Cost effectiveness of atazanavir-ritonavir vs. lopinavir-ritonavir in HIV-infected patients initiating first-line antiretroviral therapy

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BACKGROUND

- Human immunodeficiency virus (HIV) is a significant cause of morbidity, mortality, and resource expenditure in the U.S., causing opportunistic infections (OIs), acquired immunodeficiency syndrome (AIDS), treatment-related complications, and deaths.
- Protease inhibitor (PI)-based combination antiretroviral therapy (cART) is one of the preferred treatment options for antiretroviral-naïve HIV-infected patients.
- The treatment-related adverse effects (most notably gastrointestinal toxicity and increases in lipid values) of cART can negatively impact medication adherence and long-term effectiveness.
- Atazanavir used in combination with ritonavir (ATV+r) was introduced in the U.S. in 2003 as an alternative to lopinavir/ritonavir (LPV/r); ATV+r patients have less GI toxicity and lower increases in lipids, but they also have a risk of hyperbilirubinemia.
- Use of ATV+r among HIV-infected patients was shown in the CASTLE trial to be noninferior to an LPV/r-based regimen in terms of efficacy.

OVERVIEW

OBJECTIVE:

- To evaluate lifetime cost effectiveness of ATV+r versus LPV/r, both with tenofovir-emtricitabine (TDF/FTC), in U.S. HIV-infected patients initiating first-line antiretroviral treatment.

FRAMEWORK:

1) Developed a Markov microsimulation model to calculate, from a U.S. payer perspective:
   - Quality-adjusted life years (QALYs), based on CD4 and HIV RNA levels
   - Coronary heart disease (CHD)
   - AIDS diagnoses
   - OIs
   - Diarrhea
   - Hyperbilirubinemia
2) Estimated model baseline characteristics, virologic suppression, cholesterol changes, and diarrhea and hyperbilirubinemia rates from 96-week CASTLE trial results.
3) Estimated HIV mortality, OI rates, treatment adherence, costs, utilities, and CHD risk from literature and experts.

METHODS

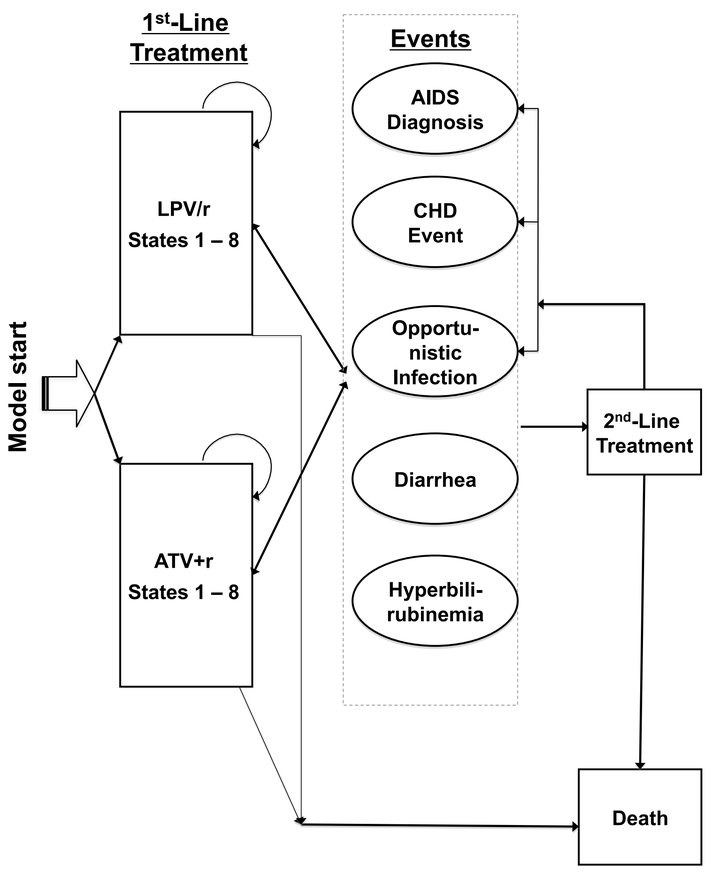
MARKOV MICROSIMULATION MODEL:

- Simulated a hypothetical cohort of 1,000,000 HIV-1-infected cART-naïve U.S. patients through two scenarios:
  1) treatment with ATV+r in combination with fixed-dose TDF/FTC, or
  2) treatment with LPV/r in combination with fixed-dose TDF/FTC
- Patients moved among eight HIV-specific health states defined by CD4 count (>350 cells/mL; 201-350; 50-200; and <50) and HIV RNA levels (viral load of <50 or ≥50 copies/mL).
- The four worst states represented the CDC's definition of AIDS.
- Individuals could transition between any state while receiving 1st-line treatment
- Patients switched to 2nd-line treatment if they experienced:
  1) virologic failure (2 consecutive model cycles in health state with RNA ≥50 copies/mL after 24 weeks of treatment)
     or
  2) severe levels of diarrhea (in LPV/r arm) or hyperbilirubinemia (in ATV+r arm)
- 2nd-line treatment consisted of a basket of cART regimens (same between treatment arms)
- Individuals did not return to 1st-line treatment once they progressed to 2nd-line treatment
- All outcomes were evaluated over 1-, 2-, 5-, 10-, 20-year, and lifetime periods

HIV State Definitions and Transition Probabilities (per 3-month cycle)

HIV state	CD4 count (cells/mL)	HIV RNA (copies/mL)	Probability of Opportunistic Infection	Probability of Transitioning from Prior State	
				LPV/r	ATV+r*
1	>350	<50	0.017	0.852†	0.864†
2		≥50	0.022	0.067	0.054
3	201–350	<50	0.028	0.074	0.086
4		≥50	0.038	0.054	0.044
5	50–200	<50	0.051	0.029	0.033
6		≥50	0.099	0.047	0.038
7	<50	<50	0.179	0.002	0.002
8		≥50	0.179	0‡	0‡

* ATV+r transitions based on a 19% lesser likelihood of transitioning to state with greater viral load (≥50 copies/mL) than when receiving LPV/r
† Probability of remaining in state 1
‡ Transitions occurred from states other than 7



Model Parameter Estimates

Age in years, mean (SD)	36.4 (9.6)			
Female, %	31.6			
CD4 cells/mL, mean (SD)	214 (133)			
HIV RNA copies/mL, mean (SD)	181,484 (204,601)			
DM, %	1.8			
CHD, %	0.7			
CHD risk (event/1,000 person-years)				
No prior CHD/DM	3.4			
Prior CHD	76.4			
Prior DM	16.4			
Prior DM and CHD	101.9			
Risk of CHD event being fatal	35.4%			
OIs (event/patient/cycle)	0.017 to 0.179 (states 1 to 8)			
	LPV/r	ATV+r		
Effect of treatment on transition to state with RNA ≥50 copies/mL (greater viral load)	N/A (Baseline)	-19%		
Effect of treatment on TC:HDL ratio	-0.17	-0.40		
Adherence:				
Rate	71%	82%		
Effect of nonadherence on transition to state with RNA ≥50 copies/mL (greater viral load)	+10%			
Diarrhea, risk (%) at varying weeks on regimen	0-48	49-96	0-48	49-96
Mild/Moderate	2.74	0.06	0.57	0.06
Severe	0.23	0.17	0.00	
Hyperbilirubinemia risk (%)				
Mild/moderate	0.46		12.24	
Severe	0.00		0.68	

Net QALYs Lost & Costs Incurred

QALY			
HIV state			
	1	0.944	
	2	0.935	
	3	0.929	
	4	0.932	
	5	0.863	
	6	0.849	
	7	0.781	
	8*	0.781	
CHD	Ongoing		Event
	0.90		0.88
Diarrhea	Mild/Moderate		Severe
	0.900		0.641
Hyperbilirubinemia	Mild/Moderate		Severe
	0.999		0.950
Costs (2008 U.S. dollars)			
First-line	LPV/r		ATV+r
	4,145		4,604
Second-line†	4,049		
Effect of nonadherence on first-line drug costs	-20%		
Nondrug costs by HIV state‡			
1, 3, 5	461		
2, 4, 6	720		
7	479		
8†	758		
CHD	Ongoing		Event
	806		12,885
Diarrhea¶	28		
Hyperbilirubinemia	0		
OI	4,442		

* Includes states beyond first-line treatment
† 40% abacavir/lamivudine+darunavir+ritonavir and 60% efavirenz/emtricitabine/tenofovir
‡ Direct medical costs of: 1 chemistry panel, 1 complete blood count, and 1 CD4 count; a 10-minute visit to a physician for states1-6, a 15-minute visit for state 7, and a 25-minute visit for state 8; 1 blood draw and 1 viral load assessment (ultrasensitive quantitation) in states 1, 3, 5, and 7; 2 blood draws and 2 viral load assessments in states 2, 4, 6, and 8.
¶ Loperamide 2 md bid

RESULTS

OVERVIEW:

- Compared with U.S. HIV-infected patients initiating LPV/r, ATV+r patients were predicted over a lifetime:
  - ➢ To receive first-line therapy for a longer time (97.3 versus 70.7 months)
  - ➢ To experience fewer cases of AIDS, OIs, CHD, and diarrhea and more cases of hyperbilirubinemia
  - ➢ To have longer quality-adjusted survival, similar absolute survival, and higher costs
- ATV+r added 0.26 QALYs at a cost of $6,826, for an incremental cost effectiveness ratio of $26,421 per QALY gained
- At a willingness-to-pay threshold of $50,000/QALY, ATV+r was cost effective 94% of the time

LIFETIME OUTCOMES:

Health-related outcomes (per 1,000 person-years)

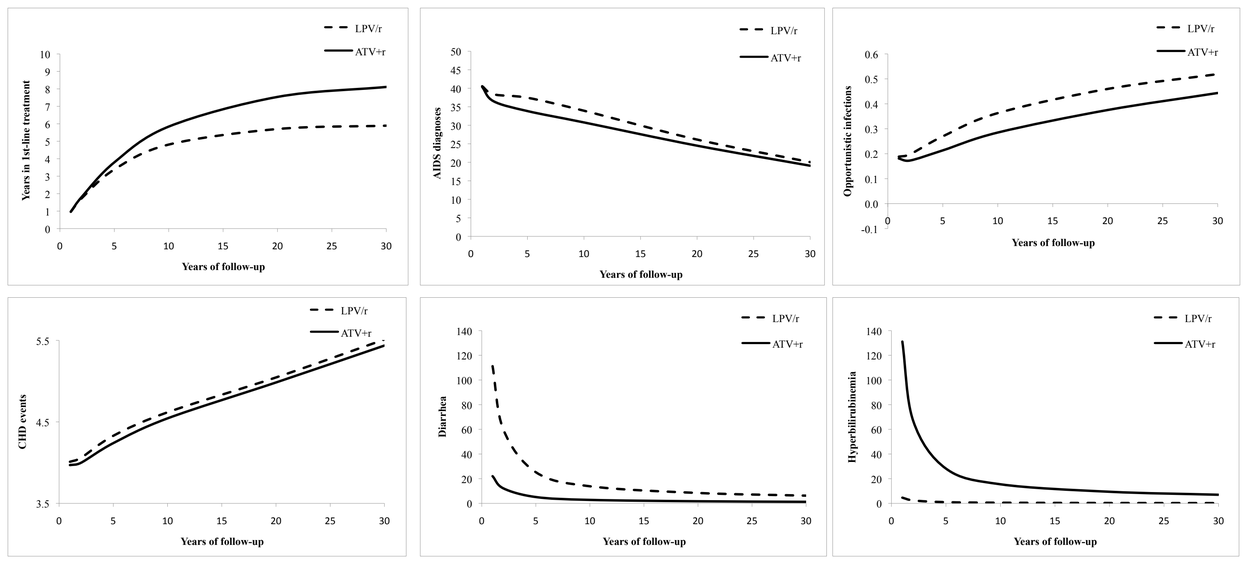
	Months in First-Line Treatment	AIDS	OI	CHD	Diarrhea	Hyperbilirubinemia
LPV/r	70.7	20.054	0.519	5.511	6.262	0.247
ATV+r	97.3	19.081	0.443	5.437	1.272	6.986

Cost and QALY outcomes

	Cost	Incremental Cost	QALY	Incremental QALY	Incremental cost-effectiveness ratio
LPV/r	$269,160	---	10.761	---	---
ATV+r	$275,986	$6,826	11.020	0.258	$26,421

ATV+r, atazanavir-ritonavir; CHD, coronary heart disease; LPV/r, lopinavir-ritonavir; OI, opportunistic infection; QALY, quality-adjusted life year; WLP, wholesale list price

EVENTS OVER TIME:



SENSITIVITY ANALYSES:

- At a willingness-to-pay threshold of $50,000 per QALY, use of ATV+r among U.S. HIV-infected patients was cost saving 15% of the time and cost effective 94% of the time.
- Incremental cost effectiveness exceeded $50,000/QALY only when the impact of ATV+r on viral load, compared with that of LPV/r, was dramatically less than that seen in CASTLE.

CONCLUSIONS

- Compared with U.S. HIV-infected patients initiating LPV/r, the model predicted that patients initiating ATV+r would, over a lifetime, continue to receive first-line treatment for two years longer; experience fewer AIDS diagnoses, OIs, CHD events, and diarrhea episodes; experience more episodes of hyperbilirubinemia; and have greater quality-adjusted survival and similar overall survival.
- Accounting for both lifetime costs and QALYs, ATV+r is cost effective (less than $50,000 per QALY) compared with LPV/r.
- In this era of ever-increasing healthcare costs, this knowledge will be useful to U.S. physicians, policymakers, and payers alike in their efforts at making clinically appropriate yet cost-conscious decisions.
- This model of the lifetime cost effectiveness of ATV+r versus LPV/r could be adapted for use outside of the U.S. to provide similar guidance and improve cost-effective care for HIV-infected patients worldwide.