A retrospective study of HIV antiretroviral treatment persistence in a commercially insured population in the United States

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This study examined factors associated with persistence (time from initiation to discontinuation of treatment) on initial antiretroviral (ARV) therapy in commercially insured HIV patients in the United States, a population not well researched. This retrospective analysis of US health insurance claims data from 1 January 2003 to 30 June 2008 included treatment-naive patients aged 18–65 years with an HIV diagnosis receiving ARV therapy consisting of at least two individual nucleoside reverse transcriptase inhibitors (NRTIs) or one fixed-dose combination NRTI, plus at least one nonnucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI), with or without ritonavir. Descriptive statistics, Kaplan-Meier survival estimation, and Cox proportional hazards regression models were completed. Patients were considered persistent until any component of the regimen was modified or there was a gap in treatment >90 days. A total of 2460 patients met full inclusion criteria (1388 NNRTI and 1072 PI). Mean (SD) time to discontinuation for NNRTI- vs PI-based regimens was 370 (346) vs 295 (338) days (p < 0.001). Female sex, substance use, low comorbidity score, index year before 2007, geographical region, and taking a lopinavir/ritonavir regimen predicted discontinuation. Relative to NNRTI-based regimens, PI-based regimens demonstrated a greater risk of discontinuation (hazard ratio [HR], 1.32; p < 0.001). The fixed-dose efavirenz/emtricitabine/tenofovir combination yielded the lowest risk of discontinuation (HR, 0.39; p < 0.001). HIV treatment persistence was longer with NNRTI-based regimens than PI-based regimens. The fixed-dose regimen of once-daily efavirenz/emtricitabine/tenofovir had the lowest risk of discontinuation.

Keywords: treatment persistence; antiretroviral therapy; HIV-1 infection

Introduction

Current US guidelines for the treatment of HIV-1 infection identify four preferred antiretroviral (ARV) regimens as initial therapy (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2009). These regimens comprise agents from four drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), ritonavir-boosted protease inhibitors (PIs), and integrase inhibitors. The current treatment paradigm calls for lifelong ARV therapy in HIV-infected individuals. Though much has been published on the efficacy of the currently preferred initial regimens, few studies have explored HIV ARV treatment persistence.

Persistence is defined as the duration of pharmacological treatment, from initiation to discontinuation (Cramer et al., 2008). This is operationally distinct from adherence, which indicates the extent to which a patient abides by the prescribed treatment regimen in terms of dose, frequency, and timing of administration (Cramer et al., 2008). Persistence is measured by the number of days taking medication without exceeding a permissible gap. Persistence is an important concept in HIV management as patients are likely to remain on lifelong ARV therapy, and the discontinuation of an ARV regimen, if associated with virological failure, may represent a permanent loss of therapeutic options.

HIV treatment persistence may be affected by a number of characteristics of the patient and the treatment regimen. Patient-related factors that may be associated with shorter persistence include disease severity (Ahdieh-Grant et al., 2005; Li et al., 2005; Mocroft et al., 2001; van Roon et al., 1999), younger age (Crystal, Sambamuthi, Moynihan, & McSpiritt, 2001; Li et al., 2005; Mocroft et al., 2001), and female sex (Spire, Carrieri, Garzot, L’henaff, & Obadia, 2004). Treatment regimen characteristics associated with shorter persistence include efficacy, tolerability profile, and regimen complexity (e.g., higher pill burden and dosing frequency; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2009; Elzi et al., 2010). The introduction of NNRTI-based treatment regimens; the arrival of new fixed-dosed NRTI combinations; a trend toward lower pill

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borders of PI-based regimens; and the introduction
of the one-pill, once-a-day ARV regimen of
efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF)
have greatly simplified HIV treatment by allowing
for lower pill burden, once-daily dosing, and longer
treatment persistence (Willig et al., 2008).

Few studies on persistence have been completed in
select HIV-infected populations, and little is known
about the factors influencing treatment persistence in
privately insured patients living with HIV/AIDS.
Much of the available data on patients with HIV
infection are from studies carried out in university
clinics and resource-limited settings. Our analysis
provides much-needed data on the factors associated
with ARV therapy persistence in privately insured
patients, a group estimated to represent 31% of HIV-
infect ed adults in the United States (Board on Health
Promotion and Disease Prevention [HPDP], 2005).
More specifically, we were interested in assessing if
the factors driving persistence in commercially in-
 sured patients are similar to those seen in published
cohort studies.

Using medical and prescription claims data from
a large US commercial claims database, we examined
persistence in commercially insured patients on initial
ARV therapy. The objectives of the analysis were to:
(1) compare the rates of persistence between NNRTI-
and PI-containing regimens, (2) assess the factors
associated with risk of treatment discontinuation, and
(3) compare the risk for discontinuation of specific
ARV regimens.

Methods

Study population and data collection

This retrospective cohort study used medical and
prescription claims data from the PharMetrics
Integrated Outcomes Database for the period from
1 January 2003 to 30 June 2008. The PharMetrics
Integrated Database is a de-identified, integrated
data base of commercial insurers that contains
patient demographics, health insurance coverage, and
medical and pharmacy claims for more than 55 million
unique members from 75 health plans across
the United States (http://www.imshealth.com). The
patients in the database are representative of the
national commercially insured US population in
terms of age, sex, and type of health plan with an
approximate distribution of health plan type:
preferred provider organization (52%), health
maintenance organization (20%), point-of-service
(18%), indemnity (7%), and other/unknown (3%).
The representativeness of the database enhances the
generalizability of study results.

Figure 1 details the study's inclusion and exclusion
criteria. Patients were required to be aged 18–65
years, to have at least one medical claim with an
International Classification of Diseases Ninth Edition

| Patients with at least one HIV diagnosis during observation window (01/2003 – 06/2008) \(N = 37,244\) |
|--------------------------------------------------|
| Patients taking ARV medications between 07/2003 and 12/2007 \(n = 15,020\) |
| Patients with required minimum length for health plan enrollment \(n = 5607\) |
| Patients aged 18 – 65 years \(n = 5462\) |
| Patients with no pregnancy-related diagnosis \(n = 5359\) |
| Patients with no ARV medication within 6 months pre-index date \(n = 2636\) |
| Patients taking recommended ARV regimen (two NRTI + PI/NNRTI) \(n = 2460\) |
| Total eligible HIV patients on ARV meeting enrollment criteria \(n = 2460\) |

Figure 1. Selection of patients with an HIV diagnosis who initiated ARV therapy involving a minimum of two NRTIs plus
one NNRTI or one PI (± ritonavir); ARV, antiretroviral; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
(ICD-9) diagnosis code for HIV infection (AIDS [042], HIV disease [042], symptomatic HIV infection [042], nonspecific serological evidence of HIV [795.71], or asymptomatic HIV infection [V08]) between 1 January 2003 and 30 June 2008, and to have initiated a prescription for an ARV regimen containing a minimum of three drugs including at least two NRTIs and one NNRTI or PI (+/− ritonavir [r]) between 1 July 2003 and 30 December 2007. Exclusion criteria included an ICD-9 diagnostic or service code for pregnancy. The integrase inhibitor raltegravir was not included in the analysis because it was not approved for treatment-naive patients until July 2009 or recommended by treatment guidelines for initial therapy until December 2009. The first claim for an ARV regimen was considered a patient’s index date. Patients were designated as treatment naive and starting initial ARV therapy if no ARV prescriptions were present for at least six months (180 days) prior to the index date. As shown in Figure 2, patients were required to be enrolled in the claims database for at least six months prior to and six months after the index date. Patients were followed until they met the study-defined criteria for nonpersistence described below.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The de-identified data-set in this study was compliant with all requirements of the Health Insurance Portability and Accountability Act (HIPAA).

**Independent variables**

Table 1 presents a list of the regimens used by patients in the main analyses. Regimen covariates included treatment category (NNRTI-based regimen vs PI-based regimen) and regimen type as defined by a specific third agent used in the regimen. In addition, use of fixed-dose combinations (FDCs) – i.e., EFV/FTC/TDF, tenofovir/emtricitabine (TDF/FTC), abacavir/lamivudine (ABC/3TC), zidovudine/lamivudine (AZT/3TC), zidovudine/lamivudine/abacavir (AZT/3TC/ABC), and lopinavir/ritonavir (LPV/r) – was included as a regimen covariate.

Patient covariates included age, sex, geographical region (Northeast, Midwest, South, West), total daily pills of non-ARV treatment, Charlson Comorbidity Index scores, calendar year at index date for regimen initiation, and psychiatric and substance abuse comorbidities per corresponding ICD-9 diagnostic codes. Charlson Comorbidity Index scores (a weighted summary score based on the presence or absence of 17 medical conditions where higher scores indicate a greater burden of comorbidity; Charlson, Pompei, Ales, & MacKenzie, 1987) were calculated for each patient after identifying comorbidities using ICD-9 diagnostic codes for the 17 associated conditions.

**Outcome measures**

The primary outcome measure was persistence (time to discontinuation) of the first-line ARV regimen. Participants were considered to be persistent until any component of the regimen was modified (including discontinuation of or addition of an ARV medication) or there was a gap in treatment >90 days. Treatment gaps (interruptions in pharmacy refill data) of >90 days were considered regimen discontinuations. A permissible gap of <90 days was chosen for this study to ensure that patients deemed nonpersistent had actually discontinued treatment. Transitions to a new fixed-dose combination (e.g., EFV + FTC/TDF to EFV/FTC/TDF) were censored and not counted as regimen modification.

**Statistical analyses**

All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC). The p-value for statistical significance was 0.05.
analyses were conducted using bivariate statistics to assess the distribution of treatment cohorts. Descriptive statistics containing treatment cohorts. Descriptive statistics examining time to persistence (time to discontinuation) by treatment category (NNRTI vs PI). A Cox proportional hazards regression model was used to assess multivariate risk of regimen discontinuation. This model was used to compare treatment category (NNRTI vs PI) and to compare more detailed regimen and patient characteristics.

A subanalysis used a Cox proportional hazards regression model to assess multivariate risk of discontinuation of specific first-line regimens in common use vs the EFV/FTC/TDF fixed-dose regimen. These regimens included: LPV/r + AZT/3TC, LPV/r + TDF/FTC, EFV + AZT/3TC, ATV/r + TDF/FTC, and EFV + TDF/FTC (excluding EFV/FTC/TDF). For a specific treatment regimen to be included in this subanalysis, at least 100 patients in the analytic sample had to be on the regimen.

Sensitivity analyses using permissible treatment gaps shorter than 90 days (i.e., 14 and 30 days, respectively) were conducted to assess the robustness of study results to the duration of permissible treatment gap.

Results
As shown in Table 2, within the cohort of 2460 patients meeting all study inclusion criteria, 1388 patients were on an NNRTI-based regimen and 1072 were on a PI-based regimen. The NNRTI cohort contained a significantly higher proportion of men than the PI cohort (81.7% vs 77.0%, respectively; \( p = 0.004 \)). Those on NNRTI-based regimens were younger (42.2 vs 43.2 years; \( p = 0.004 \)) and had lower daily pill burden (4.0 vs 9.5; \( p < 0.0001 \)) when compared with those on PI-based regimens. The proportion of patients using a fixed-dose combination as part of their index regimen was comparable between NNRTI- and PI-treated groups (72.7% vs 73.4%, respectively; \( p = 0.69 \)). Pre-index Charlson Comorbidity Index scores were identical for both treatment groups (6.2). There were no statistically significant differences in the distribution of substance abuse, depression, bipolar, and psychotic disorders between the NNRTI- and PI-based groups.

Overall, 68.2% of NNRTI-treated patients discontinued or modified their treatment in the study period, compared with 78.5% of the PI-treated group \( (p < 0.0001) \). In the period between index date and discontinuation, PI-treated patients had a lower number of prescription refills than their NNRTI counterparts (mean, 11.9 vs 13.5, respectively; \( p < 0.001 \)).

Persistence (time to discontinuation) of initial regimen by drug class
Figure 3 presents the Kaplan-Meier estimation of persistence (time to discontinuation) for the NNRTI and PI cohorts. The figure indicates that persistence was significantly longer in the NNRTI cohort relative to the PI cohort. The mean (standard deviation [SD]) time to treatment discontinuation in the NNRTI group was 370 (346) days compared with 295 (338) days in the PI group \( (p < 0.001; \) log-rank test). Similar results were observed in the sensitivity analyses when permissible treatment gaps of 14 and 30 days were used to classify regimens as discontinued.

Risk of regimen discontinuation
Table 3 presents the multivariate risk for regimen discontinuation associated with regimen and patient factors. Relative to NNRTI-based regimens, PI-based regimens demonstrated a greater risk of discontinuation (HR, 1.32; \( p < 0.001 \)). There was no association between use of a fixed-dose combination in the index regimen and risk of regimen discontinuation during the observation period (HR, 1.06; \( p = 0.345 \)). Analysis of commonly used index ARV regimens revealed that the EFV/FTC/TDF fixed-dose regimen was associated with a significantly lower risk of discontinuation than other regimens (HR, 0.39; \( p < 0.001 \)).

Table 1. Description of regimens.

| Regimen                               | n   |
|---------------------------------------|-----|
| NNRTI-based (total)                   | 1388|
| EFV-containing\(^a\)                  | 885 |
| EFV/FTC/TDF fixed-dose                | 327 |
| Other NNRTI\(^b\)                     | 176 |
| PI-based (total)                      | 1072|
| LPV/r-containing                      | 419 |
| ATV/r-containing                      | 272 |
| Other PI\(^c\)                        | 381 |
| All regimens (total)                  | 2460|

\(^a\)Excludes use of the EFV/FTC/TDF fixed-dose regimen.
\(^b\)Other NNRTI-based regimens were primarily comprised of regimens containing nevirapine or etravirine.
\(^c\)Other PI-based regimens were primarily comprised of regimens containing darunavir, fosamprenavir, or nelfinavir.

Abbreviations: ATV, atazanavir; EFV, efavirenz; FTC, emtricitabine; LPV, lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; TDF, tenofovir disoproxil fumarate.

Patients were categorized into NNRTI- or PI-containing treatment cohorts. Descriptive statistics included bivariate statistics to assess the distribution of characteristics in the two cohorts. Bivariate analyses were conducted using \( t \) tests for continuous variables and \( \chi^2 \) tests for categorical variables.

Kaplan-Meier survival estimation was used to examine time to persistence (time to discontinuation) by treatment category (NNRTI vs PI). A Cox proportional hazards regression model was used to assess multivariate risk of regimen discontinuation. This model was used to compare treatment category (NNRTI vs PI) and to compare more detailed regimen and patient characteristics.

A subanalysis used a Cox proportional hazards regression model to assess multivariate risk of discontinuation of specific first-line regimens in common use vs the EFV/FTC/TDF fixed-dose regimen. These regimens included: LPV/r + AZT/3TC, LPV/r + TDF/FTC, EFV + AZT/3TC, ATV/r + TDF/FTC, and EFV + TDF/FTC (excluding EFV/FTC/TDF). For a specific treatment regimen to be included in this subanalysis, at least 100 patients in the analytic sample had to be on the regimen.

Sensitivity analyses using permissible treatment gaps shorter than 90 days (i.e., 14 and 30 days, respectively) were conducted to assess the robustness of study results to the duration of permissible treatment gap.
Table 2. Characteristics of patients (n = 2460) included in the study cohort by type of index antiretroviral regimen (NNRTI vs PI).

| Variable                                      | NNRTI       | PI          | p-value<sup>a</sup> |
|-----------------------------------------------|-------------|-------------|----------------------|
| Age, mean (SD)                                | 42.2 (9.4)  | 43.2 (9.3)  | 0.004                |
| Male, n (%)                                   | 1134 (81.7) | 825 (77.0)  | 0.004                |
| FDC use in index regimen, n (%)               | 1009 (72.7) | 787 (73.4)  | 0.690                |
| Total daily pills in index regimen, mean (SD) | 4.0 (4.6)   | 9.5 (8.4)   | <0.0001              |
| Region, n (%)                                 |             |             | 0.084<sup>b</sup>   |
| Northeast                                     | 455 (32.8)  | 369 (34.4)  |                      |
| Midwest                                       | 379 (27.3)  | 303 (28.3)  |                      |
| South                                         | 249 (17.9)  | 209 (19.5)  |                      |
| West                                          | 305 (22.0)  | 191 (17.8)  |                      |
| Pre-index Charlson Comorbidity Index, mean (SD)<sup>c</sup> | 6.24 (2.2) | 6.24 (2.3) | 0.915               |
| Pre-index comorbidity, n (%)                  |             |             |                      |
| Depression                                    | 197 (14.2)  | 146 (13.6)  | 0.684                |
| Bipolar disorder                              | 44 (3.2)    | 50 (4.7)    | 0.055                |
| Psychotic disorder                            | 13 (0.9)    | 10 (0.9)    | 0.992                |
| Substance use disorder                        | 157 (11.3)  | 144 (13.4)  | 0.111                |
| Year of index date, n (%)                     |             |             | 0.012<sup>b</sup>   |
| 2003                                          | 156 (11.2)  | 129 (12.0)  |                      |
| 2004                                          | 296 (21.3)  | 268 (25.0)  |                      |
| 2005                                          | 290 (20.9)  | 247 (23.0)  |                      |
| 2006                                          | 410 (29.5)  | 288 (26.9)  |                      |
| 2007                                          | 236 (17.0)  | 140 (13.1)  |                      |

<sup>a</sup>p-value for difference between NNRTI- and PI-based regimens.

<sup>b</sup>Categorical analysis using $\chi^2$ test.

<sup>c</sup>Charlson Comorbidity Index, a weighted summary score based on the presence or absence of 17 medical conditions.

Abbreviations: FDC, fixed-dose combination; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

Figure 3. Persistence (i.e., time to discontinuation) by type of index ARV regimen (NNRTI-based or PI-based). The difference in time to discontinuation between PI- and NNRTI-based regimens was $p < 0.0001$ (log-rank test); ARV, antiretroviral; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
contrast, use of LPV/r in the index ARV regimen was associated with a significantly greater risk of discontinuation than regimens not containing LPV/r (HR, 1.32; p < 0.001). Sensitivity analyses using 14- and 30-day permissible treatment gaps showed similar results.

Patient variables associated with a greater risk of regimen discontinuation included a pre-index history of a substance use disorder (HR, 1.30; p < 0.001) and earlier year of index date (all years compared with 2007; p < 0.001; Table 3). Variables associated with a lower risk of regimen discontinuation included male sex (HR, 0.84; p < 0.005), location in the Midwest (HR, 0.85; p = 0.027), or West (HR, 0.69; p < 0.001) compared with the South and higher post-index and prediscontinuation Charlson Comorbidity Index scores (HR, 0.84; p < 0.001). Sensitivity analyses using 14- and 30-day permissible treatment gaps showed similar results.

Risk of discontinuation of specific regimens

Table 4 presents a subanalysis of the multivariate risk of discontinuation associated with commonly used ARV regimens. Compared with fixed-dose EFV/FTC/TDF, the following regimens were associated with a greater risk of discontinuation: EFV + AZT/3TC (HR, 1.83; p < 0.001), LPV/r + TDF/FTC (HR, 2.03; p < 0.001), and LPV/r + AZT/3TC (HR, 2.33; p < 0.001). Sensitivity analyses using 14- and 30-day permissible treatment gaps showed similar results.

Discussion

ARV treatment persistence is of paramount importance as current HIV management requires lifelong therapy and discontinuation may permanently eliminate future treatment options. This analysis provides rare insight into treatment persistence among commercially insured individuals with HIV infection, an

Table 3. Multivariate risk of regimen discontinuation (n = 2460).

| Variable | Hazard ratio | p-value |
|----------|--------------|---------|
| PI-based vs NNRTI-based | 1.32 | <0.001 |
| FDC use vs no FDC use | 1.06 | 0.345 |
| Regimens with LPV/r vs regimens without LPV/r | 1.32 | <0.001 |
| Regimens with EFV vs regimens without EFV | 1.04 | 0.496 |
| Regimens with ATV +/- r vs regimens without ATV +/- r | 0.99 | 0.993 |
| EFV/FTC/TDF fixed-dose regimen vs all other regimens | 0.39 | <0.001 |
| Age (in 5-year increments) | 1.01 | 0.338 |
| Male vs female | 0.84 | 0.005 |
| Region | | |
| Northeast vs South | 1.01 | 0.891 |
| Midwest vs South | 0.85 | 0.027 |
| West vs South | 0.69 | <0.001 |
| Charlson Comorbidity Index | 0.84 | <0.001 |
| Substance use disorder | 1.30 | <0.001 |
| Year of index date | | |
| 2003 vs 2007 | 1.66 | <0.001 |
| 2004 vs 2007 | 1.88 | <0.001 |
| 2005 vs 2007 | 1.44 | <0.001 |
| 2006 vs 2007 | 1.34 | 0.002 |

*Excludes use of the EFV/TDF/FTC fixed-dose regimen.

aCharlson Comorbidity Index, a weighted index in which a higher score indicates a greater burden of comorbid disease.

Abbreviations: ATV, atazanavir; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; LPV, lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; TDF, tenofovir disoproxil fumarate.

Table 4. Multivariate risk of discontinuation of specific regimens vs EFV/FTC/TDF fixed-dose regimen (n = 1261, including n = 316 on EFV/FTC/TDF fixed-dose regimen).

| Regimen | Hazard ratio | p-value |
|---------|--------------|---------|
| LPV/r + AZT/3TC (n = 127) | 2.33 | <0.001 |
| LPV/r + TDF/FTC (n = 104) | 2.03 | <0.001 |
| EFV + AZT/3TC (n = 279) | 1.83 | <0.001 |
| ATV/r + TDF/FTC (n = 125) | 1.19 | 0.217 |
| EFV + TDF/FTCb (n = 310) | 1.13 | 0.348 |

*Covariates included in the Cox proportional hazards regression models were age, sex, region, Charlson Comorbidity Index score, substance use, and year of index date.

bPatients who switched to EFV/FTC/TDF fixed-dose regimen were censored.

Abbreviations: ATV, atazanavir; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; LPV, lopinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.
understudied group in the HIV literature despite comprising nearly one third of all known HIV-infected patients in the United States (Board on Health Promotion and Disease Prevention [HPDP], 2005). Our study found that factors driving ARV treatment persistence in commercially insured patients were generally consistent with those seen in published cohort studies of HIV-infected patients.

Consistent with the findings of existing studies in other HIV populations (Braithwaite et al., 2007; Domingo et al., 2008; Elzi et al., 2010; Willig et al., 2008), regimen characteristics such as the utilization of NNRTIs and the use of a fixed-dose, once-daily ARV combination (EFV/FTC/TDF) were associated with greater HIV treatment persistence. In our analysis, treatment persistence was significantly longer and the risk of discontinuation was significantly lower for patients on initial regimens containing NNRTIs compared with PIs ($p < 0.001$). In regimen-level subanalyses, similar persistence was seen with EFV- and ATV/r-based regimens, while use of LPV/r in the index ARV regimen was associated with a greater risk for discontinuation. The use of LPV/r in the index ARV regimen may account for the reported difference in PI vs NNRTI persistence and may be related in part to the increased dosing frequency of LPV/r (twice daily) vs ATV/r (once daily; Li et al., 2005). The lower risk of regimen discontinuation among patients using the single-tablet EFV/FTC/TDF fixed-dose regimen is an outcome that has been previously attributed to ease and convenience of use (Willig et al., 2008). Prior to 2005, ARV regimens were not as “patient friendly” as contemporary regimens, which include more tolerable, co-formulated NRTI backbones and once-daily dosing. Ease and convenience of use may explain our finding that the risk of regimen discontinuation was greater for patients initiating ARV therapy in any year (2003–2006) prior to 2007 and that the risk of regimen discontinuation decreased over the study period (2003–2007). Further research is needed into the reasons for differences in persistence between ARV regimens and the reasons for and clinical outcomes associated with extended persistence.

Our findings are in general agreement with available data on patient-level predictors of ARV therapy durability in longitudinal analyses and in resource-limited settings (Glass et al., 2009; Lazo et al., 2007; Vo et al., 2008). Substance abuse is a well-known risk factor for decreased adherence to ARV medication in public assistance and homeless populations, and our study confirms the extent of its negative impact on privately insured individuals. The association between ARV-regimen persistence and geographical location in the United States is intriguing and warrants further investigation as to why the risk of discontinuation is lower among privately insured patients residing in the Midwest or West compared with those residing in the South. In contrast to prior studies, we found a lower risk of regimen discontinuation (nonpersistence) associated with increased Charlson comorbidity scores (Elzi et al., 2010). We speculate that patients with a higher burden of comorbidity may be more accustomed to taking medications and, due to this familiarity, are more likely to have increased persistence to an HIV treatment regimen. These findings may highlight an important challenge for clinicians, underscoring the need to closely monitor ARV treatment persistence among newly diagnosed HIV-infected patients who are otherwise healthy and therefore “inexperienced” in long-term medication compliance. The strategies of fixed-dose combinations and once-daily dosing that have proven to increase persistence are important assets to promulgating this behavior in newly HIV-infected individuals.

Clinical studies evaluating persistence to ARV therapy have shown varying results with regard to a gender difference (Clark & Squires, 2005; Kempf et al., 2009). We found a lower risk of ARV treatment discontinuation in insured men compared with their female counterparts. Although the reasons for a lower risk of ARV-regimen discontinuation among men than women are not entirely clear, several factors exclusive to women may influence the risk of discontinuation such as contraception, pregnancy, and breast feeding. A greater risk of ARV treatment discontinuation among women in the Women’s Interagency HIV Study was associated with high HIV RNA levels and high depressive symptom scores (Ahdieh-Grant et al., 2005). Further studies are needed to assess the factors negatively impacting persistence in women and men, particularly in insured vs uninsured populations and in different geographical areas within the United States.

This study has a number of limitations. First, insurance claims data are collected for administrative purposes; they are not collected to address a specific scientific question or purpose. Thus, this observational study allows us to identify associations but we cannot attribute causality. Second, patients in this study represent only those covered under health plans participating in PharMetrics. While these data are generally nationally representative, PharMetrics data were not collected using a national probability sample; therefore, care should be taken in generalizing study results too broadly. Third, since the data were obtained from a claims database, patients defined as treatment-naïve in this study may have received ARV treatment prior to the pre-index...
period in this health plan or another health plan, as treatment-naive status could not be confirmed by individual chart review. However, this limitation would have presumably affected all participants equally. Furthermore, the number of ARV regimens evaluated was limited due to a small number of patients on specific regimens and the specific reasons for treatment discontinuation were unknown. Finally, the time period over which the study was conducted (2003–2008) overlapped with a number of therapeutic advances, including the introduction of single-drug combination therapy following approval of the EFV/FTC/TDF fixed-dose combination by the US Food and Drug Administration in July 2006.

Conclusions
This study, the first of its kind to be conducted in a commercially insured population of patients newly treated for HIV with ARV therapy, demonstrated that in HIV, treatment regimen persistence is longer with NNRTI-based regimens than PI-based regimens. Patient characteristics associated with a lower risk of ARV treatment discontinuation included male sex, presence of a higher burden of comorbid conditions, and geographical region. Earlier year at index date for regimen initiation and substance abuse were associated with a greater risk of discontinuation. In regimen-level subanalyses, LPV/r-based regimens were associated with a greater risk of discontinuation and ATV/r-based regimens showed no statistically significant difference in risk of discontinuation when compared with EFV/TDF/FTC, underscoring the positive impact of once-daily dosing on long-term treatment persistence.

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References
Aldieh-Grant, L., Tarwater, P.M., Schneider, M.F., Anastos, K., Cohen, M., Khalsa, A., ... Greenblatt, R.M. & Women’s Interagency HIV Study. (2005). Factors and temporal trends associated with highly active antiretroviral therapy discontinuation in the Women’s Interagency HIV Study. Journal of Acquired Immune Deficiency Syndrome, 38(4), 500–503.

Board on Health Promotion and Disease Prevention [HPDP]. (2005). Public financing and delivery of HIV/AIDS care: Securing the legacy of Ryan white. Washington, DC: The Institute of Medicine, The National Academies Press.

Braithwaite, R.S., Kozal, M.J., Chang, C.C., Roberts, M.S., Fultz, S.L., Goetz, M.B., ... Justice, A.C. (2007). Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. AIDS (London, England), 21(12), 1579–1589.

Charlson, M.E., Pompei, P., Ales, K.L., & MacKenzie, C.R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases, 40(5), 373–383.

Clark, R.A., & Squires, K.E. (2005). Gender-specific considerations in the antiretroviral management of HIV-infected women. Expert Review of Anti-Infective Therapy, 3(2), 213–227.

Cramer, J.A., Roy, A., Burrell, A., Fairchild, C.J., Fuldeore, M.J., Ollendorf, D.A., & Wong, P.K. (2008). Medication compliance and persistence: Terminology and definitions. Value Health, 11(1), 44–47.

Crystal, S., Sambamoorthi, U., Moynihan, P.J., & McSpiritt, E. (2001). Initiation and continuation of newer antiretroviral treatments among medicaid recipients with AIDS. Journal of General Internal Medicine, 16(12), 850–859.

Domingo, P., Suarez-Lozano, I., Torres, F., Teira, R., Lopez-Aldeguer, J., Vidal, F., ... Garrido, M. (2008). First-line antiretroviral therapy with efavirenz or lopinavir/ritonavir plus two nucleoside analogues: The SUSKA study, a non-randomized comparison from the VACH cohort. Journal of Antimicrobial Chemotherapy, 61(6), 1348–1358.

Elzi, L., Marzolini, C., Furrer, H., Ledergerber, B., Cavassini, M., Hirschel, B., ... Battegay, M. & Swiss HIV Cohort study. (2010). Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. Archives of Internal Medicine, 170(1), 57–65.

Glass, T.R., Battegay, M., Cavassini, M., De Geest, S., Furrer, H., Vernazza, P.L., ... Bucher, H.C. & Swiss HIV Cohort Study. (2010). Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV Cohort Study. Journal of Acquired Immune Deficiency Syndromes, 54(2), 197–203.
Kempf, M.C., Pisu, M., Dumcheva, A., Westfall, A.O., Kilby, J.M., & Saag, M.S. (2009). Gender differences in discontinuation of antiretroviral treatment regimens. *Journal of Acquired Immune Deficiency Syndrome, 52*(3), 336–341.

Lazo, M., Gange, S.J., Wilson, T.E., Anastos, K., Ostrow, D.G., Witt, M.D., & Jacobson, L.P. (2007). Patterns and predictors of changes in adherence to highly active antiretroviral therapy: Longitudinal study of men and women. *Clinical Infectious Diseases, 45*(10), 1377–1385.

Li, X., Margolick, J.B., Conover, C.S., Badri, S., Riddler, S.A., Witt, M.D., & Jacobson, L.P. (2005). Interruption and discontinuation of highly active antiretroviral therapy in the multicenter AIDS cohort study. *Journal of Acquired Immune Deficiency Syndrome, 38*(3), 320–328.

Mocroft, A., Youle, M., Moore, A., Sabin, C.A., Madge, S., Lepri, A.C., . . . Phillips, A.N. (2001). Reasons for modification and discontinuation of antiretrovirals: Results from a single treatment centre. *AIDS (London, England), 15*(2), 185–194.

Panel on Antiretroviral Guidelines for Adults and Adolescents. (2009, December, 1). *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Retrieved from http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Spire, B., Carrieri, P., Garzot, M.A., L’henaff, M., & Obadia, Y. (2004). Factors associated with efavirenz discontinuation in a large community-based sample of patients. *AIDS Care, 16*(5), 558–564.

van Roon, E.N., Verzijl, J.M., Juttmann, J.R., Lenderink, A.W., Blans, M.J., & Egberts, A.C. (1999). Incidence of discontinuation of highly active antiretroviral combination therapy (HAART) and its determinants. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 20*(3), 290–294.

Vo, T.T., Ledergerber, B., Keiser, O., Hirschel, B., Furrer, H., Battegay, M., . . . Weber, R. & Swiss HIV Cohort Study. (2008). Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. *Journal of Infectious Diseases, 197*(12), 1685–1694.

Willig, J.H., Abroms, S., Westfall, A.O., Routman, J., Adusumilli, S., Varshney, M., . . . Mugavero, M.J. (2008). Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. *AIDS (London, England), 22*(15), 1951–1960.