Optimizing HIV Therapy in Resource Limited Settings

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Thanks RHI, WHO, NHLS, DoH, USAID, UNITAID
Disclosures...

• Part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care

• Pharma (including drug donations for studies) and managed care
What makes resource poor areas challenging?

• Obviously, less resources! And often less advocacy for more esp rural – from patients, public health care, health staff

• Often lack/inconsistent electricity, water, supply lines, internet

• Lack of skilled staff, lack of support, lack of creativity

• Information systems are poor – labs, referral

• Pregnancy, TB, hep B, children.....
My friend in New York

- HIV +
- On ART for 12 years
- Hasn’t seen a doctor or nurse in 10 years
- Barcode email, goes to lab, meds delivered
- Impossible?
Some observations...

• Biggest concerns 13 years ago – adherence and resistance – did not materialise (new drugs may make resistance irrelevant, can anticipate a very cheap, robust first line)
• % “sick” at presentation is dropping – more and more people being initiated are healthy
• Re-entry patients likely to dominate soon
• “health staffing crisis” – masks complex health staff allocation, job spec allocation
• Health staff expensive and very useful – and vested interests
• Viral load increasingly critical (and under-used)
• HIV people tend to think their’s is the only disease on the block (versus integration, other conditions)
Programmes are starting to improve
Changing disease severity over time

Adjusted proportion of patients started ART by CD4 category

- Adult CD4 below 100 cells/µl at ART start rate (adjusted)
- Adult CD4 100 to 199 cells/µl at ART start rate (adjusted)
- Adult CD4 200 to 350 cells/µl at ART start rate (adjusted)

Thanks: Andrew Boulle

Source: Consolidated National report covering monthly and quarterly ART data to end March 2014
~4 YEAR LAG BETWEEN SCALE UP OF ART AND DECLINE IN MTB INCIDENCE

Figure 1: Incidence of microbiologically-confirmed pulmonary tuberculosis (per 100,000 population) and antiretroviral treatment coverage rates in HIV-infected individuals nationally in South Africa nationally and provincially from 2004 to 2012

The solid black line represents the estimated trend in PTB incidence per 100,000 population over the study period and the dotted black line the corresponding 95% confidence interval. The overlaid dotted grey line is the ART coverage per 1000 HIV positive individuals based on data from the ASSA 2008 model.

Near-normal expectancy for adults starting ART above 200 cells/µL; Currently updating this analysis
Treatment for life

Expect a normal life expectancy:
May et al. AIDS 2014

- UK CHIC: 21,388 people started ART 2000-2010

If 35 year old man started ART:

<table>
<thead>
<tr>
<th>CD4</th>
<th>Baseline</th>
<th>1 year ART</th>
<th>5 years ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>71</td>
<td></td>
<td>&amp; VL&gt;50 54</td>
</tr>
<tr>
<td>200-349</td>
<td>78</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td>77</td>
<td>81</td>
<td>&amp; VL&lt;50 80</td>
</tr>
<tr>
<td>General population</td>
<td>78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: If diagnosed, in care and on effective ART: life expectancy is normal

Great information to give to people newly diagnosed and encourage good adherence

Thanks: Julie Fox, Guys
“Test & Treat / offer”

90% of all living with HIV will know their HIV status

90% of all living with HIV will receive sustained antiretroviral therapy

90% of all receiving antiretroviral therapy will have durable viral suppression
But...

- Average CD4 still around 300 – and significant % < 100
- Huge groups not testing – men, youth
- Some places T&T isn’t working? - ?20-somethings
So what can we improve?

- Cost
- Resistance “forgiveness”
- Side effects
- Harmonization of pediatric and adult regimens
- Demand creation
- Size of tablets and packaging
- Delivery systems
- More convenient HIV testing
New drugs will help
Game-changers that could accelerate the pace of change...

2015
- DTG and TAF-combos in high-income countries
- New LPV/r pellets

2016
- TAF/FTC approval

2017
- Long-acting PrEP
- DTG for children

2018-2020
- Nanoparticles-ARVs
- Multipurpose prevention tools
- Cabotegravir, rilpivirine long acting.
- ARVs for resistant strains
- BN Antibodies; New ARVs classes.
- DTG for infants

Changes expected from 2020+:
Vaccine? … or gene therapy for a cure

Source: UNITAID landscape analyses
We need things to go faster
World Health Organization 2015 recommendations

• Alternatives: efavirenz 400mg and dolutegravir
• Generic FDC with EFV 400mg/3TC/TDF in regulatory approval process
• Lack of DTG/TDF (or TAF) co-formulation an issue
• EFV 400mg in PMTCT and TB an issue
South Africa Snapshot June 2016

• 6-7 million HIV positive – 18% world total, 25% of Southern Africa

• 3.4 million on first line ART – Consume 25% of global generic ART

• 160,000 children on ART – PMTCT working well

• 200,000 on second line, 700 on third line
We need to cut costs!

• “Test and treat” approaches coming
• South Africa spent $350 million on ART in 2014/2015 – theoretically will double
• Equal size procurement vs PEPFAR vs GF
• Poorer countries highly donor dependant
WHO regimens pre-2015

Tenofovir + XTC + Efavirenz

AZT + Lamivudine + PI (lopinavir or atazanavir)

XTC, other nukes

Darunavir, Raltegravir, Etravirine
1\textsuperscript{st} line....

\begin{align*}
\text{TDF} & + \text{XTC} & + \text{EFV} \\
\text{AZT} & + \text{XTC} & + \text{PI} \quad \text{(lopinavir or atazanavir)} \\
\text{XTC, other nukes} \\
\text{Darunavir} & & \text{Raltegravir} & & \text{Etravirine}
\end{align*}
1\textsuperscript{st} line....

TDF + XTC + EFV

Cost driver

Side effect (and size) driver, resistance weak link
1st line....

TDF + XTC + EFV

Cost driver

400mg?
1st line....

TAF + XTC + DTG

Safer, cheaper

Safer, 2nd line need, cheaper
Dollars saved....

**Total Cost of Treatment**

**South Africa**

- Standard of Care
- Conservative
- Moderate
- Aggressive

_Millions_
WHO regimens pre-2015

- TDF
- XTC
- EFV

AZT + XTC + PI (lopinavir or atazanavir)

Cost and toxicity

XTC, other nukes

- Darunavir
- Raltegravir
- Etravirine
WHO regimens pre-2015

- TDF + XTC + EFV
- ?DTG + XTC + PI (low dose darunavir, others)

Cost and toxicity
- XTC, other nukes
- Darunavir
- Raltegravir
- Etravirine
Radical idea: Same day initiation
Why haven’t we?

- CD4 threshold, PoC N/A
- Other labs – creatinine clearance
- “Readiness” – sense that starting ART is a momentous occasion, that the adherence requirements needs careful preparation
- Historical perceptions of frailty of NNRTI regimens
- Mechanism to ration
- And I was sceptical – are we just lowering the ART bar to HT/DM?
But there are consequences!

• 2-3 visits to get ART started
• 25-40% of treatment-eligible patients don’t start treatment ≤ 6 months (Rosen references)
• Permits rationing
• Allows patients to stay on the fence
Even in settings with good testing & ART coverage, treatment cascades still show important leakages...

Hill et al. CROI 2015 [abstr 1118]
The Rosen study....

PLOS Medicine

OPEN ACCESS  PEER-REVIEWED

RESEARCH ARTICLE

Initiating Antiretroviral Therapy for HIV at a Patient’s First Clinic Visit: The RapIT Randomized Controlled Trial

Sydney Rosen, Mhairi Maskew, Matthew P. Fox, Cynthia Nyoni, Constance Mongwenyana, Given Malete, Ian Sanne, Dorah Bokaba, Celeste Sauls, Julia Rohr, Lawrence Long

Published: May 10, 2016  •  http://dx.doi.org/10.1371/journal.pmed.1002015

Article  Authors  Metrics  Comments  Related Content
Question....

• Can we give ART at first visit?
• Brief design: RCT, 2 sites in Johannesburg, (one hospital, one squatter camp primary care)
• Not pregnant
Major Programmatic Outcome: ART Initiation ≤ 90 Days

377 ART eligible patients enrolled

190 standard patients
- 54 did not initiate ≤ 90 days (28%)
  - 2 initiated ≤ 180 days
  - 52 did not initiate
- 136 initiated ≤ 90 days (72%)

187 rapid patients
- 5 did not initiate ≤ 90 days (3%)
  - 1 initiated ≤ 180 days
  - 4 did not initiate (all lost during TB workup)
- 182 initiated ≤ 90 days (97%)

Risk difference 25% (95% CI 19 to 33%)
Crude relative risk 1.36 (95% CI 1.24 to 1.49)
Table 2. ART initiation, 10-mo retention in care, and 10-mo viral suppression.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard arm(%) n = 190</th>
<th>Rapid arm(%) n = 187</th>
<th>Crude risk difference (95% CI)</th>
<th>Crude relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiated ≤ 90 d and suppressed by 10 mo (primary outcome)</td>
<td>96 (51%)</td>
<td>119 (64%)</td>
<td>13% (3%–23%)</td>
<td>1.26 (1.05–1.50)</td>
</tr>
<tr>
<td>Of those not initiated ≤ 90 d and suppressed by 10 mo</td>
<td>94 (49%)</td>
<td>68 (36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not initiated</td>
<td>54 (28%)</td>
<td>5 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiated but not suppressed</td>
<td>40 (21%)</td>
<td>63 (34%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Of those initiated but not suppressed:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retained, unsuppressed viral load test reported</td>
<td>11 (6%)</td>
<td>17 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retained, no viral load test reported</td>
<td>14 (7%)</td>
<td>16 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferred to another clinic</td>
<td>1 (1%)</td>
<td>6 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>3 (2%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>11 (6%)</td>
<td>24 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiated ≤ 90 d</td>
<td>136 (72%)</td>
<td>182 (97%)</td>
<td>25% (19%–33%)</td>
<td>1.36 (1.24–1.49)</td>
</tr>
<tr>
<td>Initiated ≤ 90 d and retained at 10 mo (secondary outcome)</td>
<td>121 (64%)</td>
<td>151 (81%)</td>
<td>17% (5%–23%)</td>
<td>1.27 (1.12–1.44)</td>
</tr>
<tr>
<td>Of those not initiated ≤ 90 d and retained at 10 mo</td>
<td>69 (36%)</td>
<td>36 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiated but not retained</td>
<td>15 (8%)</td>
<td>31 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not initiated</td>
<td>54 (28%)</td>
<td>5 (3%)</td>
<td></td>
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</tbody>
</table>

http://journals.plos.org/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1002015
### Effect Modification by Site and by Age and Sex

<table>
<thead>
<tr>
<th>Initiated ≤ 90 days and retained and suppressed by 10 months</th>
<th>Standard arm</th>
<th>Rapid arm</th>
<th>Crude relative risk [95% CI]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full sample</td>
<td>96/190 (51%)</td>
<td>119/187 (64%)</td>
<td>1.26 (1.05-1.50)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary health clinic</td>
<td>46 (43%)</td>
<td>67 (64%)</td>
<td>1.50 (1.15-1.95)</td>
</tr>
<tr>
<td>Hospital-based HIV clinic</td>
<td>50 (61%)</td>
<td>52 (63%)</td>
<td>1.04 (0.82-1.32)</td>
</tr>
<tr>
<td>Age and sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male &lt; 35</td>
<td>12/32 (38%)</td>
<td>32/45 (71%)</td>
<td>1.90 (1.17-3.08)</td>
</tr>
<tr>
<td>Male ≥ 35</td>
<td>31/53 (58%)</td>
<td>28/45 (62%)</td>
<td>1.06 (0.77-1.47)</td>
</tr>
<tr>
<td>Female &lt; 35</td>
<td>28/60 (47%)</td>
<td>32/53 (60%)</td>
<td>1.29 (0.91-1.83)</td>
</tr>
<tr>
<td>Female ≥ 35</td>
<td>25/45 (56%)</td>
<td>27/44 (61%)</td>
<td>1.10 (0.78-1.57)</td>
</tr>
</tbody>
</table>

*Effect observed in study; p-values for interaction terms for absolute risk differences were not significant
Conclusions

It is possible to initiate nearly all eligible patients on ART (75% on the same day) and improve overall health outcomes.

- ART Initiation: 36%
- Viral Suppression: 26%
Do we recommend this?

• Is this different from the private sector? Elsewhere?
• Will it overwhelm services?
• BUT: if we had a tablet that improved outcomes this dramatically, we’d be marching in the streets...
What about “mHealth”?
Jaundiced view...

- Tech ‘solutions’ have wasted time and money
- Telemedicine - ?any successful models
- Cell phones? Starting to show success
- eRecords – huge investment, little return
  - Weakness of the designer
  - Each province trying its own system
  - Disease-specific systems
  - Usually made for reporting, not for clinical management
  - Not linked to labs or pharmacy
What’s the single most useful tech currently for health care workers?
Fungal

Trying antifungal again. Will see.

Biopsy!!!
Oh, and....

• Online links to NHLS results
So, cell phones....

- End of 2017: 85% of South Africans will have smartphones
- Does beg the question: does providing wireless at health facilities become a priority?
DoH Minister...

• Stock control app at PHCs
The MDR-TB Partnership
To be used by clinicians at the Primary Health Care clinics in order to ENROLL potential MDR-TB patients. [Will also contain a Training Library in the future.]

To be used by Linkage Officers in order to receive MDR-TB results from the NHLS and CONTACT the patient to LINK them with an MDR-TB unit [Will also contain a Training Library in the future.]

To be used by clinicians at MDR-TB unit in order to REGISTER MDR-TB patients and confirm that they have been linked to care. [Will also include a Training Library and Clinical Decision Support modules in the future.]
Dashboard

Enrollment  LINKAGE  Care

6 days, 3 hrs  2340
mean time lapsed from enrollment to initiation  successful initiations in the PAST 3 MONTHS

Mean Number of Days Lapsed
From ENROLLMENT to INITIATION

Initiations
Stacked Graph
400
300
Registration and Log-in

**Username:**

**Password:**

Submit

**New User**

Lab Number / Barcode Number:

0015

Use lab number

First Name:

Vincent

Surname:

Test

ID Number:

ID00015

Date of Birth:

2015/07/15

Username:

V1

Password:

V1

Pin:

1234

Confirm Password:

V2

Confirm Pin:

1234

Cancel OK
CD4 and Viral Load Results

**CD4 Results**
(The higher the better)

Click here for more info about CD4 count...

No results yet.
Please check back later.

**Viral Load Results**
(The lower the better)

Click here for more info about Viral Load...

No results yet.
Please check back later.

click on a result to learn more about the result

---

**CD4 count of 500 or lower**

You should start antiretrovirals (ARVs) when you have a CD4 count of 500 or below, even if you are feeling well. ARVs will help to keep you healthy. Go back to your clinic and speak to your nurse or doctor so they can start you on ARV medication.

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**Viral Load (VL) higher than 1,000**

This is a sign that your treatment is not controlling the HIV virus in your blood. The most common reason for the treatment not working is if the ARVs are not taken correctly. Inform your nurse, doctor or counsellor about your high viral load result. Your doctor will then decide if you need more blood tests or different ARVs. Sometimes the virus develops resistance, which means the virus continues to multiply despite you taking your ARVs correctly. The higher the viral load, the more the virus will destroy your soldier cells (CD4 cells) and you will be more likely to become ill.

To prevent the virus becoming resistant to your ARVs, you need to take your medication every day and at the same time.
But...

- Enrolment has been slow
- Less owners of smartphones than we thought
- Battling to get young men
If I had complete control?

- Simpler, safer drug regimens
- Same day initiation – give it a try
- PoC VLs
- Ask the Americans for help - high level strategies to keep people OUT of facilities - ?NY model
- Focus on information control – single patient identifiers, lab data across the system, engagement with patients via cell phones
- Integrate all chronic illnesses into a verticalised programme