-1-infected subjects. Samir Gupta, MD, Indiana University School of Medicine, Indianapolis, Indiana, United States, presented the results of this phase 2b randomized dose trial (active controlled, blinded to BMS-986001) with worldwide recruitment.

BMS-986001 was developed to better target viral transcription and minimize the toxicities associated with current NRTIs, such as increased risk of osteoporotic fracture [Bedimo R et al. *AIDS*. 2012], renal dysfunction [Scherzer R et al. *AIDS*. 2012], and adverse metabolic outcomes [Hammond E et al. *Clin Infect Dis*. 2010]. It is active against some HIV-1 isolates with NRTI resistance-associated mutations, including the K65R and L74V substitutions and the Q151M constellation (without M184V) [Li Z et al. *Antimicrob Agents Chemother*. 2013]. In a previous study [Cotte L et al. *J Acquir Immune Defic Syndr*. 2013], BMS-986001 administration for 10 days led to substantial decreases in plasma HIV-1 RNA levels and was well tolerated.

In this study, the safety and efficacy of BMS-986001 (100, 200, and 400 mg QD) was compared with TDF (300 mg QD) in treatment-naïve subjects with HIV-1. All subjects also received 600 mg of efavirenz (EFV) plus 300 mg of lamivudine (3TC) QD. The primary study end points were the efficacy and safety of BMS-986001 at week 24, determined by measuring the proportions of subjects with plasma HIV-1 RNA < 50 counts/mL and the number of adverse events (AEs). Secondary end points included the efficacy and safety of BMS-986000 through week 48, change from baseline in CD4-positive T-cell count through weeks 24 and 48, and the number of subjects experiencing virologic failure with treatment-emergent resistance-associated mutations through weeks 24 and 48.

Patients were included in the study if they were ≥ 18 years of age and antiretroviral treatment naïve and if they had plasma HIV-1 RNA > 5000 counts/mL and a CD4-positive T-cell count > 200 cells/mm^3. The exclusion criteria were resistance to 3TC, EFV, TDF, or protease inhibitors or a positive test for hepatitis B surface antigen or hepatitis C antibodies/RNA.

Baseline demographics and characteristics in the modified intent-to-treat population (received 1 dose of study drug) were similar among the 4 groups. Subjects age ranged between 29 and 34 years, and the majority were men (62% to 71%). HIV subtypes included AE, B, and C, reflecting the worldwide distribution of the

subjects. Median HIV-1 RNA (log_{10} counts/mL) was 4.4, with ~18% having ≥100 000 counts/mL. Median CD4-positive T-cell count (cells/μL) was 312, with ~8% having <200 cells/μL.

The proportion of subjects achieving HIV-1 RNA <50 counts/mL at weeks 24 and 48 was similar among treatment groups in the modified intent-to-treat population analysis. In the BMS-986000 group, these rates at weeks 24 and 48 were, respectively, 88% and 75% in the 100-mg arm, 81% and 81% for the 200-mg arm, and 95% and 89% for the 400-mg arm. In the TDF group, these rates at weeks 24 and 48 were 89% and 82%, respectively. The observed mean change in CD4-positive T-cell counts was similar from baseline through weeks 24 (about 100 to 150 cells/μL) and 48 (about 150 to 190 cells/μL).

Emergent resistance/reduced susceptibility to the study drug was higher in patients receiving BMS-986000, particularly with the 100-mg dose (14% vs 6% in the 200- and 400-mg dose groups and 1% in the TDF group). The occurrence of serious AEs was similar in the 4 groups. There were no noticeable trends for grade 2 to 4 related AEs or new/unexpected safety signals for TDF; 1 patient died (nonstudy related). Higher doses of BMS-986001 demonstrated comparable efficacy to TDF when combined with EFV+3TC in treatment-naïve HIV-1-infected subjects.

Novel Single-Tablet Regimen Effective as Initial Treatment of HIV

Written by Maria Vinall

The first single-tablet regimen containing an integrase inhibitor for the treatment of human immunodeficiency virus (HIV) demonstrated high rates of virologic suppression, safety, and tolerability at 144 weeks in treatment-naïve patients. Richard Elion, MD, Whitman Walker Health, Washington, DC, USA, presented the results of the prespecified pooled analysis from 2 double-blind, active-control phase 3 studies of first-line treatment.

Elvitegravir (EVG; 150 mg), cobicistat (COBI; 150 mg), emtricitabine (FTC; 200 mg), and tenofovir DF (TDF; 300 mg) compose the single tablet (EVG/COBI/FTC/TDF). A previous study demonstrated that EVG/COBI/FTC/TDF was noninferior at 48 weeks when compared with coformulated efavirenz (EFV), FTC, and TDF (EFV/FTC/TDF) as initial therapy [Sax P et al. *Lancet.* 2012]. Another study showed that EVG/COBI/FTC/TDF, when compared with the ritonavir-boosted (RTV) protease inhibitor regimen of atazanavir (ATV) plus coformulated FTC/TDF (RTV-ATV/FTC/TDF) for initial therapy, was noninferior for the primary outcome of HIV RNA concentration of ≤50 copies/mL at 48 weeks [DeJesus E et al. *Lancet.* 2012]. The comparators in both studies are treatments recommended by guidelines [Gunthard HF et al. *Lancet.* 2014].

The present pooled analysis included treatment-naïve patients with HIV-1 RNA ≥5000 copies/mL and an estimated glomerular filtration rate ≥70 mL/min randomized to either EVG/COBI/FTC/TDF once daily (n=701), a fixed-dose combination pill containing EFV/FTC/TDF every night at bedtime (n=352), or RTV-ATV/FTC/TDF once daily (n=355). The patients were followed for 144 weeks.

The majority of patients were men (90%); the mean age was 38 years; and most (82% to 84%) had an asymptomatic HIV infection. The median baseline HIV-1 RNA level was 4.8 log_{10} copies/mL, and the median GFR was 114 mL/min. The mean CD4 count was 377, 382, and 375 cells/mm^3 in the EVG/COBI/FTC/TDF, EFV/FTC/TDF, and RTV-ATV/FTC/TDFgroups, respectively. Approximately 37% of the patients had viral loads >100 000 copies/mL, and 45% had CD4 counts ≤350 cells/mm^3.

The primary efficacy end point was virologic suppression (HIV-1 RNA <50 copies/mL) at week 48, which was achieved in 89%, 84%, and 87% of the EVG/COBI/FTC/TDF, EFV/FTC/TDF, and RTV-ATV/FTC/TDF groups, respectively. These rates were 79%, 75%, and 75% at week 144, respectively. Outcomes were consistent across demographics and baseline HIV-1 RNA and CD4 levels. Increases in CD4 counts were robust and comparable in each group (about 300 cells/mm^3) at week 144.

Emergent resistance was low and occurred in 2.6%, 4.0%, and 0.6% of the EVG/COBI/FTC/TDF, EFV/FTC/TDF, and RTV-ATV/FTC/TDF groups, respectively, at 144 weeks. Most of the resistance occurred in the first 24 to 48 weeks. There were relatively few adverse events (AEs). Diarrhea, upper respiratory infection, and nausea were the most frequent AEs. AEs leading to discontinuation were similar among the groups (about 7%), and discontinuation due to renal toxicity was infrequent. There were no new cases of proximal tubulopathy and no further increases in serum creatinine. Increases in creatinine usually occurred in the first 4 to 6 weeks. Patients in the EVG/COBI/FTC/TDF group had lower rates of drug-related central nervous system and psychiatric AEs.

Dr Elion stated that the overall efficacy, safety, and tolerability of EVG/COBI/FTC/TDF support its use as a first-line regimen in treatment-naïve patients.