Real-world adherence and persistence with first-line ritonavir-boosted protease inhibitor-based antiretroviral regimens

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Declarations of interest

- Funding for this research was provided by Bristol-Myers Squibb, New Jersey

- Ms. Taneja, Mr. Gertzog, and Dr. Oster are employees of Policy Analysis Inc., a contract research organization that received payment from the study sponsor

- Dr. Juday, Dr. Hebden, and Dr. Uy are employees of, and own stock in, Bristol-Myers Squibb

Background

- Adherence and persistency are interrelated but distinct concepts in pharmacotherapy:
  - Adherence reflects extent to which patients comply with their prescribed dosing regimens over defined periods of time, and is often measured as the ratio of doses taken to doses prescribed (x 100) [1]
  - Persistency reflects how long patients continue to take a prescribed regimen, and is often measured as 100 minus the percentage of patients discontinuing therapy [1, 2]
- Successful HIV treatment requires high levels of adherence and long-term persistency with combination antiretroviral therapy (cART); poor adherence and persistency may lead to treatment resistance and subsequent virological failure [2]

Background (Cont.)

- Risk factors for poor adherence and persistency include [3-6]:
  - Frequency of dosing
  - Complexity of regimens
  - Psychological and cognitive issues
  - Medication side effects
  - Comorbid diseases
  - Barriers to receipt of care
  - Patient beliefs about seriousness of disease and benefits of treatment
- Little information is available on adherence and persistency with ritonavir-boosted PI-based cART regimens

Objective

- To examine adherence and persistency in a “real-world” setting in patients with HIV who initiated first-line cART with a ritonavir-boosted protease inhibitor (PI)-based regimen, using data from a large US commercial health insurance claims database

Methods: Study Population

- Study population consisted of all persons in the PharMetrics health insurance claims database who, between January 1, 2003 and September 30, 2009, had both paid retail pharmacy claims for antiretroviral drugs and evidence of HIV

- Evidence of HIV was established based on ≥1 inpatient claims, or ≥2 claims for physician office visits and/or hospital outpatient visits on different days, with ICD-9-CM diagnosis codes 042, V08, 795.71, or 79.53

Methods: Study Population (Cont.)

- Patients were excluded from the study sample if they:
  - Did not have evidence of receipt of highly active antiretroviral therapy (combination therapy with ≥3 antiretroviral drugs) between January 1, 2004 and September 30, 2009;
  - Were aged <18 years as of their date of first receipt of an antiretroviral drug during study period ("index date");
  - Had <6 months of complete claims data prior to their index date;
  - Had invalid enrollment data for calendar month in which index date fell;
  - Had any retail pharmacy claims for antiretroviral drugs prior to their index date (i.e., they were not treatment naïve);
  - Did not receive a ritonavir-boosted PI-based regimen; or
  - Had any missing data on therapy-days supplied on any retail pharmacy claim for any drugs comprising the PI-based regimen

Methods: Treatment Groups

- Study subjects were stratified into treatment groups based on cART regimen first received (“index regimen”)
- Index regimens were defined based on outpatient pharmacy claims for antiretroviral drugs (ARVs) during 3-day period beginning with—and including—the index date
- First-line cART regimens with <100 study subjects were not considered in the analysis
  - Lopinavir and atazanavir were the only ritonavir-boosted PIs used by ≥100 patients for first-line cART during the study period

Methods: Treatment Groups (Cont.)

- Ritonavir-boosted PI-based regimens that were evaluated included:
  - Ritonavir-boosted atazanavir plus two or more nucleoside reverse transcriptase inhibitors (ATV/r + ≥2 NRTIs)
  - Ritonavir-boosted lopinavir plus two or more NRTIs (LPV/r + ≥2 NRTIs)

- LPV is available as a fixed-dose combination tablet with ritonavir; ATV is not available in such a combination

Methods: Study Measures

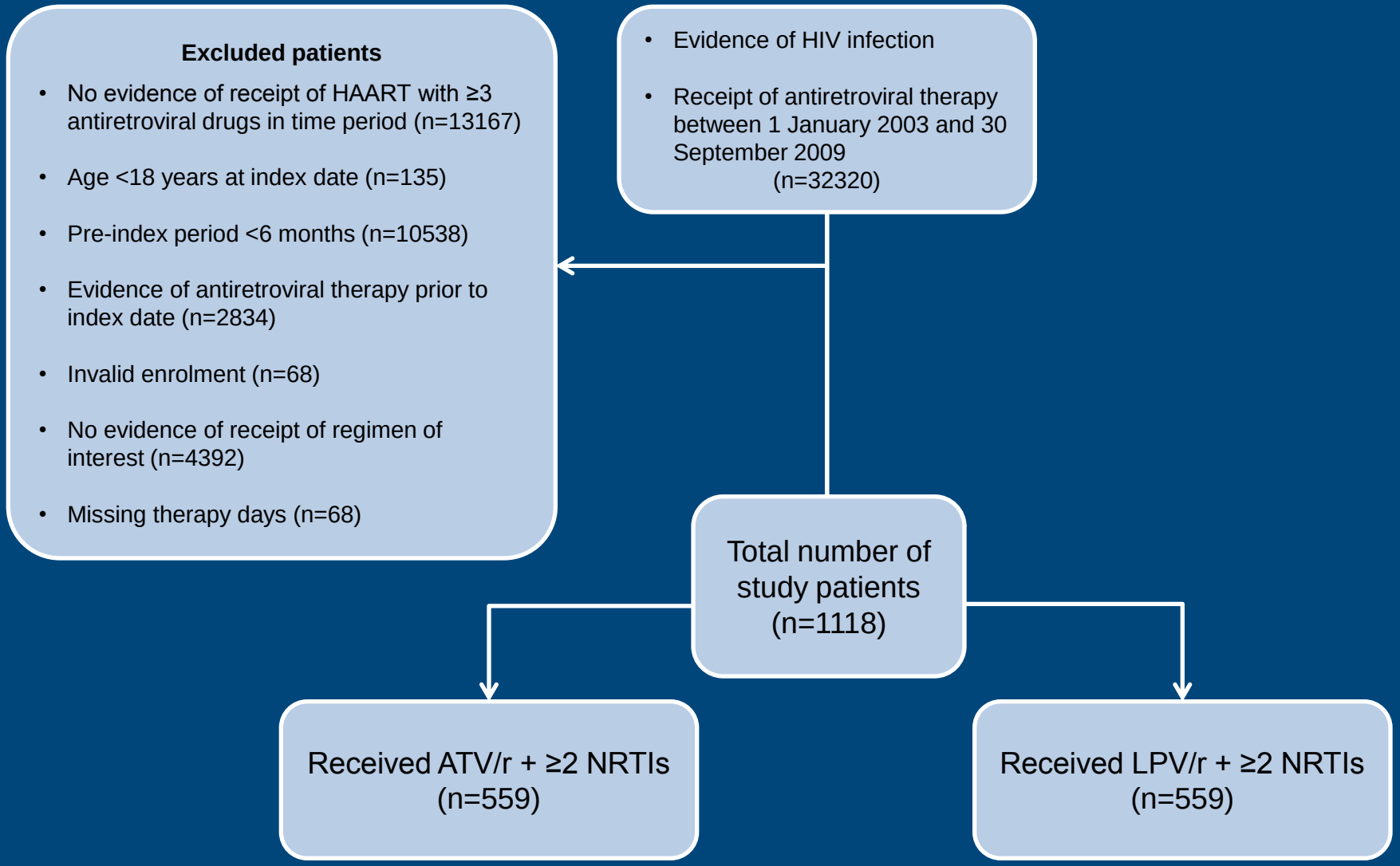
- Adherence was assessed using proportion of days covered (PDC), defined as:
  - Ratio of number of “covered days” with initial cART regimen to number of calendar days, both between index date and date of discontinuation/ switching/augmentation, end of eligibility for health benefits, or end of the study period, whichever occurred first

- Persistency was assessed based on absence of evidence of therapy discontinuation, switching, or augmentation of any component of the initial cART regimen over period beginning with index date and ending with end of eligibility for health benefits or the end of this study period, whichever occurred first

Methods: Statistical Analyses

- Demographic and clinical characteristics of study patients by index regimen were examined using descriptive statistics
- Generalized linear model (GLM) was used to assess differences in non-adherence (1-PDC) between treatment groups over 12 months after adjustment for potential confounders
  - Rate Ratio (RR) = non-adherence$^{ATV/r}$ ÷ non-adherence$^{LPV/r}$
- Multivariate Cox regression was used to assess differences in non-persistency over 12 months after adjustment for potential confounders
  - Hazard Ratio (HR)
- Adjusted Kaplan-Meier survival curves for time to non-persistency were estimated using corrected-group prognosis method

Selection of Study Subjects, by Inclusion Criteria



Characteristics of Study Subjects as of Index Date, by PI-based Regimen

	ATV/r (n=559)	LPV/r (n=559)
Age, mean (SD), years	42.3 (10.0)	42.7 (10.0)
Sex, n (%)		
Male	433 (77.5)	390 (69.8)
Female	126 (22.5)	169 (30.2)
Region, n (%)		
Northeast	151 (27.0)	192 (34.3)
Midwest	170 (30.4)	174 (31.1)
South	124 (22.2)	131 (23.4)
West	114 (20.4)	62 (11.1)
Pre-existing conditions, n (%)		
Alcohol / drug abuse	32 (5.7)	23 (4.1)
Other psychiatric illness	136 (24.3)	114 (20.4)
Hepatitis B	11 (2.0)	16 (2.9)
Hepatitis C	26 (4.7)	31 (5.5)
Pre-existing treatment, n (%)		
Proton pump inhibitors	30 (5.4)	72 (12.9)
H2-receptor antagonist	20 (3.6)	16 (2.9)
Oral contraceptives	3 (0.5)	6 (1.1)
Charlson Comorbidity Index, mean (SD)	5.4 (2.6)	5.6 (2.7)
Year of treatment initiation, n (%)		
2004	39 (7.0)	65 (11.6)
2005	41 (7.3)	72 (12.9)
2006	76 (13.6)	117 (20.9)
2007	121 (21.6)	129 (23.1)
2008	155 (27.7)	114 (20.4)
2009	127 (22.7)	62 (11.1)

Descriptive Results: Adherence

- Mean (SD) PDC over 12 months:
  - 0.883 (0.12) for ATV/r + ≥2 NRTIs
  - 0.853 (0.16) for LPV/r + ≥2 NRTIs

Multivariate GLM Regression Analysis of Non-adherence with PI-based Regimen Over 12 Months

Characteristic	Rate Ratio	95% CI	*P*-value
Regimen			
ATV/r + ≥2 NRTIs	1.00	–	–
LPV/r + ≥2 NRTIs	1.25	1.00, 1.57	0.049
Age, years			
18-34	1.00	–	–
35-44	1.04	0.75, 1.45	0.79
45-54	1.09	0.79, 1.49	0.61
≥55	0.82	0.55, 1.25	0.36
Sex			
Male	1.00	–	–
Female	1.62	1.24, 2.11	<0.01
Region			
Northeast	1.00	–	–
Midwest	0.95	0.72, 1.26	0.74
South	1.22	0.89, 1.66	0.22
West	1.18	0.83, 1.67	0.36
Charlson Comorbidity Index	1.00	0.96, 1.05	0.85

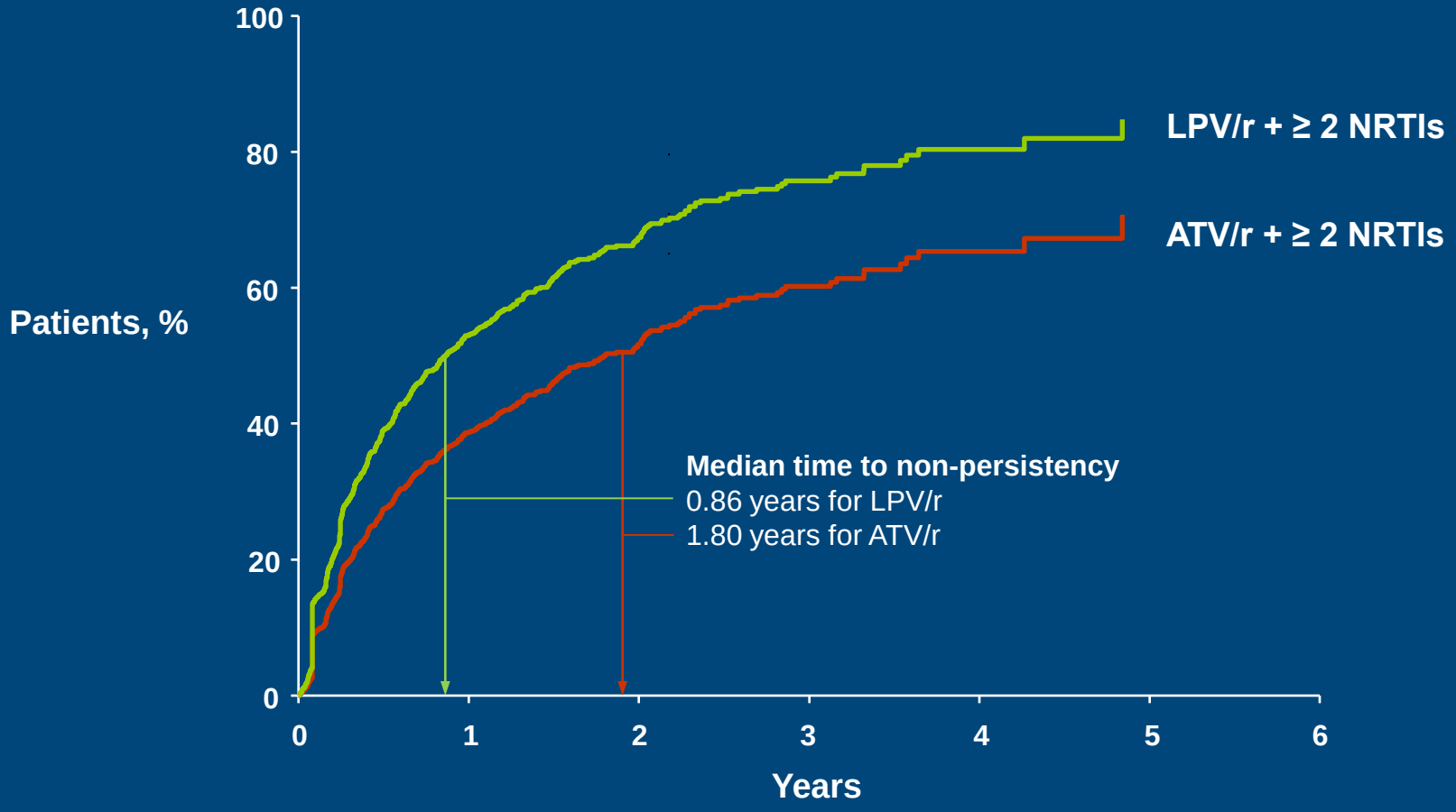
Descriptive Results: Persistency

- Incidence of non-persistency over 12 months:
  - 37.7% for ATV/r + ≥2 NRTIs
  - 49.9% for LPV/r + ≥2 NRTIs

Multivariate Cox Regression Analysis of Non-persistency with PI-based Regimens Over 12 Months

Characteristic	Hazard Ratio	95% CI	*P*-value
Regimen			
ATV/r + ≥2 NRTIs	1.00		
LPV/r + ≥2 NRTIs	1.55	1.31, 1.84	<0.01
Age, years			
18-34	1.00		
35-44	0.92	0.73, 1.16	0.49
45-54	0.83	0.66, 1.05	0.12
≥55	0.72	0.52, 1.00	0.05
Sex			
Male	1.00		
Female	1.40	1.16, 1.69	<0.01
Region			
Northeast	1.00	0.69, 1.06	0.15
Midwest	0.85	0.76, 1.20	0.72
South	0.96	0.80, 1.34	0.81
West	1.03	0.96, 1.03	0.74
Charlson Comorbidity Index	0.99	0.96, 1.03	0.74

Adjusted Kaplan-Meier Plot of Time to Non-persistency



No. at Risk							
ATV/r + ≥2 NRTIs	559	201	85	34	10	2	0
LPV/r + ≥ 2 NRTIs	559	176	80	35	10	4	0
Total	1118	377	165	69	20	6	0

Study Limitations

- Observational, non-experimental study design:
  - Treatment groups may not have been comparable

- Some potentially important covariates and potential confounders were not available in the study database, including:
  - Sociodemographic characteristics, psychosocial factors, disease characteristics, HIV-related symptoms, opportunistic infections, patient-provider relationships

- Unknown whether patients took all the medication they received from retail pharmacies

Study Limitations (Cont.)

- Reasons for treatment discontinuation/switching/augmentation are unknown
- Data did not permit examination of the relationship between adherence/persistency and clinical outcomes
- Potential channeling bias towards ATV/r cannot be excluded, but this was unlikely given that Charlson Comorbidity Index scores were comparable

Conclusions

- In a commerically-insured population of patients with HIV initiating first-line cART, those beginning treatment with ATV/r + ≥2 NRTIs had significantly better adherence—and were more likely to be persistent with therapy—than those beginning treatment with LPV/r + ≥2 NRTIs

- Further research is needed to better understand reason(s) why adherence and persistency differ between ritonavir-boosted PI-based regimens

References

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