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

- People dying from AIDS-related causes globally
- People newly infected with HIV/AIDS globally

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%
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Southern African HIV Clinicians Society adult antiretroviral therapy guidelines: Update on when to initiate antiretroviral therapy

**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>Other severe HIV-related disorders, e.g.:</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>
</tbody>
</table>

Non HIV-related disorders:

- malignancies (excluding localised malignancies)
- hepatitis B co-infection
- hepatitis C co-infection

Any condition requiring long-term immunosuppressive therapy

**CD4⁺ counts**

- <350 cells/µL                                                                                           ART recommended
- 350 - 500 cells/µL (two counts in this range)                                                          ART recommended if patient is ready and motivated to start
- >500 cells/µL                                                                                            Defer ART

HIV-infected partner in serodiscordant relationship

Regardless of CD4⁺ count or clinical diagnoses

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.

S Afr J HIV Med. 2015;16(1), 4 pages
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
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
### Recommendations

- 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. **Rating: AIII**

- ART should be offered upon detection of HIV infection. **Rating: A1a**

- Strategies for adherence support should be implemented and tailored to individual patient needs or the setting. **Rating: A1a**

- Clinicians should be alert to the nonspecific presentation of acute HIV infection and urgently pursue specific diagnostic testing (plasma HIV viral load) if suspected. **Rating: A1a**

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/mm(^3)</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\(^{(1)}\)

EACS Guidelines 2017 version 8.2
Several barriers are known to influence ART decision making and adherence to ART

<table>
<thead>
<tr>
<th>Screen for and talk about problems and facilitators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider systematic assessment of:</td>
</tr>
<tr>
<td>• Depression(^{(vii)}), see page 64-65</td>
</tr>
<tr>
<td>• Cognitive problems(^{(viii)}), see page 68</td>
</tr>
<tr>
<td>• Harmful alcohol(^{(ix)}) or recreational drug use, see page 33, 35</td>
</tr>
<tr>
<td>Consider talking about:</td>
</tr>
<tr>
<td>• Social support and disclosure</td>
</tr>
<tr>
<td>• Health insurance and continuity of drug supply</td>
</tr>
<tr>
<td>• Therapy-related factors</td>
</tr>
</tbody>
</table>

Recognise, discuss and reduce problems wherever possible in a multidisciplinary team approach.
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TEMPRANO Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAl ARTICLE

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

All Patients

30-Mo Probability

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

Months since Randomization

No. at Risk

<table>
<thead>
<tr>
<th></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: 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
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
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
D  Death from Any Cause

![Graph showing death from any cause over time with immediate and deferred initiation lines.](image-url)
TABLE 1: Summary of design, conduct and findings of the Strategic timing of antiretroviral therapy and TEMPRANO ANRS 12136 (Early antiretroviral treatment and/or early isoniazid prophylaxis against tuberculosis in HIV-infected adults) randomised controlled trials.

<table>
<thead>
<tr>
<th>Trial</th>
<th>TEMPRANO</th>
<th>START</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td>Cote 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</td>
<td>Immediate ART</td>
</tr>
<tr>
<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>
<td></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) Among patients with baseline CD4 ≥ 500, there was also a 44% reduction in primary endpoint (aHR = 0.56, 95% CI = 0.33–0.94)</td>
<td>57% reduction with immediate ART (HR = 0.43, 95% CI = 0.30–0.62) -</td>
</tr>
<tr>
<td>Main contributors to finding Reduction in AIDS events (50%, mainly TB [50%]) and invasive bacterial disease (61%)</td>
<td>Reduction in AIDS events (72%, including TB [71%]), serious non-AIDS events (25%), cancers (64%) and bacterial infections (62%)</td>
<td></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.
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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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<table>
<thead>
<tr>
<th>Class</th>
<th>Abbreviation</th>
<th>Mechanism of action</th>
<th>Specific action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside and nucleotide reverse transcriptase inhibitors</td>
<td>NRTIs and NtRTIs</td>
<td>Reverse transcriptase inhibition</td>
<td>Nucleic acid analogues mimic the normal building blocks of DNA, preventing transcription of viral RNA to DNA</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
<td>NNRTIs</td>
<td>Inhibition Reverse transcriptase</td>
<td>Alter the conformation of the catalytic site of reverse transcriptase and directly inhibit its action</td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>PIs</td>
<td>Protease inhibition</td>
<td>Inhibit the final maturation stages of HIV replication, resulting in the formation of non-infective viral particles</td>
</tr>
<tr>
<td>Integrase inhibitors (also termed integrase strand transfer inhibitors)</td>
<td>InSTIs</td>
<td>Inhibition of viral integration</td>
<td>Prevent the transfer of proviral DNA strands into the host chromosomal DNA</td>
</tr>
<tr>
<td>Entry inhibitors</td>
<td>-</td>
<td>Entry inhibition</td>
<td>Bind to viral gp41 or gp120 or host cell CD4+ or chemokine (CCR5) receptors</td>
</tr>
<tr>
<td>Generic name</td>
<td>Class of drug**</td>
<td>Recommended dosage</td>
<td>Common or severe ADR***</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tenofovir (TDF)‡</td>
<td>NtRTI</td>
<td>300 mg daily</td>
<td>Renal failure, tubular wasting syndrome, reduced bone mineral density, nausea</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>NRTI</td>
<td>150 mg 12-hourly or 300 mg daily</td>
<td>Anaemia (pure red cell aplasia) (rare)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)*</td>
<td>NRTI</td>
<td>200 mg daily</td>
<td>Palmar hyperpigmentation</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>NRTI</td>
<td>300 mg 12-hourly or 600 mg daily</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>Zidovudine (AZT)‡</td>
<td>NRTI</td>
<td>300 mg 12-hourly</td>
<td>Anaemia, neutropenia, GI upset, headache, myopathy, hyperlactataemia/steatohepatitis (medium potential), lipoatrophy</td>
</tr>
<tr>
<td>Stavudine (d4T)‡</td>
<td>NRTI</td>
<td>30 mg 12-hourly</td>
<td>Peripheral neuropathy, lipoatrophy, hyperlactataemia/steatohepatitis (high potential), pancreatitis, dyslipidaemia</td>
</tr>
<tr>
<td>Didanosine (ddl)‡</td>
<td>NRTI</td>
<td>400 mg daily (250 mg daily if &lt;60 kg) taken on an empty stomach (only enteric-coated formulation available)</td>
<td>Peripheral neuropathy, pancreatitis, nausea, diarrhoea, hyperlactataemia/steatohepatitis (high potential)</td>
</tr>
<tr>
<td>Generic name</td>
<td>Class of drug**</td>
<td>Recommended dosage</td>
<td>Common or severe ADR***</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>NNRTI</td>
<td>600 mg at night (400 mg at night if &lt;40 kg)</td>
<td>Central nervous system symptoms (vivid dreams, problems with concentration, dizziness, confusion, mood disturbance, psychosis), rash, hepatitis, gynaecomastia</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>NNRTI</td>
<td>200 mg daily for 14 days then 200 mg 12-hourly</td>
<td>Rash, hepatitis</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>NNRTI</td>
<td>25 mg daily with food</td>
<td>Rash, hepatitis, central nervous system symptoms (all uncommon)</td>
</tr>
<tr>
<td>Etravirine (ETV)</td>
<td>NNRTI</td>
<td>200 mg 12-hourly</td>
<td>Rash, hepatitis (both uncommon)</td>
</tr>
<tr>
<td>Generic name</td>
<td>Class of drug**</td>
<td>Recommended dosage</td>
<td>Common or severe ADR***</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Atazanavir (ATV)</td>
<td>PI</td>
<td>With TDF, always 300/100 mg daily and with EFV 400/100 mg daily 400 mg daily (only if ART-naive) or 300 mg with ritonavir 100 mg daily (preferable)</td>
<td>Unconjugated hyperbilirubinaemia (visible jaundice in minority of patients), dyslipidaemia (low potential), renal stones (rare), hepatitis (uncommon)</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>Boosted PI</td>
<td>400/100 mg 12-hourly or 800/200 mg daily (only if PI-naive)</td>
<td>GI upset, dyslipidaemia, hepatitis</td>
</tr>
<tr>
<td>Darunavir (DRV)</td>
<td>PI</td>
<td>600 mg 12-hourly with 100 mg ritonavir 12-hourly or 800/100 mg daily (only if PI-naive)</td>
<td>GI upset, rash, dyslipidaemia, hepatitis (uncommon) Contains sulphonamide moiety (use with caution in patients with sulpha allergy)</td>
</tr>
<tr>
<td>Saquinavir (SQV) (rarely used)§</td>
<td>PI</td>
<td>1 000 mg with 100 mg ritonavir 12-hourly, or 1 600 mg with 100 mg ritonavir daily (only if PI-naive) Take with a fatty meal, or up to 2 h after meal</td>
<td>GI disturbance (mild), hepatitis, hyperglycaemia, dyslipidaemia</td>
</tr>
<tr>
<td>Generic name</td>
<td>Class of drug**</td>
<td>Recommended dosage</td>
<td>Common or severe ADR***</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>InSTI</td>
<td>400 mg 12-hourly</td>
<td>Headache and other CNS side effects, GI upset, hepatitis and rash (rare), rhabdomyolysis (rare)</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>InSTI</td>
<td>50 mg daily</td>
<td>Insomnia, headache and other CNS side effects, GI upset, hepatitis and rash (rare)</td>
</tr>
<tr>
<td>Maraviroc (MVC)</td>
<td>CCR5 blocker</td>
<td>150 mg, 300 mg or 600 mg 12-hourly (doses depend on concomitant medication and interactions)</td>
<td>Rash, hepatitis, fever, abdominal pain, cough, dizziness, musculoskeletal symptoms (all rare)</td>
</tr>
</tbody>
</table>
ARV combinations to be avoided include:

- **AZT + D4T** (antagonism)

- **TDF + DDI** (associated with poorer virological and immunological responses and increased toxicity)

- **D4T + DDI** (associated with a very high risk for mitochondrial toxicities such as lactic acidosis and peripheral neuropathy)

- **ETV + ATV/r** (due to drug interaction)

- **ETV + DTG** unless a boosted PI is also used in the combination (due to drug interaction)
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

**Initial ART Regimens for the previously untreated patient**

<table>
<thead>
<tr>
<th>The preferred First-line regimens</th>
</tr>
</thead>
<tbody>
<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

<table>
<thead>
<tr>
<th>Recommend a regimen of 2 NRTIs and a ritonavir (RTV)- boosted (/r) PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>The preferred PI in Second-line regimens</td>
</tr>
<tr>
<td>Atazanavir (ATV) 300 mg / RTV 100mg daily</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Lopinavir (LPV)/r BD</td>
</tr>
<tr>
<td>NRTI combinations advised for second-line regimens:</td>
</tr>
<tr>
<td>AZT + 3TC</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>TDF + 3TC (FTC can be substituted for 3TC)</td>
</tr>
<tr>
<td>Draw backs of ATV:</td>
</tr>
<tr>
<td>-cannot be used with rifampicin- based TB therapy</td>
</tr>
<tr>
<td>- Important drug interactions with drugs that reduce stomach acidity such as proton pump inhibitors</td>
</tr>
</tbody>
</table>
### Choice of second-line NRTIs in relation to first-line NRTIs used

<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.*
<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>Drugs</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) 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.
Outline of talk

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