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How will new guidelines affect CD4 testing in Veterans with HIV?

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Summary: The frequency of CD4 tests in HIV positive patients treated in VA hospitals declined by 10.8% over four years, but could be reduced a further 28.9% by full implementation of new treatment guidelines, with little or no impact on the quality of care.

Abstract

Background. Guidelines now recommend limited use of routine CD4 testing in HIV positive patients with successful viral control who are not immuno-compromised.

Methods. CD4 and viral load tests for patients receiving HIV care from the U.S. Department of Veterans Affairs (VA) during 2009-2013 were evaluated to determine trends in CD4 testing frequency and the number, cost, and results of CD4 tests considered optional under the guidelines.

Results. There were 28,530 individuals with sufficient testing to be included. At the time of their last CD4 test, 19.8% of the cohort was eligible for optional monitoring and 15.6% was eligible for minimal monitoring. CD4 testing frequency declined by 10.8% over four years, reducing the direct cost of testing by $US 196 thousand per year. Full implementation of new treatment guidelines could reduce CD4 testing a further 28.9%, an additional annual saving of $US 600 thousand. CD4 tests conducted during periods of potentially reduced monitoring were rarely < 200 cells/mm^3; 1.1% of the tests conducted when minimal monitoring was recommended were less than this value and just 0.3% of tests conducted when optional monitoring was recommended.

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

Introduction

Routine evaluation of immune function with CD4 testing has long been regarded as an essential part of care for HIV positive patients. Recent studies suggest that patients who are not immunocompromised and are successfully using anti-retroviral therapy to suppress HIV do not benefit from periodic CD4 testing [1-3].

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 to 6 months except in patients with consistently suppressed virus and sustained CD4 cell count, who could be tested every 6 to 12 months [4]. The 2014 update to these guideless recommended that in individuals with viral suppression, CD4 testing be considered optional in those with sustained CD4 count of ≥ 500 cells/mm^3 and that patients with a count of between 300 and 500 cells/mm^3 for at least two years be tested only annually [5]. These recommendations were unchanged in 2016 [6].

We evaluated how these recommendations might affect HIV positive patients receiving care from the largest provider of HIV care in the United States, the U.S. 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/mm^3) 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-1 RNA and CD4 tests from the VA Corporate Data Warehouse (CDW) 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 health care product and service [8].

Cohort. We studied testing practices during the five-year period ending on September 30, 2013. We included individuals who had at least four HIV-1 RNA tests and four 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 (October 1, 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/mm^3, with the first and last of the tests be separated by at least 24 months. Minimal monitoring is recommended if CD4 ≥300 cells/mm^3. 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 pre-study 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 < 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 ≥ 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 four HIV-1 RNA assays showing viral suppression and four CD4 tests consistently ≥ 300 cells/mm^3 over 24 months. This status continued until the patient was either disqualified by HIV-1 RNA ≥ 200 copies/mL, or until CD4 test results ≥ 500 cells/mm^3 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 (i.e., intensive, minimal, or optional monitoring).

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

Statistical tests. We compared characteristics of patients grouped by their final status as eligible for optional monitoring, minimal monitoring, or ineligible for reduced monitoring. We compared these three 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 to 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 less than

365 days 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 one CD4 and at least one HIV-1 RNA assay in the five-year study period (2009-2013). We excluded 8,721 persons (23.4%) who had insufficient testing (fewer than 4 CD4 tests or fewer than 4 HIV-1 RNA assays during the three baseline years and five 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/mm^3 and 28.6% with CD4 count in the range of 300-500 cells/mm^3. A large number of subjects (71.0%) entered the study as continuing patients. Study subjects were in the study for a mean of 1,296 days (3.5 years), and had an annual average of 3.3 CD4 tests and 3.4 viral load tests.

[Insert Table 1 about here]

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 the cohort was eligible for optional monitoring, 15.6% was eligible for minimal monitoring, and 64.6% did not qualify for reduced

monitoring. A supplementary table compares test results and re-test 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.

[Insert Table 2 about here]

Most tests conducted during reduced monitoring periods had a result of >300 cells/mm^3 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/mm^3. Results of < 200 cells/mm^3 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 less than 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 less than 365 days. Table 3 provides the result of this analysis.

[Insert Table 3 about here]

Among tests that were not right-censored, the mean re-test interval was 112.7 days for tests conducted in 2009 and 126.3 days in tests conducted in 2012 (significantly different with p

< 0.001). For CD4 tests conducted in optional monitoring periods, the re-test interval increased from 123.0 to 138.5 days. The re-test 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 ($p < 0.001$).

The re-test interval exceeded 365 days for 5.5% of the tests conducted in 2009 and 5.8% of the tests conducted in 2012 ($p=0.0013$). 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 ($p<0.001$); 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 four 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 - [112.7/126.3]). Given the number of patients seen in 2012, VA clinicians ordered 5,346 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 re-testing 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 6,093 CD4 tests. (As frequency is the inverse of the re-test interval, the proportional change in frequency is 64.1% = [365 – 131.0]/365). The total of 17,178 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 36.80 limit on Medicare reimbursement that same year.

The reduction in frequency of CD4 orders saved VA $US 196 thousand in 2012 (5,346 tests at $US 34.93 each). Full implementation of guidelines would have saved an additional $US 600 thousand (17,178 tests at $US 34.93 each).

Sensitivity analyses

Using 3 (rather 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 eligible for minimal monitoring from 15.6% to 15.9%.

Conclusions

We found a significant fraction (35.4%) of persons in care for HIV infection were eligible for reduced CD4 monitoring now specified in U.S. guidelines. We determined that VA providers reduced the frequency of CD4 testing by 10.8% between 2009 and 2012. 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 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/mm^3. Our estimate is lower because we

applied the stricter definition of stable suppression specified in the new treatment guidelines-- 4 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 < 200 cells/mm^3 and that such dips are almost always temporary [1, 2, 10-13]. A recent meta-analysis of 13 studies and found very few (0.4%) patients with suppressed HIV 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/mm^3) 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 two years before the new guidelines were introduced.

Reduced frequency of CD4 testing could save the entire U.S. health care 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 thousand dollars. Full adherence to the new guidelines would further reduce the direct annual cost of CD4 testing in the VA health care system by as much as $US 600 thousand. 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 been had a solid clinical indication, such as surgery and CD4 lowering medications, including 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 situation ns 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 anti-retroviral treatment and have achieved viral suppression. Routine CD4 testing had been used to identify patients whose immune function was sufficiently compromised (<200 cells/mm^3) to merit *Pneumocystis jirovecii* pneumonia prophylaxis, but there is some doubt about the value this preventive practice in virologically suppressed HIV-infected patients [18]. Efforts to find anti-retroviral 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. Three CD4 tests a year cost 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 positive 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.

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Table 1. Cohort characteristics (N=28,530 patients)

Baseline HIV-1 RNA	
< 200 copies/mL (%)	18,503 (64.9%)
≥ 200 copies/mL (%)	10,027 (35.1%)
Baseline CD4	
<300 cells/mm^3 (%)	8,399 (29.4%)
300-500 cells/mm^3 (%)	8,148 (28.6%)
≥500 cells/mm^3 (%)	11,983 (42.0%)
Year of study entry (%)	
2009 (entered on October 1, 2008)	20,259 (71.0%)
2009 (entered after October 1, 2008)	2,074 (7.3%)
2010	2,156 (7.6%)
2011	2,323 (8.1%)
2012	1,472 (5.2%)
2013	246 (0.9%)
Mean days of follow-up (between study entry and last test) [SD]	1,296.2 [538.1]
Mean annual number of CD4 tests [SD]	3.3 [5.3]
Mean days to follow-up CD4 test [SD] (in 27,975 patients with a follow-up test)	144.3 [81.9]
Mean annual number of HIV-1 RNA tests [SD]	3.4 [5.3]
Mean days to follow-up HIV-1 RNA test [SD] (in 27,937 patients with a follow-up test)	142.5 [82.5]

Table 2. CD4 test results during different monitoring periods (N=298,587 CD4 tests)

Number (percent) of tests by type of monitoring

CD4 test result	Optional monitoring		Minimal monitoring		Not eligible for reduced monitoring	
<300 cells/mm^3 (%)	379	(0.8)	1,814	(4.4)	70,209	(33.3)
300-500 cells/mm^3 (%)	2,216	(4.8)	17,377	(41.7)	65,761	(31.2)
≥500 cells/mm^3 (%)	43,417	(94.4)	22,462	(53.9)	74,952	(35.5)
Total	46,012	(100.0)	41,653	(100.0)	210,922	(100.0)

Table 3. Time to next CD4 test by monitoring status for 2009 and 2012

Duration of intervals of 365 days or less

Monitoring status	2009		2012			
	Mean	SD	Mean	SD	Change 2009-2012	p value
Intensive	110.1	59.7	121.5	64.3	11.4	<.0001
Minimal	117.7	52.6	131.0	59.0	13.4	<.0001
Optional	123.0	53.7	138.5	60.2	15.6	<.0001
All	112.7	58.3	126.3	63.0	13.6	<.0001

Percent of intervals greater than 365 days

Monitoring status	2009	2012	Change 2009-2012	p value
Intensive	6.0	6.2	0.2	0.1438
Minimal	3.8	4.9	1.1	<.0001
Optional	3.8	5.0	1.1	<.0001
All	5.5	5.8	0.3	0.0013

p value for test that change was significantly different from zero obtained from chi-square statistic from cluster-corrected logistic regression.