Adult Guidelines

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Rustenburg | 23rd June 2017 | Molokwane Lodge
Outline of talk

• Guidelines local versus International

• TEMPRANO Trial

• START Trial

• HPTN 052

• HIV Clinicians Society Guidelines -2017

• Isoniazid Preventative Therapy

• Conclusion
Snapshot of the epidemic

**People living with HIV on antiretroviral therapy**

<table>
<thead>
<tr>
<th>Year</th>
<th>2000</th>
<th>2015</th>
<th>2020 target</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 million</td>
<td>17 million</td>
<td>30 million</td>
<td></td>
</tr>
</tbody>
</table>

**New HIV infections**

<table>
<thead>
<tr>
<th>Year</th>
<th>2000</th>
<th>2015</th>
<th>2020 target</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2 million</td>
<td>2.1 million</td>
<td>&lt;0.5 million</td>
<td></td>
</tr>
</tbody>
</table>

**New HIV infections among children**

<table>
<thead>
<tr>
<th>Year</th>
<th>2000</th>
<th>2015</th>
<th>&lt;50 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>490 000</td>
<td>150 000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**AIDS-related deaths**

<table>
<thead>
<tr>
<th>Year</th>
<th>2000</th>
<th>2015</th>
<th>&lt;0.5 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 million</td>
<td>1.1 million</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UNAIDS, 2016
People living with HIV by country

- 18% South Africa
- 9% Nigeria
- 6% India
- 5% Kenya
- 4% Mozambique
- 4% Uganda
- 4% United Republic of Tanzania
- 3% Zambia
- 3% Malawi
- 2% China
- 2% Ethiopia
- 2% Russian Federation
- 2% Brazil
- 4% United States
- 27% Remaining countries

UNAIDS, 2014
Decline in HIV incidence and mortality over time

Source: UNAIDS/WHO estimates.
Trends in AIDS-related deaths in SSA: 2005 versus 2013

UNAIDS, 2014
Improvements are needed at each stage of the cascade of HIV testing and treatment services, 2015

Source: UNAIDS/WHO estimates.
UNAIDS 90–90–90 Target by 2020

Global HIV treatment cascades from 13 countries/regions: Switzerland, Australia, UK, Denmark, Netherlands, France, Brazil, Canada (BC), USA, Sub-Saharan Africa, Georgia, Estonia, Russia

- No country or region analysed so far met the UNAIDS 90–90–90 coverage target of 73% of HIV+ patients achieving undetectable HIV RNA
South Africa

• 6.4 million South Africans are HIV-infected

• 2.6 million have started ART

• Estimated ART coverage 42%
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• Conclusion
Southern African HIV Clinicians Society adult antiretroviral therapy guidelines: Update on when to initiate antiretroviral therapy

**Adult antiretroviral therapy guidelines 2014**

### Table 3. Indications for ART*

<table>
<thead>
<tr>
<th>Clinical diagnosis (irrespective of CD4⁺ count)</th>
<th>ART recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO clinical stage 3 and 4*</td>
<td>ART recommended</td>
</tr>
<tr>
<td><strong>Other severe HIV-related disorders, e.g.⁵</strong></td>
<td>ART recommended</td>
</tr>
<tr>
<td>• immune thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>• thrombotic thrombocytopenic purpura</td>
<td></td>
</tr>
<tr>
<td>• polymyositis</td>
<td></td>
</tr>
<tr>
<td>• lymphocytic interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td><strong>Non HIV-related disorders⁵</strong></td>
<td>ART recommended</td>
</tr>
<tr>
<td>• malignancies (excluding localised malignancies)</td>
<td></td>
</tr>
<tr>
<td>• hepatitis B co-infection⁴</td>
<td></td>
</tr>
<tr>
<td>• hepatitis C co-infection</td>
<td></td>
</tr>
<tr>
<td><strong>Any condition requiring long-term immunosuppressive therapy</strong></td>
<td>ART recommended</td>
</tr>
</tbody>
</table>

### CD4⁺ counts

<table>
<thead>
<tr>
<th>CD4⁺ counts</th>
<th>ART recommended</th>
<th>ART recommended if patient is ready and motivated to start</th>
<th>Defer ART</th>
<th>Offer ART and discuss safe sex (discussion should ideally involve all partners)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350 cells/μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 - 500 cells/μL (two counts in this range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;500 cells/μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HIV-infected partner in serodiscordant relationship

Regardless of CD4⁺ count or clinical diagnoses
Southern African HIV Clinicians Society adult antiretroviral therapy guidelines: Update on when to initiate antiretroviral therapy

Adult antiretroviral therapy guidelines 2015

We recommend initiation of lifelong ART for all patients diagnosed with HIV infection. The CD4 count and clinical stage of the patient should no longer be a consideration in the decision to start ART.

For patients who are asymptomatic with CD4 > 350 cells/μL, additional time (weeks to a few months) can be spent counselling and preparing the patient for lifelong ART with good adherence before starting. In those with CD4 < 350 cells/μL (and especially < 200 cells/μL), or with clinical indication for starting, there should not be undue delay.

Within ART programmes, it is important to factor in that the absolute benefit of ART is much greater at lower CD4 counts (there is a mortality benefit at CD4 < 350 cells/μL. Therefore, planners and clinicians should prioritise and fast-track those with low CD4 counts (especially < 200 cells/μL); this is particularly relevant where there are ART shortages or anticipated stock-outs.
South African Department of Health

6.6.4 When to start: ART eligibility in late adolescents ≥15 years and adults living with HIV

Box 19: ART eligibility criteria

Eligible to start ART

CD4 count ≤500 cells/µl irrespective of clinical stage

(Prioritise those with CD4 ≤350 cells/µl)

OR

Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count

OR

Irrespective of CD4 count or clinical stage:

» Active TB disease (including drug-resistant and EPTB)

» Pregnant and breastfeeding women who are HIV-positive

» Known hepatitis B viral (HBV) co-infection

» Prioritise those with CD4 ≤350 cells/µl or advanced HIV disease
South African Department of Health (NDoH)

Eligibility Criteria for UTT:
- All HIV Positive children, adolescents and adults regardless of CD4 count will be offered ART treatment, prioritizing those with CD4 ≤ 350.
- Patients in the Pre-ART and Wellness programme shall be considered for UTT
- Willingness and readiness to start ART shall be assessed and patients who are not ready after assessment shall be kept in the wellness programme and continuous counseling
- **Baseline monitoring of CD4 count will still be done** as it is the key factor in determining the need to initiate Opportunistic Infection prophylaxis at CD4 ≤200, identify eligibility for CrAg at CD4 ≤100, prioritization at CD4 ≤350 and fast tracking at CD4 ≤200.

Timing of ART initiation:
ART should be started as soon as the patient is ready and within 2 weeks of CD4 count being Done

Immediate priority:
All HIV-positive pregnant or breastfeeding women, with no active TB or contraindication to FDC

Fast track initiation:
HIV stage 4
Patients with CD4 ≤200

6 Sept 2016
2014 Recommendations of the International IAS-USA-Society

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinicians should provide education about personal health benefits of ART and public benefits of prevention of transmission, and assess patients’ readiness to initiate and adhere to long-term ART. <strong>Rating: AIII</strong></td>
</tr>
<tr>
<td>• ART should be offered upon detection of HIV infection. <strong>Rating: A1a</strong></td>
</tr>
<tr>
<td>• Strategies for adherence support should be implemented and tailored to individual patient needs or the setting. <strong>Rating: A1a</strong></td>
</tr>
<tr>
<td>• Clinicians should be alert to the nonspecific presentation of acute HIV infection and urgently pursue specific diagnostic testing (plasma HIV viral load) if suspected. <strong>Rating: A1a</strong></td>
</tr>
</tbody>
</table>

Marrazzo et al, *JAMA*, 2014
<table>
<thead>
<tr>
<th>Target population</th>
<th>Specific recommendation</th>
<th>Strength of the recommendation</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥19 years)</td>
<td>ART should be initiated in all adults living with HIV at any CD4 cell count</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm³</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pregnant and breastfeeding women</td>
<td>ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Assessing HIV+ Person’s Readiness to start

- Pre-Contemplation: “I don’t need it, I feel good.”
- Contemplation: “I am weighing things.... and feel torn...”
- Preparation: “I want to start...”
- Action: “I will start now”

Recommendations for initiation of ART

ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts

EACS Guidelines 2017 version 8.2
Adoption of the "treat all" recommendation among adults and adolescents living with HIV, October 2016
Outline of talk

• Guidelines local versus International
• TEMPRANO Trial
• START Trial
• HPTN 052
• HIV Clinicians Society Guidelines- 2017
• Isoniazid Preventative Therapy (IPT)
• Conclusion
A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

July 20, 2015.
• Study Site
  • Ivory Coast

• Trial design
  • Unblinded, multicenter, individual-randomized controlled 2-by-2 factorial trial.

• HIV positive with CD4 count < 800 cells/mm³

• participants randomized to one of four groups
  • Deferred ART
  • Deferred ART plus IPT
  • Early ART
  • Early ART plus IPT
A Primary Outcome

All Patients

30-Mo Probability
14.1%
8.8%
7.4%
5.7%

Cumulative Probability of Death or Severe HIV-Related Illness (%)

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred ART</td>
<td>511</td>
<td>473</td>
<td>448</td>
<td>418</td>
<td>400</td>
<td>366</td>
</tr>
<tr>
<td>Deferred ART+IPT</td>
<td>512</td>
<td>489</td>
<td>473</td>
<td>459</td>
<td>440</td>
<td>419</td>
</tr>
<tr>
<td>Early ART</td>
<td>515</td>
<td>481</td>
<td>463</td>
<td>452</td>
<td>432</td>
<td>403</td>
</tr>
<tr>
<td>Early ART+IPT</td>
<td>518</td>
<td>501</td>
<td>478</td>
<td>459</td>
<td>445</td>
<td>418</td>
</tr>
</tbody>
</table>
A Primary Outcome

Patients with Baseline CD4+ Count <500/mm³

30-Mo Probability

- Deferred ART: 15.2%
- Deferred ART+IPT: 9.7%
- Early ART: 7.8%
- Early ART+IPT: 6.5%

Cumulative Probability of Death or Severe HIV-Related Illness (%)

Months since Randomization
A Primary Outcome

Patients with Baseline CD4+ Count ≥500/mm³

30-Mo Probability

- Deferred ART: 12.4%
- Deferred ART+IPT: 7.4%
- Early ART: 6.9%
- Early ART+IPT: 4.6%

Cumulative Probability of Death or Severe HIV-Related Illness (%)

Months since Randomization
Outline of talk

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Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*
• Multicontinental randomized trial
  • 215 sites in 35 countries

• Study participants
  • HIV positive > 18 years
  • Not yet initiated on ART with no history of AIDS
  • CD4+ counts >500 cells/mm³
  • Pregnant and breast feeding women not eligible

• Randomized to
  • Immediate ART or
  • Deferred initiation until the CD4+ count declined to 350 cells/mm³
A Time to First Primary Event

- Deferred initiation
- Immediate initiation
Death from Any Cause

- Immediate initiation
- Deferred initiation

Patients (%) vs. Month
<table>
<thead>
<tr>
<th>Trial</th>
<th>TEMPRANO</th>
<th>START</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td>Côte d’Ivoire</td>
<td>35 countries (21% of participants enrolled in Africa)</td>
</tr>
<tr>
<td>Number of participants</td>
<td>2056</td>
<td>4685</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>≥ 18 years old, HIV-1 (or dual HIV-1 and 2), CD4 &lt; 300, Not meeting WHO criteria for starting ART at the time (these criteria changed during the course of the trial)</td>
<td>≥ 18 years old, ART naive, No history of AIDS, General good health</td>
</tr>
<tr>
<td>Comparison arms</td>
<td>Immediate ART, ART deferred until WHO criteria for starting ART met (these criteria changed over the course of the trial)</td>
<td>Immediate ART, ART deferred until CD4 &lt; 350, AIDS diagnosis or other indication for ART (e.g. pregnancy)</td>
</tr>
<tr>
<td>Composite primary endpoint</td>
<td>AIDS, non-AIDS cancer, non-AIDS invasive bacterial disease or death</td>
<td>Serious AIDS-related event, serious non-AIDS-related event or death</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>30 months for each participant</td>
<td>Mean 3.0 years (trial stopped early by DSMB)</td>
</tr>
<tr>
<td>Number of primary events</td>
<td>Immediate arm: 64, Deferred arm: 111</td>
<td>Immediate arm: 42, Deferred arm: 96</td>
</tr>
<tr>
<td>Primary endpoint finding</td>
<td>44% reduction with immediate ART (aHR = 0.56, 95% CI = 0.41–0.76)</td>
<td>57% reduction with immediate ART (HR = 0.43, 95% CI = 0.30–0.62)</td>
</tr>
<tr>
<td>Among patients with baseline CD4 &gt; 350, there was also a 44% in primary endpoint (aHR = 0.56, 95% CI = 0.36–0.84)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Main contributors to finding</td>
<td>Reduction in AIDS events (50%, mainly TB [30%]) and invasive bacterial disease (61%)</td>
<td>Reduction in AIDS events (72%, including TB [71%]), serious non-AIDS events (29%), cancers (64%) and bacterial infections (62%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>Immediate arm: 21, Deferred arm: 26, Not significant: aHR = 0.60, 95% CI = 0.36–1.09</td>
<td>Immediate arm: 12, Deferred arm: 21, Not significant: p = 0.13</td>
</tr>
<tr>
<td>Viral load suppression</td>
<td>Viral load &lt; 100 at 12 months on ART</td>
<td>Viral load &lt; 200 at 12 months on ART</td>
</tr>
<tr>
<td>Immediate arm: 84%, Deferred arm: 80%</td>
<td>Immediate arm: 98%, Deferred arm: 97%</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Overall, the 30-month probability of a Grade 3 or 4 AE did not differ between arms although it was 2.6 times higher in the Immediate ART arm for the first 6 months</td>
<td>No difference between arms in terms of grade 4 events and hospitalisations for reasons other than AIDS</td>
</tr>
</tbody>
</table>

Note: In the TEMPRANO trial, there was a separate randomisation of participants to 6 months isoniazid preventive therapy (IPT) versus no IPT. WHO, World Health Organization; DSMB, Data and Safety Monitoring Board; aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; AE, adverse event.
Outline of talk

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• Conclusion
HPTN 052

• Worldwide multicentre randomized controlled trial
  • Early versus delayed ART
  • HIV infected adults with CD4 counts of 350-550 cells/mm$^3$
• 93% reduction in HIV transmission to sexual partner
• Delayed time to AIDS events with early treatment
Summary

HPTN 052

START

TEMPRANO

ART recommended irrespective of CD4+ count (CD4+ Count no longer a gatekeeper to ART)
Outline of talk

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• Conclusion
# First Line Regimens

Initial ART Regimens for the previously untreated patient

<table>
<thead>
<tr>
<th>The preferred First-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC (or 3TC)</td>
</tr>
<tr>
<td>plus</td>
</tr>
<tr>
<td>tenofovir</td>
</tr>
<tr>
<td>plus</td>
</tr>
<tr>
<td>dolutegravir OR efavirenz OR rilpivirine</td>
</tr>
</tbody>
</table>

Rilpivirine cannot be used with rifampicin & dolutegravir requires dose adjustment with rifampicin
Baseline resistance test

• Only recommend baseline resistance test for following situations
  • Pre-exposure prophylaxis (PrEP)- in last 6 months
  • History of sexual exposure to a person with known drug resistant HIV or who is known to have failed an ART regimen
Starting ART at the first clinic visit

• Several studies have demonstrated that it is possible to initiate ART safely on the same day as HIV diagnosis or receipt of CD4 count result.
  • These studies have demonstrated less overall loss to follow-up when ART is initiated immediately in selected patients.

• Now that treatment is recommended irrespective of CD4 count this same-day strategy should be considered as a means to improve retention in care.
Starting ART at the first clinic visit

• The patient should be motivated to start immediately.
• Same day initiation is not an adherence support “short cut”; ongoing support can occur in the days and weeks immediately after initiation.
• Patients starting TDF (which are the majority) should be contactable in the event of a creatinine clearance < 50ml/min, and told to return to the clinic immediately.
• Screen for cryptococcal meningitis with CrAg if CD4<100 cells/μL. The patient should be the contactable in the event of a positive CrAg, and advised to return to the clinic immediately.
• Patients with TB symptoms (cough, night sweats, fever, recent weight loss) should first be investigated for TB before ART initiation.
Commencing ART in patients with TB or OIs

- **CM and TBM**
  - Start 4-6 weeks

- **PCP and other OIs**
  - Start within 2 weeks

- **TB if CD4 < 50**
  - Start within 2 weeks

- **TB if CD4 > 50**
  - Start 2-8 weeks
  - IRIS risk and operational issues
When should you check a viral load?

<table>
<thead>
<tr>
<th></th>
<th>SA Dept. Health</th>
<th>SA HIV Clin. Soc.</th>
<th>DHHS (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At initiation</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Before 6 months</td>
<td>×</td>
<td>3 months</td>
<td>At 2-8 weeks, then every 4-8 weeks until suppressed</td>
</tr>
<tr>
<td>6 months</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>12 months</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Thereafter</td>
<td>Every 12 months</td>
<td>Every 6 (-12) months</td>
<td>Every 3-6 months</td>
</tr>
</tbody>
</table>

**Why check viral loads before 6 months?**

- Enables early detection of virological failure (usually due to poor adherence), before resistance develops, or worsens.
- At 3 months, most patients will be virally suppressed, but a small group of people who started with a very high viral load may still have detectable viraemia... although they’ll still show at least a $2 \log_{10}$ drop from their initiation viral loads.
When should you check a CD4 count?

• At baseline
  • Why? Allows for identification of patients at risk of OIs (and hence who will benefit from Bactrim prophylaxis, etc.)

• Every 6 months until CD4 > 200

• Can stop checking CD4 if > 200, provided that viral load is suppressed and remains suppressed
**Second-line regimens**

Recommend a regimen of 2 NRTIs and a ritonavir (RTV) - boosted (/r) PI

The preferred PI in Second-line regimens

Atazanavir (ATV) 300 mg / RTV 100mg daily

OR

Lopinavir (LPV)/r BD

NRTI combinations advised for second-line regimens:

<table>
<thead>
<tr>
<th>NRTI Combination</th>
<th>First-line Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + 3TC</td>
<td>(if TDF- or ABC-based first line)</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>TDF + 3TC</td>
<td>(if AZT- or d4T-based first line)</td>
</tr>
</tbody>
</table>

Drawbacks of ATV:
- cannot be used with rifampicin- based TB therapy
- Important drug interactions with drugs that reduce stomach acidity such as proton pump inhibitors
<table>
<thead>
<tr>
<th>First-line NRTIs used</th>
<th>Second-line NRTI combination advised</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT + 3TC</td>
<td>TDF + 3TC*</td>
</tr>
<tr>
<td>d4T + 3TC</td>
<td>TDF + 3TC*</td>
</tr>
<tr>
<td>TDF + 3TC*</td>
<td>AZT + 3TC</td>
</tr>
<tr>
<td>ABC + 3TC</td>
<td>AZT + 3TC</td>
</tr>
</tbody>
</table>

*3TC is interchangeable with FTC.
TB co-infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in concentration</th>
<th>Dose with RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions</td>
<td>Normal dose</td>
</tr>
<tr>
<td>EFV</td>
<td>Mild reduction</td>
<td>Normal dose</td>
</tr>
<tr>
<td>NVP</td>
<td>Moderate reduction</td>
<td>Omit lead-in dose phase (start at 200 mg 12-hourly)</td>
</tr>
<tr>
<td>ETV/RPV</td>
<td>Marked reduction</td>
<td>Don’t use with RIF</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Significant reduction</td>
<td>Double LPV/r dose (risk of hepatotoxicity)</td>
</tr>
<tr>
<td>Other PIs</td>
<td>Marked reduction</td>
<td>Don’t use with RIF</td>
</tr>
<tr>
<td>RAL</td>
<td>Reduction, but significance unclear</td>
<td>? Double dose (800 mg 12-hourly) ? Standard dose (400 mg 12-hourly)</td>
</tr>
</tbody>
</table>
## Dosing of ART drugs and rifabutin when prescribed concomitantly

<table>
<thead>
<tr>
<th>ART drug</th>
<th>ART dosage</th>
<th>Rifabutin dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>No change</td>
<td>Increase to 450 mg/day</td>
</tr>
<tr>
<td>NVP</td>
<td>No change</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>ATV or RTV-boosted PIs</td>
<td>No change</td>
<td>Decrease to 150 mg/day (monitor ALT, neutrophils and visual symptoms at least monthly)</td>
</tr>
</tbody>
</table>
Third-line ART Regimens

• Indicated for patients with documented PI resistance
• Requires resistance testing before regimen chosen
• Must have been on PI-based second line regimen for longer than 1 year
• Criteria for resistance testing on second-line ART
  • 2 or 3 VL > 1000 copies/mL in 6 month period
  • Exception- error of not double dosing of LPV/r with rifampicin
VL >1000 copies/mL on PI-based ART > 1 year

Adherence; compliance; tolerability; drug interactions; psychological issues

Repeat VL after 6 months

VL ≤ 1000 copies/mL
Continue second-line

VL > 1000 copies/mL
Specialist referral

GENOTYPE

Specialist decision further management
### Drugs available for third-line ART

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Darunavir (DRV)</td>
</tr>
<tr>
<td>InSTI</td>
<td>Dolutegravir (DTG)</td>
</tr>
<tr>
<td>InSTI</td>
<td>Raltegravir (RAL)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Etravirine (ETR)</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine (RPV)</td>
</tr>
<tr>
<td>CCR5 blocker</td>
<td>Maraviroc (MVC)</td>
</tr>
</tbody>
</table>

*First-generation NNRTIs (NVP & EFV) have no place in third-line therapy as they do not impair viral fitness*
Eligible for third line ART?
PI score ≥ 15

- DRV/r
  - PLUS
  - 3TC/FTC
  - PLUS
  - AZT/TDF (lowest score)

- TDF/AZT 30-59 OR
  - DRV ≥ 15

- Add DTG

- TDF/AZT > 29 AND DRV ≥ 15 AND ETR ≤ 29

- Add ETR
Outline of talk

• Guidelines local versus International
• TEMPRANO Trial
• START Trial
• HPTN 052
• HIV Clinicians Society Guidelines- 2017
• Isoniazid Preventative Therapy (IPT)
• Conclusion
Isoniazid Preventive Therapy (IPT)

- TEMPRANO: separate randomisation to 6 months of IPT
  - addition of IPT to ART- provided added protection against active TB disease
  - Benefit to patients with relatively high CD4 counts

- Khayelitsha study- placebo-controlled
  - 12 months of IPT to patients on ART
  - reduced TB incidence by 37%
**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.

*This would only apply in the case of a patient wishing to defer ART initiation.*
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Conclusion

• CD4$^+$ count no longer a barrier to ART initiation
• Earlier ART benefits all HIV-infected individuals
  • reduces risk of disease progression
  • prevents HIV transmission
• Benefits to early ART in developing countries
  • reduce TB rates
• IPT for all patients on ART