An Analysis of Cost and Health Outcomes Associated With Tenofovir/Emtricitabine and Abacavir/Lamivudine in Combination With Efavirenz or Atazanavir/Ritonavir for Treatment-Naïve Adults With HIV-1 Infection in the United Kingdom

Edmund Wilkins,[1] Martin Fisher,[2] Anita J Brogan,[3] Sandra E Talbird[3]

[1]North Manchester General Hospital, Manchester, United Kingdom; [2]Brighton and Sussex University Hospitals, National Health Service Trust, Brighton, United Kingdom; [3]RTI Health Solutions, Research Triangle Park, NC, United States

BACKGROUND

- In 2012, there were an estimated 98,400 people living with human immunodeficiency virus (HIV) in the United Kingdom (UK).[1]
- With life expectancies of people living with HIV approaching those of the general population,[2] lifelong antiretroviral therapy has resulted in rising treatment costs.[3]
- Selecting the most clinically effective and cost-effective first-line antiretroviral regimen may help to reduce costs, because first-line regimens provide the best chance for durable virologic suppression[4] and are generally less expensive[5] and associated with lower overall health care costs[6] than subsequent lines.
- With unprecedented financial pressure in the National Health Service budget, clinicians must adhere to principles of clinical and cost-effective prescribing.[7]
- Given this pressure, economic analyses are needed to determine if tenofovir and emtricitabine (TDF/FTC), which is the only preferred first-line regimen backbone in the current British HIV Association (BHIVA) guidelines,[8] is cost-effective compared with abacavir and lamivudine (ABC/3TC) when used as the backbone in first-line antiretroviral regimens.
- The AIDS Clinical Trials Group (ACTG) 5202 clinical trial provides a unique head-to-head comparison of relevant first-line regimens for an economic analysis.

OBJECTIVE

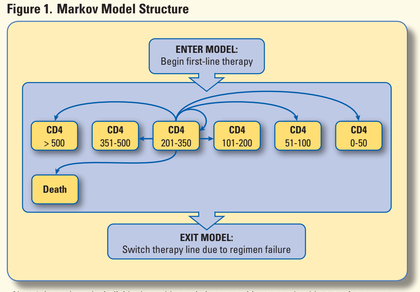
- To assess the cost-effectiveness of the four comparators examined in the ACTG 5202 clinical trial, TDF/FTC or ABC/3TC in combination with efavirenz (EFV) or atazanavir/ritonavir (ATV/r), for treatment-naïve adults with HIV-1 infection in the UK.

METHODS

Model Structure

- A Markov model with six CD4-based health states and a 1-year cycle was developed to estimate costs and health outcomes for individuals on first-line therapy (Figure 1).
- The model tracked individuals until death or regimen failure (i.e., virologic failure or discontinuation of first-line therapy due to tolerability or other reasons).
- Individuals accrued antiretroviral and other medical costs (2012 British pounds) and quality-adjusted life-years (QALYs) as they progressed through the model.

Figure 1. Markov Model Structure



Note 1: In each cycle, individuals could remain in or transition to any health state. As an example, this figure displays all possible transitions from the 201-350 CD4-based health state.

Note 2: Individuals exited the model upon regimen failure (i.e., confirmed virologic failure [HIV RNA ≥ 1,000 copies/mL at or after 16 weeks and before 24 weeks or ≥ 200 copies/mL at or after 24 weeks] or discontinuation due to tolerability or other reasons.

Model Analyses

- The ACTG 5202 study was terminated early for participants with high baseline viral load because of inferior response among participants randomized to ABC/3TC-based regimens. BHIVA guidelines restrict ABC/3TC use in the UK to patients with a viral load of < 100,000 copies/mL.
- Therefore, two analyses were conducted:
  - Full population (primary analysis)
  - Population with low baseline viral load (< 100,000 copies/mL) (secondary analysis)
- Cost-effectiveness analyses evaluate alternative treatment regimens in terms of incremental lifetime costs and incremental health outcomes, such as life-years and QALYs, to determine the best value for money.
- Although National Institute for Health and Care Excellence (NICE) guidance is currently unavailable for HIV treatments, NICE guidelines generally recommend that treatments be considered cost-effective at a maximum incremental cost per QALY gained of £30,000.[9]
- A probabilistic sensitivity analysis was performed by simultaneously sampling all model input parameters from appropriate probability distributions in 10,000 Monte Carlo simulations. This type of analysis assesses the overall impact of input parameter uncertainty on model results.
- Because therapeutic tenders are commonplace in the UK, price reduction scenarios at various levels were conducted to determine whether results were sensitive to model inputs. Other scenario analyses of interest were conducted as well.

Input Parameters

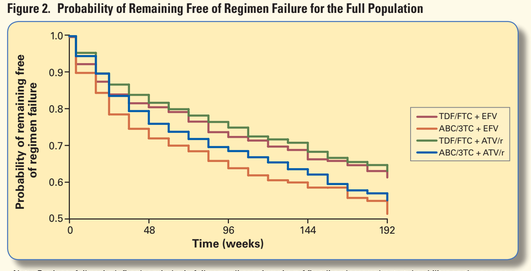
- Characteristics of the modeled populations were based on characteristics of participants in the pooled, intent-to-treat population of ACTG 5202 (Table 1).
- Head-to-head regimen efficacy data were available for up to 192 weeks for participants with low baseline viral load and up to 108 weeks for participants with high baseline viral load (due to early trial termination in this subgroup).[10-12]
  - Kaplan-Meier survival estimates for time to regimen failure (Figure 2) were used to estimate annual probabilities of switching off first-line therapies by fitting exponential curves to the data.
  - Changes in CD4 cell count (means and standard deviations [SDs]) (Table 2) were used to estimate annual transition probabilities.

Table 1. Characteristics of Modeled Population[10-12]

Characteristic	Full Population	Population With Low Baseline Viral Load[a]
Median age, years	38.0	37.0
Female	17.3%	19.0%
Starting CD4 distribution		
0-50	18.3%	9.7%
51-100	8.1%	5.7%
101-200	16.8%	15.4%
201-350	35.3%	42.1%
351-500	15.8%	20.4%
> 500	5.8%	6.7%

[a] Not all data were available for the low viral load group and were imputed using the data for all patients and patients with high baseline viral load.

Figure 2. Probability of Remaining Free of Regimen Failure for the Full Population



Note: Regimen failure is defined as virologic failure or discontinuation of first-line therapy due to tolerability or other reasons.

Table 2. Clinical Efficacy Data for First-Line Regimens for the Full Population[10-12]

Input Parameter	TDF/FTC + EFV	ABC/3TC + EFV	TDF/FTC + ATV/r	ABC/3TC + ATV/r
Immunologic response, mean (SD) CD4 cell-count increase, cells/mm³ through year 3				
Baseline to 48 weeks	181 (127)	197 (139)	206 (150)	198 (150)
Baseline to 96 weeks	245 (169)	264 (174)	283 (184)	268 (184)
Baseline to 144 weeks	289 (169)	315 (204)	324 (180)	305 (190)
Modeled immunologic response after year 3[a]				
Annual CD4 cell-count increase, cells/mm³	22	26	21	19
Reason for switching therapy line (through 192 weeks)				
Virologic failure	14.4%	18.1%	14.3%	20.9%
Tolerability or other reasons	24.5%	30.6%	22.8%	24.2%

[a] The model assumed that individuals who remained on therapy gained half as many cells in each year beyond year 3 of the trial as they did in year 3, with SDs extrapolated similarly.

- Daily antiretroviral regimen costs for TDF/FTC + EFV, ABC/3TC + EFV, TDF/FTC + ATV/r, and ABC/3TC + ATV/r were £20.63, £18.42, £24.71, and £22.50, respectively.[13]
- Costs for switching regimens due to virologic failure (£817.82) and tolerability/other reasons (£355.51) were based on physician visits and laboratory tests. The cost for switching due to virologic failure includes the cost of a resistance assay, which is not required when switching for tolerability or other reasons.
- Annual medical care costs, utility values, and HIV-related mortality rates were stratified by CD4 cell-count range (Table 3).
- Mandalia and colleagues (2010)[3] presented annual medical costs by stage of HIV infection (AIDS, symptomatic non-AIDS, asymptomatic), which were mapped to the model's CD4 health states (Table 4).
- Age- and gender-specific general population mortality was adjusted by a relative risk factor of 1.5 to account for higher non–HIV-related mortality in people with HIV.[14]

Table 3. Annual Medical Costs, Utility Values, and HIV-Related Mortality by CD4 Cell-Count Range, Mean (Range or Standard Error)

CD4 Cell-Count Range	Annual Medical Costs[3,a]	Utility Values[15,b]	Annual HIV-Related Mortality Rates[16]
0-50	£34,657 (± 20%)	0.781 (0.009)	0.176 (0.021)
51-100	£34,657 (± 20%)	0.853 (0.007)	0.055 (0.008)
101-200	£16,540 (± 20%)	0.853 (0.007)	0.022 (0.003)
201-350	£10,501 (± 20%)	0.931 (0.007)	0.008 (0.001)
351-500	£6,721 (± 20%)	0.933 (0.006)	0.004 (0.001)
> 500	£6,721 (± 20%)	0.946 (0.006)	0.004 (0.001)

[a] Annual medical costs exclude antiretroviral drug costs and were inflated to 2012 British pounds.

[b] Utility values are between 0 and 1 and quantify individual preferences for being in particular health states; 1 represents perfect health and 0 represents death.

Table 4. Stage of HIV Infection Mapped to CD4 Health States

Model CD4 Range	Stage of HIV Infection
< 100 cells	AIDS
101-200 cells	25% AIDS; 75% symptomatic, non-AIDS
201-350	Symptomatic, non-AIDS
> 350 cells	Asymptomatic

RESULTS

Primary and Secondary Analysis Results

- In both analyses, individuals using TDF/FTC-based regimens remained on first-line therapy longer (Figure 3) and accrued more QALYs (Table 5) than individuals using ABC/3TC-based regimens.
- In the primary analysis, TDF/FTC + EFV had the lowest projected average cost per year on first-line therapy (£12,902 vs. £13,087-£14,488).
- Over the duration of first-line therapy, TDF/FTC-based regimens were cost-effective compared with ABC/3TC-based regimens, using a willingness-to-pay threshold of £30,000 per QALY gained (Table 5).

Figure 3. Projected Mean Time on First-Line Therapy by Regimen

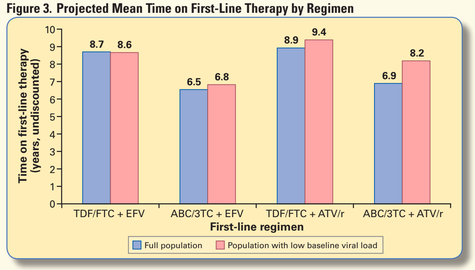


Table 5. Base-Case Results: Cost-effectiveness of TDF/FTC-Based Regimens Compared With ABC/3TC-Based Regimens

Outcome[a]	TDF/FTC + EFV	ABC/3TC + EFV	TDF/FTC + ATV/r	ABC/3TC + ATV/r
Primary analysis: full population				
Total costs	£111,882	£85,477	£124,302	£99,609
Antiretroviral drug costs	£51,002	£36,282	£62,504	£46,506
Other medical costs	£60,880	£49,195	£61,798	£53,103
Life-years	6.77	5.39	6.93	5.66
QALYs	6.30	5.02	6.45	5.26
Incremental cost per life-year gained[b]	£19,182		£19,490	
Incremental cost per QALY gained[b]	£20,545		£20,652	
Secondary analysis: population with low baseline viral load				
Total costs	£109,304	£86,030	£129,581	£110,132
Antiretroviral drug costs	£50,707	£37,627	£64,995	£53,139
Other medical costs	£58,597	£48,403	£64,586	£56,993
Life-years	6.73	5.59	7.20	6.47
QALYs	6.28	5.22	6.71	6.03
Incremental cost per life-year gained[b]	£20,464		£26,431	
Incremental cost per QALY gained[b]	£21,984		£28,651	

[a] All health and cost outcomes were discounted at 3.5% per year.[3]

[b] Incremental cost-effectiveness ratios are provided for each TDF/FTC-based regimen compared with the ABC/3TC-based regimen that contains the same third agent (EFV or ATV/r).

Sensitivity and Scenario Analysis Results

- Probabilistic sensitivity analysis results indicated that TDF/FTC-based regimens were optimal at willingness-to-pay thresholds between approximately £20,000 and £100,000 per QALY gained.
- Results of the analysis were robust in scenarios that tested discount rate, time horizon, and antiretroviral drug prices that reflect the UK market (Table 6).

Table 6. Selected Scenario Analysis Results: Cost-effectiveness of TDF/FTC-Based Regimens Compared With ABC/3TC-Based Regimens

Scenario	Incremental Cost per QALY Gained	
	TDF/FTC + EFV vs. ABC/3TC + EFV	TDF/FTC + ATV/r vs. ABC/3TC + ATV/r
Base case (primary analysis)	£20,545	£20,652
0% discount rate	£19,307	£19,779
5-year time horizon	£30,009	£27,966
10-year time horizon	£24,348	£23,468
Excluding individuals with suspected hypersensitivity reaction (HSR)[a]	£20,752	£20,219
Generic pricing for EFV[b]	£18,847	N/A
50% price reduction for ABC/3TC, UK acquisition cost for TDF/FTC	£22,833	£23,422
75% price reduction for ABC/3TC, UK acquisition cost for TDF/FTC	£27,332	£28,496

N/A = not applicable.

[a] At the time of ACTG 5202, screening for HSR was not standard of care. This scenario excluded individuals with suspected HSR and included HLA-B*5701 testing costs of £42 for all individuals receiving ABC/3TC.

[b] Daily price of £2.34 instead of the £6.68 list price.[13]

LIMITATIONS

- Modeled first-line regimens and patient characteristics were based on the ACTG 5202 clinical trial, which included United States participants only.
- The analysis evaluated outcomes for patients while on first-line therapy only.
- Individuals could switch therapy due to virologic failure or other reasons, including treatment-related adverse events. However, this analysis considered only costs related to switching and did not consider other costs or utility decrements associated with adverse events; therefore, this analysis offers a conservative estimate of the cost-effectiveness of TDF/FTC-based regimens because of the improved safety profile of TDF/FTC compared with ABC/3TC.

DISCUSSION AND CONCLUSIONS

- In an analysis of the regimens examined in ACTG 5202, TDF/FTC-based regimens yielded more favorable health outcomes and were predicted to be cost-effective compared with ABC/3TC-based regimens in treatment-naïve adults with HIV-1 infection in the UK.
- TDF/FTC-based regimens remained cost-effective even when price discounts were considered.
- Further analyses are needed using mixed-treatment comparisons and a systematic review of available trial data to further assess the cost-effectiveness of all preferred first-line and subsequent regimens in the UK.

FUNDING SOURCE AND ACKNOWLEDGEMENTS

- Funding for this study was provided by Gilead Sciences Europe, Ltd. Authors maintained independent scientific control over the study design and all analyses.
- The authors would like to thank the ACTG 5202 study team for providing additional analyses for our economic model.

REFERENCES

1. Aghaizu A, Brown AE, Nardone A, et al. London: Public Health England, 2013.
2. May M, Gompels M, Sabin C. J Int AIDS Soc. 2012;15(Suppl 4):18078.
3. Mandalia S, Mandalia R, Lo G, et al. PLoS One. 2010;5:e15677.
4. Beck EJ, Mandalia S, Youle M, et al. Int J STD AIDS. 2008 May;19(5):297-304.
5. Médecins Sans Frontières. 16th Edition. Geneva: Médecins sans Frontières, 2013.
6. Snedecor SJ, Khachatryan A, Nedrow K, et al. PLoS One. 2013;8:e72784.
7. National Health Service (NHS). Available at: http://www.england.nhs.uk/wp-content/uploads/2013/06/b06-spec-hiv-serv.pdf. Accessed June 12, 2014.
8. British HIV Association Writing Group. HIV Med. 2014;15:1-85.
9. National Institute for Health and Care Excellence. Available at: http://publications.nice.org.uk/pmg9. Accessed March 2014.
10. Daar ES, Tierney C, Fischl MA, et al. Ann Intern Med. 2011;154:445-6.
11. Sax PE, Tierney C, Collier AC, et al. J Infect Dis 2011;204 1191-201.
12. Sax PE, Tierney C, Collier AC, et al. New Engl J Med. 2009;361:2230-40.
13. Monthly Index of Medical Specialties. Available at: http://www.mims.co.uk. Accessed October 2013.
14. Lewden C, Bouteloup V, De Wit S, et al. Int J Epidemiol. 2012;41:433-45.
15. Simpson KN, Luo MP, Chumney E, et al. HIV Clin Trials. 2004;5:294-304.
16. Mocroft A, Ledergerber B, Katlama C, et al. Lancet 2003;362:22-9.

CONTACT INFORMATION

Edmund Wilkins, MD
Clinical Director of Infectious Diseases Monsall Unit,
Department of Infectious Diseases and Tropical Medicine
North Manchester General Hospital
Crumpsall Manchester M8 5RB United Kingdom
Phone: +44 (0)7976 355 171
E-mail: edmundwilkins@manch.demon.co.uk

20th International AIDS Conference (AIDS 2014)
July 20-25, 2014; Melbourne, Australia