Cost-effectiveness Analysis of Tenofovir/Emtricitabine and Abacavir/Lamivudine in Combination With Efavirenz or Atazanavir/Ritonavir for Treatment-Naïve Adults With HIV-1 Infection in France and Spain

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BACKGROUND

- In 2011, the estimated numbers of people living with human immunodeficiency virus (HIV) in France and Spain were 160,000 and 150,000, respectively.[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.[3-5]
- 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[6] and are generally less expensive and associated with lower overall health care costs than subsequent lines.[7]
- Tenofovir/emtricitabine (TDF/FTC) and abacavir/lamivudine (ABC/3TC) are both recommended nucleoside reverse transcriptase inhibitor (NRTI) backbones for use with either efavirenz (EFV) or atazanavir/ritonavir (ATV/r) as first-line treatment regimens.[8] Economic analyses are needed to determine which NRTI backbone is the cost-effective option.
- 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.
- 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. Treatment guidelines note that ABC should be used with caution in patients with a viral load of > 100,000 copies/mL.[8]

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 EFV or ATV/r, for treatment-naïve adults with HIV-1 infection in France and Spain.

METHODS

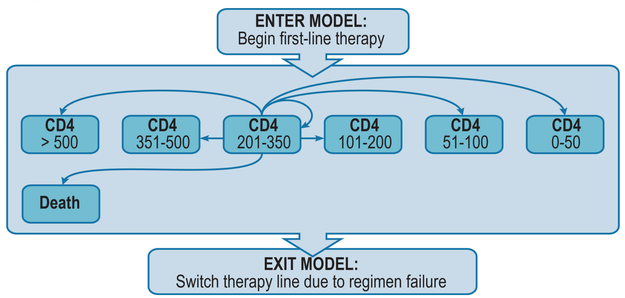
Model Structure

- 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 intolerability or other reasons).
- Individuals accrued antiretroviral and other medical costs (2014 Euros) and quality-adjusted life-years (QALYs) as they progressed through the model.

Model Analyses

- Two analyses were conducted for France and for Spain:
  - Full population (primary analysis)
  - Population with low baseline viral load (<100,000 copies/mL) (secondary analysis)
- Probabilistic sensitivity analysis was conducted to assess the impact of joint parameter uncertainty on the model results by simultaneously sampling each input parameter from an appropriate probability distribution in 10,000 Monte Carlo simulations.
- Scenario analyses were also conducted to estimate the effects of various modeling assumptions on results.
- For each country, results are shown for the primary analysis only, unless otherwise indicated.

Figure 1. Markov Model Structure



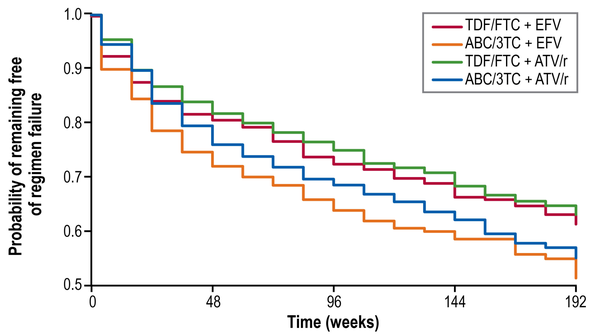
Note 1: In each cycle, individuals could remain in or transition to any health state. As an example, this figure displays all possible transitions from the 201-350 CD4-based health state.

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 of first-line therapy [i.e., discontinuation of the third agent due to intolerability or other reasons]).

Input Parameters

- Characteristics of the modeled populations were based on characteristics of participants in the pooled, intent-to-treat population of ACTG 5202.
- 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).[9-11]
  - 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 via regression analysis.
  - Changes in CD4 cell count (means and standard deviations [SDs]) (Table 1) were used to estimate annual transition probabilities.
- Daily antiretroviral regimen costs, costs for switching regimens due to virologic failure and intolerability/other reasons (based on physician visits and laboratory tests), and annual medical care costs by CD4 cell-count range were obtained from country-specific sources (Table 2).
- Utility values and HIV-related mortality rates were stratified by CD4 cell-count range (Table 3).
- Age- and sex-specific general population mortality data from the most recent national statistics[12,13] were adjusted by a relative risk factor of 1.5 to account for higher non–HIV-related mortality in people with HIV.[2]

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 intolerability or other reasons.

Table 1. Clinical Efficacy Data for First-Line Regimens for the Full Population[9-11]

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/mm^3 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/mm^3	22	26	21	19
Reason for switching therapy line (through 192 weeks)				
Virologic failure	14.4%	18.1%	14.3%	20.9%
Intolerability 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.

Table 2. Country-Specific Costs (2014 Euros), Mean (Range or Standard Error)

Input Parameter	France	Spain
Daily antiretroviral regimen costs[a]		
TDF/FTC + EFV	€17.83	€19.29
ABC/3TC + EFV	€15.19	€15.08
TDF/FTC + ATV/r	€27.83	€27.44
ABC/3TC + ATV/r	€25.19	€23.23
Costs for switching regimens, by reason for switch[b]		
Virologic failure	€530.66 (± 20%)	€682.60 (±20%)
Intolerability/other reasons	€144.83 (± 20%)	€289.89 (±20%)
Annual medical costs, by CD4 cell count range[c]		
0-50	€14,621 (€460)	€2,776 (± 20%)
51-100	€10,600 (€269)	€2,776 (± 20%)
101-200	€9,869 (€656)	€1,949 (± 20%)
201-350	€4,508 (€171)	€1,362 (± 20%)
351-500	€3,533 (€113)	€1,362 (± 20%)
> 500	€2,680 (€69)	€1,243 (± 20%)

[a] Drug regimen costs are based on manufacturer (ex-factory) prices.

[b] The cost for switching regimens due to virologic failure includes the cost of a resistance assay, which is not required when switching for intolerability or other reasons.

[c] Annual medical costs exclude antiretroviral drug costs[3,4] and were inflated to 2014 Euros.

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

CD4 Cell-Count Range	Utility Values[14]	Annual HIV-Related Mortality Rates[15,a]
0-50	0.781 (0.009)	0.176 (0.021)
51-100	0.853 (0.007)	0.055 (0.008)
101-200	0.853 (0.007)	0.022 (0.003)
201-350	0.931 (0.007)	0.008 (0.001)
351-500	0.933 (0.006)	0.004 (0.001)
> 500	0.946 (0.006)	0.004 (0.001)

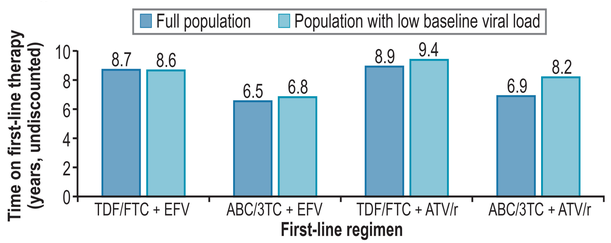
[a] Rates were converted to probabilities in the model using: probability = $1 - e^{-rate}$.

RESULTS

Primary and Secondary Analysis Results

- In France and Spain, for both the primary and secondary analyses, individuals using TDF/FTC-based regimens remained on first-line therapy longer (Figure 3) and accrued more QALYs than individuals using ABC/3TC-based regimens (Table 4).
- Over the duration of first-line therapy, in both the full population and the population with low baseline viral load, 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 4).

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



[a] Results are equivalent for France and Spain to the nearest tenth of 1 year.

Table 4. 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
France				
Primary analysis: full population				
Total costs	€72,498	€52,381	€99,944	€76,851
QALYs	6.50	5.14	6.66	5.39
Incremental cost per QALY gained[b]	€14,787		€18,202	
Secondary analysis: population with low baseline viral load				
Total costs	€71,157	€53,104	€104,258	€86,380
QALYs	6.48	5.35	6.93	6.21
Incremental cost per QALY gained[b]	€16,035		€24,768	
Spain				
Primary analysis: full population				
Total costs	€59,128	€38,435	€81,726	€57,696
QALYs	6.50	5.14	6.66	5.39
Incremental cost per QALY gained[b]	€15,220		€18,953	
Secondary analysis: population with low baseline viral load				
Total costs	€58,687	€39,718	€85,098	€65,912
QALYs	6.48	5.35	6.93	6.21
Incremental cost per QALY gained[b]	€16,860		€26,603	

[a] All health and cost outcomes were discounted at 3.0% per year.[16,17]

[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 at a willingness-to-pay threshold of €30,000 per QALY gained, TDF/FTC-based regimens were cost-effective compared with ABC/3TC-based regimens in the majority of simulations for both the full population and the population with low baseline viral load.
- Primary analysis results were generally robust in scenarios that tested alternative discount rates and time horizons (Table 5).

Table 5. 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
France		
Base case (primary analysis)	€14,787	€18,202
0% discount rate	€13,786	€17,276
5-year time horizon	€23,918	€27,655
10-year time horizon	€18,360	€21,726
Spain		
Base case (primary analysis)	€15,220	€18,953
0% discount rate	€13,951	€17,504
5-year time horizon	€27,254	€34,483
10-year time horizon	€19,736	€24,486

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.
- Estimated annual medical costs by CD4 cell count were substantially different in France and Spain, although cost estimates were based on published data.

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 France and Spain.
- Results underscore the importance of selecting a first-line regimen based on clinical effectiveness and cost-effectiveness, rather than simply regimen cost.

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