Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program

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ART COVERAGE

• ART Coverage September 2019

1,070,628 on ART
1,017,477 Adults
53,151 Pediatrics
# High Impact Practices

**Goal 1: Case Finding**

Training of Health care providers and lay counselors in Partner Notification Services, Index case finding and PITC

**Goal 2: Linkage**

Linkage registers at all HTS points

**Goal 3: Retention**

Implementation of Community & facility DSD models

**Goal 4: Viral Load**

Scale up VL coverage to 80% of TX_CURR, Documentation of timely VL results in the charts of all/100% eligible children and adolescents
Priority Areas for 2019-2020

• TLD and TAFED scale up in adult population
• Gradual phase out of EFV & NVP
• Introduction of TLD & TAFED in paediatric population
• Extension of LPV/r based regimen 2 weeks to 10 years (<20kg)
• Introduction of LPV/r granules
• Phase out of LPV/r suspension
• Setting up of the ARV active pharmacovigilance (PV) system
• HIV Testing using screening tool
• HIV Recency Testing
• 30-day LTFU introduction
• TB Preventive Therapy with introduction of 3HP
• Scale up Cervical Cancer Screening for WLHIV
• POC for EID & VL
• Treatment & VL literacy
• EMTCT of HIV & Syphilis
**Zambian Preferred First-Line ART & Alternative Regimens by Specific Population**

**Table 11 page 29_ZCG_2018**

<table>
<thead>
<tr>
<th>Specific Populations</th>
<th>Description</th>
<th>Preferred 1st line cART</th>
<th>Alternative regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant &amp; Breastfeeding Women</td>
<td>ARV naïve or Sure of tail coverage</td>
<td>TDF + XTC + DTG</td>
<td>TDF + XTC + EFV&lt;sub&gt;400&lt;/sub&gt; or TDF + XTC + ATV-r (or LPV-r) or ABC + 3TC + ATV-r (or LPV-r) or ABC + 3TC + DTG</td>
</tr>
<tr>
<td></td>
<td>Previous sdNVP exposure; or NVP monotherapy exposure (NVP without 7 days of AZT + 3TC cover); or unsure of tail coverage</td>
<td>TDF + XTC + DTG</td>
<td>TDF + XTC + ATV-r (or LPV-r) or ABC + 3TC + ATV-r (or LPV-r) or ABC + 3TC + ATV-r (or LPV-r)</td>
</tr>
<tr>
<td>Children (0-2 weeks)</td>
<td>All</td>
<td>AZT + 3TC + NVP</td>
<td>Consult or refer to expert opinion</td>
</tr>
<tr>
<td>Children (2 weeks to &lt; 5 years old)</td>
<td>All</td>
<td>ABC + 3TC + LPV-r</td>
<td>AZT + 3TC + LPV-r</td>
</tr>
<tr>
<td></td>
<td>HIV and TB co-infection</td>
<td>AZT + ABC + 3TC (if &lt; 3 months)</td>
<td>After completion of ATT, substitute to preferred 1st line with LPV-r</td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + EFV (3 months to &lt; 5yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (5 to &lt;10 years old)</td>
<td>ARV naïve</td>
<td>ABC + 3TC + EFV</td>
<td>AZT + 3TC + EFV or ABC + 3TC + NVP</td>
</tr>
<tr>
<td></td>
<td>History of maternal sdNVP; maternal or infant NVP monotherapy; mother unsure of tail coverage</td>
<td>ABC + 3TC + LPV-r</td>
<td>AZT + 3TC + LPV-r or AZT + 3TC + ATV-r</td>
</tr>
<tr>
<td>Adolescents (10 to &lt;19 years old)</td>
<td>With or without history of maternal or infant NVP exposure</td>
<td>TDF (or TAF) + XTC + DTG</td>
<td>TDF (or TAF) + XTC + EFV&lt;sub&gt;400&lt;/sub&gt; or ABC + 3TC + EFV or ABC + 3TC + DTG</td>
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<tr>
<td>Adults</td>
<td>All</td>
<td>TDF (or TAF) + XTC + DTG</td>
<td></td>
</tr>
</tbody>
</table>

**KEY**

- Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
TLD/TAFED as Primary Regimens for ART Initiation

- **TDF or TAF + XTC + DTG**
  - Is the preferred first line regimen for ARV naive adolescents and adults
  - In FDCs as
    - **Tenofovir disoproxil fumarate/Lamivudine/Dolutegravir (TLD)**
    - **Tenofovir alafenamide/Emtricitabine/Dolutegravir (TAFED)**
$TLE_{400}$ as Alternative Regimens for ART Initiation

- TDF + XTC + EFV$_{400}$
  - is the alternative first line regimen for ARV naive adolescents and adults
  - In FDCs as
    - Tenofovir disoproxil fumarate/Lamivudine/Efavirenz ($TLE_{400}$)
• Adults and adolescents with HIV-1 or HIV-2 or HIV-1/HIV-2 mixed infection who are being initiated on cART as part of combination ART as
  – TDF or TAF + XTC + DTG
DTG and TAF Use in Zambia 2

- Adults and adolescents with HIV-1 who have an undetected viral load while on NNRTI based first line as
  - TDF + XTC + **EFV** *to* TDF or **TAF** + XTC + **DTG**
  - TDF + XTC + **NVP** *to* TDF or **TAF** + XTC + **DTG**
  - ABC + 3TC + **EFV** *to* ABC or **TAF** + XTC + **DTG**
  - ABC + 3TC + **NVP** *to* ABC or **TAF** + XTC + **DTG**
DTG and TAF Use in Zambia

- Adults and adolescents with HIV-2 or HIV-1/HIV-2 mixed infection who have an undetected viral load while on PI based first-line as
  - TDF + XTC + \textbf{LPV-r} to TDF or \textbf{TAF} + XTC + \textbf{DTG}
  - ABC + 3TC + \textbf{LPV-r} to ABC or \textbf{TAF} + XTC + \textbf{DTG}
• In Patients failing PI based second line or those on Raltegravir (RAL) based third line and virologically suppressed
  – DTG to be dosed in place of RAL as 50mg once daily and as 50mg twice daily if on Rifampicin
Switching to DTG

- Patients on TDF + 3TC + EFV (TLE) with suppressed viral load (<1,000 copies/mL) can be switched to TLD or TafED, except:
  - TB patients who are on Rifampicin*
  - Pregnant and Breastfeeding women

*for TafED only
Special considerations for children and adolescents
The Risk and benefit balance for children MIGHT BE VERY different to adults!

Equitable policies: no one should be left behind
Viral suppression in children is worse than any other population

- More potent regimens are needed
- Better safety and tolerability profile is desirable to improve adherence
- Optimal sequencing remains critical in the context of life-long treatment

*Zimbabwe, Zambia, Malawi, Swaziland, Lesotho, Tanzania, Uganda, Namibia, Cameroon; <1 year n<25

Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
<table>
<thead>
<tr>
<th></th>
<th>NEONATES</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td>AZT+3TC+RAL (^1)</td>
<td>ABC+3TC+DTG (^2)</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>AZT+3TC+NVP</td>
<td>ABC+3TC+LPV/r</td>
</tr>
<tr>
<td></td>
<td>ABC+3TC+RAL (^1)</td>
<td>ABC (or AZT)+3TC+RAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ABC (or AZT)+3TC+EFV (^4)</td>
</tr>
<tr>
<td><strong>Special circumstances(^3)</strong></td>
<td>AZT+3TC+LPV/r</td>
<td>AZT+3TC+LPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZT+3TC+RAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AZT+3TC+NVP</td>
</tr>
</tbody>
</table>

ABC/3TC preferred NRTI backbone since 2013 based on the principle that sequencing with cytidine analogs as 1\(^{st}\) line and thymidine analogs as 2\(^{nd}\) line is preferable. TDF was listed as an alternative in 2013 and 2016 but later deprioritized due to concerns about bone mineral density.

Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
Why should we consider TAF for children?

- Improved durability
- More palatable
- Optimized sequencing
- Reduction in adverse impact on bone health
  - Bone accretion throughout childhood with peak in puberty
  - Multiple factors impacting bone health including nutrition, HIV and HIV treatment
TAF approvals by US FDA

<table>
<thead>
<tr>
<th></th>
<th>Approved in 12–&lt;18y; ≥35 kg (adult tablet)</th>
<th>Approved in 6–&lt;12y; ≥25 kg (adult tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC/TAF (200/25mg)</td>
<td>✓ *</td>
<td>✓ (unboosted only)</td>
</tr>
<tr>
<td>EVG/Cobi/FTC/TAF (150/150/200/10 mg)*</td>
<td>✓ *</td>
<td>✓ *</td>
</tr>
<tr>
<td>BIC/FTC/TAF (50/200/25 mg)</td>
<td>Approval expected June 20, 2019</td>
<td>Approval expected June 20, 2019</td>
</tr>
<tr>
<td>RPV/FTC/TAF (25/200/25 mg)</td>
<td>✓ *</td>
<td>Waiver</td>
</tr>
</tbody>
</table>

*Also approved in EU

Paediatric low dose TAF and Paediatric dispersible tablets for use below 25 kg are under investigation

Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
Key considerations

1. TDF offers a more favorable sequencing compared to ABC (as for adults)
2. TDF is not recommended for children because of bone toxicity and as a result paediatric formulations are not widely available
3. The only alternative NRTI to ABC is ZDV
4. Children co-infected with HBV (~8-10% among children with HIV in SSA) are not receiving treatment for Hep B.
5. If TDF>ABC and TAF=TDF therefore TAF>ABC (based on extrapolation from adult evidence)
6. TAF has a good toxicity profile in terms of surrogate markers for bone and renal health.
7. Adult formulations of TAF can be used in children over 25 kg
Acceptability and Feasibility

Would TAF introduction be well **accepted** by children and their families?

• Small pill OD
• Adults FDC from 25 kg
• Opportunity for regimen harmonization (if value to families, HCWs, programme and supply managers)

Would TAF introduction for children be **feasible** in most settings?

• Transition to TAF for 25-30 kg would be feasible and easy if recommended for adults
• By contrast, if TAF is not introduced for adults introduction for children will potentially further fragment market
WHO 2018

4 weeks

AZT + 3TC + RAL
pellets/granules

ABC / 3TC + LPVr
tablets

ABC / 3TC + DTG

20 kg

TDF / XTC / DTG

14 kg

Inclusion of TAF in children but not in adults

25 kg

Inclusion of TAF in children and adults

30 kg

Potential further Paeds market fragmentation

Maximize harmonization
TAF and Pediatric Use

• Weight <25 kg
  – Not FDA approved

• Weight ≥25 kg and no concurrent use of ritonavir or cobicistat:
  – In a fixed-dose combination tablet:
    • Emtricitabine 200 mg + TAF 25 mg, 1 tablet QD (adult dosing)
DTG 50mg and Pediatric Use

- Weight <20 kg
  - Not FDA or WHO approved
- Weight >20 kg
  - Dolutegravir 50 mg, 1 tablet QD (adult dosing)
TAF + FTC + DTG in Pediatrics

• Weight <25 kg
  - Not FDA approved

• Weight ≥25 kg
  - In a fixed-dose combination tablet:
    • Emtricitabine 200 mg + TAF 25 mg + DTG 50mg 1 tablet QD (adult dosing)
### Closer to Desired Simplified Regimen for Children and Harmonization with Adults

<table>
<thead>
<tr>
<th>POPULATIONS</th>
<th>DESCRIPTION</th>
<th>JUMPING FROM</th>
<th>JUMPING TO</th>
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<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5 to &lt;10 years)</td>
<td>ARV naïve</td>
<td>ABC + 3TC + LPV-r</td>
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<td>(&gt;25kg)</td>
<td>History of maternal sdNVP; maternal or infant NVP monotherapy; mother unsure of tail coverage</td>
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<td><strong>Adolescents</strong></td>
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<tr>
<td>(&gt;25kg)</td>
<td></td>
<td>+ XTC</td>
<td></td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>ARV naïve individuals without Creatinine available</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Individuals being transitioned from TLE or TL/N with Creatinine available but CrCl ≥ 30ml/min but ≤ 50ml/min Individuals being transitioned from ABC/3TC + EFV or NVP with Creatinine available but CrCl ≥ 30ml/min</td>
<td>+ DTG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women more than 45 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men above 50 years</td>
<td></td>
<td></td>
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Introduction: Background and pharmacovigilance of Dolutegravir in the Zambia National HIV Program
Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
TLD or TAFED?

**TLD**
- ARV naïve individuals with creatinine available and CrCl >50ml/min
- Individuals being transitioned to DTG based first line from TLE or TL/N with creatinine available and CrCl >50ml/min
- TB patients
  - with CrCl >50ml/min

**TAFED**
- ARV naïve individuals without Creatinine available
  - Same Day ART
- Individuals being transitioned from TLE or TL/N with Creatinine available but CrCl ≥ 30ml/min but ≤ 50ml/min
- Individuals being transitioned from ABC/3TC + EFV or NVP with Creatinine available but CrCl ≥ 30ml/min
- Women more than 45 years
- Men above 50 years
- Children weighing ≥ 25kg

Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
National Uptake of TLD in Zambia (Actual vs. Targets)

Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
DTG & TAF Active Pharmacovigilance

- No active PV exists
- Currently setting up active PV
- Mandatory reporting of specific data elements
- Specific options to be selected from a drop down list
- Patients to be given a paper based form which they may complement and submit at subsequent visit
- Pharmacist to be specifically assigned to the follow-up and reporting of the data

Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
Data elements to be collected

• Additional
  – Weight
  – BMI
  – Blood sugar
  – Lipids (Cholesterol)
  – Creatinine

• Pregnancy Module
  – Infant Status
    • Alive Vs Dead
    • Congenital anomalies

Introduction, Roll out and Pharmacovigilance of Dolutegravir in the Zambia National HIV Program
Criteria for selecting sites for active PV

- High volume ART sites
- Availability of electronic medical records (smart care)
  - Model Sites
- Human Resource Availability
- Strong Community Linkage system
Integrating PV into the National Electronic System (Smart Care)
ARV Pharmacovigilance Framework

ART site
- completes the ADR form
- enters data into the Electronic System (Smart Care)

ARV Pharmacovigilance of the MOH
- Collates, analyses and report to National HIV Program

HIV Unit of the MOH
- report to various stake holders

- Senior Management of the MOH
- Zambia Medicines Regulatory Authority
- WHO
**VIREND STUDY FLOW DIAGRAM**

**TLE or TLN**

- **ARM A**
  - **VL < 1000**
  - **Randomized**
  - **A1**
    - **TLD**
  - **A2**
    - **TafED**

- **ARM B**
  - **VL > 1000**
  - **Randomized**
  - **B1**
  - **B1a**
    - **TLD**
  - **B1b**
    - **TafED**
  - **B2**
    - **B2a**
      - **AZT/3TC/LPV-r**
    - **B2b**
      - **AZT/3TC/ATV-r**

**Viral Load at 0, 24, 44, 72, 96 and 144 weeks**

**VL > 1000**

**Resistance at 0, 24, 44, 72, 96 and 144 weeks**
HIVDR

• Introduced Routine HIVDR testing for
  – all individuals with VL>1,000 copies/mL after enhanced adherence counselling
  – Includes first and second line failure

• HIVDR Surveys
  – Pretreatment Drug Resistance Survey
    • Adults and Children
  – Acquired Drug Resistance Survey
    • Children and Adults