## Using Administrative Claims Data to Estimate Virologic Failure Rates among Human Immunodeficiency Virus –Infected Patients with Antiretroviral Regimen Switches


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# Using Administrative Claims Data to Estimate Virologic Failure Rates among Human Immunodeficiency Virus–Infected Patients with Antiretroviral Regimen Switches

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***Objective.*** *To develop and validate a claims signature model that estimates proportions of HIV-infected patients in administrative claims databases who switched combination antiretroviral therapy (cART) regimens because of virologic failure.* ***Methods.*** *The authors used an HIV-specific registry (development data set) to develop logistic regression models to estimate odds of virologic failure among patients who switched cART regimens. Models were validated in a sample of administrative claims with laboratory values (validation data set). The final model was applied to an application data set as a worked example.* ***Results.*** *There were 1691, 1073, and 3954 eligible patients with cART switches in the development, validation, and application data sets, respectively. In the development data set, virologic failure before a switch was observed 21.8% of the time. Failure more likely caused the regimen switch among patients who were treatment experienced, had been receiving their baseline regimen for > 180 days, had ≥ 2 or more physician visits within 90 days, had > 1 HIV RNA or CD4 cell count test within 30 days, had any resistance test within 180 days, or had a change in regimen type. The final model had good discriminatory ability (C = 0.885) and fit (Hosmer-Lemeshow P = 0.8692). Failure was estimated to occur in 18.9% (v. 18.6% observed) of switches in the validation data set and 13.8% in the application data set.* ***Conclusions.*** *This claims signature model allows payers to use claims data to estimate virologic failure rates in their patient populations, thereby better understanding plan costs of failure.* ***Key words:*** *HIV; antiretroviral; claims data; virologic failure.* ***(Med Decis Making 2012;32:118–131)***

Treatment for human immunodeficiency virus (HIV) infection has changed significantly with the introduction of multidrug regimens that suppress viral replication and typically include at least 3 drugs from 2 different drug classes. Although these combination antiretroviral treatment (cART) regimens have dramatically reduced HIV-related morbidity and mortality and have become increasingly more convenient to administer, viral resistance can develop, causing breakthrough replication (virologic failure) and swifter progression of HIV disease.[1,2] Virologic failure, which is defined by rising HIV mRNA levels, has human as well as economic consequences.[3] Understanding the impact of treatment regimen decisions on rates of virologic failure could help payers and policy makers better understand the costs of virologic failure in target populations to inform budget planning and improve decision making.

The ability of payers to assess real-world effectiveness and the economic impact of cART regimens is limited. Several specialized registries in the United States track characteristics of HIV-infected patients and can be used to examine patterns of virologic failure, but such data are often not representative of the broader

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US population and do not provide information on cost.[4,5] Administrative claims databases, on the other hand, contain information on patterns of regimen switches and costs for large numbers of HIV-infected adults[6] but do not typically include laboratory values (e.g., mRNA levels) that are needed to determine if switches are due to virologic failure or to other issues such as tolerability. We thus developed and validated a claims signature model that can use administrative data alone to estimate ex post rates of virologic failure among HIV-infected patients with cART regimen switches. We also applied the model to a larger claims database as a worked example of its ability to estimate switch and failure patterns in real-world settings.

## METHODS

In this analysis, we developed and validated several multivariate regression models to predict whether regimen switches were due to virologic failure or other reasons. An HIV-specific registry ("development data set"), in which the results of HIV mRNA testing were known for every patient, was used to develop the regression models. An administrative claims data set ("validation data set"), in which laboratory mRNA levels were also known, was used to validate the models. Finally, a large administrative claims data set ("application data set") was used to apply the final validated claims signature model as a worked example in which the final model was applied to estimate the proportion of patients with cART regimen switches that had virologic failure before their switch.

### Data Sources and Patient Selection

The model development data set was developed from HIV Insight, an HIV-specific clinical registry with longitudinal medical records containing detailed clinical and utilization data for a cohort of HIV-infected adults receiving care at 1 of 10 centers in 8 US cities. HIV Insight contains quality-reviewed and institutional review board–checked data from 1983 onwards on more than 8000 patients and 250,000 encounters and is a collaboration of the HIV Outpatient Study (HOPS) from the Centers for Disease Control and Prevention and the Cerner Corporation.[5] It includes data on patient demographics, treatments, laboratory values, and outcomes that have been abstracted from medical records by trained abstractors. The database has been used for various types of studies, including examinations of patterns of cART use and reasons for therapy discontinuation.[7,8]

Both the validation and application data sets were derived from the i3/Ingenix Lab/Rx database, a Health Insurance Portability and Accountability Act (HIPAA)–compliant administrative claims database of 8 to 10 million privately covered lives, representing all major regions of the United States. The Lab/Rx database contains de-identified adjudicated pharmacy and medical claims data from providers, health care facilities, and pharmacies as well as information on physician visits, medical procedures, hospitalizations, drugs dispensed, and tests performed. The database also contains member enrollment and benefit information as well as limited patient, provider, and hospital demographic information. A subset of the database also provides laboratory HIV mRNA values for a small number of patients and was used as the validation data set, and the entire Lab/Rx database was used as the application data set.

In all 3 data sets, patients were eligible for the study if they were HIV positive, treatment naive, or treatment experienced; were aged 18+; and had switched from one cART regimen to another between 1 January 2003 and 31 March 2008. Regimen switch definitions are specified in the model variables section. Users of investigational drugs or drugs that were not approved by the US Food and Drug Administration were excluded.

To be eligible for the application data set, patients had to be continuously enrolled for at least 1 year before and 3 months after the switch date, and treatment-naive patients had to be enrolled 6 months before starting the baseline regimen. To be eligible for the validation data set, patients had to have had at least 1 HIV mRNA value recorded within 30 days of their switch date. Data were collected for 6 months before a patient began the baseline regimen, such that the amount of time patients were followed before regimen switch equaled the amount of time they were receiving the baseline regimen plus 6 months. Study eligibility criteria were designed to ensure that all data required for analysis would be included, thus preventing any issues related to censored data.

Just as there were slight differences in the way eligibility criteria were defined among the 3 data sets because of the inherent differences between registry and claims data, eligible patients were identified using different methods for each database. For example, identifying HIV-infected adults for the development data set entailed selecting any enrolled patient from the HIV Insight registry, whereas for the validation and application data sets, it entailed identifying patients in the claims data with the appropriate birth year and *International Classification of Diseases, 9th*

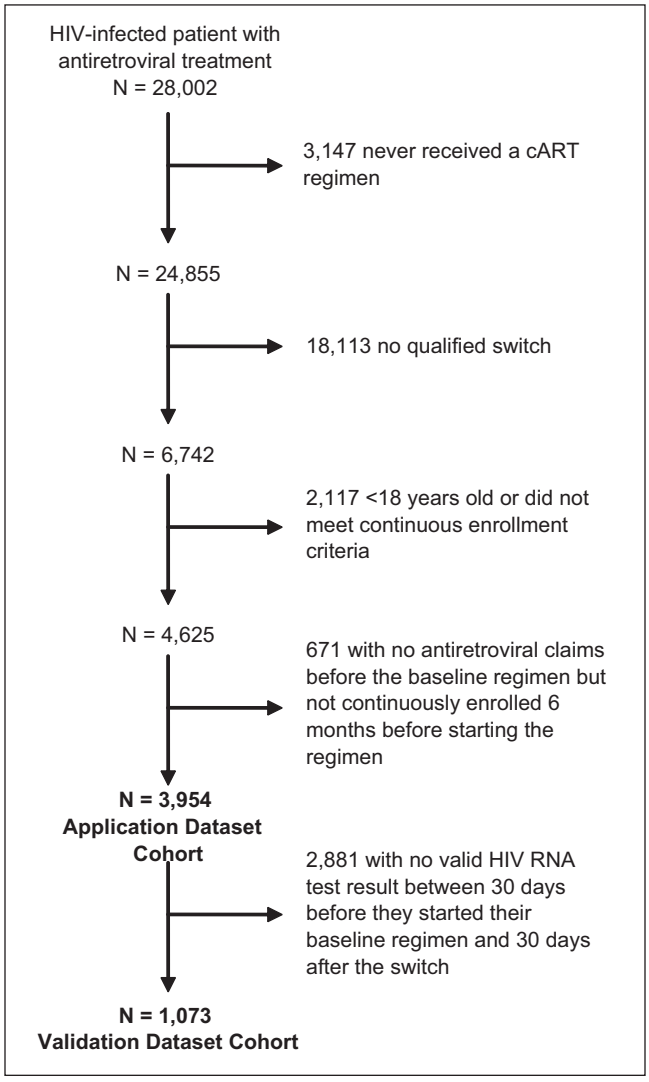


*Figure 1 Selection of patients for the validation and application data sets. cART, combination antiretroviral therapy.*

*Revision, Clinical Modification* (ICD-9-CM) codes for HIV infection (042 and V08). There were 1691 eligible adults in the development data set, and Figure 1 shows how patients were selected for the validation and application data sets. The final validation data set consisted of 1073 eligible patients, with 3954 in the final application data set.

## Model Variables

The model was designed to evaluate whether a switch in cART treatment regimen was due to virologic failure or other causes. A regimen switch was a change of at least 1 drug (except changes between lamivudine [3TC] and emtricitabine [FTC], which were considered interchangeable), and only the first switch for each patient during the study interval was considered. Regimens were defined as "baseline" or "subsequent," based on their being either before or after the switch, and the date of the regimen switch was defined as the date when all medications in the baseline regimen were no longer available. Virologic failure was defined as at least 1 instance of 1) HIV RNA level >400 copies/mL after 24 weeks of therapy, 2) detectable HIV RNA level after >48 weeks of therapy, or 3) detectable HIV RNA level after prior suppression (undetectable HIV RNA level <30 days before beginning the baseline regimen). Detectable RNA levels depended on each mRNA test's definition of a positive value and ranged from 40 to 400 copies/mL. All regimens included at least 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) as well as either 1 or more protease inhibitors (PIs) or 1 or more nonnucleoside reverse transcriptase inhibitors (NNRTIs).[9]

The amount of time that each patient was receiving baseline and subsequent regimens was calculated based on the regimen's start and stop dates. In the development data set, these start and stop dates were based on the time period between the patient's first and last records indicating regimen use. In the validation and claims data sets, these dates were estimated based on regimen fill and supply end dates; regimen start was defined as the first day that all medications in that regimen were available and regimen end as either the first day of a new regimen or the end of supply of the previous regimen. If patients refilled medications before the end of the previous fill, the end date was extended by the number of days that extra medication would be predicted to be available. A medication was considered discontinued when more than 30 days passed between the end of a medication supply and the next fill date, in which case the next fill date would then be considered that medication's new start date. Because of our 1-year minimum enrollment criteria for claims data patients, the amount of time receiving the regimen outside of the 1-year preindex period was captured by defining the variable categorically (1–180 days, 181–360 days, or ≥361 days).

Regimen switches were evaluated by the following patient- and regimen-specific factors: patient demographics (age, gender, region, race), payer type, health habits (smoking, alcohol use), route of HIV acquisition (for development data set patients only), treatment history (naive or experienced), health care utilization before switch, drug-related adverse events, regimen

characteristics (regimen type [NNRTI, PI, or NNRTI and PI based], pill burden, and time receiving regimen), and switch characteristics (year of switch, change in regimen type [e.g., from PI to NNRTI based], change in intensity, or [for development and validation data sets only] virologic failure before switch). Health care utilization included 3 factors: number of physician visits within 90 days before switch, any emergency department (ED)/hospital care within 90 days before switch, and number of HIV mRNA, CD4, and resistance tests within 180 days before switch.

Drug-related adverse events were chosen from a starting list of 39 events and narrowed down to include only those that would be available in claims data and that would be highly specific to the cause of ART medication discontinuation. This included, for example, specific drug reactions such as gastrointestinal-, ART-, and PI-related symptoms or medications that were likely to be used to treat any of these specific events. In the final list, adverse events were defined as new diagnoses (those made within 90 days before the switch) of abacavir hypersensitivity, anemia, hyperlipidemia, lipoatrophy, or lipodystrophy or as new treatment (initiated within 90 days before the switch) with erythropoietin, loperamide, or gabapentin, medications used to treat ART adverse events such as anemia, neuropathic pain, and diarrhea, respectively. Changed intensity was defined as a change in the total number of medications within a regimen class (e.g., NRTI, NNRTI, or PI) and/or a change of class.

Several variables were defined differently in the development v. the validation and claims data sets because of each source's differing data structures and elements. To identify possible drug-related adverse events, HIV Insight's specific diagnosis and treatment codes were used in the development data set, whereas *ICD-9-CM* diagnosis codes and National Drug Codes were used in the validation and claims data set. To define a patient's status as treatment naive or treatment experienced, relevant records were abstracted from the development data set; in the validation and application data sets, however, a patient's status was based on having a claim for antiretroviral medications during the 6 months before starting the baseline regimen. Race/ethnicity, smoking history, alcohol use history, and route of acquisition of HIV were available only in the development data set and were not included in the analyses of the validation or application data set.

### Statistical Analyses

Descriptive analyses of all 3 data sets were performed, and the following outcomes were reported for patients with regimen switches: demographic characteristics, payer type, health habits, route of HIV acquisition, treatment history, regimen characteristics, adverse events, health care utilization, and switch characteristics. Rates of observed virologic failure were also reported for the development and validation data sets. Univariate comparisons between outcomes were made for the development and validation data sets, using chi-square tests for categorical variables and *t* tests for continuous variables. Logistic regression models were developed to estimate the odds of virologic failure among all 3 data sets, first using a "base model" that included only the main effects for all independent variables, then applying a "final model" that included stepwise addition of significant interaction terms. To test the importance of variables found only in the development data set, another model was developed that also included smoking, alcohol use, and route of HIV acquisition.

After model development with the development data set, the base and final models' goodness-of-fit characteristics were tested in the development data set using the Hosmer-Lemeshow test, and both models were applied to the validation data set. The base and final models' predictive abilities were measured in both the development and validation data sets with C statistics and receiver operating characteristic (ROC) curves for the fraction of patients with virologic failure among all pairs of patients where one had virologic failure and one did not. Finally, the 2 models were applied to the application data set to provide a worked example of predicting virologic failure using administrative data. All data transformations and statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC), and the study was funded by Bristol-Myers Squibb Company (Plainsboro, NJ).

## RESULTS

Table 1 describes the patient populations with regimen switches that were included in this analysis for the development, validation , and claims data sets and indicates the outcomes for which there were statistically significant differences between the first 2 data sets. Mean age was similar between the 2 populations, ranging from 44.2 to 44.9 years, but there was a statistically significant difference in gender distribution between the development (20% female) and validation (13% female) data set populations. Among development data set patients, 69% had private insurance or Medicare, and 24% had public insurance or Medicaid, whereas nearly all patients in the validation population had private or Medicare coverage (99%). Among development data set patients (corresponding data were not available for

validation data set patients), approximately 50% used alcohol, 35% were current smokers, 16% were past smokers, and 61% acquired HIV infection through male-to-male sex. Between 78% and 79% of patients in both data sets were treatment experienced.

Protease inhibitor–based therapy was the most common type of regimen used among patients in the development and validation data sets, followed by NNRTI-based and combination PI- and NNRTI-based therapy. Treatment persistence was similar between patients in the 2 data sets, with more than 50% of patients in both data sets receiving their baseline regimens for more than 6 months and approximately one third for over a year. The amount of time that patients were followed before regimen switch was determined by adding 6 months to the amount of time they were receiving the baseline regimen. Therefore, approximately one third of patients in the claims data set—with more limited enrollment than the development data set—were followed for more than 1.5 years. Virologic failure before a switch was slightly more common among development than validation data set patients (21.8% v. 18.6%, respectively).

Univariate analyses of the development data set showed no statistically significant difference in age between those with virologic failure and those with no evidence of failure (44.6 v. 45.0 years; $P = 0.5196$). There was a statistically significant difference for gender, region, race/ethnicity, and smoking status between patients with and without virologic failure ($P = 0.0029$, 0.0003, 0.0028, and 0.0002, respectively), and a greater proportion of patients with virologic failure were female (25.5% v. 18.5%), were from the eastern region of the United States (35.9% v. 27.9%), were African American (40.2% v. 30.2%), and were current smokers (44.8% v. 32.8%). Among patients with virologic failure, fewer acquired HIV infection by male-to-male sex (53.0% v. 63.9%, $P = 0.0001$) or were treatment naive (14.7 v. 24.4%, $P < 0.0001$), time receiving treatment was longer ($P < 0.0001$), and more patients had prior resistance tests (33.2% v. 14.9%, $P < 0.0001$), PI-based subsequent regimens (77.7% v. 61.4%, $P < 0.0001$), increased intensity (31.0% v. 21.1%), and class switches (30.2% v. 15.5%). There were no statistically significant differences in payer type, baseline regimen type, and pill burden between patients with and without virologic failure.

Table 2 shows the base logistic regression model estimates of the cause of regimen switch (virologic failure v. other causes) among HIV-infected patients in the development data set. Although none of the demographic variables were a significant predictor of virologic failure, both treatment naïveté (odds ratio [OR] = 0.60, 95% confidence interval [CI] = 0.41–0.89) and longer time receiving baseline regimen (for 181–360 v. <180 days: OR = 45.15, 95% CI = 26.11–78.08; for >360 v. <180 days: OR = 48.50, 95% CI = 26.84–87.64) were significant predictors. Similarly, the odds of virologic failure were greater for patients with 2 v. zero physician visits during the 90 days before switching (OR = 2.25; 95% CI = 1.09–4.61), more than 1 HIV RNA or CD4 cell count test within 30 days of switching (OR = 2.12; 95% CI = 1.36–3.33), and any resistance test within 180 days before switching (OR = 4.60; 95% CI = 3.01–7.03).

In evaluating the base model's goodness-of-fit and discriminatory ability (Figure 2A), the Hosmer-Lemeshow test ($P < 0.0001$) indicated that the model had a poor overall fit to the data, although ROC curve analyses suggested it had good predictive abilities (C = 0.875). Adding the 3 significant interaction terms (age and days receiving baseline regimen, treatment history and subsequent regimen type, and days receiving baseline regimen and any resistance tests done) greatly improved the model's fit (Hosmer-Lemeshow test, $P = 0.869$). The interactions between age and days receiving baseline regimen and days receiving baseline regimen and the presence of resistance testing yielded the largest ORs. For example, among patients aged 35 to 49 years, those receiving their baseline regimen for between 181 and 360 days were 34 times more likely than those receiving their baseline regimen for ≤180 days to switch due to virologic failure (OR = 33.9; 95% CI = 74.3). Similarly, among patients with no recent resistance test, those receiving their baseline regimen for more than 360 days were 16 times more likely than those receiving their baseline regimen for ≤180 days to switch due to virologic failure (OR = 15.9; 95% CI = 8.2–30.6).

Using ROC analysis, the discriminatory ability of the model with the 3 interaction terms (C = 0.885; Figure 2B) was better than that of the base model. We also calculated integrated discrimination improvement (IDI)[10] to access the model's ability to improve average sensitivity without sacrificing average specificity; the results of this test also indicated that the model with the 3 interaction terms offered significant improvement over the base model ($P < 0.001$). This model therefore was used as the final model, and full details of this model (including all variables, coefficients, statistics, and ORs) can be found online in Technical Appendices A and B.

One additional model was developed, with variables for race/ethnicity, health habits, and route of HIV acquisition added onto the final model. These variables were not reported in the claims data for model application,

**Table 1** Characteristics of HIV-Infected Patients with Combination Antiretroviral Treatment Regimen Switches, by Data Set[a]

| Variable | Development ($n$ = 1691) | Validation ($n$ = 1073) | Claims ($n$ = 3.954) | $P$ Value[b] |
|---|---|---|---|---|
| Demographic characteristic | | | | |
| Age, y, $\bar{x}$ ($s$) | 44.9 (9.1) | 44.2 (8.1) | 44.2 (8.4) | 0.0343 |
| Female, No. (%) | 339 (20.0) | 139 (13.0) | 526 (13.3) | <0.0001 |
| Region, No. (%) | | | | <0.0001 |
| East | 501 (29.6) | 152 (14.2) | 498 (12.6) | |
| Midwest | 331 (19.6) | 85 (7.9) | 741 (18.7) | |
| South | 460 (27.2) | 747 (69.6) | 2,106 (53.3) | |
| West | 399 (23.6) | 89 (8.3) | 609 (15.4) | |
| Payer type, No. (%) | | | | <0.0001 |
| Private/Medicare | 1174 (69.4) | 1062 (99.0) | 3882 (98.2) | |
| Public/Medicaid | 408 (24.1) | 11 (1.0) | 72 (1.8) | |
| Other | 109 (6.4) | 0 (0) | 0 (0) | |
| Baseline regimen characteristic | | | | |
| Treatment naive, No. (%) | 377 (22.3) | 240 (22.4) | 836 (21.1) | 0.9643 |
| Regimen type, No. (%) | | | | <0.0001 |
| PI based | 1027 (60.7) | 564 (52.6) | 2181 (55.2) | |
| NNRTI based | 569 (33.6) | 450 (41.9) | 1522 (38.5) | |
| PI and NNRTI based | 95 (5.6) | 59 (5.5) | 251 (6.3) | |
| Pill burden (number of pills/day), No. (%) | | | | <0.0001 |
| 1–5 | 947 (56.0) | 670 (62.4) | 2402 (60.7) | |
| 6–10 | 626 (37.0) | 365 (34.0) | 1382 (35.0) | |
| ≥11 | 118 (7.0) | 38 (3.5) | 170 (4.3) | |
| Number of days receiving regimen, No. (%) | | | | 0.4873 |
| 1–180 | 768 (45.4) | 507 (47.3) | 2392 (60.5) | |
| 181–360 | 362 (21.4) | 233 (21.7) | 697 (17.6) | |
| ≥361 | 561 (33.2) | 333 (31.0) | 865 (21.9) | |
| Newly diagnosed/treated adverse events, No. (%) | 142 (8.4) | 141 (13.1) | 443 (11.2) | <0.0001 |
| Health care utilization before switch | | | | |
| MD visits within 90 days, $\bar{x}$ ($s$) | 2.4 (1.8) | 3.7 (3.9) | 3.6 (3.7) | <0.0001 |
| Emergency hospital care within 90 days, n (%) | 107 (6.3) | 130 (12.1) | 510 (12.9) | <0.0001 |
| ≥1 HIV RNA or CD4 count test within 30 days, n (%) | 228 (13.5) | 142 (13.2) | 412 (10.4) | 0.8512 |
| Any resistance test within 180 days, n (%) | 319 (18.9) | 117 (10.9) | 352 (8.9) | <0.0001 |
| Switch characteristic | | | | |
| Subsequent regimen type, No. (%) | | | | 0.0005 |
| PI based | 1098 (64.9) | 619 (57.7) | 2306 (58.3) | |
| NNRTI based | 491 (29.0) | 368 (34.3) | 1316 (33.3) | |
| PI and NNRTI based | 102 (6.0) | 86 (8.0) | 332 (8.4) | |
| Change in regimen type, No. (%) | 400 (23.7) | 282 (26.3) | 999 (25.3) | 0.1185 |
| Intensity, No. (%) | | | | <0.0001 |
| Increase intensity | 393 (23.2) | 380 (35.4) | 1388 (35.1) | |
| Class switch | 316 (18.7) | 197 (18.4) | 660 (16.7) | |
| Drug substitution | 557 (32.9) | 250 (23.3) | 919 (23.2) | |
| Decrease intensity | 425 (25.1) | 246 (22.9) | 987 (25.0) | |
| Virologic failure, No. (%) | 368 (21.8) | 200 (18.6) | — | 0.0479 |

PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

[a]Both data sets comprised HIV-infected patients treated with combination antiretroviral therapy; the development data set consisted of registry data and was used for model development; the validation data set consisted of administrative claims data with laboratory mRNA and CD4 values and was used for model validation.

[b]Statistical significance of differences between development and validation data sets.

**Table 2** Base Logistic Regression Model Estimates of Cause of Regimen Switch among HIV-Infected Patients in the Development Data Set[a]: Switch due to Virologic Failure[b] v. Other Causes

| Variable | OR (95% CI)[c] |
|---|---|
| Age group, y | |
| 50+ v. 18–34 | 0.84 (0.49–1.44) |
| 35–49 v. 18–34 | 1.13 (0.69–1.84) |
| Female v. male | 1.24 (0.83–1.86) |
| Region | |
| South v. West | 0.87 (0.56–1.35) |
| Midwest v. West | 1.00 (0.65–1.56) |
| East v. West | 1.28 (0.84–1.97) |
| Payer type | |
| Other v. public/Medicaid | 1.27 (0.66–2.44) |
| Private/Medicare v. public/Medicaid | 1.05 (0.72–1.52) |
| Treatment naive before baseline regimen: yes v. no | 0.60 (0.41–0.89)* |
| Baseline regimen type | |
| PI and NNRTI based v. PI based | 0.76 (0.32–1.81) |
| NNRTI based v. PI based | 1.11 (0.73–1.70) |
| No. of pills/day of baseline regimen | |
| 11+ v. 1–5 | 1.62 (0.87–2.99) |
| 6–10 v. 1–5 | 1.23 (0.85–1.77) |
| No. of days receiving baseline regimen | |
| 181–360 v. ≤180 | 45.15 (26.11–78.08)* |
| >360 v. ≤180 | 48.50 (26.84–87.64)* |
| Newly diagnosed/treated for adverse events: yes v. no | 0.91 (0.50–1.65) |
| No. of MD visits within 90 days before switch | |
| 5+ v. 0 | 3.39 (1.44–7.97)* |
| 3–4 v. 0 | 2.98 (1.42–6.23)* |
| 2 v. 0 | 2.25 (1.09–4.61)* |
| 1 v. 0 | 1.74 (0.84–3.60) |
| Any emergency hospital care within 90 days before switch: yes v. no | 0.64 (0.32–1.26) |
| More than 1 HIV RNA test or CD4 cell count test within (±) 30 days of switch: yes v. no | 2.12 (1.36–3.33)* |
| Any resistance test within 180 days before switch: yes v. no | 4.60 (3.01–7.03)* |
| Year of switch | |
| 2008 v. 2003 | 0.47 (0.20–1.11) |
| 2007 v. 2003 | 0.70 (0.36–1.38) |
| 2006 v. 2003 | 0.66 (0.35–1.27) |
| 2005 v. 2003 | 0.87 (0.47–1.61) |
| 2004 v. 2003 | 1.18 (0.66–2.10) |
| Subsequent regimen type | |
| PI and NNRTI based v. PI based | 0.67 (0.28–1.58) |
| NNRTI based v. PI based | 0.45 (0.30–0.66)* |
| Change in regimen type: yes v. no | 1.10 (0.50– 2.41) |
| Switch intensity | |
| Drug substitution v. decrease intensity | 0.83 (0.54–1.28) |
| Class switch v. decrease intensity | 2.27 (0.99–5.21) |
| Increase intensity v. decrease intensity | 1.78 (1.14–2.78)* |

PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; CI, confidence interval.

[a]The development data set consisted of registry data for HIV-infected patients treated with combination antiretroviral therapy and was the data set used for model development.

[b]Virologic failure defined as 1) HIV RNA level >400 copies/mL after 24 weeks of therapy, 2) detectable HIV RNA level after >48 weeks of therapy, or 3) detectable HIV RNA level after prior suppression (undetectable HIV RNA level <30 days before beginning the baseline regimen).

[c]OR and 95% CI for cause of regimen switch due to virologic failure v. other causes.

*$P < 0.05$.

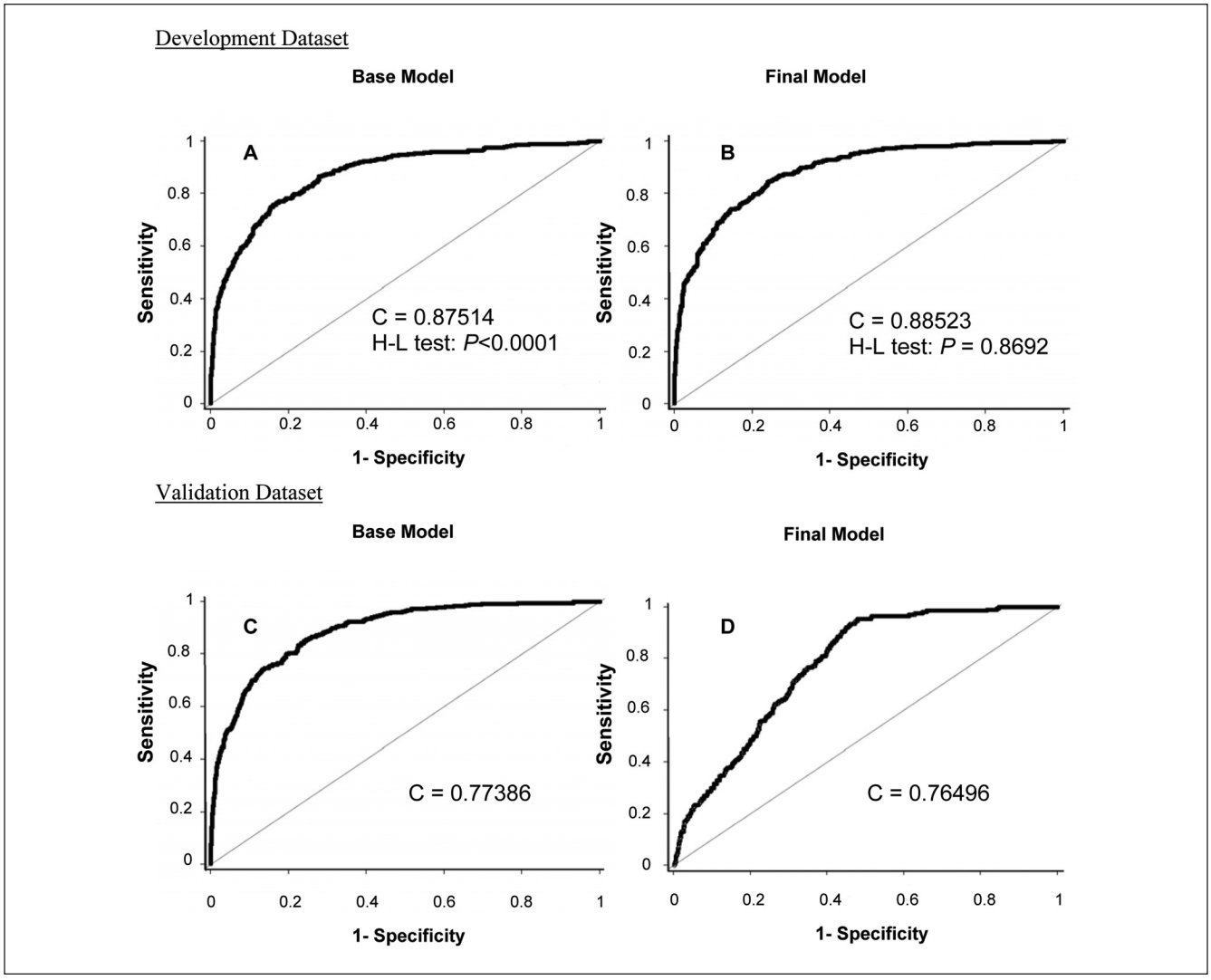


*Figure 2. Analysis of receiver operating characteristic curves to predict abilities of base and final models. H-L, Hosmer-Lemeshow goodness-of-fit test.*

so this "optimal" model could not be used for prediction and was created for comparison only. Smoking (current v. nonsmoker) was a significant predictor of virologic failure, but race/ethnicity, alcohol use, and route of HIV acquisition were not. The optimal model fit the data (Hosmer-Lemeshow test, $P = 0.9051$) and improved the C statistic marginally (C = 0.890) compared with the final model.

To validate the models, we applied both the base and final models to the validation data set. The base model predicted the proportion of patients with virologic failure to be 19.0%, and the final model predicted it to be 18.9%, compared with the observed proportion of 18.6%. As shown in Figure 2C,D, both models' C statistics were lower when applied to the validation data set than when applied to the development data set, yet they still remained high at 0.774 and 0.765 for the base and final models, respectively.

When the base and final models were applied as a worked example to the claims population in the application data set, both models predicted a 13.8% virologic failure rate, and predictions by individual characteristics were also similar between the models; thus, results for only the final model are shown (Table 3). The final validated claims signature model estimated that 15% of patients who were treatment experienced switched due to virologic failure, compared with 9.6% who were treatment naive; the model also estimated

**Table 3** Final Logistic Regression Model Estimates of Virologic Failure[a] among HIV-Infected Patients with Regimen Switches in the Application Data Set[b]

| Variable | Proportion Predicted to Have Virologic Failure (%) |
|---|---|
| Overall | 13.8 |
| Age group, y | |
| 18–34 | 10.7 |
| 35–49 | 14.9 |
| 50+ | 12.4 |
| Treatment-naïve before baseline regimen | |
| Yes | 9.6 |
| No | 15.0 |
| Baseline regimen type | |
| PI based | 14.4 |
| NNRTI based | 14.2 |
| PI and NNRTI based | 6.9 |
| No. of days receiving baseline regimen | |
| 1–180 | 2.7 |
| 181–360 | 34.5 |
| ≥361 | 28.1 |
| Newly diagnosed/treated for adverse events | |
| Yes | 11.8 |
| No | 14.1 |
| Any emergency hospital care within 90 days before switch | |
| Yes | 8.3 |
| No | 14.7 |
| Any resistance test within 180 days before switch | |
| Yes | 24.2 |
| No | 12.8 |
| Subsequent regimen type | |
| PI based | 16.1 |
| NNRTI based | 9.6 |
| PI and NNRTI based | 14.9 |
| Change in regimen type after switch | |
| Yes | 19.3 |
| No | 12.0 |
| Switch intensity | |
| Increase intensity | 15.4 |
| Class switch | 22.4 |
| Drug substitution | 10.3 |
| Decrease intensity | 9.2 |

PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.

[a]Virologic failure defined as 1) HIV RNA level >400 copies/mL after 24 weeks of therapy, 2) detectable HIV RNA level after >48 weeks of therapy, or 3) detectable HIV RNA level after prior suppression (undetectable HIV RNA level <30 days before beginning the baseline regimen).

[b]The application data set consisted of administrative claims data for HIV-infected patients treated with combination antiretroviral therapy without laboratory mRNA and CD4 values.

that 14.4% of patients receiving PI-based and 14.2% receiving NNRTI-based baseline regimens were estimated to have switched due to virologic failure, compared with 6.9% of patients receiving PI- and NNRTI-based baseline regimens. Patients who switched after receiving their baseline regimen for 181 to 360 days were more likely than were those who switched by day 180 to have virologic failure (34.5% v. 2.7%, respectively). Similarly, those without any emergency hospital care within 180 days before switching were predicted to have a greater chance of virologic failure (14.7%) compared with those with prior hospital care (8.3%). In addition, 22.4% of patients whose switch involved a different class of cART regimen were predicted to have virologic failure, compared with 9.2% of those whose change was a decrease in treatment intensity.

## DISCUSSION

We used clinical registry data containing viral load information to develop, validate, and apply a claims signature model that could use administrative claims data to estimate ex post the proportion of HIV-infected patients whose cART regimen switches were due to virologic failure v. other causes (e.g., regimen tolerability). The final model was chosen as that with the best discriminatory ability and goodness of fit, and it incorporates patients' demographic characteristics, medical and social history, and antiretroviral treatment characteristics both before and after cART regimen switch.

Model validation showed that 18.9% of switches were estimated by the model to have been due to virologic failure, compared with 18.6% observed. When applied to a large claims database as a worked example, failure rates were estimated at 13.8% among all patients who switched regimens, 15% among treatment-experienced switchers, and 9.6% among treatment-naive patients. These results are consistent with other US estimates indicating that between 5% and 23% of patients stop their regimens because of virologic failure[8,11–13] and suggest that most patients who switch cART regimens do so for reasons other than virologic failure. Thus, when interpreting the results of this analysis, lower rates of switching due to failure would not indicate more virologically potent regimens but rather would reflect situations in which the switch itself was caused less by failure and more by other factors such as regimen tolerability.

Furthermore, because this model is intended to be used as an estimation—not prediction—model to be applied to administrative claims data, it neither can nor should be used to identify specific patients with

virologic failure or to predict the future likelihood of specific failures; claims data lack the laboratory values necessary to do this, and viral and immunologic testing remains the standard for making decisions regarding clinical action. Rather, in estimating patterns of virologic failure based on data from administrative claims, these models can allow policy makers or payers to examine cost outcomes that are crucial for planning purposes, even when detailed outcomes data are lacking.

This claims signature model will therefore be valuable to payers and policy makers who could use estimated rates of virologic failure among patients who switched cART regimens to approximate the costs of failure in these populations and better inform budget planning. Such an application could be done relatively simply by using the model on a plan's population to estimate the percentage of patients who switched due to failure, multiplying this rate by estimates of short- and long-term costs of failure and thereby approximating plan-specific total costs of failure.

Alternatively, the model could more specifically be used to estimate rates and costs of failure by applying it to an individual patient in a particular population to estimate separate failure rates for each patient. From these patient-specific failure rates, one could use observed costs for patients with failure risks beyond certain extreme thresholds to again approximate plan-specific total costs of failure. For example, costs among patients below the 10th percentile of the risk distribution could be considered to represent costs of patients who did not have virologic failure, and costs among patients above the 90th percentile could represent those of patients who did have virologic failure; the difference between these would be an approximation of overall plan costs of virologic failure. Although more complicated than the former method of using the claims signature model to approximate the costs of virologic failure, this latter method may be more accurate in that it applies the model to specific patients and uses patient-specific costs rather than costs estimated from outside sources.

These results might also be used to better understand some of the factors to be considered when conducting comparative effectiveness studies of ART regimens. For example, the model estimated that patients whose regimen switch was due to virologic failure had, before the switch, an increased frequency of physician visits, more viral and immunologic testing, and fewer recent ED visits. This latter finding may appear contrary to expectations (worsening disease often accompanies virologic failure), but because our analysis evaluated switching due to virologic failure, not failure itself, this finding indicates that severe adverse events rather than virologic failure may be driving regimen switch among patients with more ED visits.

The model also estimated that longer treatment periods among claims patients were strongly associated with virologic failure. Although this is consistent with some studies in which patients who manifest regimen intolerance do so early in their course of treatment,[13,14] not all studies have shown this. Yuan and others[8] examined treatment discontinuation among patients in the HIV Insight registry (1996–2003) and found that the median time to discontinuation was shorter for virologic failure than for other reasons. Differences between the results of the current analysis and the findings of Yuan and others may reflect both changes in tolerability of cART regimens over time as well as differences in study designs, as Yuan and others studied only treatment-naive patients and defined failure by physician-reported reason rather than by laboratory results.[8]

Similarly, the current model estimated that among patients receiving PI-based regimens, those who were treatment naive were less likely to switch due to virologic failure than were those who were treatment experienced (OR = 0.50; 95% CI = 0.29–0.86). With other research indicating that treatment-naive patients have less resistance to PI-based regimens,[15] the effect found here could be due to the fact that switches among treatment-naive patients are more likely due to poorer PI tolerability than due to virologic failure. The model also estimated that patients receiving the PI- and NNRTI-based baseline regimens were less likely to have switched due to virologic failure than were other patients (6.9% v. 14.4% and 14.2% among those receiving PI- and NNRTI-based baseline regimens, respectively). This finding, which suggests that switches among patients receiving PI- and NNRTI-based baseline regimens were likely caused not by virologic failure but by other issues such as regimen tolerability, is consistent with clinical trial data showing that significantly worse adverse events (such as elevated triglycerides) occur in patients whose treatments include a combination of PI- and NNRTI-based regimens.[16]

The results of this analysis must be considered in the context of its potential limitations. The HIV Insight registry is composed of data from a limited set of specialized clinics at which HIV-infected individuals are treated by experts and where only 24% of patients are covered by public rather than private insurance. On the other hand, the administrative claims data sets (used for model validation and application) represent

claims for care delivered to millions of patients unified only by their insurance providers, all of which were private rather than public. Inferences from one data set to the other are thus best for hypothesis generation rather than testing, a problem addressed in this study by validating the models with a subset of claims data for which there was laboratory confirmation of virologic failure.

Future research should include model validation with public insurance data sets to ensure its applicability for government payers. Other limitations common to all claims studies, including the possibility of miscoding and data errors, apply to this study as well, and this is another reason why validation by other researchers would be valuable. Finally, data on medication adherence is not available in the development data set, and therefore the exact cause of virologic failure among HIV Insight patients could not be established. However, because the model's primary value is to allow payers to estimate the costs of virologic failure in their populations, and because the cause of failure (whether medication or adherence related) is not relevant to such estimates, this would not be a limitation of the analysis or of the model's application.

In conclusion, we developed and validated a claims signature model that will allow administrative claims data without viral load values to be used to estimate the proportion of cART switches that are likely to have resulted from virologic failure. This model can be applied to multiple sources of administrative claims data for HIV-infected individuals, and it can be used to supplement information from registries to estimate the impact of virologic failure on cART treatment regimen switching. Use of this model could assist payers in improving health care quality and reducing costs by allowing them to estimate and monitor both rates and costs of virologic failure in their patient populations and thereby inform budget planning and develop strategies to improve outcomes.

**Technical Appendix A** Final Logistic Regression Model in Development Data Set: Coefficients for Switch Due to Virologic Failure

| Parameter | Coefficient | Standard Error | Wald Chi-Square | *P* Value |
|---|---|---|---|---|
| Intercept | –2.1439 | 0.3374 | 40.3786 | <0.0001 |
| Age group (y): 50+ | 0.00246 | 0.1418 | 0.0003 | 0.9862 |
| Age group (y): 35–49 | 0.00551 | 0.1312 | 0.0018 | 0.9665 |
| Female | 0.1856 | 0.2152 | 0.7433 | 0.3886 |
| Region: South | –0.1858 | 0.1466 | 1.6061 | 0.2050 |
| Region: Midwest | –0.0445 | 0.1416 | 0.0987 | 0.7534 |
| Region: East | 0.2650 | 0.1369 | 3.7440 | 0.0530 |
| Payer type: Others | 0.1596 | 0.2129 | 0.5621 | 0.4534 |
| Payer type: Private/Medicare | –0.0588 | 0.1365 | 0.1854 | 0.6668 |
| Treatment naive (before beginning first regimen) | 0.5585 | 0.3643 | 2.3501 | 0.1253 |
| First regimen type: PI and NNRTI based | –0.5655 | 0.3414 | 2.7439 | 0.0976 |
| First regimen type: NNRTI based | 0.3489 | 0.2216 | 2.4797 | 0.1153 |
| No. of pills/day of first regimen: 11+ | 0.3439 | 0.2017 | 2.9071 | 0.0882 |
| No. of pills/day of first regimen: 6–10 | –0.0306 | 0.1327 | 0.0531 | 0.8178 |
| No. of days on first regimen: 361+ | 0.8803 | 0.1636 | 28.9591 | <0.0001 |
| No. of days on first regimen: 181–360 | 1.0049 | 0.1536 | 42.7786 | <0.0001 |
| Newly diagnosed/treated for adverse events | –0.1863 | 0.3208 | 0.3374 | 0.5613 |
| No. of MD visits in 90 days before switch: 5+ | 0.5232 | 0.2369 | 4.8757 | 0.0272 |
| No. of MD visits in 90 days before switch: 3–4 | 0.3275 | 0.1574 | 4.3274 | 0.0375 |
| No. of MD visits in 90 days before switch: 2 | 0.0164 | 0.1479 | 0.0123 | 0.9117 |
| No. of MD visits in 90 days before switch: 1 | –0.1627 | 0.1553 | 1.0975 | 0.2948 |
| Any emergency hospital care in 90 days before switch | –0.5428 | 0.3771 | 2.0720 | 0.1500 |
| More than 1 HIV RNA test or CD4 cell count test within (±) 30 days of switch | 0.8257 | 0.2342 | 12.4283 | 0.0004 |
| Any resistance test in 180 days before switch | 1.2500 | 0.2711 | 21.2670 | <0.0001 |
| Year of switch: 2008 | –0.4582 | 0.2933 | 2.4405 | 0.1182 |
| Year of switch: 2007 | –0.1445 | 0.1880 | 0.5908 | 0.4421 |

*(continued)*

**Technical Appendix A (continued)**

| Parameter | Coefficient | Standard Error | Wald Chi-Square | *P* Value |
|---|---|---|---|---|
| Year of switch: 2006 | –0.1938 | 0.1747 | 1.2312 | 0.2672 |
| Year of switch: 2005 | 0.1528 | 0.1591 | 0.9223 | 0.3369 |
| Year of switch: 2004 | 0.3811 | 0.1599 | 5.6804 | 0.0172 |
| Second regimen type: PI and NNRTI based | –0.0562 | 0.3130 | 0.0322 | 0.8575 |
| Second regimen type: NNRTI based | –0.3934 | 0.1966 | 4.0035 | 0.0454 |
| Change in regimen type | 0.1110 | 0.4301 | 0.0666 | 0.7964 |
| Switch intensity: Drug substitution | –0.4823 | 0.1721 | 7.8485 | 0.0051 |
| Switch intensity: Class switch | 0.5120 | 0.3287 | 2.4256 | 0.1194 |
| Switch intensity: Increase intensity | 0.2706 | 0.1690 | 2.5624 | 0.1094 |
| Age group * No. of days on first regimen: 50+ * 361+ | –0.1489 | 0.1782 | 0.6980 | 0.4035 |
| Age group * No. of days on first regimen: 50+ * 181–360 | –0.3485 | 0.1856 | 3.5246 | 0.0605 |
| Age group * No. of days on first regimen: 35–49 * 361+ | 0.3948 | 0.1630 | 5.8667 | 0.0154 |
| Age group * No. of days on first regimen: 35–49 * 181–360 | 0.1199 | 0.1686 | 0.5055 | 0.4771 |
| Treatment naive * First regimen type: yes * PI and NNRTI based | 2.1942 | 0.6805 | 10.3969 | 0.0013 |
| Treatment naive * First regimen type: yes * NNRTI based | –0.9474 | 0.4082 | 5.3882 | 0.0203 |
| Any resistance test in 180 days before switch * No. of days on first regimen: yes * 361+ | 1.1902 | 0.3518 | 11.4441 | 0.0007 |
| Any resistance test in 180 days before switch * No. of days on first regimen: yes * 181–360 | 0.7258 | 0.3410 | 4.5314 | 0.0333 |

NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

**Technical Appendix B** Final Logistic Regression Model in Development Data Set: ORs and 95% CIs for Switch Due to Virologic Failure

| Parameter | OR (95% CI) | |
|---|---|---|
| Female v. male | 1.20 | (0.79–1.84) |
| Region | | |
| South v. West | 0.86 | (0.54–1.36) |
| Midwest v. West | 0.99 | (0.63–1.55) |
| East v. West | 1.35 | (0.86–2.11) |
| Payer type | | |
| Other v. public/Medicaid | 1.30 | (0.66–2.55) |
| Private/Medicare v. public/Medicaid | 1.04 | (0.71–1.54) |
| No. of pills/day of first regimen | | |
| 11+ v. 1–5 | 1.93 | (1.02–3.65) |
| 6–10 v. 1–5 | 1.33 | (0.91–1.93) |
| Newly diagnosed/treated for AEs: yes v. no | 0.83 | (0.44–1.56) |
| No. of MD visits in 90 days before switch | | |
| 5+ v. 0 | 3.41 | (1.41–8.23) |
| 3–4 v. 0 | 2.81 | (1.31–6.00) |
| 2 v. 0 | 2.06 | (0.98–4.31) |
| 1 v. 0 | 1.72 | (0.82–3.62) |
| Any emergency hospital care in 90 days before switch: yes v. no | 0.58 | (0.28–1.22) |
| More than 1 HIV RNA test or CD4 cell count test within (±) 30 days of switch: yes v. no | 2.28 | (1.44–3.61) |
| Year of switch | | |
| 2008 v. 2003 | 0.49 | (0.20–1.18) |
| 2007 v. 2003 | 0.67 | (0.33–1.33) |

*(continued)*

**Technical Appendix B (continued)**

| Parameter | | OR (95% CI) |
|---|---|---|
| 2006 v. 2003 | 0.63 | (0.33–1.23) |
| 2005 v. 2003 | 0.90 | (0.48–1.68) |
| 2004 v. 2003 | 1.13 | (0.63–2.02) |
| Second regimen type | | |
| PI and NNRTI based v. PI based | 0.60 | (0.24–1.52) |
| NNRTI based v. PI based | 0.43 | (0.29–0.65) |
| Change in regimen type: yes v. no | 1.12 | (0.48–2.60) |
| Switch intensity | | |
| Drug substitution v. decrease intensity | 0.83 | (0.54–1.30) |
| Class switch v. decrease intensity | 2.25 | (0.93–5.47) |
| Increase intensity v. decrease intensity | 1.77 | (1.12–2.80) |
| Age * No. of days on first regimen | | |
| Age 50+: No. of days on first regimen: 361+ v. ≤180 | 8.33 | (3.59–19.28) |
| No. of days on first regimen: 181–360 v. ≤180 | 7.72 | (3.32–17.97) |
| Age 35–49: No. of days on first regimen: 361+ v. ≤180 | 39.45 | (17.74–87.71) |
| No. of days on first regimen: 181–360 v. ≤180 | 33.94 | (15.50–74.31) |
| Age 18–34: No. of days on first regimen: 361+ v. ≤180 | 25.68 | (7.09–92.98) |
| No. of days on first regimen: 181–360 v. ≤180 | 10.57 | (3.03–36.95) |
| No. of days on first regimen 361+: Age 50+ v. 18–34 | 1.11 | (0.47–2.65) |
| Age 35–49 v. 18–34 | 1.92 | (0.86–4.31) |
| No. of days on first regimen 181–360: Age 50+ v. 18–34 | 0.57 | (0.24–1.35) |
| Age 35–49 v. 18–34 | 0.91 | (0.41–2.01) |
| No. of days on first regimen ≤180: Age 50+ v. 18–34 | 1.63 | (0.48–5.60) |
| Age 35–49 v. 18–34 | 0.60 | (0.18–2.01) |
| Treatment naive (before beginning first regimen) * First regimen type | | |
| Treatment naive: First regimen type PI and NNRTI based v. PI based | 14.28 | (2.24–90.99) |
| First regimen type NNRTI based v. PI based | 1.54 | (0.69–3.43) |
| Treatment experienced: First regimen type PI and NNRTI based v. PI based | 0.46 | (0.17–1.25) |
| First regimen type NNRTI based v. PI based | 1.14 | (0.71–1.84) |
| PI- and NNRTI-based first regimen type: Treatment naive v. experienced | 15.68 | (2.21–111.42) |
| NNRTI-based first regimen type: Treatment naive v. experienced | 0.68 | (0.36–1.29) |
| PI-based first regimen type: Treatment naive v. experienced | 0.50 | (0.29–0.86) |
| No. of days on first regimen * Any resistance test in 180 days before switch | | |
| Recent resistance test: No. of days on first regimen 361+ v. ≤180 | 354.9 | (93.47–1347.26) |
| No. of days on first regimen 181–360 v. ≤180 | 252.6 | (71.44–893.47) |
| No recent resistance test: No. of days on first regimen 361+ v. ≤180 | 15.89 | (8.25–30.59) |
| No. of days on first regimen 181–360 v. ≤180 | 18.00 | (9.62–33.68) |
| No. of days on first regimen ≤180: Recent resistance test yes v. no | 0.51 | (0.17–1.58) |
| No. of days on first regimen 181–360: Recent resistance test yes v. no | 11.48 | (5.16–25.53) |
| No. of days on first regimen 361+: Recent resistance test yes v. no | 7.21 | (3.41–15.24) |

AE, adverse event; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.

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