COST-EFFECTIVENESS OF ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR COMPARED WITH EFAVIRENZ/EMTRICITABINE/TENOFOVIR AS FIRST-LINE HIV ANTIRETROVIRAL THERAPY IN THE US ADULT POPULATION

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PIN72

Introduction

- For first-line treatment of human immunodeficiency virus (HIV), February 2013 US Department of Health and Human Services (DHHS) treatment guidelines recommend efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF) as a preferred antiretroviral regimen and elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/cobi/FTC/TDF) as an alternative antiretroviral regimen.[1]
  - EFV/FTC/TDF is a once-daily single tablet combining three antiretroviral medications: the non-nucleoside reverse transcriptase inhibitor EFV and the nucleoside reverse transcriptase inhibitors FTC and TDF.
  - EVG/cobi/FTC/TDF is a once-daily single tablet regimen combining four antiretroviral medications: the integrase inhibitor EVG, the pharmacokinetic enhancer "cobi" and the nucleoside reverse transcriptase inhibitors FTC and TDF.
- While EVG/cobi/FTC/TDF and EFV/FTC/TDF were found to have similar clinical efficacy in a Phase III clinical trial,[2] each of these regimens has its own advantages; it is currently unclear how the comparative benefits and risks of these two regimens impact clinical, quality of life, and economic outcomes in HIV patients.

Objective

This study assessed the clinical and economic trade-offs involved in using EVG/cobi/FTC/TDF compared with EFV/FTC/TDF in first-line ART in US adults by evaluating the incremental costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) of EVG/cobi/FTC/TDF compared to EFV/FTC/TDF.

Methods

- Model type: Markov cohort model
- Perspective: U.S. payer
- Strategies:
  - 1st line: EFV/FTC/TDF or EVG/cobi/FTC/TDF
  - 2nd line: atazanavir/ritonavir + 2 NRTIs or darunavir/ritonavir + 2 NRTIs
  - 3rd line: darunavir + etravirine or maraviroc + raltegravir
  - Nonsuppressive therapy (NST) was considered equivalent to 3rd line treatment
- Cycle length: 12 weeks
- Annual discount rate: 3%

Model cost parameters

Parameter	Estimate[a,b]	Source
Product acquisition:		
1st Line		1,3
EFV/FTC/TDF	4,918	
EVG/cobi/FTC/TDF	6,559	
2nd Line[c]	6,977	
3rd Line[d]	9,092	
Patient monitoring[e]:		
No virologic failure[f]	914	4
Virologic failure		
CD4 ≥50 cells/mm3[g]	1,561	
CD4 <50 cells/mm3[h]	1,620	
Patient on new line of therapy[i]	113	
Treatment for adverse events:		
Rash	226	4
Elevated lipids	186	3
CNS symptoms	226	4
Renal abnormalities		
No acute kidney injury	914	4
Acute kidney injury	33,594	4, 5
Chronic kidney disease with dialysis	48,665	6
Other adverse events causing discontinuation	226	4

mg, milligrams; CNS, central nervous system

[a] All costs reported in 2012 US dollars.

[b] Gamma distributions for all cost parameters were used in probabilistic sensitivity analysis.

[c] 2nd-line treatment defined as 50% receiving atazanavir/r 2 NRTIs, 50% receiving darunavir/r + 2 NRTIs.

[d] 3rd-line treatment defined as 50% receiving darunavir/r + etravirine, 50% receiving maraviroc + raltegravir + OBT.

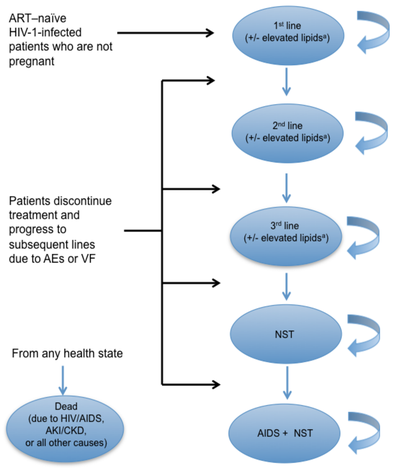
[e] All cost estimates were averages of high and low managed care rates (*Physicians' Fee & Coding Guide 2012*).

[f] Cost included baseline monitoring components, consisting of a 10-minute physician office visit, 1 blood draw, 1 chemistry panel, 1 complete blood count; 1 CD4 count; 1 viral load (ultrasensitive quantification).

[g] Cost included baseline patient monitoring plus a 15-minute physician office visit, 1 blood draw, 1 viral load assessment.

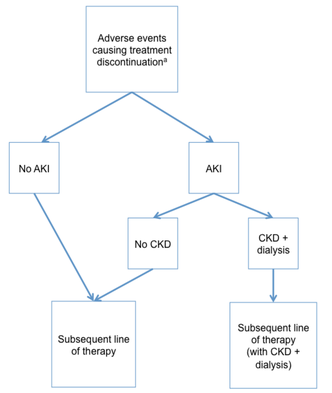
[h] Cost included baseline patient monitoring plus a 25-minute physician office visit, 1 blood draw, 1 viral load assessment.

[i] Cost included a 15-minute physician office visit.



AE, adverse event; AIDS, acquired immune deficiency syndrome; AKI, acute kidney injury; ART, antiretroviral therapy; CKD, chronic kidney disease; HIV, human immunodeficiency virus; NST, nonsuppressive therapy; VF, virologic failure.

[a] Patients with elevated lipids take lipid-lowering therapy until 6 months after progression to next line.



AKI, acute kidney injury; CKD, chronic kidney disease.

[a] Rash, renal abnormalities, CNS symptoms and other events causing discontinuation of treatment.

Utility estimates

Parameter	Estimate	Source[a]
CD4 count (cells/mm3):		
>500	0.946	7
351 to ≤500	0.933	
201 to ≤350	0.931	
50 to ≤200	0.853	
<50	0.781	
Adverse events (disutilities)		
CNS symptoms	-0.043	8
Lipid-lowering therapy	0	9
Rash	-0.034	8
Renal abnormalities		9
No acute kidney injury	0	9
Acute kidney injury[b]	-0.06	10
Chronic kidney disease with dialysis[c]	-0.06	10

mg, milligrams; CNS, central nervous system

[a] Beta distributions used for all utility parameters in probabilistic sensitivity analysis.

[b] Disutility is applied in the cycle in which the acute episode occurs.

[c] Disutility is applied during cycle of initial diagnosis and all subsequent cycles.

Clinical efficacy

Parameter	Estimate (per 12-week cycle)[a,b]	Source
Mortality		
All-cause	Age, gender-specific	11
HIV[c]	0.90%	12
AIDS[c]	3.50%	12
AKI	26.60%	13
CKD with dialysis[d]	1.90%	14
Probabilty of AIDS, given nonsuppressive regimens	1.8%	15
CD4 <50 cells/mm3 (%, among patients with AIDS)[e]	55.20%	16
Proportion achieving virologic response, mean (range per 12-week cycle):[f]		
1st Line		
EFV/FTC/TDF	0.81 (0.72-0.28)	17, 18
EVG/cobi/FTC/TDF	0.85 (0.76-0.89)	17, 18
2nd Line	0.49 (0.41-0.57)	19, 20
3rd Line	0.51 (0.49-0.57)	15, 21, 22
Change in CD4, mean (range per 12-week cycle):[f,g]		
1st Line		
EFV/FTC/TDF	263 (120-367)	2, 18
EVG/cobi/FTC/TDF	263 (140-426)	2, 18
2nd Line	105 (94-109)	23, 24
3rd Line	129 (79 – 147)	15, 21, 22

HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; mm, millimeter.

[a] Values are rounded.

[b] Beta distributions were used for all clinical parameters in the probabilistic sensitivity analysis, except where otherwise noted.

[c] Excess mortality in addition to all-cause.

[d] Average annual mortality by race weighted using EVG/cobi/FTC/TDF population distribution.

[e] CD4 count ≤200 cells/mm3 among all patients with AIDS.

[f] Values varied over time.

[g] Uniform distributions were used in the probabilistic sensitivity analysis.

Results

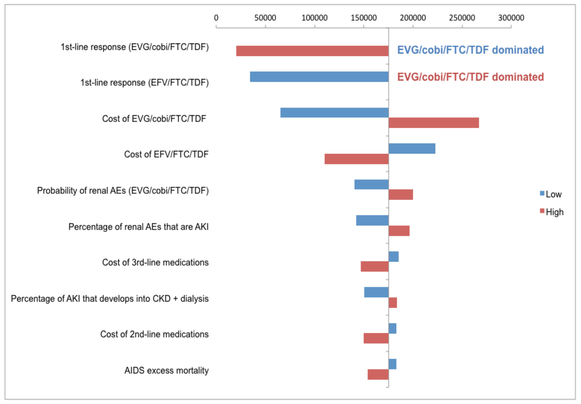
Base Case

- Compared to EFV/FTC/TDF, EVG/cobi/FTC/TDF's lifetime costs were higher by $6,886, with an ICER of $166,287/QALY.
- EVG/cobi/FTC/TDF's life expectancy and quality-adjusted life expectancy were higher than those of EFV/FTC/TDF by 0.0188 years and by 0.0414 QALY, respectively.
- First-line costs were higher for patients on EVG/cobi/FTC/TDF ($53,628) than for those on EFV/FTC/TDF ($28,486).
- For both strategies, most costs were accrued for patients receiving NST or for patients with AIDS.

	Cost		Survival (years)		QALY			
	Lifetime	Δ	Lifetime	Δ	Lifetime	Δ	ICER (LY)	ICER (QALY)
EFV/FTC/TDF	$726,728		16.8436		14.9565			
EVG/cobi/FTC/TDF	$733,615	$6,886	16.8625	0.0188	14.9979	0.0414	$365,750	$166,287

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

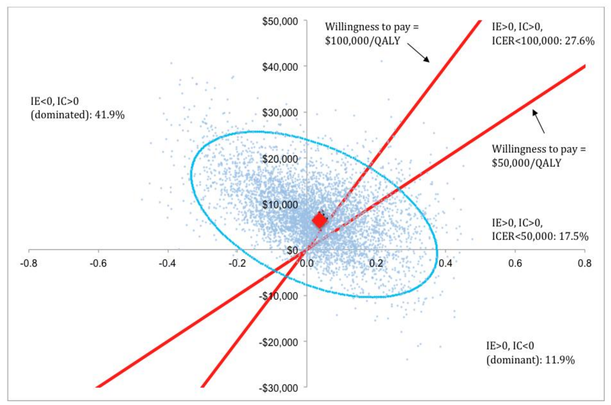
[a] Incorporating 3% annual discount rate for cost, LY, and QALY outcomes. All values are per person and rounded.



AE, adverse event; AKI, acute kidney injury; tx, therapy.

[a] Incorporating 3% annual discount rate for cost, LY, and QALY outcomes. Results expressed in $/QALY for EVG/cobi/FTC/TDF compared to EFV/FTC/TDF.

[b] All parameters varied by +/- 10%.



IC, incremental costs; ICER, incremental cost-effectiveness ratio; IE, incremental effectiveness; QALY, quality-adjusted life year..

[a] Incorporating 3% annual discount rate for cost, LY, and QALY outcomes. Results expressed in $/QALY for EVG/cobi/FTC/TDF compared with EFV/FTC/TDF. Blue dots represent ICERs when all parameters are varied simultaneously for 5,000 model simulations. Larger red box represents base case. Blue dotted line represents 95% confidence ellipse.

Sensitivity Analysis

- Results were most sensitive to 1st-line response rates of EVG/cobi/FTC/TDF and EFV/FTC/TDF, followed by the cost of EVG/cobi/FTC/TDF.
- A 10% decrease in EVG/cobi/FTC/TDF response, or 10% increase in EFV/FTC/TFG response, would result in EVG/cobi/FTC/TDF being dominated.
- Varying EVG/cobi/FTC/TDF costs resulted in ICERs ranging from $65,487 to $267,088/QALY; when EFV/FTC/TDF costs were varied this range was $109,898 to $222,676/QALY.
- Without discounting, the ICER increased to $207,273.
- When risk of CKD with dialysis among EVG/cobi/FTC/TDF patients was half that of base case, the ICER decreased to $96,557/QALY.

Conclusions

- The increased costs of EVG/cobi/FTC/TDF led to an ICER of $166,287. This finding suggests that using EVG/cobi/FTC/TDF in this patient population is not an efficient use of economic resources compared with using EFV/FTC/TDF.
- EFV/FTC/TDF was predicted in this model to lower rates of AKI and CKD events and decrease total spending compared with EVG/cobi/FTC/TDF by reducing viral load with less renal toxicity and having a lower unit cost.
- Efficacy inputs from the pivotal trial (Sax 2012) were based on point estimates. When assuming equivalent efficacy in scenario analysis, EFV/FTC/TDF dominated EVG/cobi/FTC/TDF, suggesting that our base case results may have overestimated EVG/cobi/FTC/TDF's benefit.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents, *Department of Health and Human Services* 2013; **2.** Sax, *Lancet* 2012; **3.** PriceRx, *Wolters Kluwer Health* 2012; **4.** Physicians' Fee & Coding Guide, *MAG Mutual Healthcare Solutions* 2012; **5.** Candrilli, *Clin Lymphoma Myeloma* 2008; **6.** Berger, *Am J Manag Care* 2009; **7.** Simpson, *HIV Clin Trials* 2004; **8.** Roskell, *XVI International AIDS Conference* 2006; **9.** Expert opinion; **10.** Sullivan, *Med Decis Making* 2006; **11.** NCHS (National Center for Health Statistics), *Center for Disease Control (CDC)* 2012; **12.** Center for Disease Control (CDC), *HIV Surviellance Report* 2012; **13.** Wyatt, *AIDS* 2006; 14. Choi, *Kidney Int* 2007; **15.** Gulick, *N Eng J Med* 2008 **16.** Baker, *AIDS* 2008; **17.** Gilead Sciences Inc., *Antiviral Drugs Advisory Committee Meeting Briefing Document* 2012; **18.** Rockstroh, *Clin Infect Dis* 2011; **19.** Banhegyi, *Curr HIV Res* 2012; **20.** Johnson, *AIDS* 2006; **21.** Anderson, *Curr HIV Res* 2012; **22.** Hodder *AIDS Res Hum Retroviruses* 2012; **23.** Clotet, *Lancet* 2007; **24.** Johnson, *AIDS* 2005.

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