RESEARCH

# Provider Prescribing of 4 Antiretroviral Agents After Implementation of Drug Use Guidelines in the Department of Veterans Affairs

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## ABSTRACT

BACKGROUND: The Veterans Health Administration (VHA) develops guidelines for VHA providers that delineate specific criteria for use of certain complex, costly medications indicated for specialized populations. These criteria are disseminated to all VHA facilities.

OBJECTIVE: To (a) assess the concordance with VHA guidelines for use of 4 antiretrovirals (atazanavir, darunavir, enfuvirtide, and tipranavir), and (b) to describe prescribing of these agents before and after implementation of the guideline criteria.

METHODS: In this retrospective cohort study, we evaluated all veterans in VHA care who received their first outpatient prescription for a target antiretroviral between its FDA approval date and December 31, 2007, using outpatient prescription records obtained from the VHA Human Immunodeficiency Virus (HIV) Clinical Case Registry (CCR:HIV), an observational registry database created through extraction of specific clinical data from the VHA's electronic medical record. Adherence to the VHA guideline criteria was assessed using CCR:HIV data overall and during 3 time periods: (a) *pre-criteria:* from FDA approval date to criteria implementation date (range 38 days to 192 days), (b) *early-criteria:* the first 6 months after criteria implementation, and (c) *late-criteria:* from 180 days after criteria implementation until December 31, 2007 (range 184 days to 1,525 days).

RESULTS: VHA providers prescribed target antiretroviral medications in accordance with the VHA guidelines for use more than 70% of the time. Comparing the pre-criteria with the post-criteria period (i.e., early-criteria and late-criteria combined), no significant differences in the percentages of veterans satisfying all VHA criteria were observed for any drug except atazanavir ($P=0.010$). For atazanavir in the post-criteria period compared with the pre-criteria period, significantly more antiretroviral-naïve veterans met criteria for cardiovascular disease or risk (72.8% post-criteria vs. 45.5% pre-criteria, $P=0.045$), and significantly more antiretroviral-experienced veterans met criteria for resistance to other protease inhibitors requiring the need for ritonavir-boosted atazanavir (61.7% vs. 50.5%, respectively, $P<0.001$); however, fewer antiretroviral-experienced veterans met criteria for having documented intolerance to other protease inhibitors (78.9% vs. 89.9%, respectively, $P<0.001$). Fewer darunavir-treated patients in the post-criteria period than in the pre-criteria period met the criteria for treatment experience including failure of at least 1 prior protease inhibitor regimen (87.8% vs. 96.0%, respectively, $P=0.002$). Adherence to all darunavir criteria significantly waned over time (early-criteria 78.8% vs. late-criteria 62.5%, $P<0.001$). Overall, adherence to atazanavir criteria increased over time (66.3% early-criteria vs. 72.9% late-criteria, $P<0.001$).

CONCLUSIONS: After implementation of antiretroviral specific guideline criteria, the proportion of veterans prescribed a target antiretroviral medication in accordance with VHA guideline criteria varied by agent and improved only for atazanavir. Although adherence to criteria for atazanavir, enfuvirtide, and tipranavir persisted or improved during the post-criteria period, darunavir adherence to criteria waned over time, perhaps indicating that later prescribing patterns reflected changing practice patterns and the need for updated criteria. Revisiting and updating criteria may be especially important for HIV due to the speed with which new information becomes available.

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### What is already known about this subject

- Provider adherence to institutional medication criteria guidance generally ranges from 50% to 95%. Generally accepted rates for adherence to guidelines range from 80% to 90%.
- Institutional guidelines based on currently available evidence can improve the clinical appropriateness of therapy as suggested by Owen et al. in an evaluation describing the utilization of recombinant human coagulation factor VIIa pre- versus post-implementation of an evidence-based guideline at a university hospital. Gora-Harper et al. also demonstrated significantly more instances of appropriate use of neuromuscular blocking agents post-guideline implementation compared with pre-implementation.
- Not all guideline criteria are effective in influencing provider prescribing patterns. In a study of patients in Veterans Affairs medical centers, Burk et al. found no meaningful differences in prescribing patterns before versus after posting of national formulary guidelines for use of tamsulosin.
- The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents has developed national guidelines for initiation and selection of antiretroviral regimens in individuals infected with human immunodeficiency virus (HIV-1).

### What this study adds

- In this retrospective cohort study of patients in Veterans Health Administration (VHA) care, who received their first outpatient prescription for a target antiretroviral between its FDA approval date and December 31, 2007, VHA providers prescribed target antiretroviral medications in accordance with criteria more than 70% of the time.
- After implementation of antiretroviral-specific guideline criteria, the proportion of veterans prescribed a target antiretroviral medication (atazanavir, darunavir, enfuvirtide, or tipranavir) in accordance with guideline criteria varied by drug. Comparing the pre-criteria with post-criteria periods, no significant differences in the percentages of veterans satisfying all VHA criteria were observed for any drug except atazanavir.
- Although adherence to criteria generally persisted, adherence to all darunavir criteria waned over time. Later prescribing patterns may reflect changing practice patterns and the need for updated criteria.
- Revisiting and updating criteria may be especially important for HIV due to the speed with which new information becomes available.

Four new antiretroviral agents received U.S. Food and Drug Administration (FDA) approval for the treatment of human immunodeficiency virus (HIV) infection between June 2003 and June 2006: atazanavir (June 2003), darunavir (June 2006), enfuvirtide (March 2003), and tipranavir (June 2005). Each of these agents offered antiretroviral-experienced HIV-infected patients options when previously few existed. These agents were FDA approved based on data from 24-week analyses that included very specific patient inclusion criteria.[1-7]

With the introduction of several new classes and agents, antiretroviral treatment has become increasingly complex because of resistance, long-term toxicities, regimen complexities, adherence, and drug-interactions.[8] The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents publishes national antiretroviral treatment guidelines for initiation and selection of antiretroviral regimens in HIV-1 infected individuals.[8] An evaluation of HIV-infected veterans in 2004 found that 60% were receiving a preferred or alternative regimen in accordance with these published guidelines.[9]

Although these nationally published guidelines provide recommendations on the criteria for selecting preferred components in an antiretroviral regimen and provide details on selecting appropriate agents for special populations of patients, they do not provide agent-specific criteria to follow. The influence of local criteria to help guide providers as to which HIV-infected patients may be most appropriate to receive selected antiretroviral agents has not been extensively evaluated. Although some data exist on antiretroviral prescribing patterns and utilization, provider adherence to local institutionally established antiretroviral criteria for use is understudied.[9-11]

The Veterans Health Administration (VHA) develops guidelines for VHA providers that delineate criteria for use of certain complex, costly medications indicated for specialized populations. These guideline criteria are disseminated for use by all VHA facilities. Enforcement at individual facilities varies to some extent, but criteria are available to all providers on the VHA Intranet. Once an electronic order for these medications is entered in the system, clinical pharmacists review electronic medical records (EMRs) to verify that patients prescribed these medications have met the guideline criteria.

Concerns regarding potentially inappropriate use, safety, and cost of the antiretroviral agents atazanavir, darunavir, enfuvirtide, and tipranavir led to efforts to standardize their use. VHA criteria were modeled after inclusion criteria used in the key licensing trials for each agent; current medical evidence available at the time the criteria were developed; and input from VHA HIV experts (Table 1). The guideline criteria are dynamic and are revised as new data become available.

Though such criteria are often implemented within health care delivery systems, little information has been published about adherence to such criteria or about changes in adherence over time, particularly for antiretroviral prescribing. This analysis sought to assess the concordance with VHA guidelines of 4 antiretroviral agents and to describe the prescribing of these agents before and after implementation of these criteria.

## Methods

### Patient Selection

Target medications were atazanavir, darunavir, enfuvirtide, and tipranavir. Veterans were identified using outpatient prescription records obtained from the VHA HIV Clinical Case Registry (CCR:HIV), an observational registry database created through extraction of specific clinical data from the VHA's EMR. We included all veterans in VHA care who received their first outpatient prescription for a target medication between its FDA approval date and December 31, 2007. We required that at least 1 VHA prescription for any medication be filled within 90 or more days before the first prescription for the target medication to indicate that the patient was currently receiving care from the VHA. Other than this, no specific length of time enrolled in VHA care was required. Veterans transferring into VHA care already on a target antiretroviral from another outside source were excluded, as were veterans receiving a target medication as part of a pre-approval clinical trial and continuing it after FDA approval. The present analysis includes only veterans who received the target medication, whether or not those individuals met criteria and were in concordance with VHA guidelines; we did not include veterans who may have met criteria but did not receive a target medication. Because the study data were extracted from the EMR, the data reflect only prescriptions for the target medications rather than claims indicating that the prescriptions were actually filled.

### VHA Guideline Criteria

The dates of implementation of VHA criteria for the target medications ranged between 38 days (tipranavir) and 192 days (darunavir) after FDA approval (Table 2). After guideline criteria are developed by a clinical pharmacist with expertise in the therapeutic field, they are reviewed by 2 VHA committees consisting of formulary leaders (mostly pharmacists) and a medical advisory panel (mostly physicians). The guidelines are then sent to field providers in the practice area for review and comments before final approval by the committees and posting on the VHA Intranet. Generally guidelines are posted within 90 days after FDA approval. Implementation of atazanavir criteria was delayed because this was the first antiretroviral for which VHA guidelines had been established. Darunavir guideline development was delayed because of staffing shortages and postponement of committee review. Different atazanavir criteria were established for antiretroviral-naïve and antiretroviral-experienced veterans and these were evaluated separately (Table 1).

The numbers of veterans satisfying each separate criteria and satisfying all criteria for a target medication were automatically extracted from the EMR in January 2008 using the CCR:HIV

**TABLE 1** *Criteria of Target Medications in the Veterans Health Administration*

| Target Medication | Criteria in Use at Time of Study | Criteria Currently in Use | Source and Rationale |
|---|---|---|---|
| **Atazanavir** | ***Antiretroviral naïve:***<br>1. Cardiovascular disease or multiple (3 or more) risk factors for cardiovascular disease,[a]<br>*or*<br>2. Not a candidate for other once daily medications (specifically efavirenz[b])<br>***Antiretroviral experienced:***<br>1. Documented intolerance to other PIs<br>*or*<br>2. Documented resistance to other PIs where atazanavir plus ritonavir would be expected to have activity<br>*or*<br>3. Stable on antiretroviral regimen (VL < 1,000 copies per mL) but with uncontrolled LDL-C (> 100 mg per dL) and/or triglycerides (> 300 mg per dL) | Criteria no longer in use in VHA (archived October 2006); medication is available without restriction to HIV-infected individuals in VHA care in accordance with DHHS guidelines.[8] | ***Antiretroviral naïve:***<br>1. Data from clinical trial AI424-034[6,7] demonstrating that lipids, including cholesterol and triglycerides, did not increase with short-term exposure to the drug. Atazanavir would be the preferred PI in patients for whom the potential worsening of LDL-C may place them at a high risk of a clinical event.<br>2. Patients who would likely fail any regimen administered more than once daily would be appropriate for atazanavir. Since efavirenz was also approved as a daily agent, consideration should be given as to whether the patient would benefit from an efavirenz-containing regimen in place of atazanavir.<br>***Antiretroviral experienced:***<br>1. At the time of the criteria, atazanavir was not a preferred PI according to DHHS guidelines; VHA experts agreed that other preferred PIs should be initiated first if tolerated.<br>2. In clinical trial AI424045,[7] the virologic response to ritonavir-boosted atazanavir was similar to that seen with lopinavir/ritonavir; hence, in patients sensitive to atazanavir but resistant to preferred PIs, boosted atazanavir would be appropriate.<br>3. Data from clinical trial AI424-034[6,7] demonstrating that lipids, including cholesterol and triglycerides, did not increase with short-term exposure to the drug. Atazanavir would be the preferred PI in patients for whom the potential worsening of LDL-C may place them at a high risk of a clinical event. Definition of uncontrolled dyslipidemia includes patients who do not reach VHA-recommended target goals with lifestyle changes and/or pharmacologic intervention. |
| **Darunavir** | 1. Highly treatment-experienced patients (defined in criteria as including at least 1 prior failed PI regimen)<br>*and*<br>2. Evidence of virologic failure documented by a VL > 1,000 copies per mL<br>*and*<br>3. Able to tolerate low-dose ritonavir | Criteria no longer in use in VHA (archived January 2009); medication is available without restriction to HIV-infected individuals in VHA care in accordance with DHHS guidelines.[8] | 1. FDA-approved indication is for the treatment of HIV-1 infection, with concomitant ritonavir and other antiretroviral drugs, in treatment-experienced patients, such as those with HIV-1 strains resistant to more than 1 PI.[c] Similar to inclusion criteria from POWER 1 and 2 studies.[5,24,25]<br>2. In POWER 1 and 2, patients' plasma HIV-1 RNA had to be > 1,000 copies per mL for inclusion.<br>3. Darunavir must be administered with low-dose ritonavir to achieve its desired efficacy. |
| **Enfuvirtide** | 1. Exposure to at least 2 antiretroviral classes<br>*and*<br>2. Documented VL > 5,000 copies per mL<br>*or*<br>3. Intolerance to at least 2 antiretroviral regimens | Existing criteria still in use | 1. TORO-1 and 2 inclusion criteria:[1,2] HIV-infected patients exposed to all 3 antiretroviral drug classes.<br>2. TORO-1 and 2 inclusion criteria: HIV viral load ≥ 5,000 copies per mL.<br>3. VHA expert recommendation to provide the option to use enfuvirtide if patient has intolerance to other regimens. |

**TABLE 1** Criteria of Target Medications in the Veterans Health Administration
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| | | | |
|---|---|---|---|
| **Tipranavir** | 1. Highly treatment-experienced patients (including at least 2 prior failed PI regimens)<br>*and*<br>2. Evidence of virologic failure documented by a VL > 1,000 copies per mL<br>*and*<br>3. Able to tolerate low-dose ritonavir | 1. Treatment-experienced patient (defined as 3-class experience including PI regimen)<br>2. Evidence of virologic failure documented by a VL > 1,000 copies per mL<br>3. Able to construct a multidrug regimen that includes, preferably, at least 1 additional active antiretroviral drug (if available) in addition to tipranavir/ritonavir<br>4. Under the care of an experienced HIV practitioner | 1. RESIST-1 and RESIST-2 studies[3,4] included heavily pre-treated patients with triple antiretroviral class (NRTI, NNRTI, and PI) experience.<br>2. FDA approved for patients with evidence of viral replication.[d]<br>3. Tipranavir must be administered with low-dose ritonavir to achieve its desired efficacy. |

[a]*Cardiovascular disease risk factors documented in the medical record at any time prior to starting atazanavir: (1) age in years (male ≥ 45, female ≥ 55), (2) male sex, (3) tobacco use, (4) hypertension, (5) diabetes, (6) HDL-C < 40 mg per dL, and (7) LDL-C ≥ 130 mg per dL (adapted from VA/DoD Clinical Practice Guidelines for Management of Dyslipidemia Update 2006. Available at: http://www.guideline.gov/summary/summary.aspx?doc_id=9907.*

[b]*Patients not expected to tolerate efavirenz included those with bipolar disorder, depression, post-traumatic stress disorder, or schizophrenia.*

[c]*The DHHS currently recommends darunavir as first-line treatment for both treatment-naïve and treatment-experienced patients.[8]*

[d]*Criterion was based on FDA label in place at time of study. Label history is available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist*

*DHHS = Department of Health and Human Services; dL = deciliter; FDA = U.S. Food and Drug Administration; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; mg = milligrams; mL = milliliter; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor; NRTI = Nucleoside Reverse Transcriptase Inhibitor; PI = protease inhibitor; POWER = Performance of TMC114/ritonavir When Evaluated in Treatment-experienced Patients With PI Resistance; RESIST = Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients With Tipranavir; RNA = ribonucleic acid; TORO = T-20 vs. Optimized Regimen Only Study; VHA = Veterans Health Administration; VL = viral load.*

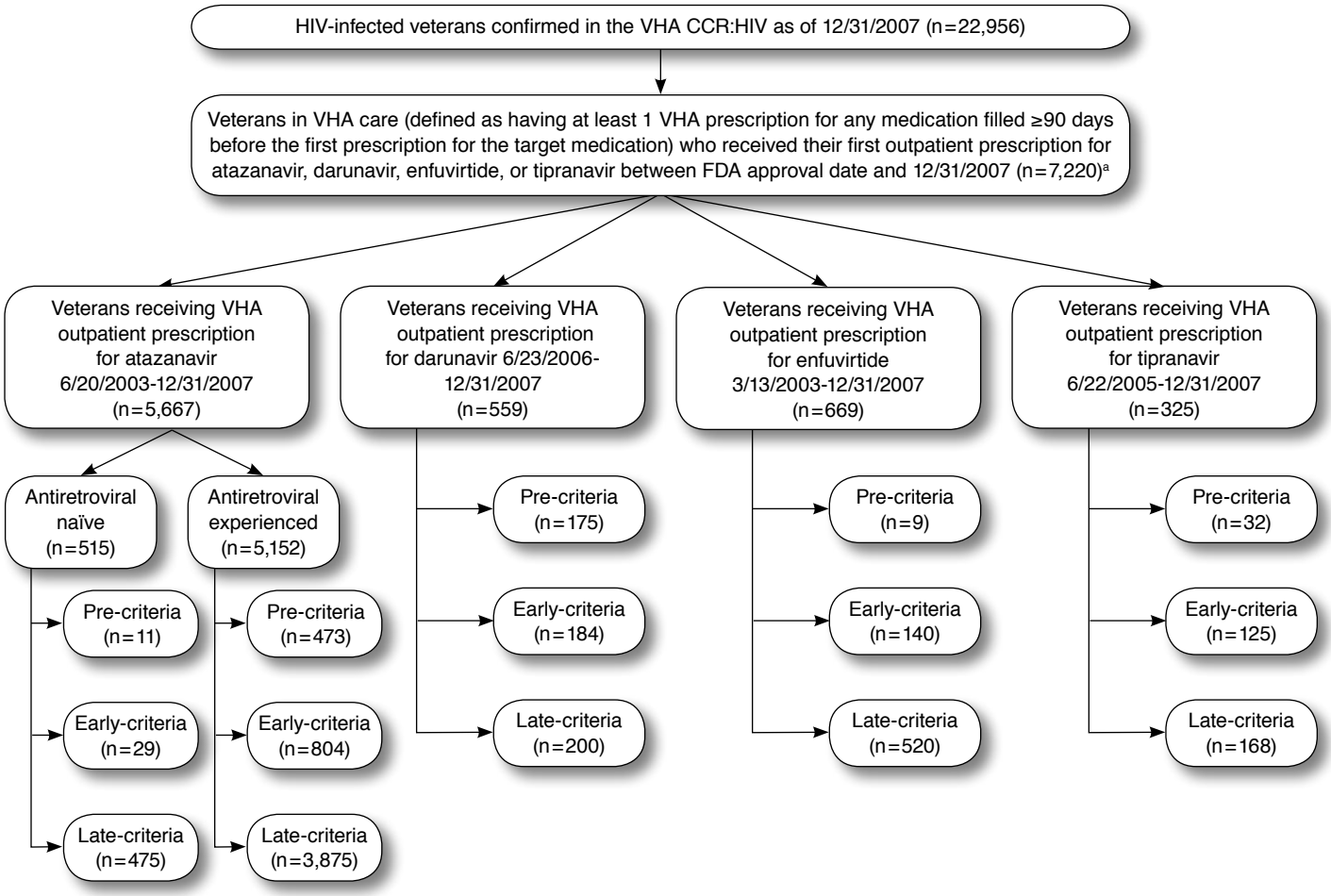
electronic database fields for allergy, demographics, diagnosis codes, laboratory, and prescription information through December 31, 2007. CCR:HIV data are derived directly from the EMR and are validated quarterly by clinical staff dedicated to routine maintenance of the database.

VHA prescription records electronically extracted from the CCR:HIV were used to identify veterans with previous antiretroviral exposure before initiation of the target drug and dating back to 1999. A patient was considered intolerant of an antiretroviral if the patient had a documented allergy to the medication or if the patient had been prescribed the medication and then the prescription was discontinued any time thereafter. This is a crude measure of intolerance; however, because this evaluation did not involve chart review, we could not confirm the reason for discontinuation. For purposes of assessing adherence to prescribing criteria, we used the less stringent measure of exposure to other protease inhibitors rather than documented intolerance. A patient was considered to be able to tolerate low-dose ritonavir if the patient had ever received low-dose ritonavir and did not have a documented allergy to ritonavir in the EMR.

Virologic cutoffs defined in the criteria were determined using laboratory results for the HIV viral load closest (but within 1 year prior) to the first target medication prescription. Per the VHA criteria and as defined in the key licensing trials for these agents, virologic failure was defined as a viral load more than 1,000 copies per milliliter (mL) for darunavir and tipranavir and a viral load more than 5,000 copies per mL for enfuvirtide.[1-5]

At the time the atazanavir guidelines were developed in the VHA, atazanavir was substantially more costly than other DHHS preferred agents (efavirenz and lopinavir/ritonavir) but offered potential benefits to patients in whom worsening lipid abnormalities may place them at a higher risk of a clinical event. Hence, VHA guidelines recommended atazanavir use in experienced patients with uncontrolled dyslipidemias and naïve patients with a history of cardiovascular disease or multiple risk factors for cardiovascular disease. For the atazanavir criteria, inpatient and outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* primary and secondary diagnoses codes were used to identify veterans with cardiovascular disease, cardiovascular risk factors, and serious mental illness documented on or anytime before the first atazanavir prescription (Table 3). Cardiovascular risk factors based on ICD-9-CM codes included tobacco use, hypertension, and diabetes. Patients were also classified as having diabetes if they had 2 or more random glucose results of 200 milligrams per deciliter (mg per dL) or more on or before (but within 1 year prior to) the first atazanavir prescription. Serious mental illness was defined as bipolar disorder, depression, post-traumatic stress disorder or schizophrenia. Low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride values were determined using the laboratory results closest (but within 1 year prior) to the first atazanavir prescription. "Uncontrolled" LDL-C values were defined as greater than 100 mg per dL in accordance with National Cholesterol Education Program Adult Treatment

**FIGURE 1** Patient Selection




*aVeterans transferring into VHA care already on a target antiretroviral from another outside source were excluded, as were veterans receiving a target medication as part of a pre-approval clinical trial and continuing it after FDA approval.*

*Pre-criteria period = FDA approval date to criteria implementation date (range 38 days to 192 days).*

*Early-criteria period = the first 6 months after criteria implementation.*

*Late-criteria period = 180 days after criteria implementation until December 31, 2007 (range 184 days to 1,525 days).*

*CCR: HIV = Human immunodeficiency virus clinical case registry; FDA = U.S. Food and Drug Administration; VHA = Veterans Health Administration.*

**TABLE 2** FDA Approval Dates and VHA Criteria Implementation Dates for Target Medications

| | FDA Approval Date | Criteria Implementation Date | Length of Pre-Criteria Period (Days)[a] | Length of Late-Criteria Period (Days)[b] |
|---|---|---|---|---|
| Atazanavir | June 20, 2003 | November 1, 2003 | 133 | 1,340 |
| Darunavir | June 23, 2006 | January 1, 2007 | 192 | 184 |
| Enfuvirtide | March 13, 2003 | April 30, 2003 | 48 | 1,525 |
| Tipranavir | June 22, 2005 | July 30, 2005 | 38 | 703 |

*[a]Number of days from FDA approval until criteria implementation.*

*[b]Number of days from end of early-criteria period (180 days after implementation) until study end date (December 31, 2007).*

*FDA = U.S. Food and Drug Administration; VHA = Veterans Health Administration.*

**TABLE 3** *Diagnosis Codes Used to Identify Veterans With Cardiovascular Disease[a] and Serious Mental Illness*

| Condition | ICD-9-CM Code* | Description |
|---|---|---|
| Cardiovascular disease | 410.xx | Acute myocardial infarction |
| | 411.xx | Other acute and subacute forms of ischemic heart disease |
| | 412.xx | Old myocardial infarction |
| | 413.xx | Angina pectoris |
| | 414.xx | Other forms of chronic ischemic heart disease |
| | 429.7x | Certain sequelae of myocardial infarction, not elsewhere classified |
| Tobacco use | 305.1, | Nondependent tobacco use disorder |
| | 989.84 | Toxic effect of tobacco |
| | V15.82 | Personal history of tobacco use |
| Hypertension | 401.xx | Essential hypertension |
| | 402.xx | Hypertensive heart disease |
| | 403.xx | Hypertensive kidney disease |
| | 404.xx | Hypertensive heart and kidney disease |
| | 405.xx | Secondary hypertension |
| Diabetes | 250.xx | Diabetes mellitus |
| Schizophrenia | 295 | Schizophrenic disorders |
| | V11.0 | Personal history of schizophrenia |
| Bipolar disorder | 296.0 | Bipolar i disorder single manic episode |
| | 296.1 | Manic disorder recurrent episode |
| | 296.4 | Bipolar i disorder, most recent episode (or current) manic |
| | 296.5 | Bipolar i disorder, most recent episode (or current) depressed |
| | 296.6 | Bipolar i disorder, most recent episode (or current) mixed |
| | 296.7 | Bipolar i disorder, most recent episode (or current) unspecified |
| | 296.8 | Other and unspecified bipolar disorders |
| | V11.1 | Personal history of affective psychosis |
| Depression | 293.83 | Mood disorder in conditions classified elsewhere |
| | 296.2 | Major depressive disorder, single episode |
| | 296.3 | Major depressive disorder, recurrent episode |
| | 296.5 | Bipolar i disorder, most recent episode (or current) depressed |
| | 298.0 | Depressive type psychosis |
| | 300.4 | Dysthymic disorder |
| | 307.44 | Persistent disorder of initiating or maintaining wakefulness |
| | 309.0 | Adjustment reaction with adjustment disorder with depressed mood |
| | 309.1 | Adjustment reaction with prolonged depressive reaction |
| | 309.28 | Adjustment disorder with mixed anxiety and depressed mood |
| | 311 | Depressive disorder not elsewhere classified |
| Post-traumatic stress disorder | 309.81 | Post-traumatic stress disorder |

[a]*Cardiovascular disease or cardiovascular disease risk factors.*
*ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.*

Program (NCEP ATP) III recommendations for the optimal LDL-C target in patients with cardiovascular disease.[12]

To determine adherence to criteria, we assessed the proportions of veterans satisfying criteria pre- and post-implementation of criteria. In an effort to assess continued adherence to criteria over time after implementation, 3 time periods were assessed based on the date of the first prescription for the target medication: immediately after FDA approval and before criteria implementation (pre-criteria); the first 180 days after criteria implementation (early-criteria); and more than 180 days after criteria implementation (late-criteria).

### Statistical Analysis

Pearson chi-square tests (a priori statistical significance level, 0.05) were used to test for differences in the proportions of veterans satisfying criteria, comparing (a) pre- versus post-criteria and (b) the 3 time periods pre-criteria, early-criteria and late-criteria. Data were analyzed using SAS version 8.2 (SAS Institute, Cary NC).

This protocol was approved by the Department of Veterans Affairs Palo Alto Health Care System Office of Research Administration, the Stanford University Institutional Review Board, and the VHA Clinical Case Registry Research Committee.

## Results

After implementation of inclusion and exclusion criteria, the sample included 7,220 initial veterans who received a new outpatient prescription for the 4 target agents: atazanavir (n=5,667), darunavir (n=559), enfuvirtide (n=669), and tipranavir (n=325; Figure 1). In veterans receiving the 3 target medications indicated solely for antiretroviral-experienced patients (darunavir, enfuvirtide, and tipranavir), 99.0% were antiretroviral-experienced, while 90.9% of veterans initiating atazanavir were antiretroviral-experienced.

### Darunavir

From the FDA approval date of darunavir in June 2006 through December 2007, 559 veterans received an initial outpatient prescription for darunavir: 175 pre-criteria, 184 early-criteria, and 200 late-criteria (Table 4). Overall, 71.0% of veterans satisfied all darunavir criteria. Although the percentages of veterans satisfying all darunavir criteria in the pre-criteria and post-criteria periods did not significantly differ ($P=0.585$), significant differences in some individual criteria and in adherence to the criteria over time were observed. Significantly fewer veterans were treatment experienced and had failed a prior protease inhibitor regimen in the post-criteria period compared with the pre-criteria period and adherence to this criteria waned over time (96.0% pre-criteria, 93.5% early-criteria, and 82.5% late-criteria [pre-criteria vs. post-criteria, $P=0.002$, early-criteria vs. late-criteria, $P<0.001$]). In fact, adherence to all darunavir criteria decreased significantly between the early- and late-criteria periods (early-criteria 78.8% vs. late-criteria 62.5%, $P<0.001$) Although immediately after criteria implementation there was an initial increase in the percentage of veterans who had evidence of virologic failure (viral load more than 1,000 copies per mL), the rate of adherence to this criterion decreased significantly from 81.5% to 72.5% between the early- and late-criteria periods ($P=0.036$).

### Enfuvirtide

During the evaluation period, 669 veterans were prescribed enfuvirtide: 9 pre-criteria, 140 early-criteria, and 520 late-criteria. Because so few patients were prescribed enfuvirtide in the 1-month interval between FDA approval and criteria implementation, statistical comparisons of the pre- and post-implementation periods could not be reasonably made.

Slightly less than 95% of veterans prescribed enfuvirtide satisfied all criteria. The proportions of veterans fulfilling each criterion and fulfilling all criteria were similar between the 3 evaluation periods with no significant differences. In accordance with VHA criteria, 98.2% of veterans had prior exposure to at least 2 antiretroviral classes, and 88.6% had evidence of intolerance to 2 previously VHA-prescribed antiretroviral regimens. Post-criteria, 81.7% of veterans had a documented viral load of more than 5,000 copies per mL just prior to initiating enfuvirtide compared with 77.8% pre-criteria.

### Tipranavir

In all, 325 veterans were prescribed tipranavir: 32 pre-criteria, 125 early-criteria, and 168 late-criteria (Table 4). Overall, 75.1% of veterans satisfied all tipranavir prescribing criteria with no significant differences between the pre- and post-criteria periods ($P=0.675$). Consistent with VHA criteria, 84.6% of veterans prescribed tipranavir had received at least 2 prior protease inhibitor regimens (90.6% pre-criteria, 88.0% early-criteria, and 81.0% late-criteria, $P=0.156$). Eighty-six percent of veterans had evidence of virologic failure (viral load of more than 1,000 copies per mL) before tipranavir initiation. Evidence of virologic failure prior to tipranavir initiation remained consistent in the post-criteria time periods (78.1% pre-criteria, 87.2% early-criteria, and 86.9% late-criteria, $P=0.941$ for comparison of early vs. late). Ninety-six percent of veterans demonstrated ability to tolerate ritonavir.

### Atazanavir

Atazanavir was prescribed to 5,667 veterans over the evaluation period: 484 pre-criteria, 833 early-criteria, and 4,350 late-criteria. Overall, 71.4% of all veterans prescribed atazanavir satisfied the criteria. Significantly more veterans met criteria in the post-criteria period compared with the pre-criteria period (71.9% vs. 66.3%, $P=0.010$). Prior to implementation of the criteria, only 2.3% (n=11) of patients prescribed atazanavir were antiretroviral-naïve. By late-criteria, a significantly higher percentage of those initiating atazanavir were antiretroviral-naïve (10.9%, $P<0.001$).

**Atazanavir-Antiretroviral Naïve:** Among antiretroviral-naïve veterans receiving atazanavir (n=515), 11 received it pre-criteria, 29 early-criteria, and 475 late-criteria. In all, 86.2% of antiretroviral-naïve veterans met all criteria for atazanavir use with no significant differences among time periods. Cardiovascular disease or multiple risk factors for cardiovascular disease were present in 72.2% of antiretroviral-naïve veterans prescribed atazanavir with significantly more veterans having cardiovascular disease or risk factors in the post-criteria period (45.5% pre-criteria, 58.6% early-criteria, and 73.7% late-criteria; pre-criteria vs. post-criteria, $P=0.045$). Fifty-six percent of veterans were unlikely to tolerate efavirenz because of a documented history of serious mental illness. No significant difference in adherence to this criteria was observed pre-criteria versus post-criteria ($P=0.497$).

**Atazanavir-Antiretroviral Experienced:** Ninety-one percent of veterans prescribed atazanavir were antiretroviral experienced (n=5,152): 473 pre-criteria, 804 early-criteria, and 3,875 late-criteria. Of antiretroviral-experienced veterans receiving atazanavir, 69.9% satisfied all criteria. Although the proportions of veterans satisfying criteria in the pre- versus post-criteria periods did not

**TABLE 4** *Veterans Satisfying VHA Criteria for Target Medications*

| Target Medication | Veterans Evaluated Total N (Pre/Early/Late) | Veterans Satisfying Criteria % (n) | Pre-Criteria % (n) | Early-Criteria % (n) | Late-Criteria % (n) | *P* Value[a] (3-way) | *P* Value[a] (Early vs. Late) | *P* Value[a] (Pre vs. Post) |
|---|---|---|---|---|---|---|---|---|
| **Atazanavir antiretroviral naïve (all criteria)** | 515 (11/29/475) | 86.2 (444) | 81.8 (9) | 75.9 (22) | 86.9 (413) | 0.222 | 0.092 | 0.669 |
| 1. Cardiovascular disease or multiple (≥3) risk factors for cardiovascular disease | | 72.2 (372) | 45.5 (5) | 58.6 (17) | 73.7 (350) | 0.029 | 0.077 | 0.045 |
| 2. Not a candidate for other once daily medications (specifically efavirenz) | | 55.5 (286) | 45.5 (5) | 58.6 (17) | 55.6 (264) | 0.754 | 0.749 | 0.497 |
| **Atazanavir antiretroviral experienced (all criteria)** | 5,152 (473/804/3,875) | 69.9 (3,601) | 66.0 (312) | 65.9 (530) | 71.2 (2,759) | 0.002 | 0.003 | 0.050 |
| 1. Documented intolerance to other PIs | | 79.9 (4,115) | 89.9 (425) | 82.6 (664) | 78.1 (3,026) | <0.001 | 0.004 | <0.001 |
| 2. Documented resistance to other PIs where atazanavir plus ritonavir would be expected to have activity | | 60.8 (3,130) | 50.5 (239) | 55.8 (449) | 63.0 (2,442) | <0.001 | <0.001 | <0.001 |
| 3. Stable on antiretroviral regimen (VL < 1,000 copies per mL) but with uncontrolled LDL-C (> 100 mg per dL) and/or triglycerides (> 300 mg per dL)[b] | | 64.8 (1,287) | 66.7 (116) | 68.8 (181) | 64.0 (990) | 0.270 | 0.127 | 0.597 |
| **Atazanavir all (naïve and experienced)** | 5,667 (484/833/4,350) | 71.4 (4,045) | 66.3 (321) | 66.3 (552) | 72.9 (3,172) | <0.001 | <0.001 | 0.010 |
| **Darunavir (all criteria)** | 559 (175/184/200) | 71.0 (397) | 72.6 (127) | 78.8 (145) | 62.5 (125) | 0.002 | <0.001 | 0.585 |
| 1. Highly treatment-experienced patients (defined in criteria as including at least 1 prior failed PI regimen) | | 90.3 (505) | 96.0 (168) | 93.5 (172) | 82.5 (165) | <0.001 | <0.001 | 0.002 |
| 2. Evidence of virologic failure documented by a VL > 1,000 copies per mL | | 76.4 (427) | 75.4 (132) | 81.5 (150) | 72.5 (145) | 0.108 | 0.036 | 0.719 |
| 3. Able to tolerate low-dose ritonavir | | 95.2 (532) | 97.7 (171) | 97.3 (179) | 91.0 (182) | 0.003 | 0.010 | 0.060 |
| **Enfuvirtide (all criteria)** | 669 (9/140/520) | 94.5 (632) | 100.0 (9) | 92.9 (130) | 94.8 (493) | NA | 0.373 | NA |
| 1. Exposure to at least 2 antiretroviral classes | | 98.2 (657) | 100.0 (9) | 99.2 (139) | 97.9 (509) | NA | 0.271 | NA |
| 2. Documented VL > 5,000 copies per mL | | 81.6 (546) | 77.8 (7) | 81.4 (114) | 81.7 (425) | NA | 0.935 | NA |
| 3. Intolerance to at least 2 antiretroviral regimens | | 88.6 (593) | 100.0 (9) | 89.3 (125) | 88.3 (459) | NA | 0.738 | NA |
| **Tipranavir (all criteria)** | 325 (32/125/168) | 75.1 (244) | 78.1 (25) | 78.4 (98) | 72.0 (121) | 0.420 | 0.214 | 0.675 |
| 1. Highly treatment-experienced patients (including at least 2 prior failed PI regimens) | | 84.6 (275) | 90.6 (29) | 88.0 (110) | 81.0 (136) | 0.156 | 0.104 | 0.321 |
| 2. Evidence of virologic failure documented by a VL > 1,000 copies per mL | | 86.2 (280) | 78.1 (25) | 87.2 (109) | 86.9 (146) | 0.382 | 0.941 | 0.166 |
| 3. Able to tolerate low-dose ritonavir | | 96.0 (312) | 100.0 (32) | 97.6 (122) | 94.0 (158) | 0.147 | 0.144 | 0.224 |

[a] *P value determined by Pearson chi-square test.*

[b] *Denominator is limited to patients with VL < 1,000 copies per mL (n = 1,985: 174 pre, 263 early, and 1,548 late).*

*dL = deciliter; LDL-C = low-density lipoprotein cholesterol; mL = milliliter; NA = not applicable (no comparison made because of small n pre-criteria); PI = protease inhibitor; VHA = Veterans Health Administration; VL = viral load.*

significantly differ ($P=0.050$), significantly more veterans in the late-criteria period met criteria compared with the early-criteria period (65.9% vs. 71.2%, $P=0.003$).

Overall, 79.9% had received prior protease inhibitor therapy; however, the proportion of veterans with prior protease inhibitor therapy decreased with each time period: 89.9% pre-criteria, 82.6% early-criteria, and 78.1% late-criteria ($P<0.001$). Although we could not assess documented resistance to other protease inhibitors from available data elements in the CCR:HIV, in veterans with resistance to other protease inhibitors where atazanavir plus ritonavir would be expected to have activity, ritonavir-boosted atazanavir was prescribed in 60.8% of patients who had previously received protease inhibitor treatment, 50.5% pre-criteria, 55.8% early-criteria, and 63.0% late-criteria (pre- vs. post- criteria $P=0.001$, early- vs. late-criteria, $P=0.001$).

Of veterans stable on another regimen prior to initiating atazanavir (n = 1,985), 64.8% had uncontrolled LDL-C or triglycerides. This percentage was similar across the 3 evaluation periods. The mean LDL-C and triglyceride concentrations in patients initiating atazanavir were 101 mg per dL and 228 mg per dL, respectively. Among those with lipids above the cutoffs, 22.1% were receiving lipid lowering medication.

## Discussion

One of the primary purposes of implementing institutional guidelines is to ensure appropriate medication use. Hence, after dissemination of such guidelines, it seems appropriate to assess adherence to criteria. Such critical evaluation is necessary to determine if guidelines are having the intended effect. This process can be particularly challenging in rapidly changing fields such as HIV treatment, where pharmacotherapy is extremely dynamic.

In the present study, we described different aspects of adherence to VHA criteria: (a) overall adherence, (b) adherence to the same criteria before and after implementation of the VHA guidelines (pre- vs. post-criteria), and (c) adherence to criteria in the early post-implementation phase versus later, after the criteria had been in place for at least 6 months. Overall adherence indicates whether providers are prescribing the target medications as intended by the guidelines. Adherence pre- versus post-criteria implementation provides insight on any changes in provider prescribing once criteria are instituted. Early- versus late-criteria assessments provide information on whether adherence to criteria diminishes over time.

Some data are available regarding the impact of institutional medication criteria on provider prescribing in the United States.[13-16] Reported provider adherence to such local guidance generally ranges between 50% to 95%.[13,14,16-20] Generally accepted rates for adherence to guidelines range from 80% to 90%.[17,18] These adherence rates were cited by studies whose scope ranges from very specific target populations (i.e., recombinant human coagulation factor VIIa prescribing at a single university teaching facility)[13] to a review of over 17,000 prescriptions written by general practitioners spanning 236 medications included on a regional formulary.[14] Previous studies also include a review of tamsulosin prescribing at 6 VHA facilities[16] and a study reviewing appropriateness, effectiveness, safety, and cost pre- and post-implementation of voluntary guidelines for neuromuscular blocking agents administered at a university hospital.[19] As suggested by these studies, implementation of guidelines based on currently available evidence may improve the clinical appropriateness of therapy. Owen et al. described improvements in the clinical appropriateness of recombinant factor VIIa upon implementation of an evidence-based guideline at a university hospital.[13] Gora-Harper et al. also demonstrated significantly more instances of appropriate neuromuscular blocking agent use post-guideline implementation compared with a pre-implementation period.[19] However, all studies were pre- versus post-implementation comparisons that lacked a control group. Not all guideline criteria have been shown to be effective in influencing provider prescribing patterns. This is evidenced by the work of Burk et al., whose data showed "no meaningful differences" in prescribing after posting of guidelines for tamsulosin use.[16]

As do many other health care institutions, the VHA routinely develops guidance for providers on the use of specific medications or classes of medications that may require special monitoring or are indicated for a highly specialized patient population. Specific evidence-based criteria are developed as part of these guidelines by clinical pharmacists with expertise in the particular disease state and are then reviewed by other VHA clinical experts. Because these criteria are generally developed soon after an agent is FDA approved, most of the currently available evidence comes from licensing trials. Often VHA criteria are modeled after inclusion criteria used in these studies with additional input from VHA experts in the field. Guideline criteria must then be presented and approved by the VHA's Medical Advisory Panel (consisting of physician volunteers and pharmacy benefit management pharmacists) and regional formulary leaders. Once approved, these guideline criteria are posted on the VHA website and disseminated through the regional pharmacy managers. Guideline criteria are reviewed and revised at periodic intervals if and when important new information becomes available. Because VHA has a national formulary, it is against VHA policy for local facilities to modify the criteria, although enforcement by the various facilities may differ. Individual facilities are responsible for implementing the guidelines; thus, the VHA lacks a standardized method to ensure guideline implementation. Generally it is the responsibility of the local clinical pharmacist assigned to that therapeutic area to enforce adherence to the guideline criteria.

Although the VHA criteria are evidence-based, many factors other than available evidence influence clinical decision making, such as the providers' clinical experience in prescribing the medication and patient-related factors such as tolerability, comorbidities, and drug interactions.[20] How much these factors contributed

to decisions regarding target drug selection in the present study is difficult to ascertain without a comprehensive chart review. Even with chart review, providers frequently do not document their decision-making process. Nevertheless, using available information from an observational database (CCR:HIV), we found that VHA providers prescribed target medications in accordance with criteria more than 70% (and as high as 95%) of the time. As expected, adherence to individual criteria for a target medication varied: atazanavir (antiretroviral naïve) 56% to 72%, atazanavir (antiretroviral experienced) 60% to 80%, darunavir 77% to 95%, enfuvirtide 82% to 97%, and tipranavir 85% to 96%.

Except for atazanavir, rates of conformity to the criteria in the pre-criteria and post-criteria periods were similar. This finding suggests that for the most part providers tended to follow current medical evidence when prescribing these agents. Since the VHA criteria were developed from the same published information available to providers, it is likely that in the pre-criteria time period, providers used similar criteria to those that would eventually be incorporated into VHA criteria to assess whether a patient was a good candidate for a therapy.

We also chose to evaluate adherence to criteria over time after implementation of the VHA guidelines (early-criteria vs. late-criteria) to see if waning adherence was an issue of concern. Waning adherence to criteria did occur for darunavir; compliance with the criteria decreased significantly by the late-criteria period. This decrease in adherence to criteria over time may have been attributable to reports describing the efficacy of darunavir in antiretroviral-naïve patients for whom it had not yet been FDA approved and to its favorable tolerability profile.[21-23] Furthermore, since many veterans receive non-nucleoside reverse transcriptase inhibitor-based regimens as first line treatment, providers may have been moving to darunavir-based regimens as a second line regimen rather than other protease-inhibitor-based regimens. According to VHA criteria in place during the time of the evaluation period, veterans must first have failed a protease-inhibitor-based regimen before initiating darunavir. Several months after the evaluation period ended, darunavir received FDA approval for use in antiretroviral naïve-patients and is now recommended as a preferred first-line agent for both naïve and experienced patients in the most recent DHHS recommendations.[8] VHA darunavir criteria have since been archived, and this agent is currently available for both antiretroviral naïve and experienced veterans as a first line protease inhibitor in accordance with DHHS recommendations.

Because of the rapid release of the criteria after FDA approval and the inherently limited number of patients for whom these agents are indicated, few veterans received enfuvirtide and tipranavir prior to the dissemination of criteria. Thus, reliable comparisons of adherence to VHA guidelines pre- versus post-criteria implementation could not be made. However, we felt it was important to include these drugs to see if adherence to the criteria changed over time, finding that it did not. Unlike the other agents evaluated, the standard of care and DHHS guideline recommendations for use of enfuvirtide and tipranavir did not change over the evaluation period, nor did VHA criteria. This consistency in guidelines may explain why no significant changes in adherence to the VHA criteria occurred over the course of the evaluation period.

The majority of veterans included in this study received atazanavir, and the atazanavir evaluation period was one of the longest evaluated. The availability of prescribing data on atazanavir over a long period of time offers a unique perspective on provider adherence to VHA guidelines of a highly prescribed agent whose place in therapy evolved over the evaluation period. Few antiretroviral-naïve patients received atazanavir either pre-criteria or early-criteria; 92% of the antiretroviral-naïve veterans who received atazanavir received it in the late-criteria period.

Touted for its lack of effect on lipids,[6,7] atazanavir offered potential benefits to patients who had hyperlipidemia or significant cardiovascular disease. Although atazanavir was available to antiretroviral-naïve veterans, few received atazanavir in the pre-criteria period, and of those that did, less than one-half met VHA criteria for cardiovascular disease or risk factors. This pattern changed in the post-criteria period, when more antiretroviral-naïve patients received atazanavir (particularly in the late-criteria period), and more patients being prescribed atazanavir met VHA cardiovascular risk criteria, although the difference was not statistically significant. This therapeutic niche for atazanavir, in addition to its favorable once-daily administration, made atazanavir a more attractive agent to patients and providers. In 2006, DHHS guidelines changed atazanavir to a preferred agent.[8] VHA atazanavir criteria were revised to reflect the change in the DHHS guidelines; atazanavir could be used in any HIV-infected veteran but was preferred in veterans with cardiovascular disease or risks for cardiovascular disease. Currently, atazanavir criteria are no longer in use in VHA—atazanavir is available as a preferred protease inhibitor in accordance with current DHHS guidelines.

The change in atazanavir status in the DHHS guidelines is reflected in the adherence to VHA criteria for atazanavir use in antiretroviral-experienced patients. Over time, significantly fewer veterans met criteria for intolerance (measured as exposure) to other protease inhibitors; this change was likely a result of atazanavir being used increasingly as a first-line protease inhibitor in VHA in accordance with the DHHS guideline recommendation. Moreover, significantly more veterans who had received prior protease inhibitor therapy were being prescribed ritonavir-boosted atazanavir in accordance with both VHA and DHHS guidelines.

Since this evaluation, the VHA has developed and implemented guideline criteria for newer agents, including maraviroc, raltegravir, and etravirine. Thus far, all available antiretrovirals have been added to and remain on the VHA national formulary.

As more and more HIV medications become available, there may come a time when VHA formulary status of these agents is revisited and comes under greater scrutiny. The existence of guideline criteria and periodic assessment of provider adherence to such criteria have been helpful in lending support to arguments for keeping all antiretroviral agents available to providers and patients.

### Limitations

First, this study employed an observational design and lacked a control group. The absence of a control group prevented us from examining the potential effect of other factors that may have influenced provider prescribing, such as published changes in other national guidelines or data presented at national conferences, although we realize that this information influences prescribing. This is particularly true in the rapidly changing field of HIV, in which information about antiretroviral resistance, sequencing of antiretrovirals, complex drug interactions, and adverse events is constantly evolving and influences prescribing decisions. Furthermore, as we assessed concordance only to VHA guidelines, our results do not address whether veterans that were appropriate for these medications actually received them. This is an area where future study may be warranted.

Second, the lack of a standardized method to ensure guideline criteria enforcement at the local facility level creates an obstacle in the ability to assess provider adherence because some facilities may be more lenient in allowing providers to prescribe outside criteria. The small sample sizes in the target medication groups, particularly enfuvirtide and tipranavir in the pre-criteria and early-criteria periods, limited our ability to perform statistical analyses comparing the pre-criteria and post-criteria periods.

Third, we did not assess outcomes (virologic or immunologic) in veterans who did or did not meet criteria, nor did we assess physician or patient characteristics as predictors of adherence with the guidelines. This assessment might have provided further information about the implementation of criteria and potential benefits of identifying veterans who would be most likely to have successful outcomes on the target antiretroviral. Because we focused only on prescribing of specific antiretrovirals, we cannot comment on prescribing of other agents in accordance with guidelines or criteria.

Fourth, although this study sample represents national VHA data, provider prescribing observed in this evaluation may not be generalizable outside of VHA. Other institutions may have different guidelines and criteria or policies relating to prescribing of antiretrovirals. HIV-infected veterans are typically male, 50 to 60 years of age, and often have other chronic diseases requiring pharmacologic treatment that might affect the selection of antiretrovirals; thus, prescribing patterns for veterans may differ from those for younger HIV-infected individuals or those seen by other health care systems.

## Conclusions

After implementation of antiretroviral specific guideline criteria, the proportion of veterans prescribed a target antiretroviral medication in accordance with the guidelines varied by agent and improved only for atazanavir. For agents for which provider adherence to evidence-based criteria is high, implementation of guidelines may not significantly change prescribing patterns. Although adherence to criteria for atazanavir, enfuvirtide, and tipranavir generally improved or persisted after guideline implementation, adherence to criteria for darunavir waned over time; these later prescribing patterns may have reflected changing practice patterns and the need for updated criteria. It is important that institutional guidelines be reassessed periodically to address changes in available evidence, including additional information and availability of newer, better tolerated agents so that providers continue to use highly specialized medications appropriately yet in accordance with the current standard of care. An ongoing process of revisiting and updating criteria is especially important for HIV due to the speed with which new information becomes available.

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### DISCLOSURES

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Study concept and design were contributed primarily by Belperio and Mole. The authors shared responsibility for data collection and data interpretation. Belperio wrote the manuscript with assistance from Backus. The revision was made primarily by Belperio. The authors would like to acknowledge Gale Yip, Health Science Specialist at the Center for Quality Management in Public Health, Department of Veterans Affairs, for her assistance in preparation of this manuscript.

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