New adult ART guidelines

Graeme Meintjes
University of Cape Town
Imperial College London

Port Alfred, 30 May 2015, SA HIV Clinicians Society CME
National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults

24 December 2014

GUIDELINE
Adult antiretroviral therapy guidelines 2014
By the Southern African HIV Clinicians Society

1. Key principles

- Adult antiretroviral therapy (ART) guidelines are evidence-driven. Internationally, the current guidelines have been written in addition to those relevant to southern Africa. The following general principles underpin the writing process:
  - South Africa is a middle-income country, whereas certain other countries in the region are low-income countries. Hence, affordability has been taken into account.
  - Only treatments and diagnostic options available in southern Africa were included.
  - We recognized the need to bridge the gap in treatment recommendations between public and private sector programmes, considering that many patients transition from the two sectors for treatment.
  - We acknowledge that current recommendations are open-ended and poorly resourced settings, the smallness of disease/treatment venues, and the factors that play a role in providing care for treatment.
  - Therapeutics-related clinical trials are an essential component of ART provision. However, clinical trial evidence has been few; the evidence from non-experimental, observational, non-comparative, and additional data from controlled community studies is awaited.

2. Goals of ART

The primary goal of ART is:
- Improve survival at 56
- Reduce HIV-related morbidity and mortality
- Provide sustained and durable suppression of viral load (VL)
- Reduce and prevent transmission.

These goals are achieved by suppressing viral replication completely for as long as possible, using well-informed and sustainable treatment plans with good adherence. With prolonged viral suppression, the CD4+ lymphocyte count steadily increases, which is accompanied by a restoration of cellular-specific immune function. For most patients, the results in a reduction in the risk of HIV-associated morbidity and mortality. It is still unclear whether immune function can reverse in HIV-infected individuals. These principles are taken into account in the design of ART for HIV-infected individuals.

3. Standard of care

Standard anti-retroviral therapy (ART) regimens should be used in HIV-positive individuals to obtain the best results and to prevent failure. However, no antiretroviral regimen has a cure in HIV prevention, e.g., in the prevention of mother-to-child transmission and the prevention of post-episode prevention (MEP) for women at risk of acquiring infection, or for those already infected. The standard of care has been developed to prevent complications, excluding complications of ART. Therefore, these regimens are probably ineffective in ART-resistant individuals. Further research is needed to assess the role of ART-resistant ART-resistant individuals. Further research is needed to assess the role of ART-resistant ART-resistant individuals.

For further information, see:
OUTLINE

• When to start ART
• ART timing in patients with TB and CM
• First line issues
• Second line issues
• IPT
• Cryptococcal antigen screening
• Return to care after ART interruption
• Reducing CD4 count monitoring
OUTLINE

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• First line issues
• Second line issues
• IPT
• Cryptococcal antigen screening
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• Reducing CD4 count monitoring
When to start ART?

• In 2013 the WHO increased the CD4 count threshold for starting ART to 500

• Also included all patients with TB, hepatitis B, pregnant women and HIV+ partner in serodiscordant couple as eligible
Number of people eligible for antiretroviral therapy in low- and middle-income countries based on the epidemic and response status at the end of 2012

- 2010 Guidelines: 15.9 million
  - eligible for ART
  - on ART
- 2013 Guidelines: 28.6 million
  - eligible for ART
  - on ART

Updated fig 1.23 (Global update on HIV treatment 2013: results, impact and opportunities: WHO report in partnership with UNICEF and UNAIDS, page 41).
HIV seroconversion added as indication for ART

<table>
<thead>
<tr>
<th>Clinical diagnoses (irrespective of CD4 count)</th>
<th>ART recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO clinical stage 3 and 4†</td>
<td></td>
</tr>
<tr>
<td>Other severe HIV-related disorders, e.g.:‡</td>
<td></td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td></td>
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<tr>
<td>Thrombotic thrombocytopenic purpura</td>
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<tr>
<td>Polymyositis</td>
<td></td>
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<tr>
<td>Lymphocytic interstitial pneumonitis</td>
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<tr>
<td>Non HIV-related disorders:§</td>
<td></td>
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<tr>
<td>Malignancies (excluding localised malignancies)</td>
<td></td>
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<tr>
<td>Hepatitis B¶</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td></td>
</tr>
<tr>
<td>Any condition requiring long-term immunosuppressive therapy</td>
<td>ART recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CD4 counts</th>
<th>ART recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350 cells/µl</td>
<td>ART recommended</td>
</tr>
<tr>
<td>350-500 cells/µl (two counts in this range)</td>
<td>ART recommended if patient ready and motivated to start</td>
</tr>
<tr>
<td>&gt;500 cells/µl</td>
<td>Defer ART</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-infected partner in serodiscordant relationship</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Regardless of CD4 count or clinical diagnoses</td>
<td>Offer ART and discuss safe sex (discussion must involve both partners)</td>
</tr>
</tbody>
</table>
SA DOH Guidelines
Implemented from 1 Jan 2015

<table>
<thead>
<tr>
<th>Eligible to start ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count &lt;500 cells/μl irrespective of clinical stage</td>
</tr>
<tr>
<td>(Prioritise those with CD4 &lt;350 cells/μl)</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Irrespective of CD4 count or clinical stage:</td>
</tr>
<tr>
<td>• Active TB disease (including drug-resistant and EPTB)</td>
</tr>
<tr>
<td>• Pregnant and breastfeeding women who are HIV-positive</td>
</tr>
<tr>
<td>• Known hepatitis B viral (HBV) co-infection</td>
</tr>
<tr>
<td>• Prioritise those with CD4 &lt;350 cells/μl or advanced HIV disease</td>
</tr>
</tbody>
</table>
HPTN 052 trial
Botswana, Brazil, India, Kenya, Malawi, SA, Thailand, Zimbabwe, USA

1736 serodiscordant, sexually active couples with HIV+ partner having CD4 350-550 randomised 1:1 to:

– Immediate ART
– Delay ART until CD4 ≤ 250 or Stage 4 event

Cohen, NEJM 2011;365:493
Early ART reduced HIV transmission

**HR = 0.11**
95% CI = 0.04-0.32

**HR = 0.04**
95% CI = 0.01-0.27

Cohen, NEJM 2011;365:493
ART scale-up associated with lower HIV incidence in rural KZN

- 16,667 HIV-negative adults followed 2004-11
- Annual HIV prevalence and ART coverage in a 3km radius around each individual was calculated
- Hazard ratio for HIV seroconversion in relation to ART coverage calculated
  - Adjusted for gender, age, HIV prevalence and various HIV risk behaviours
- 1,413 seroconversions observed over 53,605 years of observation
  - Crude HIV incidence = 2.6/100 person-years

Tanser, Science 2013;339:966
Researchers linked: HIV surveillance database ART clinics database

ART coverage 2005 - 2011

HIV prevalence 2005 - 2011

Tanser, Science 2013; 339: 966
Increased ART coverage associated with reduced HIV incidence (dose-response relationship)

Tanser, Science 2013;339:966
Haiti trial
Starting ART at $\text{CD4}<350$ vs $\text{CD4}<200$ or AIDS

HR = 4.0
HR = 2.0

Severe, NEJM 2010
Early ART & IPT in HIV-Infected African Adults With High CD4 Count (Temprano Trial)

• Randomized 2x2 factorial superiority trial conducted in 9 HIV care centers in Côte d’Ivoire
  – Immediate ART vs WHO criteria
  – 6 months IPT vs no IPT
• March 2008 - January 2015
• Inclusion criteria were:
  – HIV-1 infection
  – Age >18 years
  – CD4 nadir <800/ul
  – No criteria for starting ART according to the most recent WHO guidelines
• 2076 randomised; 2056 included in analysis
  (median CD4 = 465)

Danel, CROI 2015, 115LB
The primary endpoint was severe HIV morbidity (AIDS-defining diseases, non-AIDS-defining malignancy, or non-AIDS-defining invasive bacterial diseases), or any-cause mortality at 30 months.

<table>
<thead>
<tr>
<th>Severe morbidity</th>
<th>N</th>
<th>TAR (PY)</th>
<th>Rate (/100PY)</th>
<th>AHR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHOART</td>
<td>111</td>
<td>2,247</td>
<td>4.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EarlyART</td>
<td>64</td>
<td>2,310</td>
<td>2.77</td>
<td>0.56</td>
<td>(0.41 - 0.76)</td>
</tr>
<tr>
<td>No IPT</td>
<td>104</td>
<td>2,225</td>
<td>4.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPT</td>
<td>71</td>
<td>2,332</td>
<td>3.04</td>
<td>0.65</td>
<td>(0.48 - 0.88)</td>
</tr>
<tr>
<td><strong>Baseline CD4 &gt;500/ul</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHOART</td>
<td>38</td>
<td>918</td>
<td>4.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EarlyART</td>
<td>23</td>
<td>964</td>
<td>2.39</td>
<td>0.56</td>
<td>(0.33 - 0.93)</td>
</tr>
<tr>
<td>No IPT</td>
<td>37</td>
<td>918</td>
<td>4.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPT</td>
<td>24</td>
<td>965</td>
<td>2.49</td>
<td>0.61</td>
<td>(0.37 - 1.02)</td>
</tr>
</tbody>
</table>

N: number of events. PY: person-years; TAR: time at risk; AHR: adjusted hazard ratio; CI: confidence interval.
START Study
Strategic Timing of AntiRetroviral Treatment Study

• Adult ART naïve patients with CD4 > 500
• Randomised to:
  – Immediate ART
  – Start when CD4 < 350
• 215 sites in 35 countries
• 4,685 patients enrolled
• Due to end late 2016
• Stopped early by DSMB and results announced on 27 May 2015 (average 3 years follow-up)
FOR IMMEDIATE RELEASE
Wednesday, May 27, 2015

National Institute of Allergy and Infectious Diseases (NIAID)
http://www.niaid.nih.gov

Media Contact:
NIAID Office of Communications
(301) 402-1683
niaidnews@niaid.nih.gov

Starting Antiretroviral Treatment Early Improves Outcomes for HIV-Infected Individuals

NIH-Funded Trial Results Likely Will Impact Global Treatment Guidelines

A major international randomized clinical trial has found that HIV-infected individuals have a considerably lower risk of developing AIDS or other serious illnesses if they start taking antiretroviral drugs sooner, when their CD4+ T-cell count—a key measure of immune system health—is higher, instead of waiting until the CD4+ cell count drops to lower levels. Together with data from previous studies showing that antiretroviral treatment reduced the risk of HIV transmission to uninfected sexual partners, these findings support offering treatment to everyone with HIV.

The new finding is from the Strategic Timing of AntiRetroviral Treatment (START) study, the first large-scale randomized clinical trial to establish that earlier antiretroviral treatment benefits all HIV-infected individuals. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, provided primary funding for the START trial. Though the study was expected to conclude at the end of 2016, an interim review of the study data by an independent data and safety monitoring board (DSMB) recommended that results be released early.
Event rate of primary endpoint

- Primary endpoint = AIDS, serious non-AIDS event* or death
  - Early arm = 0.60/100 person years
  - Deferred arm = 1.25/100 person years
  - Hazard ratio = 0.47 (95%CI=0.32-0.68)  
    (53% reduction in early arm)

* Serious non-AIDS event = Major CVS, renal or hepatic disease or non-AIDS cancer
<table>
<thead>
<tr>
<th>Category</th>
<th>Early arm (A)</th>
<th>Later arm (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: AIDS, serious non-AIDS, or death (primary)</td>
<td>41</td>
<td>86</td>
</tr>
<tr>
<td>Category 2: AIDS or AIDS death</td>
<td>14</td>
<td>46</td>
</tr>
<tr>
<td>Category 3: Serious non-AIDS or non-AIDS death</td>
<td>28</td>
<td>41</td>
</tr>
</tbody>
</table>
Tony Fauci (NIAID Director), 27 May 2015

“We now have clear-cut proof that it is of significantly greater health benefit to an HIV-infected person to start antiretroviral therapy sooner rather than later.”

“Moreover, early therapy conveys a double benefit, not only improving the health of individuals but at the same time, by lowering their viral load, reducing the risk they will transmit HIV to others. These findings have global implications for the treatment of HIV.”
Guidelines are likely to change soon

CD4 < 500

All HIV+ patients regardless of CD4

Prioritise those with lowest CD4 counts
Patients must be motivated for lifelong ART
Fig. 5.1. Actual and projected numbers of people receiving antiretroviral therapy in low- and middle-income countries by WHO region and in high-income countries across WHO regions, 2003–2015\(^a\)

\(^a\)Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS)
By end of 2013

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ART timing in patients with TB and CM

<table>
<thead>
<tr>
<th>Timing of ART initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART should be started as soon as the patient is ready, and within at least 2 weeks of CD4 count being done</td>
</tr>
<tr>
<td>In TB co-infection, start with TB treatment first, followed by ART as soon as possible and within 8 weeks</td>
</tr>
<tr>
<td>If CD4 &lt;50 cells/µl initiate ART within 2 weeks of starting TB treatment, when the patient’s symptoms are improving and TB treatment is tolerated</td>
</tr>
<tr>
<td>If CD4 &gt;50 cells/µl initiate ART within 2-8 weeks of starting TB treatment</td>
</tr>
<tr>
<td>In cryptococcal or TB meningitis: Defer ART initiation for 4-6 weeks</td>
</tr>
</tbody>
</table>

IMMEDIATE INITIATION: All HIV-positive pregnant or breastfeeding women, as long as no active TB

FAST TRACKING (within 7 days:)

- Patients with CD4 <200 cells/µl
- HIV stage 4, even if CD4 is not yet available

DOH guidelines
Randomised strategy trials of ART timing during TB treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion criteria</th>
<th>Early ART</th>
<th>Deferred ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPiT* (South Africa)</td>
<td>Smear + PTB CD4 &lt; 500</td>
<td>Within 4 weeks</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>STRIDE ACTG A5221 (Multi-country)</td>
<td>Smear + and – PTB CD4 &lt; 250</td>
<td>Within 2 weeks</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>CAMELIA (Cambodia)</td>
<td>Smear + PTB and EPTB CD4 ≤ 200</td>
<td>2 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>TB meningitis trial (Vietnam)</td>
<td>TB meningitis</td>
<td>Within 1 week</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

* SAPiT had 3rd arm (ART within 4 weeks of completing TB treatment) that was stopped early by DSMB due to significant excess mortality

ART timing and primary endpoints

**Death**
- p = 0.006
- 38% ↓

**Death/AIDS**
- Early (~2 wk) p = 0.45
- Later (~8 wk) p = 0.73

CAMELIA (percentage)

STRIDE (percentage)

SAPIT (incidence rate)
ART timing and primary endpoints in patients with CD4 < 50

<table>
<thead>
<tr>
<th>Study</th>
<th>Early (~2 wk)</th>
<th>Later (~8 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELIA (percentage)</td>
<td>38% ↓</td>
<td>42% ↓</td>
</tr>
<tr>
<td>STRIDE (percentage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>38% ↓</td>
<td>42% ↓</td>
</tr>
<tr>
<td>Death/AIDS</td>
<td>p=0.006</td>
<td>p=0.02</td>
</tr>
<tr>
<td>Death/AIDS</td>
<td>p=0.06</td>
<td></td>
</tr>
</tbody>
</table>

*SAPiT (incidence rate) 68% ↓

*CAMELIA data represents all patients in trial, majority had CD4 < 50 (median CD4 =25)*
SAPiT IRIS incidence
(IRIS cases/100 person years)

Naidoo, Annals Intern Med 2012
“These data support deferred initiation of ART in HIV-associated TBM, particularly in resource-limited settings”

Torok Clin Infect Dis 2011;52:1374
ART Timing in TB patients

- **CD4 < 50**
  - Start at 2 weeks
  - Increased TB-IRIS risk (2-5x)
  - *PredART clinical trial evaluating prednisone to prevent TB-IRIS*

- **CD4 > 50**
  - Can defer up to 8 weeks
  - Unless clinical reasons to start earlier

- **CD4 > 220**
  - Can defer longer but for programmatic reasons start by 8 weeks

- **TBM**
  - Defer 4-6 weeks
Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis


Randomized Strategy Trial
Cryptococcal Optimal ART Timing (COAT) Trial
Uganda and South Africa

HIV-infected ART-naïve Cryptococcal meningitis

EARLY ARM
ART 1-2 weeks

DEFERRED ARM
ART 5-6 weeks

PRIMARY ENDPOINT
SURVIVAL AT 26 WEEKS

HYPOTHESIS
Early ART will reduce mortality

Target enrollment = 500
177 participants enrolled
Enrollment halted after 17 months by NIAID Africa DSMB

Boulware et al, NEJM 2014
Recognised cryptococcal IRIS events
Early ART = 17/87 (20%)  Deferred ART = 9/69 (13%)  p=0.32

Boulware et al, NEJM 2014
OUTLINE

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• IPT
• Cryptococcal antigen screening
• Return to care after ART interruption
• Reducing CD4 count monitoring
# First line ART

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td>TDF</td>
<td>FTC/3TC</td>
<td>Efavirenz</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>ABC AZT Short term D4T</td>
<td>-</td>
<td>Rilpivirine Nevirapine</td>
</tr>
</tbody>
</table>

Raltegravir or PI/r to be used as 3rd drug when NNRTI contra-indicated eg. life-threatening hypersensitivity reaction

SA HIV Clinicians Society 2014
TDF and the kidney: Meta-analysis

- 17 studies
  - 9 RCT
  - 8 Observational
- Tenofovir vs other regimens
  - Mean difference in calculated CrCl: -3.9 ml/min
  - Risk difference for ARF: 0.7%
- But many studies exclude higher risk patients

Cooper, Clin Infect Dis 2010
First line ART & renal function

- Assess creatinine clearance at baseline
  - MDRD or modified Cockgraf-Gault formula
  - Avoid TDF if < 50ml/min
  - Could later use TDF if normalises

- Monitor Creatinine on TDF
  - Timepoints: month 3, 6 and 12 then annually
  - If creatinine rises: recalculate creatinine clearance

- Generally avoid TDF while on injectable for MDR TB
The modified Cockroft-Gault equation:

\[
\text{Creatinine clearance} = (140 - \text{age}) \times \text{ideal weight} \times \frac{\text{serum creatinine}}{}
\]

*For women, multiply the total by 0.85*
NDOH 1st line if TDF contra-indicated

<table>
<thead>
<tr>
<th>TDF contraindication:</th>
<th>ABC+ 3TC + EFV (or NVP)</th>
<th>Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance of &lt;50 mL/min</td>
<td></td>
<td>MDR treatment</td>
</tr>
</tbody>
</table>
Abacavir Drug Hypersensitivity (1)

• Features
  – Fever (usually 39-40 degrees)
  – Rash in 70% (maculopapular or urticarial)
  – Fatigue, malaise
  – GI symptoms (N&V, diarrhoea, abdominal pain)
  – Arthralgias
  – Cough, dyspnoea, pharyngitis
  – Usually > 1 system
  – Temporally related to taking dose

• Timing
  – Median onset 9 days
  – 90% in first 6 weeks
Abacavir Drug Hypersensitivity (2)

• Incidence
  – 4-8% in people of European descent
  – Much less common in people of African descent
  – Strongly associated with HLA-B5701
    • White Americans 8%
    • African-Americans 2.5%
    • Africa < 1%

• Can be fatal
  – 3/10,000 people on abacavir-based ART (trial data)
  – Rechallenge is an important risk
Use of Abacavir in 30 HIV-infected Children From Durban, South Africa

Report From a Pilot Study

To the Editors:

We report on the use of Abacavir from a pilot study conducted between February 3, 2004 and August 29, 2006 at King Edward VIII Hospital in Durban, South Africa. Ethical approval was obtained from the University of KwaZulu Natal.

Thirty ART (antiretroviral therapy) naïve children aged between 2 and 12 years with vertically transmitted HIV-1 infection were enrolled in the study to assess the use of structured treatment interruptions. The children received a combination of 3 nucleoside reverse transcriptase inhibitors, namely Zidovudine, Lamivudine, and Abacavir. The use of a triple nucleoside regimen was based on the unavailability of protease inhibitors at the time of the study, as well as on the possible risk of resistance developing if a non-nucleoside reverse transcriptase inhibitor was used in the interrupted subjects. ART was received for a mean of 84.27 weeks (2.96 weeks). Follow-up was done at regular intervals and the children were monitored for side effects.

During the course of the study, there were no significant adverse events. There was one instance of suspected hypersensitivity. This occurred in a 5-year-old child, who presented with fever and a rash 2 weeks after starting ART. A septic workup and skin biopsy were done on the child. All investigations were normal and the histopathology of the biopsy was nonspecific. It was therefore unclear whether the rash was drug related or due to an intercurrent viral infection. The rash cleared on stopping Abacavir and was therefore not recommended. The child remained well on follow-up.

All children on the study had molecular class I HLA (human leukocyte antigen) typing done at baseline through the South African National Blood Bank. The most prevalent allele in this cohort was HLA-B1503. No patient, including the child with the suspected hypersensitivity, had the HLA-B5701 allele.

Abacavir has been recommended for use in both first and second line therapy.1 However, there are safety concerns, as hypersensitivity to Abacavir can present with idiosyncratic symptoms.1 Reintroduction can be potentially fatal. Studies have shown a strong association between the presence of the (HLA) B*5701 allele and Abacavir hypersensitivity.1 HLA-B*5701 is more prevalent among Caucasians.1

In an HIV-1 infected childle C. Zulu Xhosa population of both children and adults in Durban, South Africa, there was zero prevalence of B*5701.1 2 Prospective screening for HLA-B5701 has a positive predictive value of 100% in preventing hypersensitivity reactions to Abacavir.1 It has been suggested that patients be screened for possible hypersensitivity prior to treatment; however these tests are prohibitively expensive, and possibly not indicated in patients of African origin.

This is the first report on the use of Abacavir in African children. It appears to be safe in a population of children where the prevalence of HLA-B5701 is low; however, it would be prudent to maintain surveillance in view of some reports of Abacavir hypersensitivity in the absence of HLA-B*5701.1

Razia Bobat, FCP(Paed), MD
Gurpreet Kindra, MB BS, Dip(Epi)
Department of Paediatrics and Child Health
Nelson R Mandela School of Medicine
Photini Kiwipi, PhD
Shabashini Reddy, BSc(Hons)
HIV Pathogenesis Program
Doris Duke Medical Research Institute
Prakash M. Jeeva, FCP(Paed)
Miriam Adhihari, FCP(Paed), MD
Department of Paediatrics and Child Health
Nelson R Mandela School of Medicine
University of KwaZulu-Natal
Corrallla, South Africa
Hoonch M. Coovadia, FCP(Paed), MD
HIV Pathogenesis Program
Doris Duke Medical Research Institute
University of KwaZulu Natal
Durban, South Africa

REFERENCES
Virological efficacy of abacavir: systematic review and meta-analysis

Mario Cruciani¹*, Carlo Mengoli², Marina Malena¹, Giovanni Serpelloni¹, Saverio G. Parisi², Graeme Moyle³ and Oliviero Bosco¹
Findings

• In a meta-analytical pooling of RCTs with a direct comparison of ABC/3TC and TDF/FTC at 48 weeks (6 trials, 4118 patients) proportion with VL < 50 similar in
  – in overall comparison (RR 0.98; 95% CI 0.94–1.03),
  – in the low baseline VL strata (RR 1.01; 95% CI 0.99–1.03)
  – in the high baseline VL strata (RR 0.96; 95% CI 0.90–1.03)

• Similar virological results were found at 96 weeks (4 trials, 2003 patients)
Figure 4. Forest plot of comparison: rates of patients with VL <50 copies/mL at 48 weeks and 96 weeks in studies comparing abacavir (ABC) and tenofovir (TDF) according to baseline VL values. Cumulative results and subgroup analyses based on screening values: <100000 copies/mL (analyses 2.1.1 and 2.2.1) or >100000 copies/mL (analyses 2.1.2 and 2.2.2).
OUTLINE

• When to start ART
• ART timing in patients with TB and CM
• First line issues
• Second line issues
• IPT
• Cryptococcal antigen screening
• Return to care after ART interruption
• Reducing CD4 count monitoring
# 2nd line

<table>
<thead>
<tr>
<th>1st LINE</th>
<th>2nd LINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + FTC + NNRTI</td>
<td>AZT + 3TC + Lopinavir/ritonavir</td>
</tr>
<tr>
<td>AZT/D4T + 3TC + NNRTI</td>
<td>TDF + FTC + Lopinavir/ritonavir</td>
</tr>
</tbody>
</table>

If on rifampicin-based TB treatment: Double dose lopinavir/ritonavir
## Contra-indication or Intolerance

<table>
<thead>
<tr>
<th>Reason</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidaemia (total cholesterol &gt;6 mmol/L) or diarrhoea associated with LPV/r</td>
<td>Switch LPV/r to ATV/r</td>
</tr>
<tr>
<td>Anaemia and renal failure</td>
<td>Switch to ABC</td>
</tr>
</tbody>
</table>
Atazanavir

• Causes **mild unconjugated hyperbilirubinaemia** in up to 50% of patients
• Competitive inhibition of uridine diphosphate-glucuronosyl transferase (UGT) 1A1 enzyme similar to Gilbert’s syndrome
• If other LFTs normal and no hepatitis symptoms then this does not represent liver injury
• Cannot be used with Rifampicin
OUTLINE

• When to start ART
• ART timing in patients with TB and CM
• First line issues
• Second line issues
  • IPT
• Cryptococcal antigen screening
• Return to care after ART interruption
• Reducing CD4 count monitoring
IPT guidelines

Table 13. Indications for and duration of IPT

<table>
<thead>
<tr>
<th>TST</th>
<th>Pre-ART</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not done</td>
<td>IPT for 6 months</td>
<td>IPT for 12 months</td>
</tr>
<tr>
<td>Negative</td>
<td>IPT not indicated</td>
<td>IPT for 12 months</td>
</tr>
<tr>
<td>Positive</td>
<td>IPT for at least 36 months</td>
<td>IPT for at least 36 months</td>
</tr>
</tbody>
</table>

IPT = isoniazid preventive therapy; TST = tuberculin skin test; ART = antiretroviral therapy.

SA HIV Clin Soc guidelines, 2014
Cochrane meta-analysis: IPT in HIV+

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment (INH)</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>2152</td>
<td>1984</td>
<td></td>
<td>100.0 %</td>
<td>0.67 [ 0.51, 0.87 ]</td>
</tr>
</tbody>
</table>

Total events: 85 (Treatment (INH)), 123 (Control).
Heterogeneity: $\chi^2 = 13.80, df = 12 (P = 0.31); I^2 = 13\%$
Test for overall effect: $Z = 2.95 (P = 0.0032)$

Akolo, 2010
### Analysis 2.1. Comparison 2 Isoniazid vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: Isoniazid vs placebo

Outcome: Incidence of active TB (confirmed, probable or possible)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment (N=H)</th>
<th>Control (N=H)</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PPO+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hawken 1997</td>
<td>5/67</td>
<td>8/69</td>
<td></td>
<td>6.3 %</td>
<td>0.64 [0.22, 1.87]</td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>4/52</td>
<td>11/60</td>
<td></td>
<td>8.2 %</td>
<td>0.42 [0.14, 1.24]</td>
</tr>
<tr>
<td>Pape 1993</td>
<td>2/38</td>
<td>6/25</td>
<td></td>
<td>5.8 %</td>
<td>0.22 [0.06, 1.00]</td>
</tr>
<tr>
<td>Whalen 1997</td>
<td>7/536</td>
<td>2/1464</td>
<td></td>
<td>18.0 %</td>
<td>0.29 [0.12, 0.67]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>693</strong></td>
<td><strong>618</strong></td>
<td></td>
<td><strong>38.3 %</strong></td>
<td><strong>0.36 [0.22, 0.61]</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 18 (Treatment (N=H)), 46 (Control)</td>
<td>Heterogeneity: Chi² = 1.88, df = 3 (P = 0.69); I² = 0.0%</td>
<td>Test for overall effect: Z = 3.78 (P = 0.00015)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment (N=H)</th>
<th>Control (N=H)</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 PPO-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzgerald 2001</td>
<td>6/126</td>
<td>4/111</td>
<td></td>
<td>3.4 %</td>
<td>1.32 [0.38, 4.56]</td>
</tr>
<tr>
<td>Gordin 1997</td>
<td>4/260</td>
<td>6/257</td>
<td></td>
<td>4.8 %</td>
<td>0.66 [0.19, 2.31]</td>
</tr>
<tr>
<td>Hawken 1997</td>
<td>11/235</td>
<td>8/224</td>
<td></td>
<td>6.6 %</td>
<td>1.31 [0.54, 3.20]</td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>14/178</td>
<td>17/166</td>
<td></td>
<td>14.1 %</td>
<td>0.77 [0.39, 1.51]</td>
</tr>
<tr>
<td>Pape 1993</td>
<td>2/20</td>
<td>5/35</td>
<td></td>
<td>2.9 %</td>
<td>0.70 [0.16, 3.01]</td>
</tr>
<tr>
<td>Rivero 2003</td>
<td>3/83</td>
<td>4/77</td>
<td></td>
<td>3.3 %</td>
<td>0.70 [0.16, 3.01]</td>
</tr>
<tr>
<td>Whalen 1997-nergy</td>
<td>9/395</td>
<td>10/323</td>
<td></td>
<td>8.8 %</td>
<td>0.74 [0.30, 1.79]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1297</strong></td>
<td><strong>1193</strong></td>
<td></td>
<td><strong>43.9 %</strong></td>
<td><strong>0.86 [0.59, 1.26]</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 49 (Treatment (N=H)), 54 (Control)</td>
<td>Heterogeneity: Chi² = 1.87, df = 6 (P = 0.93); I² = 0.0%</td>
<td>Test for overall effect: Z = 0.76 (P = 0.45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 PPO unknown

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment (N=H)</th>
<th>Control (N=H)</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H/Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawken 1997</td>
<td>9/40</td>
<td>7/49</td>
<td></td>
<td>5.0 %</td>
<td>1.58 [0.64, 3.85]</td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>9/122</td>
<td>16/124</td>
<td></td>
<td>12.7 %</td>
<td>0.57 [0.26, 1.24]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>162</strong></td>
<td><strong>173</strong></td>
<td></td>
<td><strong>17.7 %</strong></td>
<td><strong>0.86 [0.48, 1.52]</strong></td>
</tr>
<tr>
<td></td>
<td>Total events: 18 (Treatment (N=H)), 23 (Control)</td>
<td>Heterogeneity: Chi² = 2.82, df = 1 (P = 0.09); I² = 65%</td>
<td>Test for overall effect: Z = 0.53 (P = 0.59)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overall (n=1995)
- 43% reduction in TB

TST positive
- 74% reduction in TB

TST negative
- No significant reduction in TB
- Unexplained increased mortality (21 vs 7 deaths after 5 months)
Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial


1329 patients starting ART/on ART randomised to 12 months IPT vs placebo

Figure 2: Time to tuberculosis from randomisation
The placebo group was given antiretroviral therapy plus placebo and the isoniazid group was given antiretroviral therapy plus isoniazid. Numbers show the number of participants followed up at each timepoint, and the numbers in parentheses show new tuberculosis cases in each period. Log-rank test p value for equality of survival curves = 0.02.

Lancet, 2014
TB SCREENING ALGORITHM FOR IPT IN ADOLESCENTS & ADULTS

HIV POSITIVE ADOLESCENTS/ADULTS

TB SYMPTOM SCREEN
Current cough, Fever, Loss of weight, drenching night sweats

- YES
  - INVESTIGATE FOR TB, as per national TB management guidelines. If patient has silicosis, a chest x-ray must be done
    - TB
      - Treat for TB
      - Assess for IPT eligibility after completion of TB treatment
    - NO TB
      - Review after 3 months
      - Assess for IPT eligibility after 3 months
  - NO
    - OTHER DIAGNOSIS
      - Give appropriate treatment
      - Assess for IPT eligibility after 3 months

- NO
  - ASSESS FOR CONTRAINDICATIONS TO IPT
    - Exclude excessive alcohol use, liver disease, peripheral neuropathy, and history of adverse reactions to INH
    - Contraindications Present
      - CONTRAINDICATIONS PRESENT
      - DEFER IPT
    - No Contraindications
      - Do TST
        - Read within 48-72 hours
        - TST negative
          - Pre ART
          - On ART
            - No IPT
            - IPT for 12 months
        - TST positive
          - IPT for 36 months

SCREEN FOR TB REGULARLY
At every consultation with the patient
Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Haileyesus Getahun¹*, Wanitchaya Kittikraisak², Charles M. Heilig³, Elizabeth L. Corbett⁴, Helen Ayles⁴,⁵, Kevin P. Cain³, Alison D. Grant⁴, Gavin J. Churchyard⁶, Michael Kimerling⁷, Sarita Shah⁸, Stephen D. Lawn⁴,⁹, Robin Wood⁹, Gary Maartens¹⁰, Reuben Granich¹, Anand A. Date³, Jay K. Varma²,³

The best performing rule was the presence of any one of:
• current cough (any duration)
• fever
• night sweats
• or weight loss

The overall sensitivity was 78.9% and specificity was 49.6%

Published 2011
OUTLINE

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• Cryptococcal antigen screening
• Return to care after ART interruption
• Reducing CD4 count monitoring
<table>
<thead>
<tr>
<th>Phase of HIV management</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Confirm HIV result with rapid antibody test if no test results are available</td>
<td>To confirm HIV-positive status in patients who present without documented proof of positive HIV status</td>
</tr>
<tr>
<td>WHO clinical staging if HIV-positive</td>
<td>To assess eligibility for ART and timing of initiation</td>
</tr>
<tr>
<td>CD4 count</td>
<td>To identify eligibility for ART (CD4 &lt;500/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for prioritisation (CD4 &lt;350/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for fast-tracking (CD4 &lt;200/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for Cotrimoxazole (CD4 &lt;200/μl)</td>
</tr>
<tr>
<td></td>
<td>To identify eligibility for CrAg or CLAT (CD4 &lt;100/μl)</td>
</tr>
<tr>
<td>Screen for pregnancy or ask if planning to conceive</td>
<td>To identify women who need ART for PMTCT and offer appropriate family planning</td>
</tr>
<tr>
<td>Assessment of hypertension and diabetes with blood pressure and urine glycosuria</td>
<td>To identify any concomitant chronic diseases</td>
</tr>
<tr>
<td>Screen for TB symptoms using the TB screening tool</td>
<td>To identify those suspected of TB and refer them for investigation and to assess eligibility for INH</td>
</tr>
<tr>
<td>Screen for HBV (HBsAg)</td>
<td>To identify those co-infected with HBV so that they can be initiated on ART regardless of CD4 count</td>
</tr>
<tr>
<td>Screening for STIs and syphilis</td>
<td>To identify and treat STIs</td>
</tr>
<tr>
<td>Weight and height in adolescent</td>
<td>To check if the weight is above or below 40kg to determine which ARV drugs to use</td>
</tr>
<tr>
<td>Cryptococcus Antigen (CrAg) test if CD4 &lt;100 cells/μl</td>
<td>To assess if there is disseminated Cryptococcal infection and if fluconazole treatment/prophylaxis is indicated</td>
</tr>
<tr>
<td>Do Hb or FBC if requires AZT</td>
<td>To detect anaemia or neutropenia</td>
</tr>
<tr>
<td>Creatinine if requires TDF</td>
<td>To assess renal sufficiency</td>
</tr>
<tr>
<td>ALT if requires NVP</td>
<td>To exclude liver dysfunction</td>
</tr>
<tr>
<td>Fasting cholesterol and triglycerides if requires LPV/r</td>
<td>To identify at risk of LPV/r related hyperlipidaemia. If above 6 mmol/L, consider (ATV/r) instead of LPV/r (if available)</td>
</tr>
</tbody>
</table>
In a Ugandan study: Antigenaemia preceded meningitis by median 22 days (>100 days in 11%)
Retrospective testing of plasma of 707 patients who started ART 2002-2005

336 with CD4 ≤ 100

42 CrAg + (13%)

21 no history of CM

6 (29%) developed CM on ART

21 history of CM

4 (19%) others died or lost to follow-up

Among those who were CrAg negative none developed CM
% of patients without prior CM who were CrAg +

Jarvis et al, Clin Infect Dis 2009;48:856
CrAg Lateral Flow Assay

1. Add 1 drop LF specimen diluent to tube
2. Add 40 µL patient specimen to tube
3. Insert strip as shown
4. Wait 10 minutes
5. Positive or negative

Source: Immy CrAg LFA package insert
Cryptococcal antigen screening when CD4+ T-lymphocyte count <100 cells/µl

**Initiate ART**
No fluconazole

**Lumbar puncture may be considered if available.**

**Special situations include:**
- Prior cryptococcal meningitis
- Pregnancy or breastfeeding mothers
- Clinical liver disease

*Symptomatic for meningitis if either of the following is present:
1. Headache
2. Confusion

*Symptomatic* for meningitis if either of the following is present:

- Contact patient for urgent follow-up
- Screen for symptoms of meningitis
- Check for special situations

**Asymptomatic**

Start fluconazole 1200 mg daily and refer immediately for lumbar puncture

Lumbar puncture (+)

Start **Amphotericin B plus fluconazole**
800 mg daily for 2 weeks *in hospital*

Lumbar puncture (-)

Start **Fluconazole 800 mg daily for 2 weeks as outpatient**

**Fluconazole 400 mg daily for 2 months then 200 mg daily**
Continue fluconazole for minimum of 1 year in total and discontinue when patient has had two CD4 counts >200 taken at least 6 months apart

Start **ART after 4-6 weeks of antifungal therapy**

Start **ART after 2 weeks of antifungal therapy**

No clinical trials data regarding pre-emptive treatment

SA HIV Clinicians Society 2013
Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial

Sayoki Mfinanga, Duncan Chanda, Sokonne L. Kivuyo, Lorna Guinness, Christian Bottomley, Victoria Simms, Carol Chijoka, Ayubu Masasi, Godfather Kimaro, Bernard Ngowi, Amos Kahwa, Peter Mwaba, Thomas S Harrison, Saidi Egwaga, Shabbar Jaffar, on behalf of the REMSTART trial team*

Lancet, published online March 10, 2015
28% reduction in mortality

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Clinic plus community support</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic plus community support</td>
<td>1001</td>
<td>998</td>
</tr>
<tr>
<td>Standard care</td>
<td>899</td>
<td>869</td>
</tr>
<tr>
<td></td>
<td>869</td>
<td>834</td>
</tr>
<tr>
<td></td>
<td>854</td>
<td>811</td>
</tr>
<tr>
<td></td>
<td>842</td>
<td>794</td>
</tr>
</tbody>
</table>
OUTLINE

• When to start ART
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• Cryptococcal antigen screening
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Return to care after 1\textsuperscript{st} line interruption

• Issues to consider
  – History of adherence prior to default episode
  – Viral load measure prior to default episode
  – CD4 nadir and current CD4
  – Current clinical status

• Individualised decision weighing up
  – Not wanting to unnecessarily switch to 2\textsuperscript{nd} line (less well tolerated)
  – Not wanting to restart patient on failing regimen if very immunosuppressed

• If restart first line (especially in patients with CD4 < 200)
  – Do viral load when restart then at 2-3 months, anticipate > 2 log drop if adherent and no resistance
  – Most will have VL < 1000 by 3 months
Return to care after interruption (1)

- We recommend restarting the same regimen if patients return to care after defaulting therapy.
- A VL should preferably be performed before restarting. We then recommend that the VL is measured 3 months after restarting ART; switching to a second-line regimen should be considered if the VL is not <1 000 copies/mL at this point.
- In patients with multiple episodes of interruption, particularly beyond the first year of ART, many clinicians would consider switching to a second-line regimen, making the assumption that the multiple interruptions resulted in first-line resistance.
- Reasons for defaulting should be addressed and adherence support increased.

SA HIV Clin Soc guidelines, 2014
Return to care after interruption (2)

- Hospitalisation with an AIDS-defining condition and a CD4+ count of <50 cells/μL represents another situation where a patient may be restarted immediately on second-line ART when returning to care after defaulting.

- The reason being that the patient is considered to be at high risk of mortality if restarted on a first-line therapy to which their virus may be resistant, and that they require a guaranteed effective ART regimen immediately.

- This decision should usually be taken by the clinicians at a hospital level.

SA HIV Clin Soc guidelines, 2014
6.6.9 Management of patients previously on ART

If a patient is referred in (e.g. from the private sector), and is still on ART and the regimen is successful (VL undetectable and no side-effects), where possible, the patient should be continued on the same regimen.

If the patient has interrupted treatment and was on a previous regimen as above, or where the prior regimen is unknown, take a full history to establish why the treatment was stopped. If the interruption was NOT due to toxicity or clear virological failure, check the VL and restart first line treatment as above, and repeat the VL after 2 months.

If patients have failed a previous regimen, initiate appropriate second line treatment.

If patient was previously on ART but has interrupted treatment, establish the cause of the interruption. If it is due to social or psychological factors, address these and follow up on interventions. If the patient stopped as a result of side effects, evaluate other drug choices and offer appropriate options. If the interruption was due to drug supply issues, and there were no non-adherence, resistance or toxicity issues, the previous ART regimen should be reinitiated as soon as possible.

NB: If NVP is restarted after an interruption of >1 week, re-commence with the 2 week lead-in dose and check the ALT if the patient becomes symptomatic.
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# Monitoring on ART

<table>
<thead>
<tr>
<th>On ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen for TB symptoms at each visit</td>
<td>To identify TB/HIV co-infected</td>
</tr>
<tr>
<td>WHO clinical staging at every visit</td>
<td>To identify new OIs</td>
</tr>
<tr>
<td>Ask about side effects at each visit</td>
<td>To identify ARV related toxicity</td>
</tr>
<tr>
<td>CD4 at 1 year on ART</td>
<td>To monitor immune response to ART</td>
</tr>
<tr>
<td>VL at month 6, month 12 on ART and then every 12 months</td>
<td>To identify treatment failures and problems with adherence</td>
</tr>
<tr>
<td>ALT if on NVP and develops rash or symptoms of hepatitis</td>
<td>To identify NVP toxicity</td>
</tr>
<tr>
<td>FBC at month 3 and 6 if on AZT and then every 12 months</td>
<td>To identify AZT toxicity</td>
</tr>
<tr>
<td>Creatinine at month 3 and 6, month 12, then every 12 months if on TDF</td>
<td>To identify TDF toxicity</td>
</tr>
<tr>
<td>Fasting cholesterol and triglycerides at month 3 if on LPV/r</td>
<td>To identify LPV/r toxicity</td>
</tr>
</tbody>
</table>

SA NDOH guidelines
The future role of CD4 cell count for monitoring antiretroviral therapy

Nathan Ford, Graeme Meintjes, Anton Pozniak, Helen Byrne, Andrew Hill, Trevor Peter, Mary-Ann Davies, Beatriz Grinsztejn, Alexandra Calmy, N Kumarasamy, Prapahn Phanuphak, Pierre deBeauparl, Marco Vitoria, Meg Doherty, Wendy Stevens, George K Siberry

For more than two decades, CD4 cell count measurements have been central to understanding HIV disease progression, making important clinical decisions, and monitoring the response to antiretroviral therapy (ART). In well resourced settings, the monitoring of patients on ART has been supported by routine virological monitoring. Viral load monitoring was recommended by WHO in 2013 guidelines as the preferred way to monitor people on ART, and efforts are underway to scale up access in resource-limited settings. Recent studies suggest that in situations where viral load is available and patients are virologically suppressed, long-term CD4 monitoring adds little value and stopping CD4 monitoring will have major cost savings. CD4 cell counts will continue to play an important part in initial decisions around ART initiation and clinical management, particularly for patients presenting late to care, and for treatment monitoring where viral load monitoring is restricted. However, in settings where both CD4 cell counts and viral load testing are routinely available, countries should consider reducing the frequency of CD4 cell counts or not doing routine CD4 monitoring for patients who are stable on ART.
Consideration for Genotype & 3\textsuperscript{rd} line

- Repeated VL > 1000 on 2\textsuperscript{nd} line ART
- On 2\textsuperscript{nd} line > 1 year
- Of those with virological failure on 2\textsuperscript{nd} line majority do not have resistance*
- Critical to ensure adherence
  - Pharmacy claims records for the last 6 months is objective method (specific but not sensitive)
- Adherence counseling and address side effects
- Ask re previous exposure to rifampicin without lopinavir/ritonavir dose adjustment

*Van Zyl, PLoSONE 2013; Wallis, AIDS Res and Treatment 2011
HIV RNA >1000 copies/ml on second-line ART for longer than one year

Check for adherence, compliance, tolerability and drug-drug interaction and assess psychological issues

Repeat VL after 6 months

VL ≤1000 copies/ml
- Continue second-line regimen

VL >1000 copies/ml
- Specialist referral as needed
  - Genotypic resistance testing
  - Specialist decision regarding further management
Third line options

• NRTIs with best resistance profile
• New generation NNRTIs
  – Etravirine (and rilpivirine)
  – NNRTI genotype unreliable at 2nd line failure
• Ritonavir-boosted darunavir
• Raltegravir

• Maraviroc (cost+++; only if purely CCR5 tropic)
• Dolutegravir (to be registered later this year)
HIVdb Program: Mutation List Analysis

Protease, RT, and integrase mutations can be entered using either the text box or pull down menus (detailed usage is found below).

The output can then be customized to display mutation comments, mutation scores, and an optional identifier and date. For further explanations and sample datasets please see the Release Notes.

### Reverse Transcriptase

<table>
<thead>
<tr>
<th>Enter Mutation List:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

OR

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>41  44  62  65  67  69  70  74</td>
</tr>
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<td>75  77  90  98  100  101  103  106</td>
</tr>
<tr>
<td>108 115 116 118 138 151 179 181</td>
</tr>
<tr>
<td>184 188 190 210 215 219 221 225</td>
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<tr>
<td>227 230 234 236 238 318 333 348</td>
</tr>
</tbody>
</table>

### Protease

http://hivdb.stanford.edu/
## Mutation Scoring

<table>
<thead>
<tr>
<th>PR</th>
<th>ATV/r</th>
<th>DRV/r</th>
<th>FPV/r</th>
<th>IDV/r</th>
<th>LPV/r</th>
<th>NFV</th>
<th>SQV/r</th>
<th>TPV/r</th>
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<tr>
<td>I54V+V82A</td>
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<td>V82A+M46I</td>
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</table>

## RT 3TC ABC AZT D4T DDI FTC TDF EFV ETR NVP RPV

<table>
<thead>
<tr>
<th>RT</th>
<th>3TC</th>
<th>ABC</th>
<th>AZT</th>
<th>D4T</th>
<th>DDI</th>
<th>FTC</th>
<th>TDF</th>
<th>EFV</th>
<th>ETR</th>
<th>NVP</th>
<th>RPV</th>
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</tr>
<tr>
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<td>-</td>
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<td>10</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>

| F227L  | -   | -   | -   | -   | -   | 15  | 0   | 30  | 0   | -   | -   |
| D67N+K70R+K219Q | 10 | 10 | 10 | 10 | 10 | 10 | - | - | - | - | - |
| Total: | 70 | 45 | 60 | 50 | 70 | 70 | 20 | 25 | 10 | 60 | 15 |
MUTATION SCORING

Mutation scoring

The mutation penalty score for an antiretroviral drug is obtained by adding together the scores of each mutation associated with resistance to that drug. The scores are titrated to fall within the following ranges:

- 0-9: Drug susceptible
- 10-14: Potential low level resistance
- 15-29: Low level resistance
- 30-59: Intermediate resistance
- >60: High level resistance
**Drug Resistance Interpretation: RT**

<table>
<thead>
<tr>
<th>NRTI Resistance Mutations:</th>
<th>M41L, K70R, Q151M</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI Resistance Mutations:</td>
<td>None</td>
</tr>
<tr>
<td>Other Mutations:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nucleoside RTI</th>
<th>Non-Nucleoside RTI</th>
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</thead>
<tbody>
<tr>
<td>lamivudine (3TC)</td>
<td>Low-level resistance</td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td>Intermediate resistance</td>
</tr>
<tr>
<td>zidovudine (AZT)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>stavudine (D4T)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>didanosine (DDI)</td>
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</tr>
<tr>
<td>emtricitabine (FTC)</td>
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<tr>
<td>tenofovir (TDF)</td>
<td>Intermediate resistance</td>
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<tr>
<td>delavirdine (DLV)</td>
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</tr>
<tr>
<td>efavirenz (EFV)</td>
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</tr>
<tr>
<td>etravirine (ETR)</td>
<td>Susceptible</td>
</tr>
<tr>
<td>nevirapine (NVP)</td>
<td>Susceptible</td>
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</table>

**RT Comments**

- M41L usually occurs with T215Y. Together these mutations confer intermediate-to-high level resistance to AZT and d4T and a lower level of resistance to ddl, ABC, and TDF.
- K70R causes low-level AZT, d4T, and possibly TDF resistance.
- By itself, Q151M causes intermediate-to-high level resistance to AZT, ddl, d4T, and ABC; and low-level resistance to TDF. With changes at the associated positions 75, 77, and 116, Q151M confers high-level resistance to AZT, ddl, d4T, and ABC; intermediate resistance to TDF, and low-level resistance to 3TC and FTC.
CASE 1: GT while failing 2\textsuperscript{nd} line

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>M184V</td>
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<tr>
<td>NNRTIs</td>
<td>K103N</td>
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<tr>
<td>PIs</td>
<td>Mo major mutations</td>
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- Explanation?
- Management?
CASE 2: GT while failing 2\textsuperscript{nd} line

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutations</th>
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<tbody>
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<td>NRTI</td>
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</tr>
<tr>
<td>NNRTI</td>
<td>A98G, F227L</td>
</tr>
<tr>
<td>PI</td>
<td>M46I, I54V, L76V, V82A, L10IV, Q85E, A71I</td>
</tr>
</tbody>
</table>
### Mutation Scoring

<table>
<thead>
<tr>
<th>PR</th>
<th>ATV/r</th>
<th>DRV/r</th>
<th>FPV/r</th>
<th>IDV/r</th>
<th>LPV/r</th>
<th>NFV</th>
<th>SQV/r</th>
<th>TPV/r</th>
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<tr>
<td>M46I</td>
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</tbody>
</table>

L76V+M46I | - | - | 10 | 10 | 10 | - | - |
I54V+V82A | 10 | - | 10 | 10 | 10 | 10 | - |
V82A+M46I | 10 | - | 10 | 10 | 10 | - | - |

**Total:**

<table>
<thead>
<tr>
<th>RT</th>
<th>3TC</th>
<th>ABC</th>
<th>AZT</th>
<th>D4T</th>
<th>DDI</th>
<th>FTC</th>
<th>TDF</th>
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<th>NVP</th>
<th>RPV</th>
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D67N+K70R+K219Q | 10 | 10 | 10 | 10 | 10 | 10 | - | - | - | - | - |

**Total:**

<table>
<thead>
<tr>
<th>RT</th>
<th>3TC</th>
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<td>20</td>
<td>25</td>
<td>10</td>
<td>60</td>
<td>15</td>
</tr>
</tbody>
</table>
Management

• 3\textsuperscript{rd} line:
  – TDF/FTC + Raltegravir + Darunavir/ritonavir

• Follow-up viral loads:
  – Less than 40 for over 2 years
Efficacy of third line ART in Africa: outcomes on ART salvage regimens in the Southern African private sector

Liezl Dunn¹, Marla Coetsee¹, Michael Hislop¹, Leon Regensberg¹, Gary Maartens¹,², Graeme Meintjes¹,²

¹Aid for AIDS
²University of Cape Town

7th EDCTP Forum, Berlin, 1 July 2014
Resistance patterns

185 resistance tests in 152 patients
111/113 were subtype C

<table>
<thead>
<tr>
<th>Mutations</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>1-2 TAMs</td>
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<td>23%</td>
</tr>
<tr>
<td>≥ 3 TAMs</td>
<td>72</td>
<td>47%</td>
</tr>
<tr>
<td>No major PI mutations</td>
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<tr>
<td>1-2 major PI mutations</td>
<td>38</td>
<td>25%</td>
</tr>
<tr>
<td>≥ 3 major PI mutations</td>
<td>114</td>
<td>75%</td>
</tr>
</tbody>
</table>

TAMs = Thymidine analogue mutations
Virological suppression

145 (95.4%) of 152 had at least one viral load performed on salvage ART

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% of those who had VL performed (n=145)</th>
<th>% of whole cohort (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppressed &lt; 400</td>
<td>126</td>
<td>86.9%</td>
<td>82.9%</td>
</tr>
<tr>
<td>Suppressed &lt; 50</td>
<td>108</td>
<td>74.5%</td>
<td>71.1%</td>
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</table>
CD4 count recovery on salvage ART (median and IQR)

Medians: 153, 307, 365, 448

CD4 count

Time on salvage ART (with +/- 3 month windows)
Cumulative survival by KM estimate = 87.2%
(95%CI = 79.8 – 92.0)

Vital status available for all patients on administrative censor date (30 April 2014)