WHO recommendations on the use of Dolutegravir and other ARVs in adults and adolescents with HIV

*Update from IAS 2019*

Giovanni Ravasi, Advisor HIV/STI Care and Treatment

PAHO/WHO

PANCAP Webinar Series
Outline

• Context (treatment, policies, HIV resistance)
• Rapid evolution of WHO recommendations (2018-2019)
• Focus on 1st and 2nd line ART update (adults, adolescents, women of child bearing potential – WCBP and pregnancy)

Next webinar will focus on ART in children!

https://www.who.int/hiv/pub/arv/en/
Increase in people receiving ART over time (62% ART coverage in 2018)

Source: UNAIDS/WHO estimates
Uptake of major HIV treatment policies in LMICs

**Treat All**

**DTG transition**
Nationally Representative Surveys of Pretreatment HIVDR (PDR) among Adults Initiating ART (2014-2018)

39 countries started
• 25 completed
• 14 ongoing
18 planned

2019 WHO HIVDR Report

Status of HIV pre-treatment drug resistance surveillance in Caribbean countries (Aug 2019)

<table>
<thead>
<tr>
<th>Completed</th>
<th>Ongoing</th>
<th>Planning</th>
<th>No information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuba, Jamaica, OECS, Suriname</td>
<td>Haiti, Barbados</td>
<td>Dominican Republic, Trinidad and Tobago</td>
<td>Bahamas, Belize, Guyana</td>
</tr>
</tbody>
</table>

Survey ongoing: 🔵
Survey planned: 🔵
Data not available: 📸
Not applicable: 🗑

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER) World Health Organization
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Prevalence of PDR to NNRTI, by Country

Honduras 2016
Cuba 2017
South Africa 2017
Nicaragua 2016
Papua New Guinea 2017
Uganda 2016
Namibia 2015
Guatemala 2016
Argentina 2014
Zimbabwe 2015
Eswatini 2016
Nepal 2016
Mexico 2017
Cameroon 2015
Brazil 2013
Colombia 2016
Myanmar 2016
Vietnam 2017

PDR NNRTI >10%
Africa (5): South Africa, Uganda, Namibia, Zimbabwe, Eswatini; Central/South America (5): Argentina, Honduras, Cuba, Nicaragua, Guatemala; South East Asia (2): Nepal, PNG.
Prevalence of PDR, by Drug and by Country

- Honduras 2016
- Cuba 2017
- Nicaragua 2016
- Papua New Guinea 2017
- Uganda 2016
- Namibia 2015
- Guatemala 2016
- Argentina 2014
- Zimbabwe 2015
- Eswatini 2016
- Nepal 2016
- Mexico 2017
- Cameroon 2015
- Brazil 2013
- Colombia 2016
- Myanmar 2016
- Vietnam 2017

- NVP
- EFV
- EFV/NVP and NRTI
- TDF 0-4.5%
- XTC 0-5.7%
Prevalence of NNRTI PDR, by Gender

Pooled analysis of country data:
NNRTI PDR is significantly higher in women (11.8%) vs men (7.8%) p=0.005
Prevalence of NNRTI PDR among First-Line Initiators, by Reported Prior Exposure to ARV Drugs

NNRTI PDR is nearly 3 times higher in ART re-initiators reporting prior ARVs exposure: 21.1% (prior ARV drug exposed) vs 7.8% (naive); p≤0.0001.
2018 WHO recommendations: First-line ART regimens

1. A dolutegravir (DTG)-based regimen is recommended as the preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)
   - Adults and adolescents (moderate-certainty evidence)
   - Women and adolescent girls of childbearing potential (very-low-certainty evidence)
   - Infants and children with approved DTG dosing (low-certainty evidence)

2. A raltegravir (RAL)-based regimen may be recommended as an alternative first-line regimen for infants and children for whom approved DTG dosing is not available (conditional recommendation, low-certainty evidence).

3. A RAL-based regimen is recommended as the preferred first-line regimen for neonates (conditional recommendation, very-low-certainty evidence)

*WHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.
In mid-2016, dolutegravir rolled out nationally in Botswana to all adults (including pregnant women), allowing for inclusion of DTG exposure in comparative analyses.

Tsepamo provided the first data on safety of DTG when starting during pregnancy.

- No increased signal for congenital abnormalities among 280 women who started DTG during the first trimester (median 10 weeks GA).

Zash et al. Lancet GH, 2018
In April 2018, we were asked by WHO to provide any preliminary data available for upcoming HIV guidelines committee meeting for women on DTG from conception.

<table>
<thead>
<tr>
<th>NTDs/Exposures</th>
<th>4/426</th>
<th>14/11,300</th>
<th>3/5,787</th>
<th>0/2,812</th>
<th>61/66,057</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.94% (0.37%, 2.4%)</td>
<td>0.12% (0.07%, 0.21%)</td>
<td>0.05% (0.02%, 0.15%)</td>
<td>0% (0%, 0.13%)</td>
<td>0.09% (0.07%, 0.12%)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>0.82% (0.24%, 2.3%)</td>
<td>0.89% (0.31%, 2.3%)</td>
<td>0.94% (0.35%, 2.4%)</td>
<td>0.85% (0.27%, 2.3%)</td>
</tr>
</tbody>
</table>

May 2018: Possible DTG Safety Signal Reported
Note of caution for using DTG in women and adolescent girls of childbearing potential

• Exposure to DTG at the time of conception may be associated with NTD risk among infants.

• DTG appears to be safe when started after the period of risk of neural tube defects (ie, up to 8 weeks after conception).

• Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent contraception (hormonal contraception and DTG have no reported or expected drug–drug interactions).

• An EFV-based regimen is a safe and effective first-line regimen and can be used among women of childbearing potential during the period of potential risk for developing NTDs.

• National programmes should consider the balance of benefits and risks when selecting the optimal ARV regimen for women and adolescent girls of childbearing potential (fertility levels, contraceptive availability and coverage, pretreatment resistance to NNRTIs at the population level, drug availability and the maternal and infant toxicity profile).

**BOX 3. A WOMAN-CENTRED APPROACH**

Woman-centred health services involve an approach to health care that consciously adopts the perspectives of women and their families and communities. This means that health services see women as active participants in and beneficiaries of trusted health systems that respond to women’s needs, rights and preferences in humane and holistic ways. Care is provided in ways that respect women’s autonomy in decision-making about their health, and services must provide information and options to enable women to make informed choices. The needs and perspectives of women, their families and communities are central to providing care and to designing and implementing programmes and services. A woman-centred approach is underpinned by two guiding principles: promoting human rights and promoting gender equality.

Source: Consolidated guideline on sexual and reproductive health and rights of women living with HIV (3).
Access to DTG as preferred 1\textsuperscript{st} line among WCBP, April 2019

24 countries

- 24 countries

- All WCBP
  - NO-DTG based regimen
  - 4 countries
    - Burundi, Eswatini, Mozambique, Rwanda

- WCBP on Contraception
  - Access DTG
  - 15 countries
    - ANY contraception
      - 2 countries
        - Haiti
        - Ukraine
      - 7 countries
        - Botswana, Brazil, DRC, Kenya, Nigeria, South Africa, Venezuela
    - Long Acting Contraception
      - 6 countries
        - Cote d'Ivoire, Ethiopia, Ghana, Niger, Senegal, Zambia

- Informed Choice
  - 5 Countries
    - Lesotho, Malawi, Tanzania, Uganda, Zimbabwe
PICO questions for 2019 update

**DTG in 1\(^{st}\) line**

- **PICO 1a**: Should DTG-based regimens be recommended as the preferred first-line with an NRTI backbone for the treatment of HIV in adults and adolescents?

- **PICO 1b**: Should PI-based regimens be recommended as the alternative first-line for the treatment of HIV in women and adolescent girls of childbearing potential in settings with poor access to contraception and high levels of NNRTI resistance?

**DTG in 2\(^{nd}\) line**

- **PICO 2**: Should DTG be recommended as the preferred second-line antiretroviral agent in combination with an optimized NRTI backbone for the treatment of HIV?

**Role of EFV\(_{400}\)**

- **PICO 3**: Should EFV\(_{400}\) be used as an alternative to EFV\(_{600}\) in combination with an NRTI backbone for the treatment of HIV in adults and adolescents?

**Role of TAF**

- **PICO 4**: Should TAF be used as an alternative to TDF in combination with 3TC (or FTC) in the NRTI backbone for the treatment of HIV?

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**What is new relative to 2018 review?**

- New data from key studies (ADVANCE, DAWNING, DOLPHIN, NAMSAL, TSEPAMO) – some data is confidential
- Additional outcomes were included/expanded
  - Time to VL suppression
  - Maternal & birth outcomes (including NTDs)
  - Adverse events: body weight gain, CNS, bone, renal and metabolic effects (grade 3-4)
- More subpopulations: women and adolescents in childbearing age
### Safety and Efficacy of DTG and EFV$_{600}$ in 1$^{st}$ line ART

(summary 2019 WHO Sys Review & NMA)

<table>
<thead>
<tr>
<th>major outcomes</th>
<th>DTG vs EFV$_{600}$</th>
<th>quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment discontinuation (any or due AEs)</td>
<td>DTG better</td>
<td>high</td>
</tr>
<tr>
<td>Viral suppression (4-96 weeks), viral suppression at delivery (PW), transmission (PW)</td>
<td>DTG probably better</td>
<td>high to moderate</td>
</tr>
<tr>
<td>CD4 recovery (24-144 weeks)</td>
<td>DTG probably better</td>
<td>high to moderate</td>
</tr>
<tr>
<td>Mortality</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>Neuropsychiatric AEs (any grade), depression (grade 3 or 4), dizziness (any grade)</td>
<td>DTG probably better</td>
<td>moderate to low</td>
</tr>
<tr>
<td>Sleep disorders (any grade)</td>
<td>comparable</td>
<td>very low</td>
</tr>
<tr>
<td>Body weight gain</td>
<td>EFV probably better</td>
<td>moderate</td>
</tr>
<tr>
<td>NTD</td>
<td>EFV may be better</td>
<td>low</td>
</tr>
<tr>
<td>HIVDR (overall, NRTI or anchor drug)</td>
<td>DTG probably better</td>
<td>high to moderate</td>
</tr>
</tbody>
</table>

Reference: Steve Kanters, For WHO ARV GDG, 5-7 June 2019
Safety and Efficacy of EFV$_{400}$ and EFV$_{600}$ in 1$^{\text{st}}$ line ART (PICO 3) (summary 2019 WHO Sys Review & NMA)

<table>
<thead>
<tr>
<th>major outcomes</th>
<th>EFV$<em>{400}$ vs EFV$</em>{600}$</th>
<th>quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment discontinuation (due AEs)</td>
<td>EFV400 better</td>
<td>high to moderate</td>
</tr>
<tr>
<td>Viral suppression (48-96 weeks), VL suppression if baseline &gt; 100,000 (48 weeks)</td>
<td>comparable</td>
<td>moderate</td>
</tr>
<tr>
<td>CD4 recovery (24-96 weeks)</td>
<td>comparable</td>
<td>moderate</td>
</tr>
<tr>
<td>Mortality</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>Neuropsychiatric AEs (any grade), depression (grade 3 or 4), dizziness (any grade), sleep disorders (any grade)</td>
<td>comparable</td>
<td>low to very low</td>
</tr>
<tr>
<td>Body weight gain</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>Treatment related adverse events</td>
<td>EFV400 better</td>
<td>moderate</td>
</tr>
<tr>
<td>HIVDR (overall, NRTI or anchor drug)</td>
<td>comparable</td>
<td>very low</td>
</tr>
</tbody>
</table>

Reference: Steve Kanters, For WHO ARV GDG, 5-7 June 2019
### Current optimization profiles of new ARV drugs comparative analysis

<table>
<thead>
<tr>
<th>Optimization criteria</th>
<th>DTG</th>
<th>EFV&lt;sub&gt;400&lt;/sub&gt;</th>
<th>TAF</th>
<th>DRV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy and safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic potency</td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
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<tr>
<td>Lower toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High genetic barrier to resistance</td>
<td></td>
<td>yes</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Simplification</strong></td>
<td></td>
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<tr>
<td>Available as generic FDC</td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
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<tr>
<td>Low pill burden/pill size</td>
<td></td>
<td>yes</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Harmonization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in pregnant women</td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in childbearing age women</td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in children</td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in HIV-associated TB</td>
<td></td>
<td>yes</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Few drug interactions</td>
<td></td>
<td>yes</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low price</td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:
- **Green**: yes
- **Red**: no
- **Yellow**: ongoing studies
2019 WHO recommendations: First-line ART regimens

First-line ART regimens*

1. Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART
   - Adults and adolescents* (strong recommendation, moderate-certainty evidence)
   - Infants and children with approved DTG dosing (conditional recommendation, low-certainty evidence)

2. Efavirenz at low dose (EFV 400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART* (strong recommendation, moderate-certainty evidence)

3. A raltegravir (RAL)-based regimen may be recommended as the alternative first-line regimen for infants and children for whom approved DTG dosing is not available (conditional recommendation, low-certainty evidence)

4. A RAL-based regimen may be recommended as the preferred first-line regimen for neonates (conditional recommendation, very-low-certainty evidence)

*See Table 1 for ARV drug selection.
*See Box 2 on women and adolescent girls of childbearing potential using DTG.
*Except in settings with pretreatment HIV drug resistance to EFV/nevirapine (NVP) exceeding 10%.
2019 WHO recommendations: First-line ART regimens

Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential.

DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester).

If women identify pregnancy after the 1st trimester, DTG should be initiated/continued for the duration of the pregnancy.
Since May 2018
1 NTD/1275 additional exposures to DTG at conception

<table>
<thead>
<tr>
<th>NTDs/Exposures</th>
<th>5/1683</th>
<th>15/14792</th>
<th>3/7959</th>
<th>1/3840</th>
<th>70/89372</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.30% (0.13, 0.69)</td>
<td>0.10% (0.06, 0.17)</td>
<td>0.04% (0.01, 0.11)</td>
<td>0.03% (0.0, 0.15)</td>
<td>0.08% (0.06, 0.10)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>0.20% (0.01, 0.59)</td>
<td>0.26% (0.07, 0.66)</td>
<td>0.27% (0.06, 0.67)</td>
<td>0.22% (0.05, 0.62)</td>
</tr>
</tbody>
</table>
### Adverse Birth Outcomes: Conception EFV vs. DTG*

<table>
<thead>
<tr>
<th></th>
<th>DTG-conception (N=1,271)</th>
<th>EFV-conception (N=4,430)</th>
<th>Adjusted RR (95% CI)#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse birth outcome</td>
<td>422 (33.2%)</td>
<td>1,550 (35.0%)</td>
<td>0.94 (0.86,1.02)</td>
</tr>
<tr>
<td>Any severe birth outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SB, NND, vPTB, vSGA)</td>
<td>151 (11.9%)</td>
<td>568 (12.8%)</td>
<td>0.89 (0.74,1.05)</td>
</tr>
</tbody>
</table>

No difference between DTG and EFV for any individual adverse birth outcome:
1. Preterm <37 weeks
2. Very Preterm <32 weeks
3. Small for Gestational Age (<10th %tile)
4. Very Small for Gestational Age (<3rd %tile)
5. Stillbirth
6. In-hospital Neonatal Death <28 days

*Analysis conducted among singleton births since October 2016 # All models adjusted for maternal age, gravida and low education

A Modeling Study

Caitlin M. Dugdale, MD; Andrea L. Ciaranello, MD, MPH; Linda-Gail Bekker, MD, PhD; Madeline E. Stern, BA; Landon Myer, MBChB, PhD; Robin Wood, MMed, DSc (Med); Paul E. Sax, MD; Elaine J. Abrams, MD; Kenneth A. Freedberg, MD, MSc; and Rochelle P. Walensky, MD, MPH
WCP newly initiating ART in South Africa
219,300 WCP per year (5 years) (~1.1 million)
NNRTI PTDR of 10.7%;
SA-age specific fertility
and their 250,000 HIV-exposed infants

ART strategies
EFV / DTG / DTG-C (DTG if LA contraception)

Assumed efficacy and adverse events with DTG vs EFV based on NMA

<table>
<thead>
<tr>
<th>Treatment efficacy &amp; adverse event assumptions</th>
<th>EFV</th>
<th>DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 week virologic suppression to &lt;50 c/mL for new ART starts without NNRTI PDR, %</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Adverse events leading to switch to PI-based ART, %</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

• VL monitoring: SA guidelines
• NTD risk per Tseampo May 2019; 100% mortality
• MTCT calculated for in utero / intrapartum / postpartum ± ART ± viral suppression (until end BF)

Outcomes: WCP – VL<50, death, sexual transmission; Children – NTDs, MTCT, death, HIV-free survival

HIV SYNTHESIS

WCP wanting more children & newly initiating ART in SSA in population 10 million adults (20 years)
500 setting scenarios (epidemic & program settings generated from epidemic start & projected forward; scenarios are also varied)

Median values over setting scenarios
HIV prevalence 13%
HIV incidence 0.86/100py
3 90s 85 / 90 / 86
NNRTI PDR 9%
Fertility 12% of women age 15-65 give birth/yr

ART strategies
TLE/ZL-PI: TDF + 3TC + EFV or TLD: TDF + 3TC + DTG

Potency of DTG = EFV; 13x lower rate of resistance
• DTG weight gain: in WCP: ↑ death/morbidity; in pregnancy: ↑ stillbirths & neonatal deaths
• VL monitoring: WHO guidelines; varying coverage
• NTD risk per Tseampo May 2019; 100% mortality (1 DALY added to mother until end of analysis)
• MTCT depends on maternal VL (9% until end BF)

Outcomes: WCP – VL<50, death, sexual transmission; Children – NTDs, MTCT; Both: DALYs & costs
CEPAC: Tsepamo May 2019 NTD risk, NMA ARV efficacy, PDR 10.7%
For every 1 NTD averted with use of EFV compared to DTG, it is predicted that there will be this many additional outcomes:

**EFV vs DTG**
- 5 Deaths among women
- 22 Sexual transmissions
- 4 MTCT transmissions
- <1 child deaths*
- 0.3 more child deaths

**DTG**
- 1 more NTDs
- <1 fewer child deaths* Fewer child deaths with DTG vs EFV

**DTG-C**
- 0 more NTDs*
- 0 more child deaths*
- 1 more women alive
- 3 more women alive
- 13 more men without HIV
- 5 more men without HIV
- 3 fewer MTC transmissions
- 0 fewer MTC transmissions*
- 3 more children alive and HIV-free
- 0 more children alive and HIV-free*

*<n<0.5; #n=0; numbers ≥0.5 rounded up

What would be the negative outcomes of avoiding any excess NTDs by using EFV?

With Tsepamo May 2019 assumptions, there would be **0.3 more child deaths per NTD averted with use of EFV**, due to the additional HIV-infected children with EFV vs DTG.

CEPAC: May 2019 Tsepamo ARV efficacy per NMA, PDR 10.7%
For every 1000 South African WCP with HIV starting ART, per year, compared with EFV (average over 5 yrs):
HIV SYNTHESIS

What would be the negative outcomes of avoiding any excess NTDs by using EFV?

SYNTHESIS does not model mortality of children with HIV explicitly, but child HIV-related morbidity/mortality included in mother’s DALYs → Each NTD/NND averted using TLE would result in 125 additional child DALYs lost.

SYNTHESIS: Tsepamo May 2019 NTD risk, incl. ADVANCE/NAMSAL, PDR 9%
For every 1 adverse infant outcome (NTD+NND) averted with use of TLE compared to TLD, it is predicted that there will be this many additional outcomes:

**TLDA vs TLE**
- 21 Deaths among women
- 26 Sexual transmissions
- 14 MTCT transmissions
- Difference in child deaths not modelled
- 125 additional DALYs

SYNTHESIS: May 2019 Tsepamo Incl. NAMSAL/ADVANCE, PDR 9%
For every 1000 WCP wanting more children starting ART, per year, compared with TLE (average over 20 years):

- 2 more NTD
- 1 more NND
- 38 more women alive
- 35 fewer sexual transmissions
- 29 fewer MTC transmissions
- 125 additional DALYs

SYNTHESIS does not model mortality of children with HIV explicitly, but child HIV-related morbidity/mortality included in mother’s DALYs → Each NTD/NND averted using TLE would result in 125 additional child DALYs lost.

*numbers ≥0.5 rounded up*
Conclusions

Both models show that for WCP initiating ART use of EFV rather than DTG in order to avoid NTDs would likely lead to other substantial negative impacts at population level.

**CEPAC: Tsepamo May 2019 NTD risk, NMA ARV efficacy, PDR 10.7%**

For every 1 NTD averted with use of **EFV** compared to **DTG**, it is predicted that there will be this many additional outcomes:

**EFV vs DTG**
- 5 Deaths among women
- 22 Sexual transmissions
- 4 MTCT transmissions
- <1 more child deaths*
- 0.3 more child deaths

**SYNTHESIS: Tsepamo May 2019 NTD risk, incl. ADVANCE/NAMSAL, PDR 9%**

For every 1 adverse infant outcome (NTD+NND) averted with use of **TLE** compared to **TLD**, it is predicted that there will be this many additional outcomes:

**TLD vs TLE**
- 21 Deaths among women
- 26 Sexual transmissions
- 14 MTCT transmissions
- Difference in child deaths not modelled
- 125 additional DALYs
Community Voices Clear

Unanimous decision based on the data currently available that DTG’s benefits – reduced side effects, improved efficacy, and a high barrier to resistance – outweigh its potential risks.

Concluded that blanket exclusions that deny women equitable access to this optimal HIV treatment are not warranted or justified.
Safety and Efficacy of DTG and PIs (LPVr) in 2nd line ART (summary 2019 WHO Sys Review & NMA)

<table>
<thead>
<tr>
<th>major outcomes</th>
<th>DTG vs LPVr</th>
<th>quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression (4-96 weeks)</td>
<td><strong>DTG better</strong></td>
<td>high</td>
</tr>
<tr>
<td>Viral suppression baseline VL &gt; 100,000 (48 weeks)</td>
<td>comparable</td>
<td>moderate</td>
</tr>
<tr>
<td>CD4 recovery (24-48 weeks)</td>
<td>comparable</td>
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<td>Mortality</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>Neuropsychiatric AEs (any grade)</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>Treatment related SAE</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>Treatment emergent AE, related AEs</td>
<td><strong>DTG probably better</strong></td>
<td>high</td>
</tr>
<tr>
<td>Treatment discontinuation (any or due AEs)</td>
<td><strong>DTG probably better</strong></td>
<td>high</td>
</tr>
<tr>
<td>HIVDR (overall)</td>
<td>comparable</td>
<td>very low</td>
</tr>
</tbody>
</table>

Reference: Steve Kanters, For WHO ARV GDG, 5-7 June 2019
2019 WHO recommendations: Second-line ART regimens

**Second-line ART regimens**

1. DTG in combination with an optimized NRTI backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.
   - Adults and adolescents\(^a\) (conditional recommendation, moderate-certainty evidence)
   - Children with approved DTG dosing (conditional recommendation, low-certainty evidence)

2. Boosted protease inhibitors in combination with an optimized NRTI backbone is recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing (strong recommendation, moderate-certainty evidence)

\(^a\)Table 2 for ARV drug selection.
\(^b\)See Box 2 on women and adolescent girls of childbearing potential using DTG.
2019 WHO recommendations: Second-line ART regimens

Table 2. Preferred and alternative second-line ART regimens

<table>
<thead>
<tr>
<th>Population</th>
<th>Failing first-line regimen</th>
<th>Preferred second-line regimen</th>
<th>Alternative second-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents</td>
<td>TDF&lt;sup&gt;b&lt;/sup&gt; + 3TC (or FTC) + DTG&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AZT + 3TC + ATV/r (or LPV/r)</td>
<td>AZT + 3TC + DRV/r&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + EFV (or NVP)</td>
<td>AZT + 3TC + DTG&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AZT + 3TC + ATV/r (or LPV/r or DRV/r)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV (or NVP)</td>
<td>TDF&lt;sup&gt;b&lt;/sup&gt; + 3TC (or FTC) + DTG&lt;sup&gt;c&lt;/sup&gt;</td>
<td>TDF&lt;sup&gt;b&lt;/sup&gt; + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children and infants</td>
<td>ABC + 3TC + DTG&lt;sup&gt;e&lt;/sup&gt;</td>
<td>AZT + 3TC + LPV/r (or ATV/r)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>AZT + 3TC + DRV/r&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ABC (or AZT) + 3TC + LPV/r</td>
<td>AZT (or ABC) + 3TC + DTG&lt;sup&gt;e&lt;/sup&gt;</td>
<td>AZT (or ABC) + 3TC + RAL</td>
</tr>
<tr>
<td></td>
<td>ABC (or AZT) + 3TC + EFV</td>
<td>AZT (or ABC) + 3TC + DTG&lt;sup&gt;e&lt;/sup&gt;</td>
<td>AZT (or ABC) + 3TC + LPV/r (or ATV/r)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + NVP</td>
<td>ABC + 3TC + DTG&lt;sup&gt;e&lt;/sup&gt;</td>
<td>ABC + 3TC + LPV/r (or ATV/r&lt;sup&gt;g&lt;/sup&gt; or DRV/r&lt;sup&gt;g&lt;/sup&gt;)</td>
</tr>
</tbody>
</table>

<sup>a</sup> DRV, d4T, efavirenz, NVP, tenofovir, lamivudine, abacavir, zidovudine, raltegravir, etraviudine, indinavir, lopinavir/ritonavir, atazanavir/ritonavir, nevirapine, ritonavir.
INSTI and new story of weight gain among PLHIV

**FIGURE 1.** Weight change at 18 months among patients switching to an integrase inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel A), switching to a protease inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel B), switching to DTG/ABC/3TC versus a raltegravir or elvitegravir-based regimen (panel C), or switching to DTG/ABC/3TC versus remaining on EFV/TDF/FTC (panel D). Models adjusted for age, sex, race, total duration of ART, and baseline CD4+ T-cell count and weight.
## Important drug-drug interactions with DTG

<table>
<thead>
<tr>
<th>Key drug interaction</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodaquine</td>
<td>Use an alternative antimalarial agent</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Use DTG twice daily or substitute with an alternative anticonvulsant agent</td>
</tr>
<tr>
<td>Phenytoin and phenobarbital</td>
<td>Use an alternative anticonvulsant agent</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Use an alternative antiarrhythmic agent</td>
</tr>
<tr>
<td>Metformin</td>
<td>Limit daily dose of metformin to 1000mg when used with DTG &amp; monitor glycemic control</td>
</tr>
<tr>
<td>Polyvalent cation products containing Al, Ca, Fe, Mg and Zn (eg: antacids, multivitamins &amp; supplements)*</td>
<td>Use 2 hours before or 6 hours after DTG</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Use DTG twice daily or substitute with rifabutin</td>
</tr>
</tbody>
</table>

* There is no drug interaction of DTG with folic acid. However, folic acid is frequently included in multivitamin preparations which may also contain polyvalent cations.
<table>
<thead>
<tr>
<th>Topic</th>
<th>2018 interim guidelines</th>
<th>2019 updates</th>
</tr>
</thead>
</table>
| Use of DTG in 1\textsuperscript{st} line | DTG as preferred option  
• Conditional recommendation  
• Moderate certainty evidence for adults  
• Very low certainty evidence for women of reproductive age (note of caution on DTG and use of effective contraception)                                                                                           | DTG as preferred option  
• Strong recommendation  
• Moderate certainty evidence for all adults (programmatic considerations and informed by risk/benefit analysis for women of reproductive age)  
• Strong focus on women centred approach                                                                                                                                   |
| Use of EFV in 1\textsuperscript{st} line   | EFV 400 and EFV600 as alternative options  
• Conditional recommendation  
• Moderate certainty of evidence  
• Limited evidence on EFV400 efficacy in TB and pregnant women                                                                                                                                                                                   | EFV400 as alternative option (including TB and PW)  
• Strong recommendation  
• Moderate certainty of evidence  

**EFV600 used in special situations** |
| Use of DTG in 2\textsuperscript{nd} line  | DTG as preferred option if not used in 1\textsuperscript{st} line  
• Conditional recommendation  
• Moderate certainty of evidence (note of caution on DTG use for women of reproductive age)                                                                                                                                     | DTG as preferred option if not used in 1\textsuperscript{st} line  
• Conditional recommendation  
• Moderate certainty of evidence (informed by risk/benefit analysis for women of reproductive age)  

**PI as preferred option if DTG used in 1\textsuperscript{st} line**  
• Strong recommendation  
• Moderate certainty of evidence |
HIV treatment and Contraceptive Services Integration Implementation Tool

1. ENSURING ACCESS TO INTEGRATED, RIGHTS-BASED, CLIENT-CENTRED, HIGH-QUALITY CONTRACEPTIVE CARE

2. ENSURING CONTRACEPTIVE OPTIONS AND EFFECTIVENESS FOR WOMEN AND ADOLESCENT GIRLS LIVING WITH HIV

3. CONTRACEPTIVE CONSIDERATIONS FOR WOMEN AND ADOLESCENT GIRLS RECEIVING ART

4. CONTRACEPTIVE CONSIDERATIONS ACROSS THE LIFE-COURSE IN HIV TREATMENT PROGRAMMES

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• https://hivtx.org/iphone
• https://hivtx.org/android

This is a Beta Launch-- We want your feedback!
Thank you!

WHO documents available at:
https://www.who.int/hiv/pub/arv/en/