Cost-effectiveness of HIV Monitoring Strategies in Resource-Limited Settings

A Southern African Analysis

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Background: Although the number of infected persons receiving highly active antiretroviral therapy (HAART) in low- and middle-income countries has increased dramatically, optimal disease management is not well defined.

Methods: We developed a model to compare the costs and benefits of 3 types of human immunodeficiency virus monitoring strategies: symptom-based strategies, CD4-based strategies, and CD4 counts plus viral load strategies for starting, switching, and stopping HAART. We used clinical and cost data from southern Africa and performed a cost-effectiveness analysis. All assumptions were tested in sensitivity analyses.

Results: Compared with the symptom-based approaches, monitoring CD4 counts every 6 months and starting treatment at a threshold of 200/µL was associated with a gain in life expectancy of 6.5 months (61.9 months vs 68.4 months) and a discounted lifetime cost savings of US $464 per person (US $4069 vs US $3605, discounted 2007 dollars). The CD4-based strategies in which treatment was started at the higher threshold of 350/µL provided an additional gain in life expectancy of 5.3 months at a cost-effectiveness of US $107 per life-year gained compared with a threshold of 200/µL. Monitoring viral load with CD4 was more expensive than monitoring CD4 counts alone, added 2.0 months of life, and had an incremental cost-effectiveness ratio of US $5414 per life-year gained relative to monitoring of CD4 counts. In sensitivity analyses, the cost savings from CD4 count monitoring compared with the symptom-based approaches was sensitive to cost of inpatient care, and the cost-effectiveness of viral load monitoring was influenced by the per test costs and rates of virologic failure.

Conclusions: Use of CD4 monitoring and early initiation of HAART in southern Africa provides large health benefits relative to symptom-based approaches for HAART management. In southern African countries with relatively high costs of hospitalization, CD4 monitoring would likely reduce total health care expenditures. The cost-effectiveness of viral load monitoring depends on test prices and rates of virologic failure.

Arch Intern Med. 2008;168(17):1910-1918

Two-thirds of the world’s HIV-infected population resides in Africa, and most of the world’s new infections occur in low- and middle-income countries. In the southern cone of Africa, which includes heavily affected countries such as Angola, Botswana, Malawi, Mozambique, Namibia, South Africa, Zambia, and Zimbabwe, approximately 11 million persons are infected with HIV.² Despite substantial progress in access to treatment, only 20% of adults who need highly active antiretroviral therapy (HAART) receive it.¹ In addition, in many resource-limited regions, the conditions of individuals who receive HAART are managed without access to monitoring of CD4 T-cell counts or human immunodeficiency viral load, which may substantially reduce the effectiveness of HAART.³ Therefore, key questions in the management of HIV infection in resource-constrained settings are whether and how to monitor persons infected with HIV and when to initiate HAART. Little is known about the effectiveness and cost-effectiveness of evaluation and treatment initiation criteria in southern Africa, and monitoring of infected individuals remains a major challenge for clinicians and health care systems.⁴ ⁵

In high-income countries, viral load, CD4 counts, and clinical monitoring are the most common tools used to determine treatment eligibility and to monitor HIV-infected patients.⁶ Multiple clinical trials examined strategies for choosing initial and sequential anti-
retroviral regimens in which viral load and CD4 counts are used for treatment decisions and serve as the primary measurements of efficacy.7,8 In resource-limited regions, however, where laboratory monitoring is often unavailable, HAART is initiated in many HIV-infected individuals when they develop a severe opportunistic disease.9 Previous studies in sub-Saharan Africa estimate the cost-effectiveness of HAART and the timing of treatment initiation.10-12 In the present study, we used an HIV treatment and monitoring model to estimate the effectiveness and cost-effectiveness of several strategies for initiation, change, and discontinuation of HIV treatment in infected individuals in southern Africa.

METHODS

OVERVIEW AND MODEL STRUCTURE

Using commercially available software (TreeAge Pro; TreeAge Software, Inc, Williamstown, Massachusetts), we developed a simulation model of the lifetime history of HIV-positive patients from time of presentation for care until death. The purpose of the model was to evaluate the relative cost-effectiveness of 3 types of currently practiced management strategies for caring for patients with HIV in southern Africa: 2 symptom-based strategies with which the conditions of patients are managed using clinical criteria without CD4 counts or viral load monitoring; 4 CD4-based strategies that include CD4 count monitoring in addition to clinical monitoring for treatment initiation and regimen change; and 4 strategies that include both CD4 counts and viral load measurements, comparable to routine management of patients in resource-rich countries (see the Appendix [online only] for more details; http://lsi.stanford.edu/people/eranbendavid/).

Each patient’s health was characterized by viral load, CD4 counts, medication toxicity, and severe opportunistic diseases. The model followed each patient’s health status monthly, but clinical and laboratory data were only available to decision makers during follow-up visits or sooner in the case of acute clinical events.

Data for the model were taken from 2 established HIV cohorts in the Cape Town area: the Cape Town AIDS Cohort, a group of HIV-positive patients cared for in local hospital clinics; and the Médecins Sans Frontières community clinics in Khayelitsha (Table 1).13-16 For the base-case analyses, we simulated a population of 100,000 patients, and for the sensitivity analyses, we simulated independent cohorts of 50,000 patients.

DISEASE PROGRESSION

Disease progression was determined by each patient’s CD4 counts, viral load, history of opportunistic diseases, and treatment record. We modeled the CD4 counts as a continuous variable that determined the patient’s risk of death and of developing opportunistic diseases. Viral load, also modeled as a continuous variable, guided the rate of change in CD4 counts in the absence of suppression of viral replication.17,18 After successful initiation of HAART, a patient’s viral load decreased to less than 400 copies/mL and CD4 counts rose based on empirical data.19,20 When a patient developed a severe opportunistic disease, the risk of death increased by an amount inversely related to the CD4 counts at the time of the infection (Table 1).20,21

TREATMENT OPTIONS

In resource-limited regions, the World Health Organization formulary advises a first-line regimen consisting of a dual nucleoside reverse transcriptase inhibitor backbone with a non-nucleoside reverse transcriptase inhibitor, and a second-line protease inhibitor-based regimen.21 We used safety and effectiveness data for first- and second-line regimens, similar to the World Health Organization formulary; however, consistent with current practice in resource-limited countries, we assumed no additional HAART regimens.22,23,24 At the start of the model, patients were antiretroviral naive and, after starting a first-line regimen, were switched to a second-line regimen for 2 reasons: medication toxicity and failure of therapy (based on measured viral load, decrease in CD4 counts, or opportunistic diseases in the various strategies; Table 2).25,26,27

MANAGEMENT STRATEGIES

We examined 10 strategies: 2 symptom-based strategies and 4 versions each of the CD4 counts only and CD4 and viral load strategies, in which HAART was started at 200/µL or 350/µL, and monitoring frequency was 3 or 6 months (Table 2). In the symptom-based strategies, HAART was started when patients developed their first severe opportunistic disease, and treatment was changed when patients experienced medication toxicity related to the first-line regimen or after developing their second or third opportunistic disease, suggesting failure of therapy. In the CD4-based strategies, the CD4 counts were checked regularly, and HAART was started when the measured CD4 counts decreased to below an initiation threshold, unless a patient first developed an opportunistic disease. The treatment regimen was changed with medication toxicity or if the measured CD4 counts decreased to half of the highest measured CD4 counts, suggesting failure of therapy. In the CD4 viral load strategies, patients were switched to a second-line regimen with measured virologic failure (>1000 copies/mL).28 In all strategies, treatment was discontinued in patients who experienced a severe medication toxicity with second-line HAART but was continued in patients with treatment failure during second-line treatment because of the survival advantages of a nonsuppressive regimen compared with HAART cessation.

COSTS

We considered all direct HIV costs obtained from costing reports of the study cohorts.10,20,30,31 Cost of care included inpatient costs, outpatient costs, HAART costs, and testing costs. Per-test cost included cost of reagents, labor, parts, data management, maintenance, and the rental or acquisition of CD4 or viral load enumeration equipment.10,31 Viral load was measured only after a patient had started HAART because no therapeutic decisions were made using viral load before onset of HAART. We measured the incremental cost-effectiveness of each strategy compared with the next least-effective strategy in 2007 US$ per life-year gained. All costs were converted to 2007 US dollars using a currency converter and a gross domestic product deflator.32 We adopted a societal perspective, although some indirect costs such as travel or lost wages were excluded. We discounted all costs and benefits at 3% annually.

SENSITIVITY ANALYSIS

We evaluated all of our assumptions and parameters in sensitivity analyses. In particular, we examined clinical parameter estimates including rates of virologic failure, treatment discontinu-
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<tr>
<th>Variable</th>
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<td>Demographic data, mean (SD), range</td>
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<tr>
<td>Age at presentation, y</td>
<td>32.8 (9.2), 14-50</td>
<td>Holmes et al16</td>
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<td>Additional risk of death from severe opportunistic disease, %/mo</td>
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<td>Robbins et al25 Orrell et al26 Calmy27 and Amoroso28</td>
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<td>Badri et al1811</td>
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<td>&gt;350</td>
<td>0.14/1.9, ±50%</td>
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<td>0.39/3.1, ±50%</td>
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<td>≤200</td>
<td>4.7/6.6, ±50%</td>
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(continued)
ation owing to medication toxicity, and opportunistic diseases, and the increased mortality risk of opportunistic diseases. We also examined the sensitivity of the results to inpatient costs, outpatient costs, HAART costs, and testing costs independently and jointly (assuming that costs covary among regions and a reduction in one cost is related to other reduced costs).

**RESULTS**

**MODEL VALIDATION**

We calibrated our model against established models of HIV in resource-limited settings and cost studies from Cape Town, and validated the outcomes of the model by comparing model predictions to cost of care, life expectancy, and observed rates of development of severe opportunistic diseases (Table 3). Our model correlated well with expected values.

**BASE-CASE ANALYSES**

**CD4 Count Monitoring**

All CD4-based strategies resulted in higher life expectancy and were less costly than the symptom-based approaches (Table 4 and Figure 1). The most effective symptom-based strategy yielded a discounted estimated life expectancy of 61.9 months at a lifetime cost of $4069, whereas the least effective CD4-based strategy (in which HAART was started at 200/µL) cost $3605 and yielded an estimated life expectancy of 68.4 months (Figure 1), that is, a lifetime cost saving of $464 and an increase in life expectancy of 6.5 months. The increase in life expectancy was associated with a large decrease in the number of severe opportunistic diseases (314 fewer severe opportunistic diseases per 1000 persons over their lifetime), and the increased treatment and testing costs when the CD4 counts were monitored were more than offset by the decrease in inpatient costs compared with the symptom-based approach (Table 3).

**CD4 Count Threshold**

Starting HAART at CD4 350/µL was always more effective than starting at 200/µL, regardless of the monitoring strategy. When the CD4 count alone was monitored every 6 months, starting HAART at 350/µL rather than 200/µL was associated with a gain of 5.3 months of life expectancy at an incremental lifetime cost of $48, or $107 per life-year.
Compared with a symptom-based approach, the gain in life expectancy was 11.8 months. Starting HAART at 350/µL led to higher HAART, testing, and outpatient costs but decreased inpatient costs. Compared with the lower threshold for initiation of therapy, individuals also had 18% fewer severe opportunistic diseases (589 per 1000 persons vs 719 per 1000 persons).

**Viral Load Monitoring**

We estimated the costs and benefits of viral load monitoring for determining treatment failure and the timing of a regimen change. Adding viral load to CD4 count monitoring was associated with further increase in life expectancy. When testing every 6 months and starting HAART at 350/µL, adding viral load to CD4 count testing was associated with a 2-month gain in life expectancy. However, viral load testing was associated with an increased lifetime cost of $899 per person, mostly because of increased testing costs. Compared with monitoring CD4 counts every 6 months and starting HAART at 350/µL, the incremental cost-effectiveness ratio of adding viral load was $5414 per life-year gained.

**Monitoring Frequency**

Testing every 3 months rather than every 6 months was associated with modest increases in life expectancy and significant increases in lifetime costs. For equivalent strategies, testing every 3 months was associated with a life expectancy gain of 2 to 19 days. The incremental cost-effectiveness ratio of monitoring CD4 counts and viral load every 3 months and starting HAART at 350/µL was about $100 000 per life-year gained compared with a similar strategy with monitoring every 6 months.

**SENSITIVITY ANALYSIS**

Monitoring of CD4 counts reduced net costs compared with symptom-based management because it reduced ex-
sensitivity analyses changed our results substantively. Of variability we examined (Table 1), none of these sen-
sitive toxicities in sensitivity analyses. Within the range
continuation because of the cost of HAART, rates of CD4
rates of failure increased the ratio to US $8776 per life-
creased to US $3257 per life-year gained, and halving the
US $20, the ratio was US $1635. In addition, high rates
US $2869 per life-year gained and, at a per-test cost of
CD4 counts were monitored every 6 months and HAART
(based on data from South Africa) to US $120 for an in-
tient was further reduced, CD4 count monitoring
increased total costs compared with symptom-based man-
however, the incremental cost-effectiveness ratio
remained less than US $700 per life-year gained even
when inpatient costs were reduced to US $20 per day,
the lowest value reported for southern Africa.38
The cost-effectiveness of viral load monitoring was sen-
sitive to the cost of testing and virologic failure
(Figure 3). In a comparison with strategies in which
CD4 counts were monitored every 6 months and HAART
was started at 350/µL, halving the cost of viral load test-
ing decreased the incremental cost-effectiveness ratio to
US $2869 per life-year gained and, at a per-test cost of
US $20, the ratio was US $1635. In addition, high rates of
virologic failure, which might occur when adherence
is low or rates of resistance are high, increased the im-
portance of viral load monitoring. Where rates of failure
were twice as high as our base-case estimate, the in-
cremental cost-effectiveness ratio of viral load testing
decreased to US $3257 per life-year gained, and halving the
rates of failure increased the ratio to US $8776 per life-
year gained.
We evaluated changes in the rates of treatment dis-
continuation because of the cost of HAART, rates of CD4
counts change, rates of virologic suppression, and medica-
tion toxicities in sensitivity analyses. Within the range of
variability we examined (Table 1), none of these sen-
sitivity analyses changed our results substantively.

We evaluated the relative merits of alternative HIV moni-
toring strategies in resource-limited settings using data
from southern Africa. We found that CD4 count moni-
toring could substantially increase life expectancy and
reduce total costs relative to the symptom-based ap-
proaches currently practiced in many regions, espe-
cially outside of major urban areas. Monitoring CD4
counts increased life expectancy through earlier initia-
tion of HAART and prevention of severe opportunistic
diseases. Compared with the most effective symptom-
based strategy, initiation of HAART at CD4 counts of
200/µL or 350/µL increased life expectancy by almost 7
and 12 months, respectively.
These gains in life expectancy are substantial. Previ-
ous studies suggest that use of HAART compared with
no HAART increases life expectancy by approximately
20 months. Thus, addition of CD4 count monitoring and initiation of treatment when CD4 counts reach 350/µL provides a 60% additional gain in longevity compared with introduction of antiretroviral therapy. For the population eligible for HAART in southern Africa, the achievable gains in life expectancy are large: initiating antiretroviral therapy in 1 million persons at CD4 counts of 200/µL would yield 542 000 life-years compared with providing HAART without CD4 count monitoring, and initiating HAART at 350/µL would yield an additional 440 000 life-years.

In South Africa, and perhaps in several other countries, much of this gain in life expectancy could be obtained while reducing total expenditures for HIV care by averting expensive hospitalizations because of opportunistic diseases, which outweighed the higher costs of HAART and CD4 testing. The reduction in total costs is large in South Africa, in part because of the relatively high cost of inpatient care, and our analysis suggests that CD4 count monitoring may also reduce costs of HIV care in Botswana, Swaziland, and Namibia, where the quality of the epidemic is similar and inpatient care costs are relatively high. However, even in Malawi, where the health care infrastructure is basic, health care costs are low, and use of inpatient care is inconsistent, the incremental cost-effectiveness ratio of monitoring CD4 counts every 6 months and starting HAART at 200/µL was US $670 per life-year gained. A threshold of twice the per capita gross domestic product is often cited as an acceptable incremental cost-effectiveness ratio for developing countries. By that standard, monitoring CD4 counts is cost-effective in all parts of southern Africa. Our analysis also suggests that, even in the most resource-limited settings, starting HAART at 350/µL is an effective and cost-effective intervention.

Our analysis highlights that the sizeable worldwide investments that would make HAART available could be strongly leveraged by using CD4 count monitoring to initiate treatment before onset of serious opportunistic diseases and severe immunocompromise. Recent evidence shows that, in resource-limited settings, where HAART is commonly started at low CD4 counts or with opportunistic diseases, mortality after treatment initiation is much higher than in Europe and North America, especially in the first few months of treatment.

Addition of viral load monitoring resulted in an additional increase in life expectancy of 2 months relative to use of only CD4 count monitoring. Two months is an important additional benefit. However, this gain in effectiveness came at a less favorable incremental cost-effectiveness ratio than did CD4 count monitoring because viral load testing is substantially more expensive and provides about a fourth of the benefit of CD4 testing. If the price of viral load testing were substantially reduced, the cost-effectiveness would improve markedly. In developed countries, where cost-effectiveness acceptability thresholds are substantially higher, viral load monitoring is considered a cost-effective intervention. Viral load monitoring has other benefits, such as reduced transmission by limiting the number of persons with non-suppressed HIV replication, and fewer accumulated resistance mutations. Because we did not include these potential benefits, we may have underestimated the overall benefits of viral load testing.

Why has CD4 count monitoring not been universally adopted in resource-limited settings? The initial investment in CD4 technology and infrastructure is expensive. The cost of CD4 flow cytometers, which require highly trained personnel and laboratories with refrigeration, is high, and ministries of health and public health programs may be unable or unwilling to make the investment. In addition, the cost of an individual CD4 test, while modest in comparison with the cost of HAART or viral load monitoring, may limit access to testing and treatment. The World Health Organization guidelines encourage using a CD4 count threshold of 200/µL for HAART initiation, but they acknowledge the limited capability to expand monitoring capacity.

These challenges are increasingly surmountable. Recent advances in CD4 enumeration technology enable lower per-test cost, as well as smaller machines that require relatively little infrastructure, maintenance, and technical expertise. Alternative financing mechanisms may enable health care systems to minimize the initial investment in equipment through reagent rental agreements and amortization. Both the reductions in technical challenges and our finding that CD4 count monitoring is cost-effective or cost saving support expanding CD4 count monitoring as a valuable tool in improving treatment in southern Africa. Use of CD4 count monitoring to determine treatment initiation and initiating HAART early will benefit a substantial percentage of individuals in whom treatment would be otherwise delayed until life-threatening symptoms develop.

Our analysis has several limitations. Although the phase and prevalence of the epidemic in South Africa is similar to that in other countries in the region, most of the data for our model are from a single region. Some opportunistic diseases, most notably tuberculosis, place a unique burden on that region and may limit the generalizability of our results. In addition, although our estimates of the health benefits of alternative management strategies are likely applicable more broadly in Africa, the study cohorts in Cape Town received care in a setting with potential access to clinics and hospitals. In settings in which individuals with opportunistic diseases have no access to hospitals, mortality will be higher and the cost of care will be lower than we projected. In those settings, more efforts to prevent severe opportunistic diseases may have additional mortality benefits.

We also used some data from clinical trials. While clinical trials may provide the best or only source of data, events such as treatment failure and response to HAART may differ in other settings. In addition, we used a societal perspective for this analysis, in which all costs and benefits are included. However, additional perspectives may be relevant to parts of southern Africa where costs and benefits are accrued by different parts of the health care system. For example, the perspective of a donor organization that bears costs but realizes no direct benefits may be important where donors have an important role in the health care system. Our model is not intended to restrict the use of viral load monitoring in southern Africa. Rather, we highlight the importance of CD4
count monitoring and early treatment initiation as the priority in improving health care in southern Africa. The rapid increase in access to treatment in resource-limited regions represents major progress toward reducing HIV-related morbidity and mortality. Our analysis shows that, where HAART is available, CD4 count monitoring with earlier treatment initiation provides a substantial increase in life expectancy, which in some settings may be achievable while reducing total expenditures for HIV infection. As the number of persons receiving HAART increases, the potential health benefit and cost savings from use of CD4 monitoring will also increase.

Accepted for Publication: March 30, 2008.

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Author Contributions: Dr Bendavid had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bendavid, Young, Katzenstein, and Owens. Acquisition of data: Bendavid and Young. Analysis and interpretation of data: Bendavid, Bayoumi, Sanders, and Owens. Drafting of the manuscript: Bendavid, Young, Katzenstein, and Owens. Critical revision of the manuscript for important intellectual content: Bendavid, Young, Katzenstein, Sanders, and Owens. Statistical analysis: Bendavid, Bayoumi, and Owens. Administrative, technical, and material support: Bayoumi. Study supervision: Bayoumi, Sanders, and Owens.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grants T32-HS000028 from the Agency for Healthcare Research and Quality and R01 DA15612-01 from the National Institute on Drug Abuse; and the Department of Veterans Affairs.

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