Adult Guidelines

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University of Cape Town
Groote Schuur Hospital

eMalahleni, Saturday 18th November 2017
Outline of talk

• Guidelines local versus International
• TEMPRANO Trial
• START Trial
• HPTN 052
• HIV Clinicians Society Guidelines -2017
• Isoniazid Preventative Therapy
• Conclusion
Global Scale of Problem

- 36.7 million people living with HIV
- 51% of people with HIV know their status
  - HIV testing reached its limit
- 18.2 million people receiving ART
- WHO targets to end HIV pandemic
  - New guidelines to increase ART coverage
  - New set targets for 2020 & 90-90-90 strategy
  - End AIDS epidemic by 2030
Decline in HIV incidence and mortality over time

Source: UNAIDS/WHO estimates.
Improvements are needed at each stage of the cascade of HIV testing and treatment services, 2015

Source: UNAIDS/WHO estimates.
Adoption of the "treat all" recommendation among adults and adolescents living with HIV, October 2016
South Africa

- 6.4 million South Africans are HIV-infected
- 2.6 million have started ART
- Estimated ART coverage 42%
Outline of talk

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### 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></td>
</tr>
<tr>
<td>Other severe HIV-related disorders, e.g.</td>
<td></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>Non HIV-related disorders*</td>
<td>ART recommended</td>
</tr>
<tr>
<td>• malignancies (excluding localised malignancies)</td>
<td></td>
</tr>
<tr>
<td>• hepatitis B co-infection*</td>
<td></td>
</tr>
<tr>
<td>• hepatitis C co-infection</td>
<td></td>
</tr>
<tr>
<td>Any condition requiring long-term</td>
<td>ART recommended</td>
</tr>
<tr>
<td>immunosuppressive therapy</td>
<td></td>
</tr>
</tbody>
</table>

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

*Regardless of CD4+ count or clinical diagnoses

**Notes:**
* ART = Antiretroviral Therapy
* CD4+ = CD4-positive T lymphocytes
* WHO = World Health Organization
* ART recommended
* ART recommended if patient is ready and motivated to start
* Defer ART
* Offer ART and discuss safe sex (discussion should ideally involve all partners)
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.
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
### 2014 Recommendations of the International IAS-USA-Society

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Rating</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.</td>
<td>AIII</td>
</tr>
<tr>
<td>ART should be offered upon detection of HIV infection.</td>
<td>A1a</td>
</tr>
<tr>
<td>Strategies for adherence support should be implemented and tailored to individual patient needs or the setting.</td>
<td>Ali</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.</td>
<td>All a</td>
</tr>
</tbody>
</table>

Marrazzo et al, *JAMA*, 2014
## Recommendation 1: When to start ART among people living with HIV

<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 a (&gt;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>
Outline of talk

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TEMPRANO Trial

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*
• Study Site  
  • Ivory Coast  

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

• HIV positive with CD4 count < 800 cells/mm$^3$  

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

![Graph showing cumulative probability of death or severe HIV-related illness over months since randomization for different ART strategies.](image)

<table>
<thead>
<tr>
<th>No. at Risk</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>512</td>
<td>515</td>
<td>518</td>
<td>518</td>
<td>518</td>
</tr>
<tr>
<td>Deferred ART + IPT</td>
<td>473</td>
<td>489</td>
<td>481</td>
<td>501</td>
<td>501</td>
<td>501</td>
</tr>
<tr>
<td>Early ART</td>
<td>448</td>
<td>473</td>
<td>463</td>
<td>478</td>
<td>478</td>
<td>478</td>
</tr>
<tr>
<td>Early ART + IPT</td>
<td>418</td>
<td>459</td>
<td>452</td>
<td>459</td>
<td>459</td>
<td>459</td>
</tr>
</tbody>
</table>

30-Mo Probability
- Deferred ART: 14.1%
- Deferred ART + IPT: 8.8%
- Early ART: 7.4%
- Early ART + IPT: 5.7%
A Primary Outcome

Patients with Baseline CD4+ Count ≥500/mm³

<table>
<thead>
<tr>
<th>Intervention</th>
<th>30-Mo Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred ART</td>
<td>12.4%</td>
</tr>
<tr>
<td>Deferred ART + IPT</td>
<td>7.4%</td>
</tr>
<tr>
<td>Early ART</td>
<td>6.9%</td>
</tr>
<tr>
<td>Early ART + IPT</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

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

Months since Randomization
A Primary Outcome

Patients with Baseline CD4+ Count <500/mm³

<table>
<thead>
<tr>
<th>30-Mo Probability</th>
<th>Deferred ART</th>
<th>Deferred ART+IPT</th>
<th>Early ART</th>
<th>Early ART+IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability (%)</td>
<td>15.2%</td>
<td>9.7%</td>
<td>7.8%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

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

Months since Randomization

0  6  12  18  24  30
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The START Trial

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/mm$^3$
  • Pregnant and breast feeding women not eligible

• Randomized to
  • Immediate ART or
  • Deferred initiation until the CD4+ count declined to 350 cells/mm$^3$
A Time to First Primary Event

- Deferred initiation
- Immediate initiation

Patients (%) vs. Month
D  Death from Any Cause

![Graph showing death from any cause over time for immediate initiation and deferred initiation.](image)
<table>
<thead>
<tr>
<th>Trial</th>
<th>TEMPRANO</th>
<th>START</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Countries</strong></td>
<td>Côte d’Ivoire</td>
<td>55 countries (21% of participants enrolled in Africa)</td>
</tr>
<tr>
<td><strong>Enrollment years</strong></td>
<td>2008–2012</td>
<td>2009–2013</td>
</tr>
<tr>
<td><strong>Number of participants</strong></td>
<td>2050</td>
<td>4685</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>≥ 18 years old</td>
<td>≥ 18 years old</td>
</tr>
<tr>
<td></td>
<td>HIV-1 (or dual HIV-1 and 2)</td>
<td>ART naive</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 800</td>
<td>No history of AIDS</td>
</tr>
<tr>
<td></td>
<td>Not meeting WHO criteria for starting ART at the time (these criteria changed over the course of the trial)</td>
<td>General good health</td>
</tr>
<tr>
<td><strong>Comparison arms</strong></td>
<td>Immediate ART</td>
<td>Immediate ART</td>
</tr>
<tr>
<td></td>
<td>ART deferred until WHO criteria for starting ART met (these criteria changed over the course of the trial)</td>
<td>ART deferred until CD4 ≤ 350, AIDS diagnosis or other indication for ART (e.g., pregnancy)</td>
</tr>
<tr>
<td><strong>Composite primary endpoint</strong></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><strong>Duration of follow-up</strong></td>
<td>30 months for each participant</td>
<td>Mean 3.0 years (trial stopped early by DSMB)</td>
</tr>
<tr>
<td><strong>Number of primary events</strong></td>
<td>Immediate arm: 64</td>
<td>Immediate arm: 42</td>
</tr>
<tr>
<td></td>
<td>Deferred arm: 111</td>
<td>Deferred arm: 96</td>
</tr>
<tr>
<td><strong>Primary endpoint finding</strong></td>
<td>44% reduction with immediate ART (aHR = 0.56, 95% CI = 0.41–0.76)</td>
<td>5.7% reduction with immediate ART (HR = 0.43, 95% CI = 0.30–0.62)</td>
</tr>
<tr>
<td></td>
<td>Among patients with baseline CD4 ≥ 500, there was also a 44% in primary endpoint (aHR = 0.55, 95% CI = 0.33–0.94)</td>
<td></td>
</tr>
<tr>
<td><strong>Main contributors to finding</strong></td>
<td>Reduction in AIDS events (50%, mainly TB (50%)) and invasive bacterial disease (62%)</td>
<td>Reduction in AIDS events (72%, including TB (71%)), serious non-AIDS-related events, mainly infections (22%)</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>Immediate arm: 21</td>
<td>Immediate arm: 12</td>
</tr>
<tr>
<td></td>
<td>Deferred arm: 26</td>
<td>Deferred arm: 21</td>
</tr>
<tr>
<td></td>
<td>Not significant: aHR = 0.60, 95% CI = 0.34–1.09</td>
<td>Not significant: p = 0.13</td>
</tr>
<tr>
<td><strong>Viral load suppression</strong></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></td>
<td>Immediate arm: 94%</td>
<td>Immediate arm: 98%</td>
</tr>
<tr>
<td></td>
<td>Deferred arm: 80%</td>
<td>Deferred arm: 97%</td>
</tr>
<tr>
<td><strong>Adverse events</strong></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.
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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 gate keeper to ART)
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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 known to have failed an ART regimen
# First Line Regimens

<table>
<thead>
<tr>
<th>Initial ART Regimens for the previously untreated patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The preferred First-line regimens</strong></td>
</tr>
<tr>
<td>TDF + emtricitabine (FTC) (or 3TC) + efavirenz (EFV)</td>
</tr>
<tr>
<td>Or</td>
</tr>
<tr>
<td>TDF + emtricitabine (FTC) (or 3TC) + dolutegravir (DTG)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>TDF + emtricitabine (FTC) (or 3TC) + rilpivirine (RPV) provided VL &lt; 100,000 copies/mL</td>
</tr>
</tbody>
</table>

- Rilpivirine cannot be used with rifampicin & dolutegravir requires dose adjustment with rifampicin
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
# 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:**

- **AZT + 3TC**
  - or
- **TDF + 3TC (FTC can be substituted for 3TC)**

**Draw backs 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.*
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>Class</th>
<th>Drug</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)

Add DTG

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

Add ETR

TDF/AZT 30-59
OR
DRV ≥ 15
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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