ART Optimization (New emerging molecules)

KPA PRE-CONFERENCE 24th April 2018
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Outline

• Introduction
• New ART molecules already adopted
  • Dolutegravir
  • Efavirenz 400mg
• The Kenyan landscape
• The case of Machakos Level 5 Hospital
### WHO ARV Guidelines Evolution: 2002 to 2016

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<tr>
<td>When to start</td>
<td>CD4 ≤200</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 350</td>
<td>CD4 ≤ 500</td>
<td>Treat All</td>
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<td>- consider 350</td>
<td>-TB at CD4 ≤350</td>
<td>-CD4 ≤ 350 as priority</td>
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<td>-TB, HBV at any CD4</td>
<td>-TB, HBV, PW, SDC at any CD4</td>
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<tr>
<td>1st Line ART</td>
<td>8 options</td>
<td>4 options</td>
<td>8 options</td>
<td>6 options (FDC)</td>
<td>1 preferred option (FDC)</td>
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<td>2nd Line ART</td>
<td>Boosted PIs</td>
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<tr>
<td>3rd Line ART</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DRV/r, RAL, ETV, DTG</td>
<td>DRV/r, RAL, ETV, DTG</td>
<td>DRV/r, RAL, ETV, DTG</td>
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<tr>
<td>Viral Load Testing</td>
<td>No</td>
<td>No (Desirable)</td>
<td>Yes (Tertiary centers)</td>
<td>Yes (Phase in approach)</td>
<td>Yes (preferred for monitoring, use of PoC, DBS)</td>
<td>Yes (preferred for monitoring, scale up all technologies)</td>
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**Key Changes:**
- **Earlier initiation**
  - CD4 ≤ 350 as priority
  - Programmatic focus on KPs
- **Simpler treatment**
  - New alternative options (DTG, EFV)
- **Less toxic, more robust regimens**
  - New alternative options (DRV/r, LPV/r + RAL)
- **Better and simpler monitoring**
  - CD4 monitoring can be stopped if patient virally suppressed

Vitoria et al. Curr Opin HIV/AIDS, 2013, 8: 12-18
HIV Life Cycle & ARV Action Sites

CCR5 inhibitors - Maraviroc
Fusion inhibitors - Enfuvertide
NRTIs and NNRTIS
Integrase inhibitors - DTG, RAL
Protease inhibitors
What is ART optimization?

WHO recommends adoption of ART regimen that fulfil the following:

• High potency
• Good tolerability/Reduced pill burden/ easy to take or administer
• High genetic barrier to resistance/durable
• Improve sequencing/switching options
• Lower costs
• Used across different population groups -“ Harmonization”

WHO 2017, Transition to antiretrovirals in HIV programming
New ART molecules already adopted

- Dolutegravir 50mg
- Efavirenz 400mg (EFV 400MG)
- Darunavir/Ritonavir
- Raltegravir
- LPV/r pellets 40/10mg
- LPV/r 100mg/25mg
- Abacavir/lamivudine 120/60mg
- Abacavir / lamivudine 600/300mg (ABC/3TC) FDC
Integrase Inhibitors

Approved INSTIs
• Raltegravir, 2007
• Elvitegravir, 2012
• Dolutegravir, 2013
• Bictegravir, 2018

INSTIs in clinical studies
• Cabotegravir
Dolutegravir

- An Integrase inhibitor
- Well tolerated
- Low toxicity
- High genetic barrier to resistance
- Once daily dosing
- Twice daily in TB treatment
- No interaction with hormonal contraceptives
- Emerging safety data in pregnancy

- Small tablet- 9mm
- Tablets: 10 mg, 25 mg, and 50 mg
- FDC-
  - TDF/3TC/DTG 300mg/300mg/50mg
  - ABC/3TC/DTG 600mg/300mg/50mg
- Lower cost than TDF/XTC/EFV
Use of Dolutegravir

1. Newly initiating ART naïve patients
2. Patients already on ART
   • Stable first line
   • Second line patients
   • Third line patients
3. Heavily experienced treatment patients
4. ? In Pregnancy
5. In TB co-infection

WHO recommends 1st line DTG use in countries where Primary HIVDR to NNRTI >10% in ART naïve patients
(Argentina, Guatemala, Namibia, Nicaragua, Uganda and Zimbabwe).
NEWLY INITIATING ART naïve patients

SINGLE STUDY

DTG/ABC/3TC superior to TDF/FTC/EFV

- Virological suppression (71% vs. 63%)
- Fewer adverse events
- No Resistance development

Abstract:

The SINGLE study was a randomized, double-blind, noninferiority study that evaluated the safety and efficacy of 50 mg dolutegravir + abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine in 833 ART naïve HIV-1 + participants. Of 833 randomized participants, 71% in the dolutegravir + abacavir/lamivudine arm and 63% in the efavirenz/tenofovir/emtricitabine arm maintained viral loads of <50 copies per milliliter through W144 (P = 0.01). Superior efficacy was primarily driven by fewer discontinuations due to adverse events in the dolutegravir + abacavir/lamivudine arm (dolutegravir + abacavir/lamivudine arm vs. efavirenz/tenofovir/emtricitabine arm 27 vs. 35; P = 0.02). No resistance was found in the efavirenz/tenofovir/emtricitabine arm. (J Acquir Immune Defic Syndr. 2015 Dec 15;70(5):515-519. doi: 10.1097/QAI.0000000000000750.)
FLAMINGO STUDY
DTG with 2 NRTI’s superior (VL suppression <50copies/ml at 90%) to 83% of DRV/r with 2 NRTI’s over 48 weeks

THE LANCET
Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study

Dr Bonaventura Clotet, MD, Prof Judith Feinberg, MD, Prof Jan van Lunzen, MD, Marie-Aude Khuong-Josses, MD, Andrea Antinori, MD, Irina Dumitru, MD, Prof Vadim Pokrovskiy, MD, Jan Fehr, MD, Roberto Ortiz, MD, Prof Michael Saag, MD, Julia Harris, MA, Clare Brennan, DPT, Tamio Fujwara, PhD, Sherene Min, MD on behalf of the ING114915 Study Team

Published: 21 March 2014
SPRING-2 STUDY
DTG non inferior to RAL over a 48 week period regardless of baseline VL and NRTI back bone (88% vs. 85%)
Similar safety profiles
Resistance in RAL arm

Once-daily dolutegravir versus raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study

Prof Francois Raffi, MD, Prof Anita Rachlis, MD, Prof Hans-Jurgen Stellbrink, MD, W David Hardy, MD, Carlo Torti, MD, Chloe Orkin, MD, Mark Bloch, MD, Daniel Podzamczer, MD, Prof Vadim Pokrovsky, MD, Federico Pulido, MD, Steve Almond, MMath, David Margolis, MD, Clare Brennan, DPT, Sherene Min, MD on behalf of the SPRING-2 study group
Published: 08 January 2013
PlumX Metrics
Use of DTG in patients already on ART

• Stable First line Patients

**STRIIVING**: non-inferior of switch to ABC/3TC/DTG v continuing current regimen in adults with stable viral suppression

• Second-line patients

**DAWNING**: New evidence suggest DTG superior to LPV/r when combined with 1 equally fully active NRTI

• Third-line patients

**SAILING**: In patients with viral failure and resistance to > 2 drug classes DTG superior to RAL when combined with 1-2 other fully active drugs

**VIKING**: In patients with viral failure and INSTI resistance, DTG is effective when combined with >1 fully active drug.
DTG in clients heavily experienced on ART

• DTG still active in patients with ART experience
• High suppression rates in STRIIVING regardless to genotypic susceptibility score after switching to DTG-based in patients with viral suppression
• DOLULAM: DTG +3TC maintains virological suppression even in heavily treatment experienced patients
Dolutegravir in Pregnancy

“Reports of dolutegravir use in pregnancy from Botswana, Europe and the Antiretroviral Pregnancy Registry to date did not show an increased risk of adverse outcomes compared with other antiretrovirals.”- IAS Paris 2017
### Tsepamo: Birth Outcomes When Initiating First-line DTG vs EFV in Pregnancy

- Prospective cohort study in HIV-infected women in Botswana initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

<table>
<thead>
<tr>
<th>Adverse Birth Outcomes, n (%)</th>
<th>DTG (n = 845)</th>
<th>EFV (n = 4593)</th>
<th>aRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ▪ Severe</td>
<td>291 (34.4)</td>
<td>1606 (35.0)</td>
<td>1.0 (0.9-1.1)</td>
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<tr>
<td></td>
<td>92 (10.9)</td>
<td>519 (11.3)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>18 (2.1)</td>
<td>105 (2.3)</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td>Neonatal death (&lt; 28 d)</td>
<td>11 (1.3)</td>
<td>60 (1.3)</td>
<td>1.0 (0.5-1.9)</td>
</tr>
<tr>
<td>Preterm birth (&lt; 37 wks)</td>
<td>149 (17.8)</td>
<td>844 (18.5)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td>▪ Very preterm (&lt; 32 wks)</td>
<td>35 (4.2)</td>
<td>160 (3.5)</td>
<td>1.2 (0.8-1.7)</td>
</tr>
<tr>
<td>SGA (&lt; 10th percentile weight)</td>
<td>156 (18.7)</td>
<td>838 (18.5)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>▪ Very SGA (&lt; 3rd percentile weight)</td>
<td>51 (6.1)</td>
<td>302 (6.7)</td>
<td>0.9 (0.7-1.2)</td>
</tr>
</tbody>
</table>

*For DTG vs EFV; adjusted for maternal age, education, gravida.

- Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396); most second/third trimester
- Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)
- ABO risks similar when initiating first-line DTG vs EFV in pregnancy
Dolutegravir PK in HIV-infected children 2-<6 yrs Ruel T et al. CROI 2017, Seattle, WA. Poster 806

- 10 HIV+ children 2-<6 years - DTG granules for suspension
IMPAACT P1093
(NCT01302847) Data expected in May 2018

Approved in Europe
≥15-<20 kg- 20 mg daily
20-<30 kg - 25 mg once daily
30-<40 – 35 mg once daily
≥40 – 50 mg once daily

ODYSSEY(NCT02259127)
Randomised Trial of Dolutegravir (DTG)-Based Antiretroviral Therapy vs. Standard of Care (SOC) in Children With HIV Infection Starting First-line or Switching to Second-line ART Data expected in June 2019
Dolutegravir use in Children - WHO

• Approved for adolescents by WHO
• WHO still reviewing data for younger children

• As of June 2017, DTG has been approved by the FDA for use among children 6 years and older (> 30 kg), and by the European Medicines Agency for children weighing more than 15 kg.
Multiple countries are planning to phase in the use of DTG singles and TDF/3TC/DTG
Reduced dose Efavirenz 400mg

- **ENCORE1**: In treatment naïve patients, 400mg EFV was non inferior to 600mg
- A lower dose of EFV has the potential to
  - Lower cost for the program
  - Decrease side effects
- Not enough evidence for use in pregnancy
- Not enough evidence for use in TB/HIV co-infection
- Has significant interactions with hormonal contraception
### Key items for consideration of a safe transition to new first-line ARVs

<table>
<thead>
<tr>
<th>Optimization criteria</th>
<th>DTG containing regimens</th>
<th>EFV400 containing regimens</th>
<th>Preferred Choice</th>
</tr>
</thead>
</table>
| **Efficacy**          | • Highly efficacy in context of NNRTI resistance (cost saving)  
                        • Efficacy data on PW and TB co-infection pending | • Efficacy data on PW and TB co-infection pending  
                        • Concerns with rising NNRTI resistance | **Favours DTG** |
| **Safety**            | • Limited safety data in young children, pregnancy, TB co-infection and advanced HIV disease (IRIS risk) | • Used for decades in LMICs and is proved safe in PW and PLHIV with TB  
                        • Lower doses are better tolerated. | **Favours EFV400** |
| **Simplification**    | • Generic single formulation available, but FDC expected only in 2018  
                        • Need dose adjustment in TB co-treatment (twice daily dose) | • Generic FDC already available  
                        • No dose adjustment needed and maintenance of once daily dose | **Favours EFV400** |
| **Harmonization**     | • Strategically preferred choice in long term | • Limitations for use in all populations (young children, IDU)  
                        • Some important drug interactions | **Favours DTG** |
| **Cost**              | • Cheaper than EFV600 and higher potential for further cost reduction (strong generic competition) | • Cheaper than EFV600 but less potential for further cost reduction | **Favours DTG** |
DTG phase in- Kenya HIV programming

- Included in the 2016 ART national guidelines
- Phased adaptation
- Alternative 1st Line for those not tolerating Efavirenz
- Preferred 1st line for initiation in PWID (instead of ATV/r)
- Substitution for patients who are virally-suppressed on PI/r-based 1st line (PWID)
- Patients failing PI-based regimen based on DRT results and recommendation by regional & national TWG
Lopinavir/Ritonavir 40mg/10mg pellets per capsules

- Approved by WHO in 2015
- Developed due to need of heat stable and favourable taste
- **CHAPAS 2 Trial study** - similar efficacy between LPV/r syrup, oral pellets, and 100/25mg tablets
- Given to those > 14 days old & > 3kg, MOH recommended above 9 months
- Adm with food/milk/juice by sprinkling on them
- should not be chewed, crushed, stirred or dissolved
- Twice daily dosing
LPV/R (100mg/25mg) tablet

- Heat stable
- Administered to >10kg and must be able to swallow
- Cannot be crashed, chewed, broken or dissolved
SIMPLIFIED WEIGHT BAND DOSING SCHEDULE FOR LPV/r oral pellets 40mg/10mg, oral liquid 80mg/20mg/ml and heat stable tablets 100mg/25mg

<table>
<thead>
<tr>
<th>WEIGHT BAND [KG]</th>
<th>NUMBER OF LPV/R ORAL PELLETS 40MG/10MG CAPSULES</th>
<th>LPV/R 80MG/20MG/ML ORAL LIQUID</th>
<th>NUMBER OF LPV/R 100MG/25MG TABLETS</th>
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<tbody>
<tr>
<td></td>
<td>AM</td>
<td>PM</td>
<td>AM</td>
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<tr>
<td>3-4.9 kg</td>
<td>2</td>
<td>2</td>
<td>1 ml</td>
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<tr>
<td>5-5.9 kg</td>
<td>2</td>
<td>2</td>
<td>1 ml</td>
</tr>
<tr>
<td>6 - 9.9 kg</td>
<td>3</td>
<td>3</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>10 - 13.9 kg</td>
<td>4</td>
<td>4</td>
<td>2 ml</td>
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<tr>
<td>14 - 19.9 kg</td>
<td>5</td>
<td>5</td>
<td>2.5 ml</td>
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<tr>
<td>20 - 24.9 kg</td>
<td>6</td>
<td>6</td>
<td>3 ml</td>
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<tr>
<td>25 - 29.9 kg</td>
<td>7</td>
<td>7</td>
<td>NR</td>
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<tr>
<td>30 - 34.9 kg</td>
<td>8</td>
<td>8</td>
<td>NR</td>
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NR=NOT RECOMMENDED

Adapted from Cipla package insert approved by USFDA and WHO 2013 dosages of recommended antiretroviral drugs
Pediatric Optimized ART does not exist yet!

Dr Nandita S, ICAP
Kenyan landscape

• DTG already in country for those not tolerating EFV 1st line and for thirdline
• DTG for above 12 years and > 35 kg
• Not used in pregnancy and in TB co-infected
• EFV 400mg piloted in Nairobi
• Lpv/r 40mg/10mg pellets use in selected regions but challenges with manufacturer supply
• LPV/R 100mg/25mg tablet use country wide
• Darunavir/ritonavir used for thirdline ART or PI based treatment failure
The Naishi experience

Machakos Level 5 Hospital
Pre implementation Plan

- Facility selection criteria:
  - Number of PLHIV on TDF/3TC+NVP
  - Strong multidisciplinary team and partner support
  - Regional representation
- CHMT notification
- Site sensitization: HMT and CCC
- CHS-Naishi program sensitization
- HCW Training
- Line listing eligible patients
- Ordering of commodities
# DTG ‘Phase-in’ Timeline

<table>
<thead>
<tr>
<th>Action</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
<th>Jan</th>
<th>Feb</th>
<th>March</th>
<th>Apr</th>
<th>May</th>
<th>June</th>
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<tr>
<td>Sensitization and activation</td>
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<td>16/10/2017</td>
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<tr>
<td>Review of NVP stocks in facility, orders for DTG in place of NVP</td>
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<td>200 DTG packs ordered</td>
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<tr>
<td>Monthly monitoring of NVP stocks in facility</td>
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<tr>
<td>Line listing of patients on TDF/3TC/NVP, check viral load results in last 12 months</td>
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<td>Transition from NVP to DTG</td>
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<td>Facility review meetings from November 2017</td>
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<td>Monthly reports on phase in TA visits</td>
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<td>TA visits</td>
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<td>Final reports and review meeting</td>
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</tbody>
</table>
Clients On 3TC/TDF/DTG Regimen

Data source: ADT/IQCARE
Feb 2018
DTG Switch Trend - Cumulative

National roll out

Number of patients

Aug-17 4
Sep-17 49
Oct-17 113
Nov-17 300
Dec-17 592
Jan-18 858
Feb-18 1015

Data source: ADT/IQCARE
Categories for DTG use at ML5 Hospital

- EFV intolerance - 7 with neuropsychiatric effects
  - 1 male with gynaecomastia
- DTG phase in – (1015)
- TB coinfection for patients on 2nd line ART – (4)
- 3rd line ART – No client yet
- PWID on PI regimen – No client yet
Pharmacovigilance

Adverse drug Reactions

- Generalised body itchiness
- Generalised ody weakness
- Dizziness/fainting
- Hyperglycaemia
- Skin eruptions
- Increased appetite
- Amenorrhea
- Lower limb weakness
- Severe headache
- Tongue discoloration

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>Generalised body itchiness</td>
<td>3</td>
</tr>
<tr>
<td>Generalised ody weakness</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness/fainting</td>
<td>6</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>18</td>
</tr>
<tr>
<td>Skin eruptions</td>
<td>1</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>17</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>2</td>
</tr>
<tr>
<td>Lower limb weakness</td>
<td>4</td>
</tr>
<tr>
<td>Severe headache</td>
<td>8</td>
</tr>
<tr>
<td>Tongue discoloration</td>
<td>10</td>
</tr>
</tbody>
</table>

Data source: ADT/IQCARE

Action following Adverse Drug reaction

- Total No. developed ADR: 18
- Total No. substituted: 1
- Total No still on DTG: 17
Strategies to improve VL uptake

- Appointment of a focal clinician and Peer educator
- Special appointment booking for DTG clients
- Color coding of client files
- Flagging out of clients with missed VLs
- Call back of clients for VL testing
Summary

• Integrase inhibitors being redesigned for 1st line ART for treatment naïve adolescents and adults

• ART optimization for adolescents and adults realized

• Optimized pediatric ART regimen is yet to be realized

• Promising Ongoing studies for children< 12 years- IMPAACT 1093

• Need for continued pharmacovigilance on new drugs to inform policy
References

• MOH, Kenya 2016 , ART guidelines
• WHO technical update on transition to new ARVs, 2017
• New Horizon Network
• HIV learning Network, The CQUIN Project
• Appreciate Dr Virginia Karanja, CHS