New ART Regimen

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Then - “Prevention is the only Treatment”
Now - “Treatment as Prevention”
Anti-Retroviral Treatment: Different Phraseology

- ART
- HAART
- MEGA HAART
- GIGA HAART
- cART (Combination ART)
- rART (Robust ART) Latest!
- Individualised ART ... Future

Gilada/UMRC, Mumbai
Newer trends in HIV treatment and management

Strategies in treatment:
• Starting ART earlier than later
• Treatment as Prevention (TasP)

Prevention:
• Using PrEP- One or two drugs to prevent infection

Drugs:
• Efficacy of newer drugs- Change in First line drugs
• Triple therapy/dual therapy/monotherapy
• Changing therapy after viral suppression
• TAF Vs TDF
• EFV600mg Vs 400mg
• IPT

Monitoring
• Viral load Vs CD4 Count

Life expectancy
• Almost full life
What is new and news?

- WHO’s Test & Treat strategy
- Introduction of an INSTI Dolutegravir
- STR with lower dose of Efavirenz-TLE400
- Tenofovir Alafenamide Fumarate (TAF) and TAF+FTC combo
- TLD made available, TED/TAFED/TAFLD in pipeline
- Darunavir-Ritonavir – DRV/r Combo 800+100, 400+50
- PrEP, Bridge PrEP, PEPSE
- 92% of PLHIV in world access Indian ARVs, with full basket
- Injectable ARVs may be coming next year
- Vanishing Paediatric ARVs
## Antiretroviral Agents Approved by US FDA

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>Integrase Inhibitors</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine (AZT)</td>
<td>Raltegravir (RAL)</td>
<td>saquinavir (SQV)</td>
</tr>
<tr>
<td>didanosine (ddI)</td>
<td>Elvitegravir (ELV)</td>
<td>indinavir (IDV)</td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td>Dolutegravir (DTG)</td>
<td>ritonavir (RTV)</td>
</tr>
<tr>
<td>lamivudine (3TC)</td>
<td>Bictegravir (BIC)</td>
<td>nelfinavir (NFV)</td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td></td>
<td>lopinavir/ritonavir (LPV/r)</td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td></td>
<td>atazanavir (ATV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darunavir (DRV)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>NNRTIs</th>
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<tbody>
<tr>
<td>Nevirapine (NVP)</td>
<td></td>
<td></td>
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<tr>
<td>Efavirenz (EFV)</td>
<td></td>
<td></td>
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<tr>
<td>Rilpivirine (RLP)</td>
<td></td>
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<tr>
<td>Etravirine (ETV)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nucleotide RTIs</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Tenofovir DF (TDF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry Inhibitors</th>
<th></th>
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<tbody>
<tr>
<td>Maraviroc (CCR5)</td>
<td></td>
<td></td>
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<tr>
<td>enfuvirtide (ENF, T20)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Post Attachment Inhibitor</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibalizumab</td>
<td></td>
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</tr>
</tbody>
</table>
New Art regimen: ARVs

- E400
- DTG
- ABC/L
- DRV/r
- TAF

Heroes:
DTG, DRV/r, TAF, 3TC (longest in use)
What is expected of an Ideal ART regimen

• Co-administration with other medications especially TB t/t
• Specific populations: women- children, adolescent, aging
• Efficacy
• Safety, tolerability (minimal ADEs)
• Minimal Drug-drug interaction
• Affordability and global access
• Potent enough to bring down VL to undetectable level ASAP
• Pill Burdon : STR or minimal number of pill
• No or minimal food restrictions
• Suitable dosage convenience

Cheaper, acceptable and tolerable ART is essential to increase retention in care and viral suppression, to achieve the 90-90-90
# Target Prices: MPP

## Table 1. Target prices for key first-line combination treatments in low or low-middle income countries

<table>
<thead>
<tr>
<th>Combination treatment</th>
<th>Estimated price per patient-year</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/3TC/ATV/r</td>
<td>$279</td>
<td>13</td>
</tr>
<tr>
<td>TDF/FTC/ELV/COBI</td>
<td>$184</td>
<td>14</td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td>$179</td>
<td>14</td>
</tr>
<tr>
<td>TDF/FTC/EFV600</td>
<td>$144</td>
<td>13</td>
</tr>
<tr>
<td>TDF/3TC/EFV600</td>
<td>$130</td>
<td>13</td>
</tr>
<tr>
<td>TDF/3TC/EFV400</td>
<td>$100 to $110</td>
<td>13</td>
</tr>
<tr>
<td>TAF/3TC/DTG</td>
<td>$60</td>
<td>14</td>
</tr>
<tr>
<td>DTG/3TC</td>
<td>$46</td>
<td>14</td>
</tr>
</tbody>
</table>

3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; COBI, cobicistat; DTG, dolutegravir; EFV400, efavirenz 400 mg; EFV600, efavirenz 600 mg; ELV, elvitegravir; FTC, emtricitabine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.
HAART Evolution: NNRTI based
Reduce Pill-Burdon: Combo ARVs
Oral – Inj., Daily - Monthly

AZT,3TC,SQV  AZT,3TC,NVP  d4T,3TC,NVP  DDI,3TC,EFV  TDF,FTV,EFV  CBV,RPV

Thanks to our pharma companies that for first line they combined all in one pill

Daily  Daily  Daily  Daily  Daily  Monthly

Gilada/UMRC, Mumbai
Treatment Failure

Viral load more >1000 copies on 2 consecutive measurements in 3 months with adherence support after 1st VL

Virologic failure

Immunologic failure

Clinical failure

Drug Resistance

CD4 Count

Viral Load

Courtesy: Dr N Kumarasamy, Chennai
About resistance

Develops under sub-optimal drug pressure

Mutations in the RT, Protease and Integrase genes

Permanently archived

Some drugs have low genetic barrier

Class cross resistance

Increasing degree if patient continues on failing regimen

Transmitted Resistance
Pre-treatment HIV drug resistance to EFV or NVP among I ART initiators in selected countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage with EFV/NVP Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>20%</td>
</tr>
<tr>
<td>Namibia</td>
<td>15%</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>10%</td>
</tr>
<tr>
<td>Cameroon</td>
<td>5%</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>25%</td>
</tr>
<tr>
<td>Guatemala</td>
<td>15%</td>
</tr>
<tr>
<td>Argentina</td>
<td>20%</td>
</tr>
<tr>
<td>Mexico</td>
<td>5%</td>
</tr>
<tr>
<td>Brazil</td>
<td>10%</td>
</tr>
<tr>
<td>Columbia</td>
<td>10%</td>
</tr>
<tr>
<td>Myanmar</td>
<td>5%</td>
</tr>
<tr>
<td>Kenya</td>
<td>13%</td>
</tr>
<tr>
<td>India</td>
<td>&gt;5-10%</td>
</tr>
<tr>
<td>Thailand</td>
<td>7.9%</td>
</tr>
<tr>
<td>Indonesia</td>
<td>4.3%</td>
</tr>
<tr>
<td>Philippines</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

2. Salvana E et al., Open Forum Infectious Diseases 2017; 4(suppl 1): S423
Primary DRMs in Asia: Prevalence

Percentage (%)

M41L 0.7
D67E/G/N 0.3
T69D 0.2
K70R 0.2
L74I/V 0.1
V75M 0.1
F77L 0.1
F116Y 0.1
Q151M 0.2
M184I/V 0.6
L210W 0.6
T215D/E/F/I/S/Y 0.8
K219E/Q/R 0.9
K103N/S 0.3
V106A 0.1
Y181C 0.4
G190A/E 0.4
P225H 0.1

NRTI Mutations

Percentages of resistance-associated mutations are calculated in comparison to the total number of patients.

Resistance Guidelines

Use non NNRTI (Dolutegravir-DTG) for initiation or HIVDR testing to guide initiation

When?

• National prevalence of pre-treatment HIVDR to NNRTI is >10%

WHO Guidelines on The public Health Response to pretreatment HIV DR- July 2017
### WHO ARV Guidelines Evolution 2002 to 2016

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>When to start</strong></td>
<td>CD4 ≤200</td>
<td>CD4 ≤ 200</td>
<td>CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB</td>
<td>CD4 ≤ 350 - Regardless CD4 for TB and HBV</td>
<td>CD4 ≤ 500 - Regardless CD4 for TB, HBV PW and SDC - CD4 ≤ 350 as priority</td>
<td></td>
</tr>
<tr>
<td><strong>Towards treatment initiation at any CD4 cell count</strong></td>
<td><strong>Towards treatment initiation at any CD4 cell count</strong></td>
<td><strong>Towards treatment initiation at any CD4 cell count</strong></td>
<td><strong>Towards treatment initiation at any CD4 cell count</strong></td>
<td><strong>Towards treatment initiation at any CD4 cell count</strong></td>
<td><strong>Towards treatment initiation at any CD4 cell count</strong></td>
<td><strong>Towards treatment initiation at any CD4 cell count</strong></td>
</tr>
<tr>
<td><strong>1st Line ART</strong></td>
<td>8 options - AZT preferred</td>
<td>4 options - AZT preferred</td>
<td>8 options - AZT or TDF preferred - d4T dose</td>
<td>6 options &amp; FDCs - AZT or TDF preferred - d4T phase out</td>
<td>1 preferred option &amp; FDCs - TDF and EFV preferred across all pops</td>
<td></td>
</tr>
<tr>
<td><strong>Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)</strong></td>
<td><strong>Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)</strong></td>
<td><strong>Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)</strong></td>
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<td><strong>Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3rd Line ART</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DRV/r, RAL, ETV</td>
<td>DRV/r, RAL, ETV</td>
<td>Encourage HIV DR to guide</td>
</tr>
<tr>
<td><strong>Viral Load Testing</strong></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></td>
</tr>
<tr>
<td><strong>Better and simpler monitoring</strong></td>
<td><strong>Better and simpler monitoring</strong></td>
<td><strong>Better and simpler monitoring</strong></td>
<td><strong>Better and simpler monitoring</strong></td>
<td><strong>Better and simpler monitoring</strong></td>
<td><strong>Better and simpler monitoring</strong></td>
<td><strong>Better and simpler monitoring</strong></td>
</tr>
</tbody>
</table>

**Notes:**
- CD4: CD4 count
- AZT: Zidovudine
- TDF: Tenofovir Disoproxil Fumarate
- d4T: Stavudine
- DRV: Darunavir
- DRV/r: Darunavir/Ritonavir
- FPV: Fosamprenavir
- FPV/r: Fosamprenavir/Ritonavir
- IDV: Indinavir
- IDV/r: Indinavir/Ritonavir
- LPV: Lopinavir
- LPV/r: Lopinavir/Ritonavir
- SQV: Saquinavir
- SQV/r: Saquinavir/Ritonavir
- ATV: Atazanavir
- ATV/r: Atazanavir/Ritonavir
- RAL: Raltegravir
- ETV: Etravirine
- DRV: Darunavir
- DRV/r: Darunavir/Ritonavir
- EFV: Efavirenz
- ETV: Etravirine
- DR: Drug Resistance
- VL: Viral Load
- PoC: Point of Care
Treatment Guidelines

When to start? Has become History
What to Start? Almost the same combo
When to change? Becoming easier
WHO Treatment Guidelines: What to Start in Adults

<table>
<thead>
<tr>
<th>TARGET POPULATION</th>
<th>2010 ART GUIDELINES</th>
<th>2013 ART GUIDELINES</th>
<th>2016 ART GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+ ADULTS</td>
<td>AZT or TDF + 3TC (or FTC) + EFV or NVP</td>
<td>TDF + 3TC (or FTC) + EFV (as fixed dose combination)</td>
<td>Preferred: TDF + 3TC (or FTC) + EFV (as fixed dose combination)</td>
</tr>
<tr>
<td>HIV+ PREGNANT WOMEN</td>
<td>AZT + 3TC + NVP or EFV</td>
<td></td>
<td>Alternate: TDF + 3TC (or FTC) + DTG*</td>
</tr>
<tr>
<td>HIV/TB CO-INFECTION</td>
<td>AZT or TDF + 3TC (or FTC) + EFV</td>
<td></td>
<td>TDF+3TC (or FTC) + EFV400mgs</td>
</tr>
<tr>
<td>HIV/HBV CO-INFECTION</td>
<td>TDF + 3TC (or FTC) + EFV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Current first line ART options

Currently 3 molecules are looked into in greater detail to construct an ideal ART regimen – **Efavirenz 400, Dolutegravir (DTG) and Tenofovir Alafenamide Fumarate (TAF)**

- TDF(TAF) + XTC + EFV$_{600}$
- TDF + 3TC + EFV$_{400}$
- TDF(TAF)/ABC + XTC + DTG
Efavirenz 600mg

• 15 million person-years of experience supports the use of EFV 600 mg in a range of settings when combined with TDF and 3TC¹

• **Efavirenz**: Well demonstrated antiretroviral efficacy and favorable pharmacokinetics

• There are growing concern about its adverse effects related to neurological and neuropsychiatric reactions

<table>
<thead>
<tr>
<th>Skin</th>
<th>Liver</th>
<th>Nervous</th>
<th>Metabolic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV²</td>
<td>Rash</td>
<td>Hepatitis</td>
<td>Dyslipidaemia, Gynaecomastia</td>
<td>↓ plasma 25(OH) vitamin D, Teratogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression, Sleep disturbances, Headache, <strong>Suicidal ideation</strong>Φ</td>
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</tbody>
</table>

Φ "Severe effects" (events that can put a person's life at risk and represent a medical emergency)

ENCORE1 study:
(EFV 400 mg Vs 600 mg QD) + TDF/FTC

ENCORE-1 was a double-blind, placebo-controlled, non-inferiority trial done at 38 clinical sites in 13 countries

Argentina, Australia, Chile, Germany, Hong Kong, Israel, Malaysia, Mexico, Nigeria, Singapore, South Africa, Thailand, and the UK

The primary endpoint was the difference in the proportions of patients in the two treatment groups with a plasma HIV-1 viral load below 200 copies per mL at week 96.

ENCORE-1 Study
EFV 600mg Vs 400mg

• Findings suggest that EFV400 is non-inferior to standard dose of EFV600 (with BMI) with TDF/FTC during 48 wks in ART-naive adults with HIV-1 inf.
• Adverse events related to the study drug were more frequent with EFV-600 mg than with EFV-400 mg.
• Lower dose EFV should be recommended as part of routine care.
• At 96 weeks also finding remain the same
ENCORE1 (w96): Virologic response

- **HIV RNA < 200 c/mL**
  - mITT: 90.0% vs. 90.6%
  - Difference (95% CI): -0.6% (-5.2 to 4.0)

- **HIV RNA < 50 c/mL**
  - mITT: 86.7% vs. 86.3%
  - ITT, NC= F: 81.7% vs. 78.2%
  - Difference (95% CI): -0.4% (-5.8 to 4.9)

- **HIV RNA < 5 log**
  - mITT: 86.3% vs. 87.5%
  - ITT, NC= F: 83.1% vs. 82.1%

- **HIV RNA > 5 log**
  - mITT: 81.7% vs. 78.2%
  - ITT, NC= F: 83.1% vs. 82.1%

**Per protocol**

- **HIV RNA < 200 c/mL**
  - All patients: 94.3% vs. 95.3%
  - Difference (95% CI): -0.6% (-5.2 to 4.0)

- **HIV RNA < 50 c/mL**
  - All patients: 94.1% vs. 95.6%
  - Difference (95% CI): -0.6% (-5.2 to 4.0)

- **HIV RNA < 5 log**
  - All patients: 94.5% vs. 94.8%
  - Difference (95% CI): -0.6% (-5.2 to 4.0)

*Lancet Infect Dis 2015;15(7):793-802*
# Adverse events and serious adverse events

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz 400 mg group (n=321)</th>
<th>Efavirenz 600 mg group (n=309)</th>
<th>Difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events (total=3337)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Total number of adverse events</td>
<td>1653 (49.5%)</td>
<td>1684 (50.5%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>1202 (73%)</td>
<td>1236 (73%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>381 (23%)</td>
<td>363 (22%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>62 (4%)</td>
<td>77 (5%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>8 (1%)</td>
<td>8 (1%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Patients reporting adverse events</td>
<td>291 (91%)</td>
<td>285 (92%)</td>
<td>-1.6 (–2.8 to 5.9)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Patients with adverse event related to efavirenz</strong>*</td>
<td>126 (39%)</td>
<td>148 (48%)</td>
<td>–8.6 (–16.4 to –0.8)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Patients stopping efavirenz because of treatment-related adverse event</strong>*</td>
<td>16 (13%)</td>
<td>34 (23%)</td>
<td>–10.3 (–19.2 to –1.4)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of serious adverse events</td>
<td>32 (40%)</td>
<td>48 (60%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Patients reporting serious adverse events</td>
<td>24 (8%)</td>
<td>32 (10%)</td>
<td>–2.9 (–7.3 to 1.5)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Patients reporting serious adverse events related to efavirenz</strong>*</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
<td>–0.7 (–2.4 to 1.1)</td>
<td>0.44</td>
</tr>
</tbody>
</table>
How did we manage our pts in the pre-TLE400 era?

- 50% dose of TLE for pts below 35 kg wt, (up to even 40 kg)
- 75% dose of TLE for pts between 40-50 kg wt
- (One tab first day, ½ tab next day)
- Priming with ½ dose x 10 days
- Patients on their own did it
Is Dose Reduction in medicines new?

- **Chlorpheneramine Maleate** - 50%
- **Diadonosine (DDI)** - 250 mg for <50 kg, 400 mg for >60 kg
- **Stavudine (d4T)** - 30 mg BD <50 kg, 40 mg BD for >60 kg
- **Zidovudine (AZT)** - 600 mg to 400 mg in PMTCT, 300 mg in Thailand
- **Lamivudine (3TC)** - 300 mg in HIV, 100 mg in HBV
- **Ritonavir (with 3TC/AZT)** - 800 mg BD, in boosting 100 mg BD/OD
- **Indinavir (with backbone)** - 800 mg BD, then 800 BD and then 400 mg BD with boosting
- **DRV/r** - 600/100 BD ->900/100 OD -> 800/100 OD
TLE400 Advantages

- TLE400- licensed for use in naïve and t/t experienced PLHIV
- Pill burden maintained to one STR
- Safety profile, good CNS penetration, relatively few AE and few drug-drug interactions are advantages
- FDC size 1200 mg to 1000 mg—Reduced
- Cost ---- Reduced by 20%
- Adverse drug reactions --- Reduced
- Long term sustainability on TLE---Assured
- Suitable for low weight patients---Improved
- Long-term experience using EFV---Advantage
- Future regimens ----- Spared
- Hence over-all survival of HIV pts-Remains high

Gilada/UMRC, Mumbai
Pharmacokinetics of EFV 400mg with INH/RMP in people with HIV, Cerrone M et al, CROI 2018

- EFV Cmax, C24h and AUC0-24 were respectively 9%, 15% and 9% lower after four weeks of co-administration with INH/RIF vs EFV400 alone.
- Co-administration of EFV400 with INH/RIF was well-tolerated in 20/22 participants but resulted in >grade 3 ALT elevations in the remaining two.
- All participants maintained viral load <50 copies/mL.
- The investigators concluded that EFV400 can be co-administered with anti-TB treatment.
Dolutegravir in ART naive patients
SINGLE : Walmsley et al NEJM 2013

• Randomized, double-blind, phase 3 study involving adult participants who had not received previous therapy for HIV-1 infection and who had an HIV-1 RNA level of \( \geq 1000 \text{ copies per ml} \)

• Participants were randomly assigned to DTG at a dose of 50 mg plus ABC/L once daily (DTG–ABC–3TC group) or combination therapy with EFV–TDF/FTC once daily (EFV–TDF–FTC group).

• The primary end point was the proportion of participants with an HIV-1 RNA level of less than 50 c/ml at week 48.
Single: DTG vs EFV$_{600}$
SINGLE : Results : CD4

Change in CD4+ T-Cell Count

Adjusted Mean Change from Baseline (cells/mm³)

Difference in response at wk 48, 59 cells/mm³ (95% CI, 33–84) P<0.001

DTG–ABC–3TC, 267 cells/mm³
EFV–TDF–FTC, 208 cells/mm³

Baseline 2 4 8 12 16 24 32 40 48

Week
SINGLE : adverse events of DTG Vs EFV

<table>
<thead>
<tr>
<th>Event</th>
<th>Dolutegravir and Abacavir–Lamivudine (N=414)</th>
<th>Efavirenz–Tenofovir DF–Emtricitabine (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of participants (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of study drug†</td>
<td>10 (2)</td>
<td>42 (10)</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>2 (&lt;1)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>0</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Skin and subcutaneous-tissue disorder</td>
<td>2 (&lt;1)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>0</td>
<td>8 (2)</td>
</tr>
<tr>
<td>General disorder or administration-site condition</td>
<td>0</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Adverse event of grade 2–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8 (2)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21 (5)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (2)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17 (4)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (2)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (2)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (3)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (&lt;1)</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (1)</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Liver aminotransferase abnormality of grade 2–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated level of alanine aminotransferase</td>
<td>10 (2)</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Elevated level of aspartate aminotransferase</td>
<td>7 (2)</td>
<td>23 (5)</td>
</tr>
</tbody>
</table>
TB: DTG with RMP interaction

Journal of Acquir Immune Defic Syndrome 2013; 62:21
Lower DTG exposure in pregnancy

![Graph showing Dolutegravir Concentration (mcg/mL) vs Time Post-Dose (hours) for 2nd Trimester, 3rd Trimester, and Postpartum phases.]
## DTG and The competitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DTG</th>
<th>EFV&lt;sub&gt;600&lt;/sub&gt;</th>
<th>EFV&lt;sub&gt;400&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic Potency</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tolerability</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Genetic barrier to resistance</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>QD</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>STR</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Concomitant RMP</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Rapid viral decline</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Impact of transmitted resistance</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cost</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total score</td>
<td><strong>27</strong></td>
<td><strong>24</strong></td>
<td><strong>22</strong></td>
</tr>
</tbody>
</table>
NAMSAL ANRS 12313 study, Cournil A et al (Glasgow 2018)

- Conducted in Cameroon, where there is a high background rate of TDR
- **TDF/3TC/EFV400 Vs TDF/3TC/DTG** in treatment naïve patients
- Two-thirds of study participants had high VL >100,000 copies/ml, 30.5% had a VL >500,000 copies/ml
- After 48 weeks on treatment there was no significant difference in the proportion of participants in each arm who had a VL <50 copies/ml
- 74.5% in the DTG arm and 69% in the EFV arm
- 19 participants had VL >1000 copies/ml: 16 in EFV Vs 3 in DTG
- None of those on DTG showed any evidence of DRMs
- 9 people who received EFV 400mg developed drug resistance, in three cases to all the drugs in the regimen
- No significant difference in adverse events
Clinical trials of DTG use in treatment experienced patients

- **DAWNING**: DTG Vs LPV/r

- **SAILING**: DTG Vs RAL
  Activity of DTG in INSTI-Naive Pts With NRTI and/or PI Resistance

- **VIKING**: In RAL resistant pts
  The first clinical demonstration of the activity of any integrase inhibitor in subjects with HIV-1 resistant to Raltegravir.

  Subjects received DTG 50 mg OD (cohort I) or 50 mg BD (cohort II) while continuing a failing regimen (without RAL) through day 10 after which the background regimen was optimized
HIV, Pregnancy and ART

- HIV is associated with significant morbidity/mortality for the pregnant woman and her fetus/infant – treatment is required for both maternal health and to prevent MTCT

- Only limited data on ARVs in pregnancy/lactation;
  - of the 31 approved ARVs, mean lag between approval and any pregnancy data is 5 years
  - No data on 3/7 drugs approved since 2010

- Big unknowns, particularly for newer drugs:
  - Pharmacokinetics and safety in pregnancy and lactation
  - Fetal/infant safety

Courtesy: IAS President Anton Pozniak, Consultant Physician UK
Gilada/UMRC, Mumbai
Timing of *In Utero* ARV Exposure and Fetal Risk

![Diagram showing the timing of in utero ARV exposure and fetal risk.](image-url)
Timing of In Utero ARV Exposure

Greatest risk for serious defects is NOT in women starting during pregnancy but in those who conceive while receiving drug -

but most studies do not distinguish between 1st trimester exposure and preconception exposure.

Courtesy: IAS President Anton Pozniak, Consultant Physician UK
However, HIV-Uninfected Women Still Have Better Outcomes than HIV+ Women on DTG or EFV ART

Risk benefit

→ When started during pregnancy, EFV and DTG appear equivalent in terms of pregnancy outcomes (including birth defects)

→ But adverse outcomes with EFV or DTG ART are still higher than in HIV-uninfected women
Dolutegravir in Pregnancy

Balancing act

Benefit of Maternal Treatment

- DTG:
  - Rapid VL decline
  - Better tolerated
  - Less expensive

Risk of Adverse Fetal Effects

- DTG:
  - Potential signal for neural tube defect with preconception exposure

Courtesy: IAS President Anton Pozniak, Consultant Physician UK
## WHO 2018 recommendations for first-line

<table>
<thead>
<tr>
<th>Population</th>
<th>Preferred</th>
<th>Alternatives</th>
<th>Special situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult men and adolescent boys</td>
<td>TLD&lt;sup&gt;a&lt;/sup&gt;&lt;br&gt;TDF/3TC/DTG</td>
<td>TLE600&lt;br&gt;TLE400</td>
<td>AZT+3TC+EFV600&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pregnant (from eight weeks after conception) and breastfeeding women and adolescent girls</td>
<td></td>
<td></td>
<td>TDF+3TC (or FTC)+PI/r&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women and adolescent girls with effective contraception or not of childbearing potential</td>
<td>TLE600&lt;br&gt;TDF/3TC/EFV</td>
<td>TLE400&lt;br&gt;TDF+3TC (or FTC)+PI/r&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AZT+3TC+EFV600&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Women and adolescent girls of childbearing potential who want to become pregnant and have no effective contraception</td>
<td>TLE600&lt;br&gt;TDF/3TC/EFV</td>
<td>TLE400&lt;br&gt;TDF+3TC (or FTC)+PI/r&lt;sup&gt;c&lt;/sup&gt;</td>
<td>TDF+3TC (or FTC)+RAL</td>
</tr>
</tbody>
</table>

<sup>a</sup> TLD: TDF/3TC/DTG

<sup>b</sup> EFV600

<sup>c</sup> FTC, PI, RAL
Comparing preferred and alternative 1\textsuperscript{st} line ART options in adults/adolescents with HIV

DHHS, EACS and WHO ART guidelines

<table>
<thead>
<tr>
<th>GUIDELINES</th>
<th>NRTI BACKBONE</th>
<th>NNRTI</th>
<th>INSTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAF/XTC</td>
<td>TDF/XTC</td>
<td>ABC/3TC</td>
<td>AZT/3TC</td>
</tr>
<tr>
<td>EACS (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHHS (2018)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO (2018)</td>
<td><em>red</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- preferred
- alternative
- not recommended/use in special situations

* In childbearing age women and adolescent girls, DTG should be used with consistent and reliable contraception.

[World Health Organization Logo]
Dolutegravir: Special Advantages

• Barrier to resistance
• Forgiving
• No cross resistance, can be still used in RAL resistant pts
• Requires less frequent lab support
• Pts who are averse to taking large pills
• Circumstance like - Immigration, surgery, pt reports late in pregnancy, discordant couples, wanting to conceive from PLHIV
• When u need robust response
  - Very bad clinical condition
  - Very poor CD4
Reasons to Choose or Change Therapy

Substitution v/s Switch

- Toxicity – silent medicines preferred
- Treatment Failure
  - Clinical failure
  - Immunologic failure
  - Virologic failure – Robust medicines preferred
- Pregnancy (DTG dose double)-Adv. DRV/r
- Treatment of active TB (DTG dose double)
- Non-adherence
TDF risk factors for bone disease and renal dysfunction

- Older than 60 years of age
- Postmenopausal females
- Osteoporosis based on hip and/or spine T-score
- CKD - stage ≥ 2 (baseline eGFR_{CG} < 90 mL/min)
- Urine albumin: Creatinine > 30 mg/g
- Serum phosphate < 2.5 mg/dL
- Body mass index < 18.5 or ≥ 30
- Hypertension, diabetes mellitus, CVD or hyperlipidemia
- Use of TDF with protease inhibitors
- Concomitant use of nephrotoxic drugs like NSAID’s

Gilada/UMRC, Mumbai
# TDF vs TAF

<table>
<thead>
<tr>
<th>No</th>
<th>TDF</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tenofovir Disoproxil Fumarate</td>
<td>Tenofovir Alafenamide Fumarate</td>
</tr>
<tr>
<td>2.</td>
<td>In blood TDF-TFV- cells- TDFDP (active form)</td>
<td>In blood TAF-Cells- TFV-TDFDP (active form)</td>
</tr>
<tr>
<td>3.</td>
<td>Increased level of TFV in blood- Causing renal tubulopathy and decrease in bone mineral density</td>
<td>Plasma levels of TFV 90% lower with TAF, Smaller decreases in BMD in DEXA Scans</td>
</tr>
<tr>
<td>4.</td>
<td>300 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>5.</td>
<td>-</td>
<td>Smaller increase in S.creatinine levels</td>
</tr>
<tr>
<td>6.</td>
<td>-</td>
<td>Smaller decrease in eGFR rates</td>
</tr>
</tbody>
</table>

All statistically significant

Gilada/UMRC, Mumbai
TAF vs TDF: Mechanism of Action

TAF use in treatment naïve patients

- Cobicistat/Elvitegravir/Emtricitabine/TAF (Quad)
- RAL /FTC/TAF
- DTG /FTC/TAF

are recommended as first-line HIV regimens in the DHHS and the International Antiviral Society-USA panel guidelines

In addition

- FTC/RPV/TAF
- DRVr / FTC/TAF
- Cobi/DRVr /FTC/TAF are included as recommended first-line regimens in the EACS guidelines
TAF in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study (Pozniak et al, JAIDS 2016)

- Enrolled VL suppressed HIV-1-infected subjects with estimated creatinine clearance (CrCl) 30–69 mL/min in a single-arm, open-label study to switch regimens to E/C/F/TAF
- Enrolled and treated 242 patients with mean age 58 years, 18% Black, 39% hypertension, 14% diabetes
- Two patients (0.8%) discontinued study drug for decreased CrCl, neither had evidence of renal tubulopathy and both had uncontrolled hypertension
- 92% percent (222 patients) maintained HIV-1 RNA < 50 copies/ml at week 48.
Studies 104/111: TAF-Based Regimen Superior to TDF Through 144 Weeks in Treatment-Naive Patients (CROI 2017)

• Week 144 analysis of studies 104 and 111: 2 parallel, randomized, double-blind, controlled phase III studies
• Summary of Key Conclusions
• In 2 phase III trials, treatment with TAF superior to TDF for treatment-naive patients at Week 144 when both coformulated with EVG/COBI/FTC
  – Rate of HIV-1 RNA < 50 copies/mL: 84% vs 80%
  – Rate of HIV-1 RNA < 20 copies/mL: 81% VS 76%
• Low rates of emergent resistance at virologic failure in both arms
• TAF-based regimen associated with significantly less deleterious effects on renal biomarkers and bone mineral density over 144 weeks vs TDF regimen
• TAF-based regimen associated with significantly increased levels of fasting lipids through 144 weeks vs TDF regimen
• Investigators concluded that long-term data on safety, tolerability, and durability support initiating and continuing HIV treatment with TAF-containing regimen

Gilada/UMRC, Mumbai
# Recommendations for ART in Pts With Selected O.Is.

## Opportunistic Infection | DHHS Recommendation for ART
--- | ---
**Pneumocystis pneumonia** | Start ART within 2 wks of PCP diagnosis

**Toxoplasma gondii encephalitis** | Many clinicians start ART within 2-3 wks
   | Based on A5164 study, in which the 282 pts with OIs included 13 pts (5%) with toxoplasmosis

**Mycobacterium tuberculosis** | Start ART within 2 wks if CD4+ < 50 cells/mm³, by 8-12 wks for all others
   | Consider DDIs, adherence support

**Cryptosporidiosis** | Start ART as part of OI management

**Cryptococcal meningitis** | Consider delaying ART until after antifungal induction (2 wks) or induction/consolidation (10 wks)

DHHS Guidelines. November 2015
## ATV/r Vs LPV/r Vs DRV/r

<table>
<thead>
<tr>
<th>Major parameters</th>
<th>ATV/r</th>
<th>LPV/r</th>
<th>DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency with paediatric regimens</td>
<td>No&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Yes</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of pills per day (standard dose as a fixed-dose combination)</td>
<td>1</td>
<td>4</td>
<td>2–4</td>
</tr>
<tr>
<td>Convenience (once- versus twice-daily regimen)</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Safety in pregnancy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gastrointestinal intolerance (diarrhoea)</td>
<td>Not frequent</td>
<td>Common</td>
<td>Not frequent</td>
</tr>
<tr>
<td>Availability of co-formulations (as heat-stable fixed-dose combinations)</td>
<td>Yes</td>
<td>Yes</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Use with a TB treatment regimen that contains rifampicin</td>
<td>No</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Accessibility in countries (registration status)</td>
<td>Moderate</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Availability of generic formulations</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**2018**

- Reduced to 1-2
- DRV/r avl
- Yes

---


Gilada/UMRC, Mumbai
Positioning of DRV/r

1. Simplification of 600/100mg BD to 800/100 OD

2. As a second line agent
   • Vs LPV/r: Pill burden, toxicity (GI and lipids)
   • Vs ATZ/r: Intolerance- Hyperbilirubinemia, icterus

3. As a third line agent
   • Along with OBR
   • Low prevalence of DRM in second line failure
Advantage – DRV/r

• Older two Ds (d4T and DDI) changed to new two Ds (DTG and DRV)
• If pills burden is the issue, it is reduced
• If BD is the issue, it is now OD
• If FDC is the issue, it is now FDC
• If cost is the issue – it is reduced
• If resistance is suspected- use DTG or DRV
• Excellent genetic barrier to resistance
## Summary of Uses of ARVs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EFV400</th>
<th>DTG</th>
<th>TAF</th>
<th>DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/t naïve pts</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>T/t experienced pts</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (preferred in pts with low VL, no baseline DRM)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Yes (But RCT pending)</td>
<td>Conception- No Afterwards -Yes</td>
<td>No (RCT awaited)</td>
<td>Yes</td>
</tr>
<tr>
<td>HIV/TB co-infection</td>
<td>Yes (But RCT pending)</td>
<td>Yes But double dose</td>
<td>May be Yes (But RCT awaited)</td>
<td>Yes along with Rifabutin</td>
</tr>
<tr>
<td>PEP</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Alternative to DTG</td>
</tr>
</tbody>
</table>

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TEMPRANO Study

- Was a study conducted in 9 HIV care centers in Ivory Coast
- From March 2008 to January 2015
- 2076 patients
- Inclusion Criteria: HIV-1 inf., >18 years, CD4 Count >800 cells/cu.mm
- TDF+FTC+EFV, ZDV, or LPV/r
- 2x2 factorial study: EarlyART, EarlyART+IPT, WHO ART, WHO ART+IPT
- Primary end point: Severe HIV morbidity ((AIDS-defining diseases, non-AIDS-defining malignancy, or non-AIDS-defining invasive bacterial diseases), or any-cause mortality at 30 months.
- The secondary endpoint was any other grade 3-4 defining morbidity.
- Tested for interaction between Early ART and IPT
Injectable drugs in HIV infection

- LATTE-2 study
- Injection Cabotegravir (INSTI)
- Injection Rilpivirine (NNRTI)

Long-acting drugs given in combination every 4 or 8 weeks after oral suppression

Some people may prefer long acting injections to daily oral medication

94%/95%/91%
By 3 methods we may learn wisdom

1. First, by reflection, which is noblest;
2. Second, by imitation, which is easiest; &
3. Third by experience, which is the bitterest.

- Confucius
Thank you all very much &
Wish you a Happy, Healthy and Promising New Year 2019!