HIV Management in Resource-Poor Settings

Research in Progress

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Outline

• Context
• Methods
• Results
• Conclusions
• Discussion
The number of people on HIV treatment in many less developed countries has increased by more than 10-fold since 2003.
Context

While much emphasis has been placed on increasing the numbers starting HAART, relatively little has been placed on how to manage the millions now on treatment.

“WHO recognizes the importance of laboratory monitoring for efficacy and safety but does not want restricted infrastructure for these tests to place undue limitations on the scale-up effort”

“The 3 by 5” Guidelines, WHO
Highly Active Antiretroviral Therapy (HAART) has the ability to suppress HIV replication indefinitely (as far as we know).

As long as viral suppression is maintained, HIV is a chronic disease.
Our Question

What is the relative effectiveness and cost effectiveness of various HIV disease management strategies in the context of resource-poor settings?
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• Discussion
Management Strategies

HIV Management

- VL, CD4, and Sx
  - Alive
  - Dead

- CD4 and Sx
  - Alive
  - Dead

- Sx alone
  - Alive
  - Dead
Management Guidelines

<table>
<thead>
<tr>
<th>US (DHHS):</th>
<th>Developing countries (WHO):</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Monitor CD4 at baseline and every 3-6 months.</td>
<td>-Clinical monitoring</td>
</tr>
<tr>
<td>-Monitor viral load at baseline, with initiation of treatment, every 3-4 months thereafter, and with any clinical event.</td>
<td>-No lab monitoring at primary care sites, CD4 at district hospitals, and CD4 at regional referral centers, recognizing viral load may be important.</td>
</tr>
</tbody>
</table>
HIV Modeling

Markov models of disease

- Suited for following disease progression over time.
- Generally have a finite number of health states and discrete time progression.
- Intrinsically incapable of keeping history.
- One way to get around that is to create health states that incorporate history.
- Number of states can quickly become intractably large.
HIV Modeling

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- Suited for following disease progression over time.
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HIV Modeling

Monte Carlo simulation

- Simulate one patient at a time.
- Patient-level parameters are monitored (CD4, viral load, treatment regimen, etc).
- No limit on relevant patient-level parameters.
- History is tracked from time of entry into the model until death.
CD4 & Viral Load

CD4 T cells
• the major indicator of the patient’s immunocompetence.
• The strongest predictor of risk of opportunistic disease and death.
• Used to determine when to start treatment and response to treatment.

Viral load
• A measure of the HIV viral genetic material.
• Limited role in determining initiation of treatment.
• Helps determine response to treatment initiation.
• Helps ascertain continued suppression of viral replication.
Relationship of VL and CD4
Relationship of VL and CD4
Relationship of VL and CD4
Relationship of VL and CD4

Estimated CD4 T-cell change, cells/μL per year vs. Median Plasma HIV RNA, log_{10} copies/mL

R² = 0.09
n = 974

Rodriguez et al, JAMA 2006
CD4 on HAART

Staszewski, NEJM, 1999
HAART Failure

1. Inability to tolerate the medicines (severe toxicity).

2. Virologic failure.
   a. Emergence of resistance.
   b. Non-adherence.
Change of HAART

WHO guidelines recommend a first and second line regimen.

For failure on:
- d4T or ZDV
- 3TC
- NVP or EFV

Change to:
- TDF or ABC
  - ddI $^a$
  - LPV/r or SQV/r $^b$

“3 by 5” Guidelines, WHO
Recap

• CD4 determines disease status.
• Viral load affects change of CD4.
• HAART suppresses viral replication, allowing a rise in CD4 counts.
• Higher CD4 lowers the risk of AIDS and death.
• Treatment may need to be changed due to toxicity or virologic failure.
Model Decisions

HIV+

Need Rx?

Clinical monitoring
CD4 monitoring?

Start Rx

Toxicity?

Failure?

Change Rx

Follow-up

Clinical monitoring
CD4 monitoring?

VL monitoring?
Example Using CD4 and VL

HIV+

<200 or OD?

First line HAART

Toxicity?

Virol failure?

Y Y N

2\textsuperscript{nd} line HAART

Rpt CD4 & VL testing

N
Risk of Death

- HIV/AIDS
- Dead

Risk factors:
- CD4 count
- Acute opportunistic disease
- Treatment history
- Age-related mortality

Transition probabilities:
- $p$ from HIV/AIDS to Dead
- $1-p$ from HIV/AIDS to itself
- $1$ from Dead to itself
How the Model Functions

• All parameters are monitored by the model (the model is omniscient).
• Only some of the parameters are available to the patients and care providers (e.g. CD4 only every 3 months).
• Groups of 10,000 patients were simulated one at a time.
South Africa
Cape Town
Cape Town
Data Inputs

- Initial CD4 and viral load.
- Age at presentation.
- Rates of developing AIDS by CD4.
- Rates of mortality by CD4.
- Rates of toxicity by regimen and time on regimen.
- Rates of treatment failure by regimen and time on regimen.
## Costs

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (2004 USD)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Day</td>
<td>$182</td>
<td>Badri; Cleary</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>$28</td>
<td>“</td>
</tr>
<tr>
<td>Annual inpt days (no HAART)</td>
<td>1.9-7.7</td>
<td>“</td>
</tr>
<tr>
<td>Annual outpt visits (no HAART)</td>
<td>4.1-5.6</td>
<td>“</td>
</tr>
<tr>
<td>Annual inpt days (HAART)</td>
<td>0.14-0.26</td>
<td>“</td>
</tr>
<tr>
<td>Annual outpt visits (HAART)</td>
<td>3.9-4.6</td>
<td>“</td>
</tr>
</tbody>
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## Costs

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<thead>
<tr>
<th>Item</th>
<th>Cost (2004 USD)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per CD4 test</td>
<td>$20</td>
<td>Badri; Cleary</td>
</tr>
<tr>
<td>Cost per viral load test</td>
<td>$70</td>
<td>“</td>
</tr>
<tr>
<td>First line treatment regimen</td>
<td>$322</td>
<td>Badri; MSF</td>
</tr>
<tr>
<td>Second line treatment regimen</td>
<td>$840</td>
<td>“</td>
</tr>
<tr>
<td>CD4 flow cytometer</td>
<td>$35,000</td>
<td>Renault</td>
</tr>
<tr>
<td>Annual CD4 maintenance</td>
<td>$1,000</td>
<td>“</td>
</tr>
<tr>
<td>PCR machine for VL</td>
<td>$5,000</td>
<td>Elbeik</td>
</tr>
<tr>
<td>Annual PCR maintenance</td>
<td>$1,000</td>
<td>“</td>
</tr>
</tbody>
</table>
Benefits

• Life years gained.
  – Previous use.
  – Limited QOL data.

• All future costs and benefits were discounted at 3%.
Analyses

1. Clinical symptoms alone versus symptoms and CD4 versus symptoms and CD4 and viral load.

2. Different CD4 treatment initiation thresholds.

Management Strategies

HIV Management

- VL, CD4, and Sx
  - Alive: 1
  - Dead
- CD4 and Sx
  - Alive: 1
  - Dead
- Sx alone
  - Alive: 1
  - Dead
Symptom-based Strategy

- No HAART before...
  - Development of any AIDS-defining illness.

- HAART started when...
  - Patient develops any AIDS-defining illness.

- HAART switched after...
  - Patient develops severe toxicity to first line regimen.
  - Development of a 3rd severe opportunistic disease.

- HAART stopped with...
  - Severe toxicity to second line treatment.
CD4-based Strategy

• No HAART before...
  – Development of AIDS-defining illness AND
  – CD4, when checked, remains above treatment threshold.

• HAART started when...
  – Any AIDS-defining illness.
  – CD4 is checked and found to be below specified threshold.

• HAART switched after...
  – Patient has severe toxicity to first line regimen.
  – Treatment failure, defined by a dropping CD4 over four consecutive monitoring intervals.

• HAART stopped with...
  – Severe toxicity to second line treatment.
CD4 and VL-based Strategy

• No HAART before...
  - Development of AIDS-defining illness AND
  - CD4, when checked, remains above treatment threshold.

• HAART started when...
  - Any AIDS-defining illness.
  - CD4 is checked and found to be below specified threshold.
  - (VL is only checked once HAART is started)

• HAART switched after...
  - Patient has severe toxicity to first line regimen.
  - Treatment failure, defined by a log increase in the patient’s viral load.

• HAART stopped with...
  - Severe toxicity to second line treatment.
CD4 Threshold Strategies

Diagram showing thresholds and outcomes for CD4 counts:
- Threshold 350:
  - Alive: Stay alive
  - Dead: Overall Death
- Threshold 340:
  - Alive: Stay alive
  - Dead: Overall Death
- Threshold 240:
  - Alive: Stay alive
  - Dead: Overall Death
- Threshold 200:
  - Alive: Stay alive
  - Dead: Overall Death
"I think you should be more explicit here in step two."
Outline

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CD4 Behavior

• While not receiving HAART, CD4 falls at a rate roughly related to the VL.

• While on effective HAART, CD4 rises to a maximum that is related to lowest CD4.
CD4 Decline Without HAART

- CD4
- Time (mo)
- VL 400K
- VL 100K
- VL 24K
- VL 5K
CD4 Recovery on HAART

Model Cape Town data

Lawn, BMC, 2006
Viral Load Behavior

• While on effective suppressive therapy, viral load drops rapidly in the first month and more slowly in the next 6 months to a minimum of “below 400.”

• During virologic failure, the viral load rises.
Viral Load Behavior

1) Normal response to treatment
2) Treatment toxicity
3) Treatment failure
## Risk of AIDS

Rate of severe OD by CD4:

<table>
<thead>
<tr>
<th>CD4</th>
<th>Cape Town (per 100 PY)</th>
<th>Model (per 100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>51-200</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>201-350</td>
<td>9.2</td>
<td>6.1</td>
</tr>
<tr>
<td>&gt;350</td>
<td>2.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Holmes, JAIDS, 2006
Results – Basic Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (2004 USD)</th>
<th>Effectiveness (LY)</th>
<th>ICER ($/LYG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms only</td>
<td>4038.7</td>
<td>4.81</td>
<td></td>
</tr>
<tr>
<td>CD4 and VL</td>
<td>5368.9</td>
<td>6.33</td>
<td>$875</td>
</tr>
</tbody>
</table>

Cost (2004 USD)

Life Years

CD4 and VL

Sx only
Results – Basic Strategies

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<tr>
<td>Symptoms only</td>
<td>4038.7</td>
<td>4.81</td>
<td></td>
</tr>
<tr>
<td>CD4 only</td>
<td>4111.9</td>
<td>6.26</td>
<td>$50.5</td>
</tr>
<tr>
<td>CD4 and VL</td>
<td>5368.9</td>
<td>6.33</td>
<td>$17,957</td>
</tr>
</tbody>
</table>
Results – More Strategies

Incremental ratios:
1) $296/LYG
2) $4,295/LYG
3) $99,110/LYG
Results – CD4 threshold

Life Years

Cost (2004USD)

5.8 - 6.4

4800 - 5400
### Results – CD4 threshold

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incr Cost</th>
<th>Eff</th>
<th>Incr Eff</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>240</td>
<td>5034.8</td>
<td></td>
<td>6.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>5078.9</td>
<td>44.1</td>
<td>6.06</td>
<td>0.046</td>
<td>951.0</td>
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<tr>
<td>260</td>
<td>5122.0</td>
<td>43.2</td>
<td>6.10</td>
<td>0.045</td>
<td>956.7</td>
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<tr>
<td>270</td>
<td>5158.2</td>
<td>36.1</td>
<td>6.14</td>
<td>0.035</td>
<td>1027.9</td>
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<tr>
<td>280</td>
<td>5188.7</td>
<td>30.5</td>
<td>6.17</td>
<td>0.031</td>
<td>990.4</td>
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<tr>
<td>290</td>
<td>5217.9</td>
<td>29.2</td>
<td>6.20</td>
<td>0.028</td>
<td>1045.6</td>
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<tr>
<td>300</td>
<td>5245.9</td>
<td>28.0</td>
<td>6.22</td>
<td>0.025</td>
<td>1122.4</td>
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<tr>
<td>310</td>
<td>5271.8</td>
<td>26.0</td>
<td>6.25</td>
<td>0.025</td>
<td>1056.3</td>
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<td>320</td>
<td>5293.8</td>
<td>22.0</td>
<td>6.27</td>
<td>0.019</td>
<td>1169.5</td>
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<tr>
<td>330</td>
<td>5316.6</td>
<td>22.7</td>
<td>6.29</td>
<td>0.021</td>
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<tr>
<td>340</td>
<td>5336.0</td>
<td>19.4</td>
<td>6.30</td>
<td>0.018</td>
<td>1097.4</td>
</tr>
<tr>
<td>350</td>
<td>5355.0</td>
<td>19.0</td>
<td>6.32</td>
<td>0.016</td>
<td>1187.2</td>
</tr>
</tbody>
</table>
## Sensitivity – Cost of CD4 Testing

<table>
<thead>
<tr>
<th>Machine</th>
<th>Cost of Machine</th>
<th>Annual maintenance</th>
<th>Cost per test</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPICS</td>
<td>$60,000</td>
<td>$15,000</td>
<td>$6</td>
</tr>
<tr>
<td>FACS</td>
<td>$35,000</td>
<td>$1,000</td>
<td>$15</td>
</tr>
<tr>
<td>CyFlow</td>
<td>$30,500</td>
<td>$1,000</td>
<td>$2</td>
</tr>
</tbody>
</table>

The diagram above illustrates the cost (2004USD) versus life years for different testing methods:
- CD4 and VL FACS
- CD4 and VL EPICS
- CD4 and VL CyFlow
- CD4 only FACS
- CD4 only EPICS
- CD4 only CyFlow
- Sx only
Sensitivity – All Costs

Median ICER: $62/LYG (Mean -$117/LYG)
Acceptability – CD4 Monitoring

Proportion Cost-Effective

Willingness to Pay

Malawi $596
Acceptability Curve - Viral load monitoring

Proportion Cost-Effective

Willingness to Pay

Malawi $596
Tanz $723
Ethiopia $823
Zim $2,607
S. Africa $12,161
Sensitivity – Failure Strategy

![Graph showing the relationship between Cost and Effectiveness for different strategies: CD4 Fail 50%, CD4 Fail 4 checks, CD4 and VL 350, and Sx only. The graph indicates that as the cost increases, the effectiveness also increases, with specific points for each strategy at different cost levels.](image-url)
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CD4 Monitoring is Fundamental

• Monitoring HIV with CD4 counts has an enormous impact on life expectancy, and a relatively minor impact on cost per person.

• With the current diagnostic technology, using CD4 monitoring is highly cost effective.
Costs and Benefits

- Using CD4 monitoring involves multiple additional costs.
  - Costs of machines
  - Costs of testing
  - Maintenance costs
  - More people on HAART for longer

- But they involve great benefits.
  - Fewer opportunistic diseases
  - Lower direct medical costs
  - Overall healthier population
Viral Load Monitoring, Optional?

- Viral load monitoring confers little additional benefit above CD4 monitoring for an individual.

- The benefits of preventing spread of resistant virus and preventing treatment failures were not measured, but may alter the cost effectiveness of VL monitoring.

- The ICER of viral load monitoring puts it squarely out of reach for most developing countries.
Co-trimoxazole for HIV+TB+ $15
Treatment of Latent TB $25
CD4 Monitoring $50
HAART $725

Intervention

Creese, Lancet, 2002
Other Conclusions

- Despite the increased cost of starting at a higher CD4 count, using 350 as the threshold is cost effective compared with 200.

- Monitoring every six months instead of every three is a good option for health systems strapped for resources.

- By and large, resources should be directed towards expanding CD4 monitoring, especially if the tradeoff is expanding viral load monitoring.
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Can This be Implemented?

- In order to truly scale up monitoring capacity, monitoring must be done in both urban and rural settings.

- Can we make the tools we have now more widely available?

- Is the challenge to expanding CD4 monitoring strictly a matter of funding?
On CEA in the Developing World

“How can CEA for medical devices be compared with such basic needs as elementary, secondary, or higher education, government stability, trade barriers, fair court systems, infrastructure, and clean water?”
Piecemeal Implementation

• How can analysis help?
  – Local government
  – Guidelines

• Complex realities on the ground.
  – Historical problems
  – Practical problems

• Opportunity cost
Limitations

• No population-level parameters measured.
• South African data is unique for SSA.
• Opportunistic diseases measured all together.
• Limited validation to date.
Future Directions

• Effectiveness and cost effectiveness of different treatment strategies.
• Implications of adherence.
• Implications of pre-exposure prophylaxis.
• Viral resistance in the developing world.
"What's your exit strategy?"