THE MODELLED HEALTH BENEFITS OF TREATMENT WITH FOSTEMSAVIR IN HEAVILY TREATMENT EXPERIENCED PEOPLE LIVING WITH HIV

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Introduction

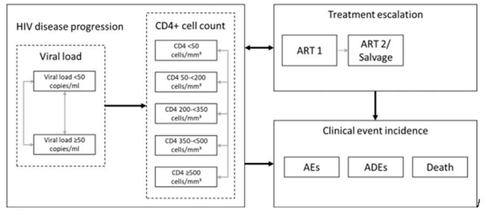
- Heavily treatment experienced (HTE) people living with HIV (PLHIV) have few if any remaining treatment options and are at increased risk of progression to AIDS and death. Consequently, there is an urgent need for effective new treatments in this population.
- In the BRIGHTE study fostemsavir (FTR), a first-in-class oral attachment inhibitor prodrug, led to a significantly greater reduction in mean baseline HIV-1 RNA at Day 8 compared to placebo (p<0.0001) when added to the participant's current failing regimen. After Day 8, all participants received fostemsavir in combination with Optimised Background Therapy (OBT). Continued clinically meaningful improvements in CD4+ T-cell count were observed and viral suppression maintained through 96 weeks [1].
- Disease progression modelling aims to predict the real-world effectiveness of new interventions based on observed clinical trial data. However, the design of the BRIGHTE trial means that comparative effectiveness data is only available for the first 8 days.
- As such, to inform analysis of the long-term effectiveness of fostemsavir plus OBT versus OBT alone, matching-adjusted indirect comparisons (MAICs) were conducted. These data were used to inform key model parameters determining the clinical progression of patients to examine longer-term health benefits.
- This study evaluated the modelled health benefits of management with fostemsavir plus OBT versus OBT alone informed by comparator data from two relevant studies (BENCHMRK and VIKING-3).

Methods

Model Structure

- A deterministic hybrid Markov state-transition model was developed in combination with a decision tree to incorporate treatment allocation based on reasons for discontinuation. A schematic depicting the modelled treatment lines, within therapy health states, and clinical events is provided in Figure 1.
  - Here ART 1 refers to treatment with fostemsavir plus OBT or OBT alone, after which all patients progress to ART 2, a failing salvage regimen. In each modelled monthly cycle, simulated patients' virologic and immunologic status may improve, worsen, or remain constant, represented by transitions through the respective health states.
  - From each viral load and CD4+ cell count health state, patients are subject to the risk of discontinuation due to virologic or non-virologic causes, AIDS-defining events (ADEs) and death. Event rate and utility profiles were informed by published literature [2-4]. Whilst on treatment, patients are subject to the risk of experiencing adverse events (AEs). On discontinuation, simulated patients progress to the subsequent treatment line with initial health state assignment determined by the cause of discontinuation.
- The model was used to estimate life years (LYs) and quality-adjusted life years (QALYs) over a lifetime horizon. Health benefits were discounted at 1.5% per annum.

Figure 1. Schematic summarising the model structure



Comparator Data Sources

- Two MAICs were conducted to inform model inputs (Table 1 & 2), using data from the BENCHMRK study [5] and the VIKING-3 study [6].
  - The BENCHMRK-1 and -2 studies had a comparable patient population to those in BRIGHTE and this trial included an 'OBT alone' arm with sensitivity scores reported and available for matching. However, as BENCHMRK began in 2006 it will not reflect the most contemporary clinical practice.
  - VIKING-3 is a more recent study in the HTE population and the regimens used more closely reflect current clinical practice. However, the matching process (including accounting for the fact all patients received dolutegravir in addition to OBT) means that the comparison will only reflect some of the PLHIV eligible for FTR in clinical practice, excluding those with fewer treatment options available.
  - The MAIC informed inputs reflect predicted greater viral suppression and greater increase in CD4+ cell count with the addition of fostemsavir for both comparisons (Table 1), and comparable rates of discontinuation in the BENCHMRK comparison for Week 0-96 but lower discontinuation with the addition of fostemsavir in the VIKING-3 comparison for Week 0-48 (Table 2). After these timepoints discontinuations were assumed to be the same across both arms for each comparison.

Table 1. MAIC Informed Viral Suppression and CD4+ Cell Count Change

Efficacy profile	Assessment point	Percent suppressed (HIV-1 RNA <50 copies/mL)	Baseline CD4 cell count (cells/mm³)		Change in CD4 cell count (cells/mm³)		Source
			Mean	SD	Mean	SD	
FTR + OBT [BENCHMRK]	Week 96	53.59%	158.00	151.00	184.78	208.88	BENCHMRK MAIC
OBT alone [BENCHMRK]		26.00%	158.00	150.40	49.00	106.00†	Eron et al. 2013 [5]
FTR + OBT [VIKING-3]	Week 48	69.81%	199.90	192.43	141.66	299.39	VIKING-3 MAIC
OBT alone [VIKING-3]		63.39%	199.90	192.43	114.80	130.69	VIKING-3 48 week CSR [7]

†Estimated from reported 95% CI and assuming normally distributed sample statistic

Table 2. MAIC Informed Discontinuation Probabilities

Efficacy profile	Monthly discontinuation probability [mean (SE)]						Source
	Virologic			Non-virologic			
	Week 0-48	Week 48-96	Week 96+	Week 0-48	Week 48-96	Week 96+	
FTR + OBT [BENCHMRK]	0.0090 (0.0084)	0.0090 (0.0084)	0.0085 (0.0071)	0.0005 (0.0021)	0.0005 (0.0021)	0.0005 (0.0017)	BENCHMRK MAIC
OBT alone [BENCHMRK]	0.0080 (0.0058)	0.0080 (0.0058)	0.0085 (0.0071)	0.0005 (0.0014)	0.0005 (0.0014)	0.0005 (0.0017)	Eron et al. 2013 [5]
FTR + OBT [VIKING-3]	0.0050 (0.0080)	0.0122 (0.0091)	0.0122 (0.0091)	0.0007 (0.0030)	0.0017 (0.0034)	0.0017 (0.0034)	VIKING-3 MAIC
OBT alone [VIKING-3]	0.0195 (0.0102)	0.0122 (0.0091)	0.0122 (0.0091)	0.0026 (0.0038)	0.0017 (0.0034)	0.0017 (0.0034)	VIKING-3 48 week CSR [7]

Results

- Table 3 presents the results for each comparison (i.e. FTR+OBT versus OBT alone, (1) informed by the BENCHMRK MAIC and (2) informed by the VIKING MAIC). Incremental LYs and QALYs for fostemsavir plus OBT vs OBT were estimated to be 1.318 and 1.068 for the BENCHMRK MAIC. For the VIKING-3 MAIC, gains in LY and QALYs of 0.737 and 0.592 were predicted.
- The distribution of QALYs accrued by CD4+ cell count category reflects the amount of time individuals spend in each state. Examining QALYs accrued by CD4+ cell count category, incremental values indicate less time spent in worse (lower CD4+ cell count) health states, positive incremental values suggest more time spend in better (higher CD4+ cell count) health states with the addition of fostemsavir for both BENCHMRK and VIKING comparisons.

Table 3. Model Outcomes

Outcomes		Comparison informed by BENCHMRK MAIC			Comparison informed by VIKING MAIC		
		FTR + OBT	OBT alone	Incremental	FTR + OBT	OBT alone	Incremental
Total LYs		9.684	8.366	1.318	8.540	7.803	0.737
Total QALYs		7.288	6.220	1.068	6.460	5.868	0.592
QALYs accrued	CD4+ cell count <50	1.155	1.348	-0.193	1.153	1.290	-0.137
	CD4+ cell count 50-<200	1.300	1.927	-0.627	1.059	1.153	-0.094
	CD4+ cell count 200-<350	1.591	1.841	-0.250	0.902	0.926	-0.025
	CD4+ cell count 350-<500	1.830	0.883	0.947	1.066	0.995	0.071
	CD4+ cell count ≥500	1.466	0.277	1.190	2.336	1.560	0.776
QALYs lost	ADEs	0.003	0.004	-0.001	0.003	0.003	0.000
	Death	0.051	0.053	-0.001	0.052	0.053	-0.001

Conclusions

- Fostemsavir is a new treatment option with demonstrable safety and efficacy that is predicted to provide meaningful improvements in survival and quality of life for HTE PLHIV in this modelling study. Both comparisons suggest that treatment with fostemsavir is associated with substantial gains in LY and QALYs; interpretation of the most appropriate comparison depends on the clinical context and treatments available to the patient population.

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References

1. Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. The lancet HIV. 2020;7(11):e740-e51.
2. Kauf TL, Roskell N, Shearer A, et al. A predictive model of health state utilities for HIV patients in the modern era of highly active antiretroviral therapy. Value in Health. 2008;11(7):1144-53.
3. Paltiel AD, Scharfstein JA, Seage GR, et al. A Monte Carlo Simulation of Advanced HIV Disease Application to Prevention of CMV Infection. Medical Decision Making. 1998;18(2 suppl):S93-S105.
4. Anis AH, Nosyk B, Sun H, et al. Quality of Life of Patients With Advanced HIV/AIDS: Measuring the Impact of Both AIDS-Defining Events and Non-AIDS Serious Adverse Events. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2009;51(5):631-9.
5. Eron JJ, Cooper DA, Steigbigel RT, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. Lancet Infect Dis. 2013;13(7):587-96.
6. Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study. Journal of Infectious Diseases 2014;210(3):354-62 doi: 10.1093/infdis/jiu051[published Online First: Epub Date]|.
7. GlaxoSmithKline and ViiV Healthcare. Clinical Study Report: A Phase III Study to Demonstrate the Antiviral Activity and Safety of Dolutegravir in HIV-1 Infected Adult Subjects with Treatment Failure on an Integrase Inhibitor Containing Regimen (ING112574 – Week 48 Results of All Subjects Enrolled [N=183]). 2013.

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