How Will New Guidelines Affect CD4 Testing in Veterans With HIV?

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CD4 testing, but further reductions may still be warranted. Optional monitoring was recommended were less than this value. An additional annual savings of US$600,000. CD4 tests conducted during periods of potentially reduced monitoring were rarely <200 cells/µL: 1.1% of the tests conducted when minimal monitoring was recommended and just 0.3% of tests conducted when optional monitoring was recommended were less than this value.

Conclusions. Reduced CD4 monitoring of HIV-infected patients would result in modest cost savings and likely reduce patient anxiety, with little or no impact on the quality of care. Veterans Affairs has made substantial progress in reducing the frequency of optional CD4 testing, but further reductions may still be warranted.

Keywords. HIV; CD4 testing; veterans; guidelines; cost.

Routine evaluation of immune function with CD4 testing has long been regarded as an essential part of care for human immunodeficiency virus (HIV)-infected patients with successful viral control who are not immunocompromised. The reduced emphasis on CD4 testing has been incorporated into treatment guidelines issued by the Department of Health and Human Services. Guidelines issued in 2012 recommended CD4 testing every 3–6 months except in patients with consistently suppressed virus and sustained CD4 cell count, who could be tested every 6–12 months [4]. The 2014 update to these guidelines recommended that, in individuals with viral suppression, CD4 testing be considered optional in those with sustained CD4 count of >500 cells/µL and that patients with a count of 300–500 cells/µL for at least 2 years be tested only annually [5]. These recommendations were unchanged in 2016 [6].

We evaluated how these recommendations might affect HIV-infected patients receiving care from the largest provider of HIV care in the United States, the US Department of Veterans Affairs (VA) [7]. We determined how many VA patients with HIV were eligible for minimal and optional monitoring, the time intervals between CD4 tests, and the frequency of meaningfully low CD4 values (<200 cells/µL) when minimal or optional monitoring was appropriate. We evaluated recent trends in testing frequency and the potential cost savings from full application of the new guidelines.

METHODS

Data Source
We obtained results of HIV type 1 (HIV-1) RNA and CD4 tests from the VA Corporate Data Warehouse chemistry laboratory file. We obtained information on the cost of CD4 laboratory testing from the laboratory test file of the VA Managerial Cost Accounting System (formerly called Decision Support System), an activity-based costing system that determines a facility-specific cost based on the resources (including staff time, labor expense, supplies, equipment, and overhead) used to provide each healthcare product and service [8].

Cohort
We studied testing practices during the 5-year period ending on 30 September 2013. We included individuals who had at least 4
HIV-1 RNA tests and 4 CD4 tests over the study and baseline period. To place the study in context, we reported the number of persons excluded because of insufficient testing. Persons entered the study on the date of their first CD4 test, or if they were continuing in care, on the first day of the study (1 October 2008, the first day of Federal Fiscal Year 2009; all references to a specific year are to the Federal Fiscal Year unless otherwise noted). Cohort members were followed until their last CD4 test in the 5-year study period.

Definitions
According to the guidelines, CD4 monitoring is optional when the person had at least 4 prior HIV-1 RNA measurements all showing viral suppression and at least 4 prior CD4 tests, all with CD4 ≥ 500 cells/µL, with the first and last of the tests being separated by at least 24 months. Minimal monitoring is recommended if the CD4 count is ≥ 300 cells/µL. We identified monitoring status after each CD4 test using the most recent 36 months of data. This provided a consistent look-back period for every CD4 test over all 5 study years (2009–2013). It required laboratory results from a 3-year prestudy baseline period (2006–2008). Persons tested during the baseline period entered the study with the monitoring status at the time of their last baseline CD4 test. We defined viral suppression as an HIV-1 RNA level <200 copies/mL, a standard that could be consistently applied to all tests conducted since 2006. The optional monitoring period began on the day following the CD4 test that confirmed eligibility, and continued until the person had a single HIV-1 RNA result ≥200 copies/mL, irrespective of subsequent CD4 test results.

We defined minimal CD4 monitoring periods in a similar way. Among individuals not eligible for optional monitoring, minimal monitoring was appropriate if there were 4 HIV-1 RNA assays showing viral suppression and 4 CD4 tests consistently ≥300 cells/µL over 24 months. This status continued until the patient was either disqualified by HIV-1 RNA ≥200 copies/µL, or until CD4 test results >500 cells/µL qualified the individual for optional monitoring. Intensive monitoring was indicated if the individual was not eligible for minimal or optional monitoring. We identified the number of days spent under each by type of monitoring (ie, intensive, minimal, or optional monitoring).

We evaluated the sensitivity of findings to less restrictive criteria for eligibility, requiring only 3 consistently suppressed HIV-1 RNA and 3 CD4 tests in the recommended range over the 24- to 36-month time frame.

Statistical Tests
We compared characteristics of patients grouped by their final status as eligible for optional monitoring, eligible for minimal monitoring, or ineligible for reduced monitoring. We compared these 3 groups defined with logistic regression and regression, using independent variables to represent final monitoring status.

We compared the number of days between CD4 tests in 2009–2012 with generalized estimating equations with indicators of monitoring status, year of test, and their interaction as the independent variables. The proportion of intervals that were right-censored (exceeded 365 days) were compared with logistic link function, and the length of intervals that were <365 days were compared with an identity link function. Standard errors were corrected to account for the correlation of observations from the same person.

Simulation
Annual CD4 testing frequency was estimated as the reciprocal of mean uncensored testing interval. The trend in testing frequency was estimated by comparing annual frequency in 2009 to 2012. The change in the proportion of testing intervals that was right-censored was ignored. As the proportion of intervals of 365 days increased, this assumption resulted in a conservative estimate of the reduction in testing frequency.

RESULTS
There were 37 251 persons potentially eligible for the study because they had at least 1 CD4 and at least 1 HIV-1 RNA assay in the 5-year study period (2009–2013). We excluded 8721 persons (23.4%) who had insufficient testing (<4 CD4 tests or <4 HIV-1 RNA assays during the 3 baseline years and 5 study years).

The baseline characteristics of the 28 530 members of the study cohort are presented in Table 1. Most of the cohort (65%) entered the study with viral control. Most subjects also entered the study with good immune function, with 42.0% having a CD4 count of >500 cells/µL and 28.6% with CD4 count in the range of 300–500 cells/µL. A large number of subjects (71.0%) entered the study as continuing patients. Study subjects were in the study for a mean of 1296 days (3.5 years), and had an annual average of 3.3 CD4 tests and 3.4 viral load tests.

We determined each cohort member’s eligibility for reduced monitoring at the time of their last CD4 test. At the end of the study, 19.8% of subjects were eligible for optional monitoring, 15.6% were eligible for minimal monitoring, and 64.6% did not qualify for reduced monitoring. Supplementary Table 1 compares test results and retest intervals of cohort members grouped by their final monitoring status.

Table 2 presents information on 298 587 CD4 tests conducted during the study according to patients’ monitoring status at the time of the test. Most tests (70.6%) were conducted during an intensive monitoring period. Tests conducted when minimal monitoring was possible accounted for 14.0% of total testing. Those performed when optional monitoring was possible accounted for 15.4% of total CD4 testing.
Mean days of follow-up (between study entry and last Year of study entry, No. (%)

Mean days to follow-up HIV-1 RNA test (SD) (in 27,937 patients with a follow-up test)

Mean days to follow-up CD4 test (SD) (in 27,975 patients with a follow-up test)

Baseline CD4 count, No. (%)

Baseline HIV-1 RNA, No. (%)

Mean annual number of HIV-1 RNA tests (SD) 3.4 (5.3)

Mean annual number of CD4 tests (SD) 3.3 (5.3)

Mean days to follow-up HIV-1 RNA tests (SD) 3.4 (5.3)

Mean days to follow-up CD4 test (SD) (in 27,975 patients with a follow-up test) 144.3 (81.9)

Mean days to follow-up HIV-1 RNA test (SD) (in 27,937 patients with a follow-up test) 142.5 (82.5)

Abbreviations: HIV-1, human immunodeficiency virus type 1; SD, standard deviation.

Table 2. CD4 Test Results During Different Monitoring Periods (n = 298,587 Tests)

<table>
<thead>
<tr>
<th>CD4 Test Result</th>
<th>Optional Monitoring</th>
<th>Minimal Monitoring</th>
<th>Not Eligible for Reduced Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300 cells/µL</td>
<td>379 (0.8)</td>
<td>1814 (4.4)</td>
<td>70,209 (33.3)</td>
</tr>
<tr>
<td>300–500 cells/µL</td>
<td>2216 (4.8)</td>
<td>17,377 (41.7)</td>
<td>65,761 (31.2)</td>
</tr>
<tr>
<td>&gt;500 cells/µL</td>
<td>43,417 (94.4)</td>
<td>22,462 (53.9)</td>
<td>74,952 (35.5)</td>
</tr>
<tr>
<td>Total</td>
<td>46,012 (100.0)</td>
<td>41,653 (100.0)</td>
<td>210,922 (100.0)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%).

Most tests conducted during reduced monitoring periods had a result of >300 cells/µL. This threshold was exceeded by 95.6% of the tests conducted during minimal monitoring periods, and by 99.2% of the CD4 tests conducted during optional monitoring periods. Few tests conducted during periods of reduced monitoring were <200 cells/µL. Results of <200 cells/µL accounted for 1.1% of the tests conducted when minimal monitoring was appropriate and 0.3% of tests conducted when optional monitoring was appropriate.

We characterized the change in CD4 testing frequency by comparing retest intervals in the first year of the study (2009) to the penultimate year of the study (2012). We compared the retest intervals that were <365 days and the proportion of tests with an interval that was right-censored at 365 days. We used 2012 as the endpoint for this analysis, as all 2013 observations were right-censored by a follow-up period of <365 days. Table 3 provides the result of this analysis.

Among tests that were not right-censored, the mean retest interval was 112.7 days for tests conducted in 2009 and 126.3 days for tests conducted in 2012 (significantly different with \( P < .001 \)). For CD4 tests conducted in optional monitoring periods, the retest interval increased from 123.0 to 138.5 days. The retest interval increased from 117.7 to 131.0 days for tests conducted during minimal monitoring periods, and from 110.1 to 121.5 days for tests conducted during intensive monitoring. The increases were all statistically significant (\( P < .001 \)).

The retest interval exceeded 365 days for 5.5% of the tests conducted in 2009 and 5.8% of the tests conducted in 2012 (\( P = .0013 \)). There was a significant increase in the proportion of tests with a follow-up period that was right-censored at 365 days in both reduced monitoring groups (\( P < .001 \)); the change in proportion of intervals that were right-censored for tests conducted when intensive monitoring was indicated was not statistically significant.

### Actual and Potential Changes in Testing Frequency

The testing interval increased by 12.1% over the 4 years studied (from 112.7 days to 126.3 days). Since test frequency is the reciprocal of testing interval, this represents a 10.8% decline in test frequency (0.108 = 1 / 112.7 – 1 / 126.3). Given the number of patients seen in 2012, VA clinicians ordered 5624 fewer CD4 tests that year than they would have ordered had this reduction in frequency not occurred.

We estimated the potential of full application of the guidelines to reduce CD4 testing in patients eligible for reduced monitoring. If all CD4 tests were avoided in patients eligible for optional monitoring, 11,085 fewer tests would have been conducted in 2012. If the retesting interval for minimal monitoring was increased from the current interval of 131.0 days to 365 days, CD4 testing of patients eligible for minimal monitoring would be reduced by 64.1%, a reduction of 6093 CD4 tests.

### Table 3. Time to Next CD4 Test by Monitoring Status for 2009 and 2012

<table>
<thead>
<tr>
<th>Monitoring Status</th>
<th>2009 Mean (SD)</th>
<th>2012 Mean (SD)</th>
<th>Change 2009–2012</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>110.1 (59.7)</td>
<td>121.5 (64.3)</td>
<td>11.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Minimal</td>
<td>117.7 (52.6)</td>
<td>131.0 (59.0)</td>
<td>13.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Optional</td>
<td>123.0 (53.7)</td>
<td>138.5 (60.2)</td>
<td>15.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>All</td>
<td>112.7 (58.3)</td>
<td>126.3 (63.0)</td>
<td>13.6</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Percentage of intervals >365 days

<table>
<thead>
<tr>
<th>Monitoring Status</th>
<th>2009 Mean (SD)</th>
<th>2012 Mean (SD)</th>
<th>Change 2009–2012</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>6.0 (6.2)</td>
<td>0.2 (0.1)</td>
<td>0.6 (0.1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Minimal</td>
<td>3.8 (4.9)</td>
<td>1.1 (1.0)</td>
<td>2.7 (1.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Optional</td>
<td>3.8 (5.0)</td>
<td>1.1 (1.0)</td>
<td>2.7 (1.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>All</td>
<td>5.5 (5.8)</td>
<td>0.3 (0.3)</td>
<td>5.2 (0.3)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

\( P \) value for the test that the change was significantly different from zero was obtained from \( \chi^2 \) statistic from cluster-corrected logistic regression.

Abbreviation: SD, standard deviation.


(As frequency is the inverse of the retest interval, the proportional change in frequency is $\frac{64.1\%}{100\%} = \frac{\frac{365}{365} - 1}{1}$.)

The total of 17187 potentially avoidable tests was 28.9% of the total CD4 tests conducted in 2012.

**Cost Implications**

The mean cost of a CD4 test in 2013 was US$34.93, according to the VA Managerial Cost Accounting System. This is slightly less than the US$36.00 limit on Medicare reimbursement that same year.

The reduction in frequency of CD4 orders saved the VA US $196,000 in 2012 (5624 tests at US$34.93 each). Full implementation of guidelines would have saved an additional US$600,000 (17178 tests at US$34.93 each).

**Sensitivity Analyses**

Using 3 (rather than the 4) tests to define viral suppression and sustained immune function increased the proportion of individuals eligible for optional monitoring by the end of the study from 19.8% to 20.1%, and the proportion of individuals eligible for minimal monitoring from 15.6% to 15.9%.

**DISCUSSION**

We found a significant fraction (35.4%) of persons in care for HIV infection were eligible for the reduced CD4 monitoring now specified in US guidelines. We determined that VA providers reduced the frequency of CD4 testing by 10.8% between 2009 and 2012. In addition, we found that full implementation of the guidelines would have resulted in an additional 28.9% reduction in testing overall.

We believe that this is one of the largest studies to evaluate the potential impact of reduced CD4 monitoring. A prior, smaller study estimated that 55% of patients would be eligible for reduced monitoring [9]. This earlier study evaluated viral suppression and CD4 count at only one time point using a CD4 threshold of >300 cells/µL. Our estimate is lower because we applied the stricter definition of stable suppression specified in the new treatment guidelines—a tests showing viral suppression and CD4 maintenance over 24 months’ time.

A number of studies have found that treated HIV patients who achieve sustained viral suppression rarely had a CD4 count <200 cells/µL and that such dips are almost always temporary [1, 2, 10–13]. A recent meta-analysis of 13 studies found that very few (0.4%) patients with suppressed HIV RNA had a CD4 decline that was confirmed yet unexplained [14]. We confirmed that CD4 monitoring rarely yielded clinically meaningful information (CD4 was rarely <200 cells/µL) among patients eligible for reduced monitoring. CD4 was below this level in 1.1% of the tests conducted when minimal monitoring was appropriate and in 0.3% of tests conducted when optional monitoring was appropriate.

Most often practice changes lag guidelines, but we found evidence that the frequency of CD4 testing was already changing ahead of the guidelines. We found that between 2009 and 2012, the testing interval increased by 13.4 days in those eligible for minimal monitoring, and by 15.6 days in those eligible for optional monitoring. This occurred 2 years before the new guidelines were introduced.

Reduced frequency of CD4 testing could save the entire US healthcare system a modest amount, perhaps US$10 million per year, according to one estimate [15]. The authors of that estimate noted a lack of data on testing frequency. We found that reduction in CD4 testing by VA providers even before the promulgation of the guidelines had reduced annual testing expenditures by US$196,000. Full adherence to the new guidelines would further reduce the direct annual cost of CD4 testing in the VA healthcare system by as much as US$600,000. Using less restrictive criteria for reduced monitoring—3 rather than 4 tests to document viral suppression and immune function—resulted in a very small increase in eligibility for reduced monitoring.

We acknowledge several limitations. First, we only considered the direct cost of testing and did not consider the cost of provider time spent discussing CD4 results with patients, any additional visits prompted by testing, travel or other patient-borne costs, or the cost of any interventions prompted by clinically meaningless changes in CD4 counts.

We did not explore whether the small number of low CD4 results found in persons eligible for minimal or optional monitoring were persistent or clinically significant. Other studies have investigated this question and found that low CD4 counts are usually transitory and not clinically significant [1, 2, 9, 10, 12]. We did not distinguish when testing may have had a solid clinical indication, such as surgery and CD4-lowering medications (eg, chemotherapy, interferon treatment, and prescription of corticosteroids), as well as a variety of viral and other infections [3,9,16]. Our estimate of adherence to guidelines may thus be a lower bound.

In resource-limited situations where viral load testing is difficult to obtain, CD4 testing can have an important role in selecting patients most in need of antiviral treatment, but HIV-1 RNA testing is more useful once treatment has been started [17]. In developed countries, CD4 testing rarely yields actionable information in patients who have initiated antiretroviral treatment and have achieved viral suppression. Routine CD4 testing had been used to identify patients whose immune function was sufficiently compromised (<200 cells/µL) to merit Pneumocystis jirovecii pneumonia prophylaxis, but there is some doubt about the value of this practice in virologically suppressed HIV-infected patients [18]. Efforts to find antiretroviral therapies that increase CD4 counts in stable virologically suppressed patients have either been unsuccessful [19] or resulted in slight increases in CD4 levels that did not correlate with any clinical benefit [1, 2, 10, 12, 19].

It must be acknowledged that CD4 testing is a small part of the cost of HIV care. Performing 3 CD4 tests a year costs little...
more than US$100. This is a small part of the US$20 000 average annual cost of HIV care in industrialized countries [10]. More importantly, reduced CD4 monitoring of healthy patients can reduce patient anxiety or concerns about normal fluctuation in CD4 count [9]. Time currently spent reviewing CD4 results could instead be used to address other health issues, such as lipid management, smoking cessation, weight loss, or alcohol use. We determined that VA clinicians had already made significant progress in reducing the frequency of CD4 testing of HIV-infected patients even before the new guidelines were issued. Full implementation of these guidelines would further reduce CD4 testing in healthy individuals, reducing patient anxiety and health system cost.

Supplementary Data
Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes
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