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

Update from IAS 2019

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PAHO/WHO

PANCAP Webinar Series

PAN CARIBBEAN PARTNERSHIP AGAINST HIV & AIDS

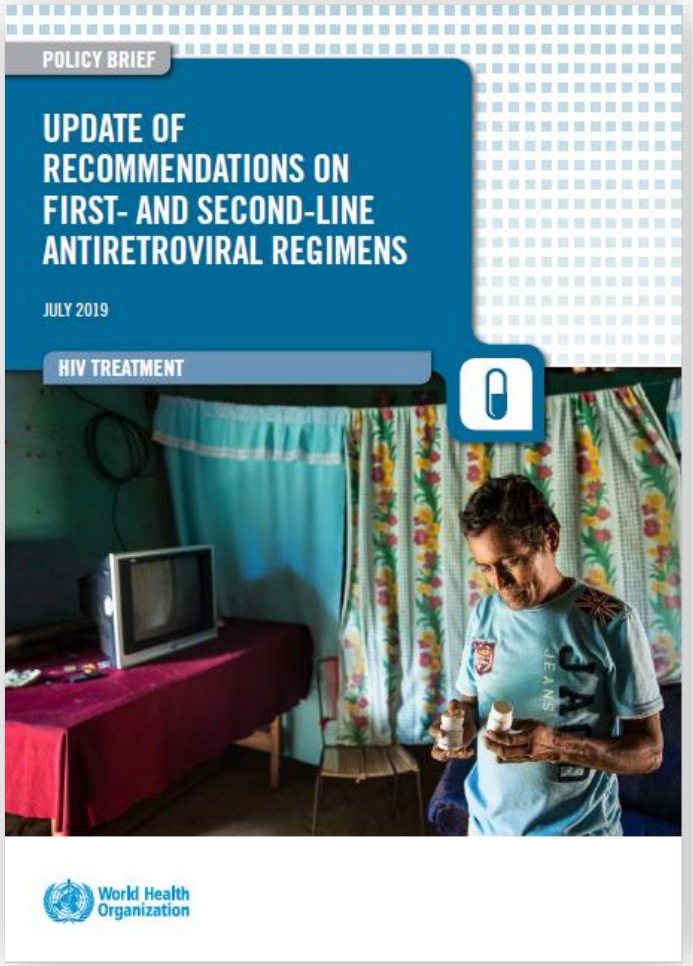
IAS 2019
10TH IAS CONFERENCE ON HIV SCIENCE
Mexico City, Mexico 21-24 July 2019

Pan American Health Organization
World Health Organization
REGIONAL OFFICE FOR THE Americas

Outline

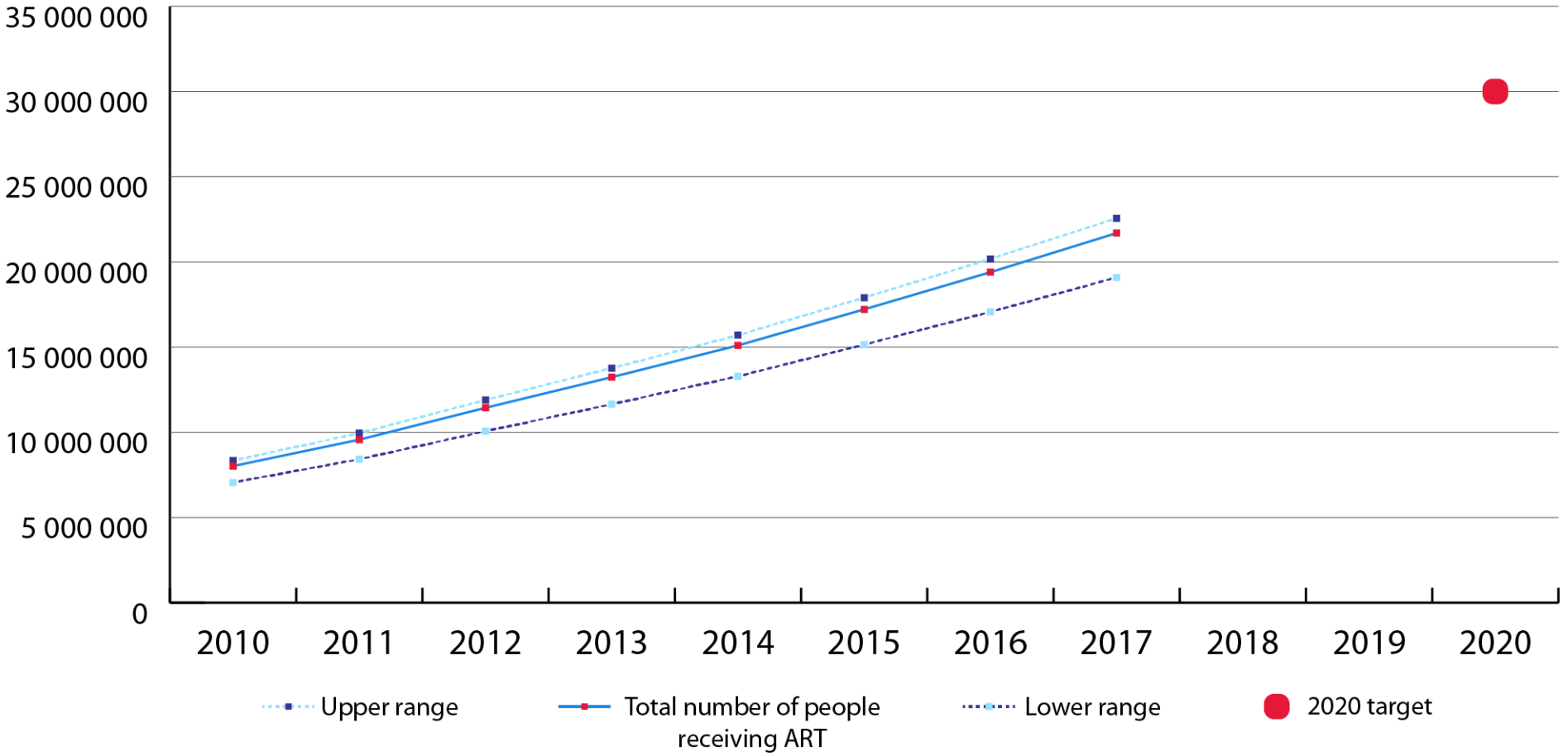
- Context (treatment, policies, HIV resistance)
- Rapid evolution of WHO recommendations (2018-2019)
- Focus on 1st and 2nd line ART update (adults, adolescents, women of child bearing potential – WCBP and pregnancy)

Next webinar will focus on ART in children!



https://www.who.int/hiv/pub/arv/en/

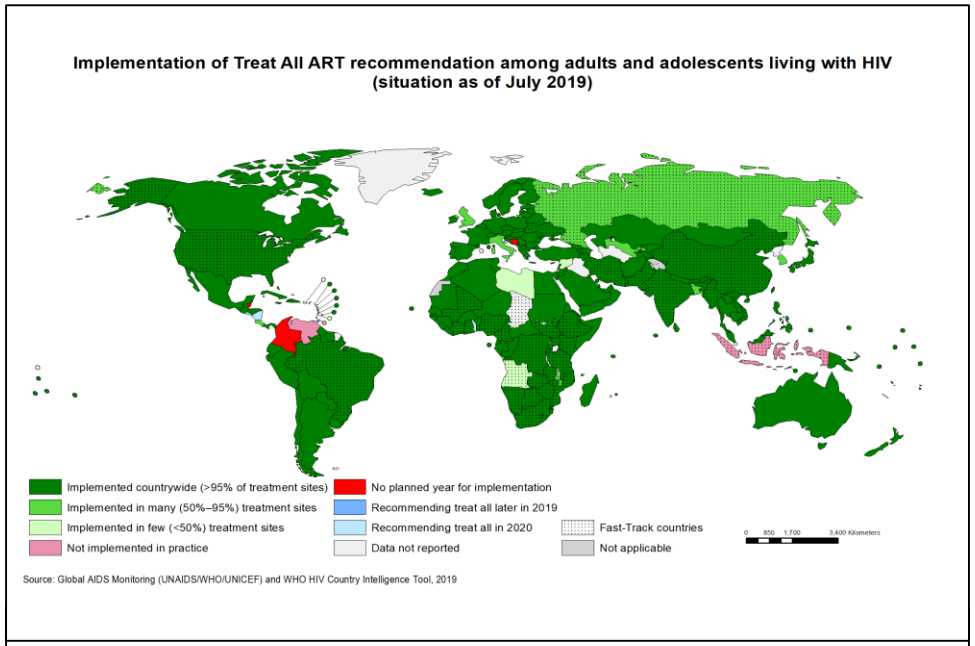
Increase in people receiving ART over time (62% ART coverage in 2018)

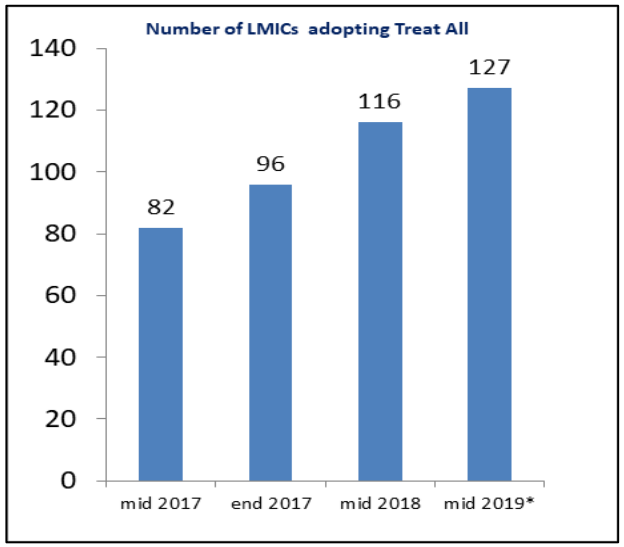


Source: UNAIDS/WHO estimates

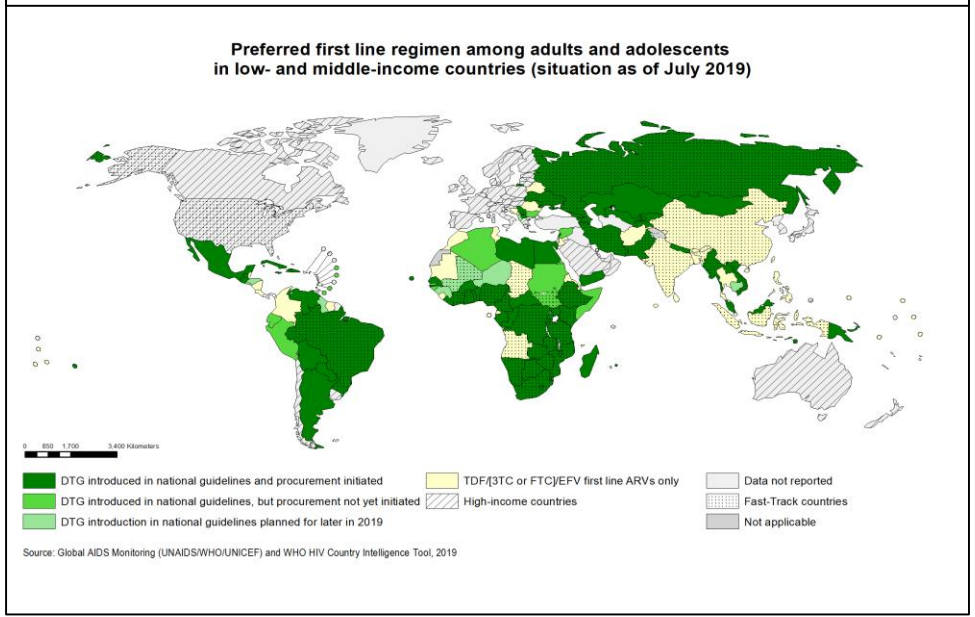
Uptake of major HIV treatment policies in LMICs

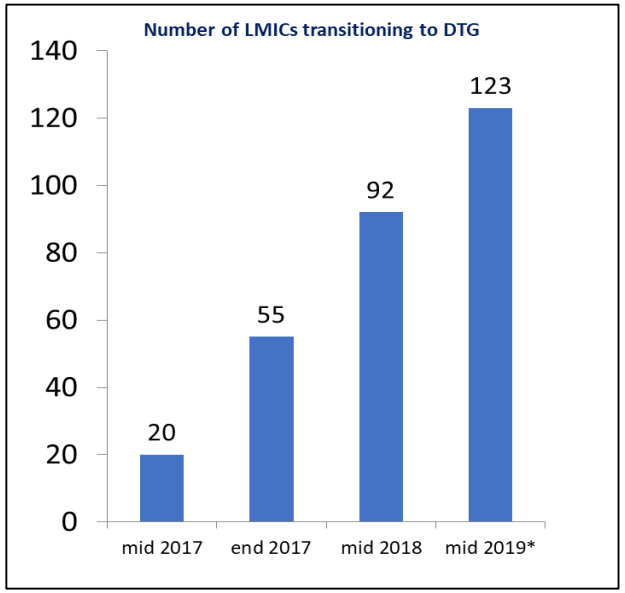
Treat All





DTG transition





* Preliminary data

World Health Organization

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

39 countr
- 25 con
- 14 ong

18 planne

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

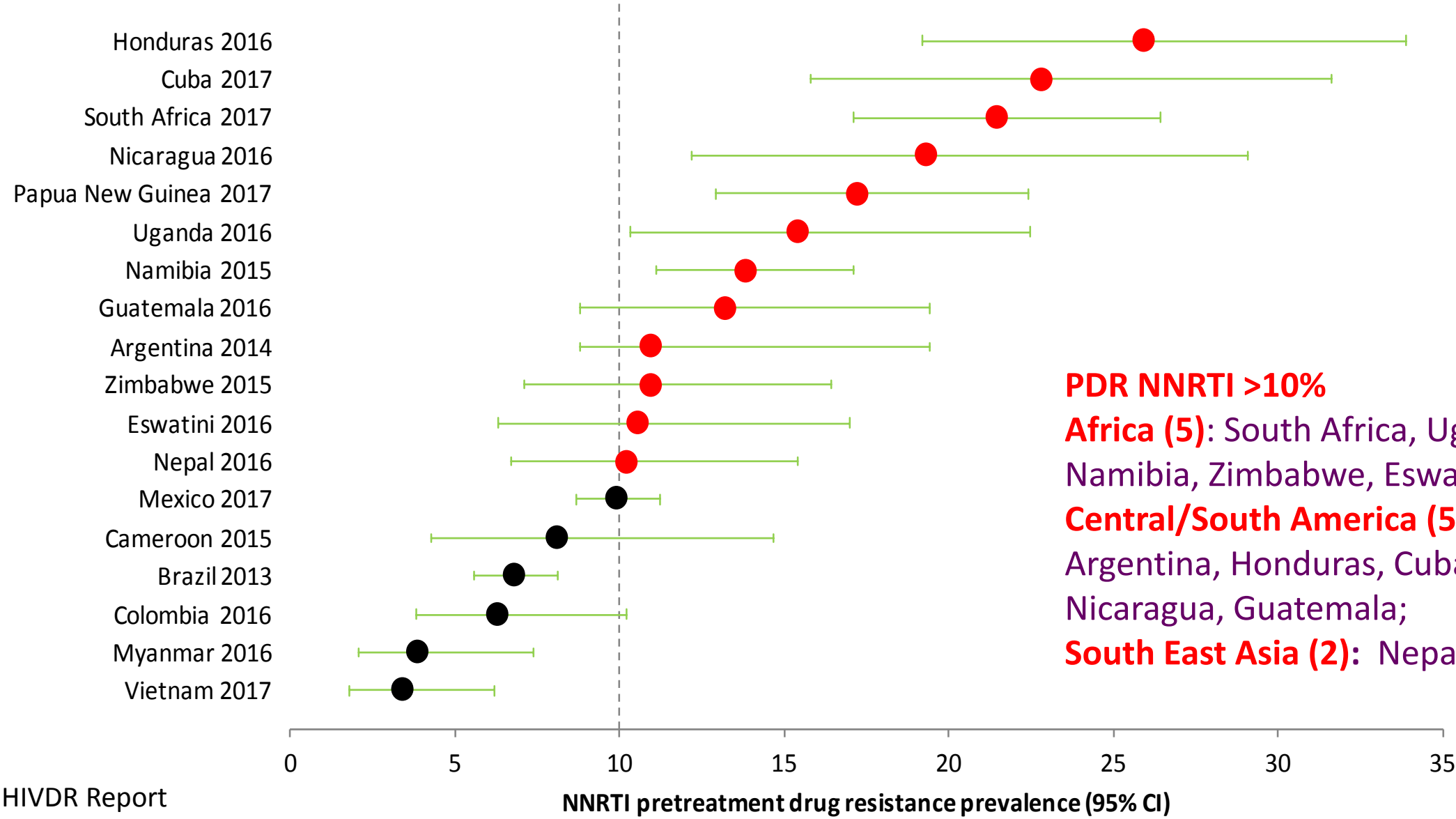
Completed	Ongoing	Planning	No information
Cuba, Jamaica, OECS, Suriname	Haiti, Barbados	Dominican Republic, Trinidad and Tobago	Bahamas, Belize, Guyana

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

World Health Organization

2019 WHO HIVDR Report

Prevalence of PDR to NNRTI, by Country



PDR NNRTI >10%

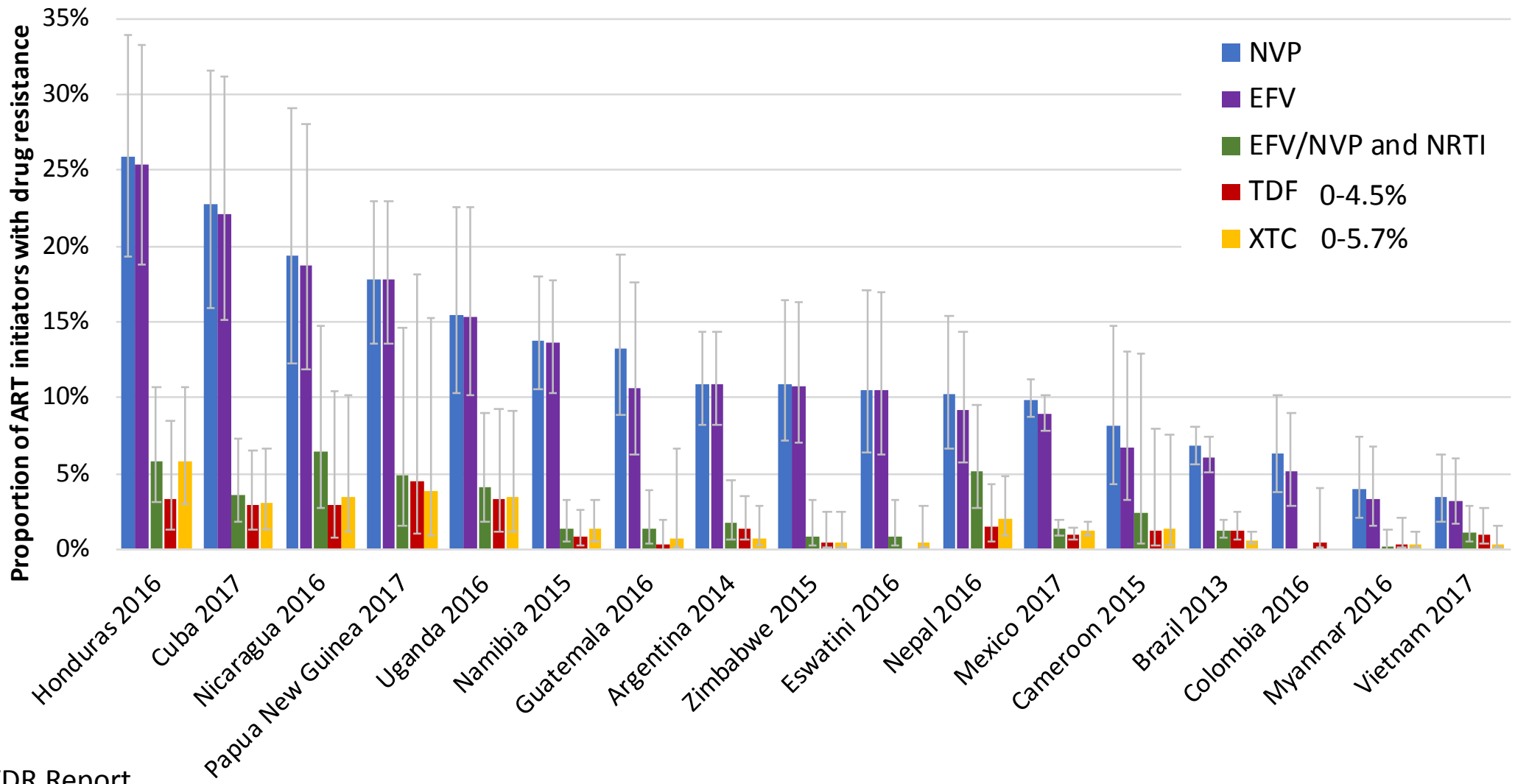
Africa (5): South Africa, Uganda, Namibia, Zimbabwe, Eswatini;

Central/South America (5): Argentina, Honduras, Cuba, Nicaragua, Guatemala;

South East Asia (2): Nepal, PNG.

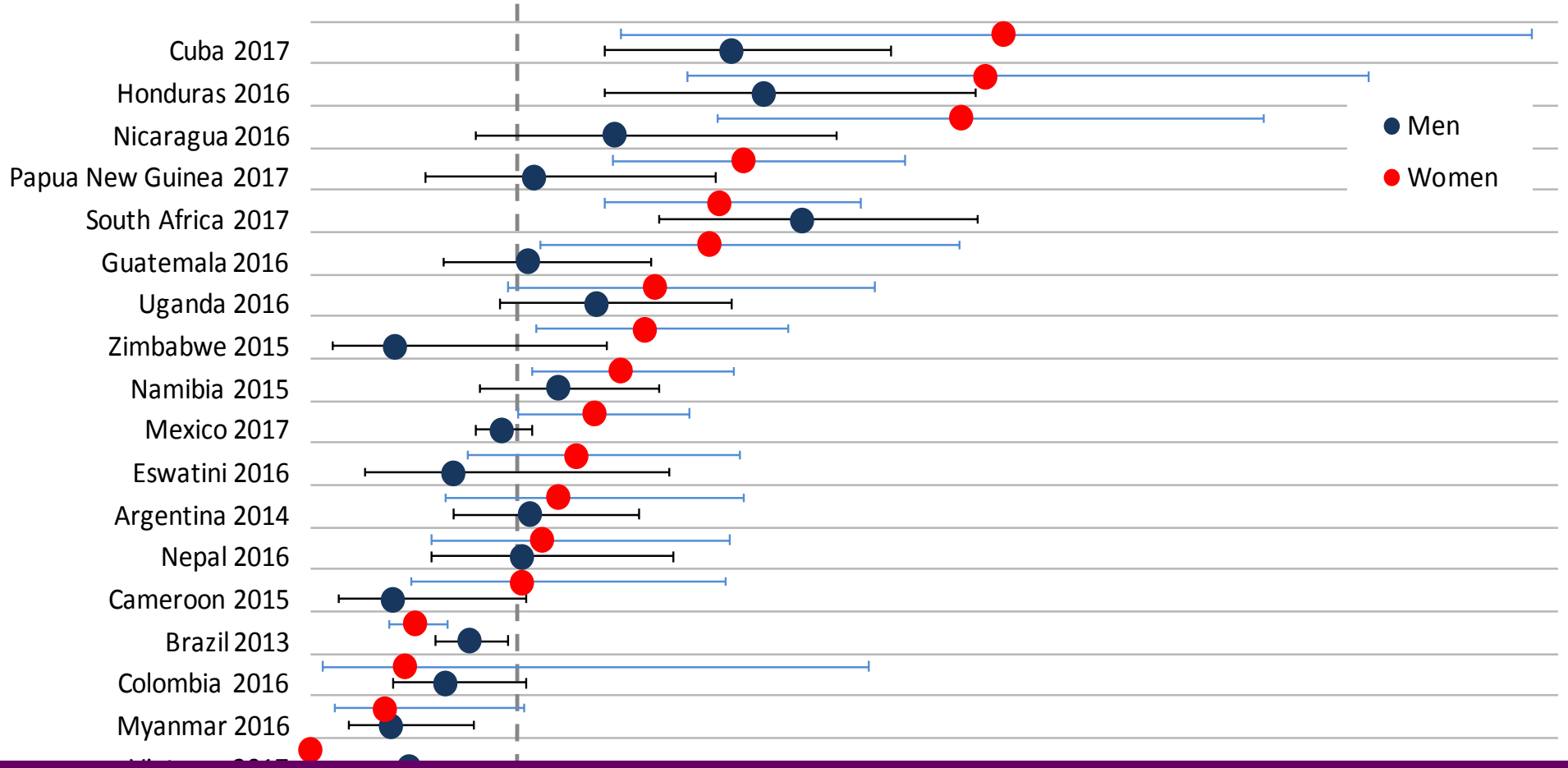
2019 WHO HIVDR Report

Prevalence of PDR, by Drug and by Country



2019 WHO HIVDR Report

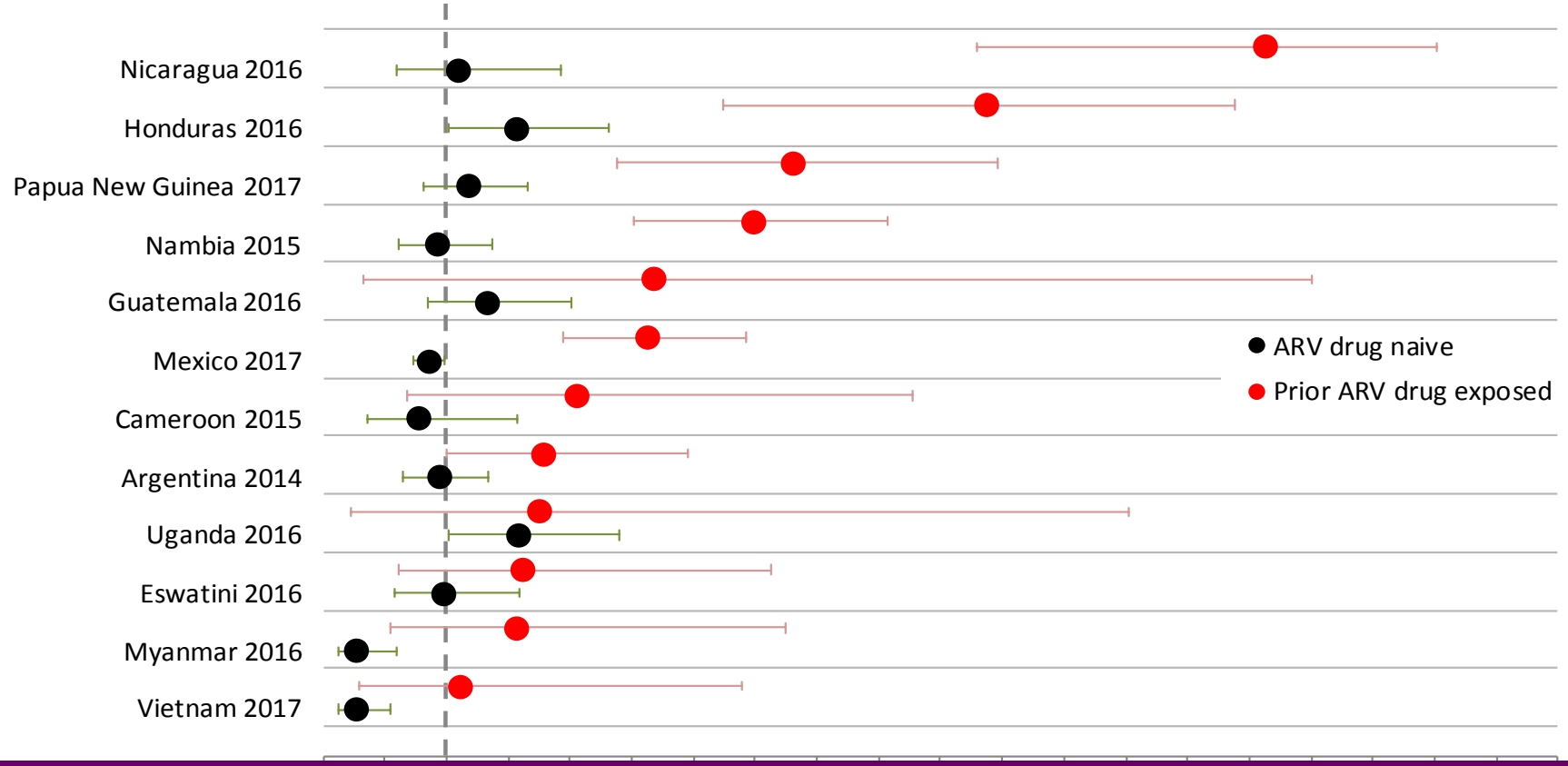
Prevalence of NNRTI PDR, by Gender



Pooled analysis of country data:

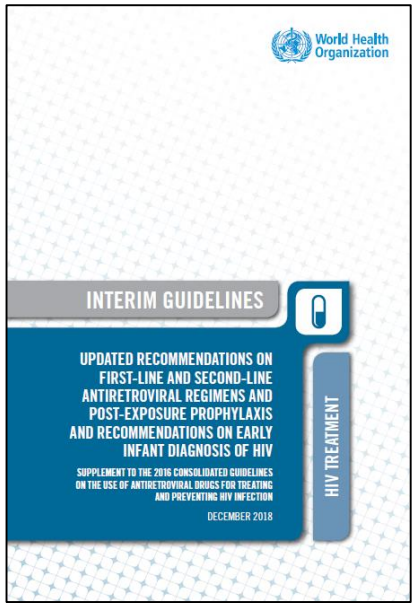
NNRTI PDR is significantly higher in **women (11.8%) vs men (7.8%)** p=0.005

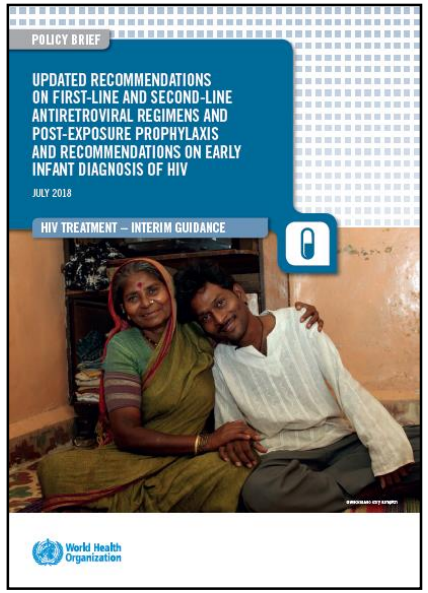
Prevalence of NNRTI PDR among First-Line Initiators, by Reported Prior Exposure to ARV Drugs



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)*

NEW

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).*

NEW

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

NEW

[a]WHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.

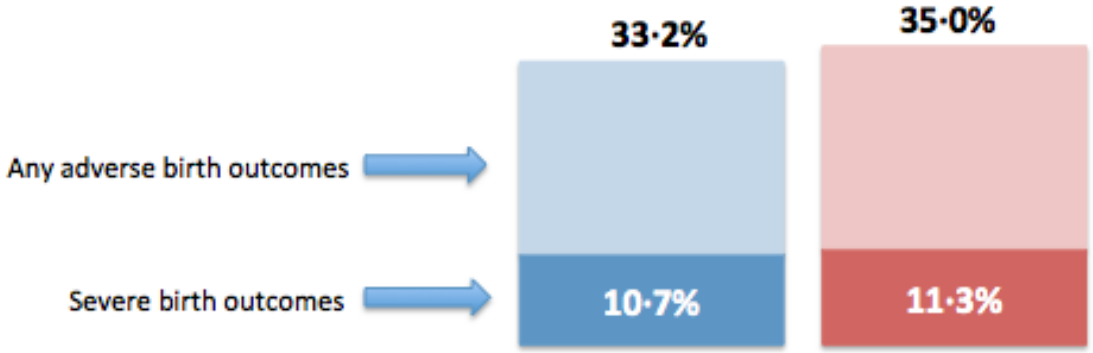
World Health Organization

Tsepamo and Dolutegravir

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)

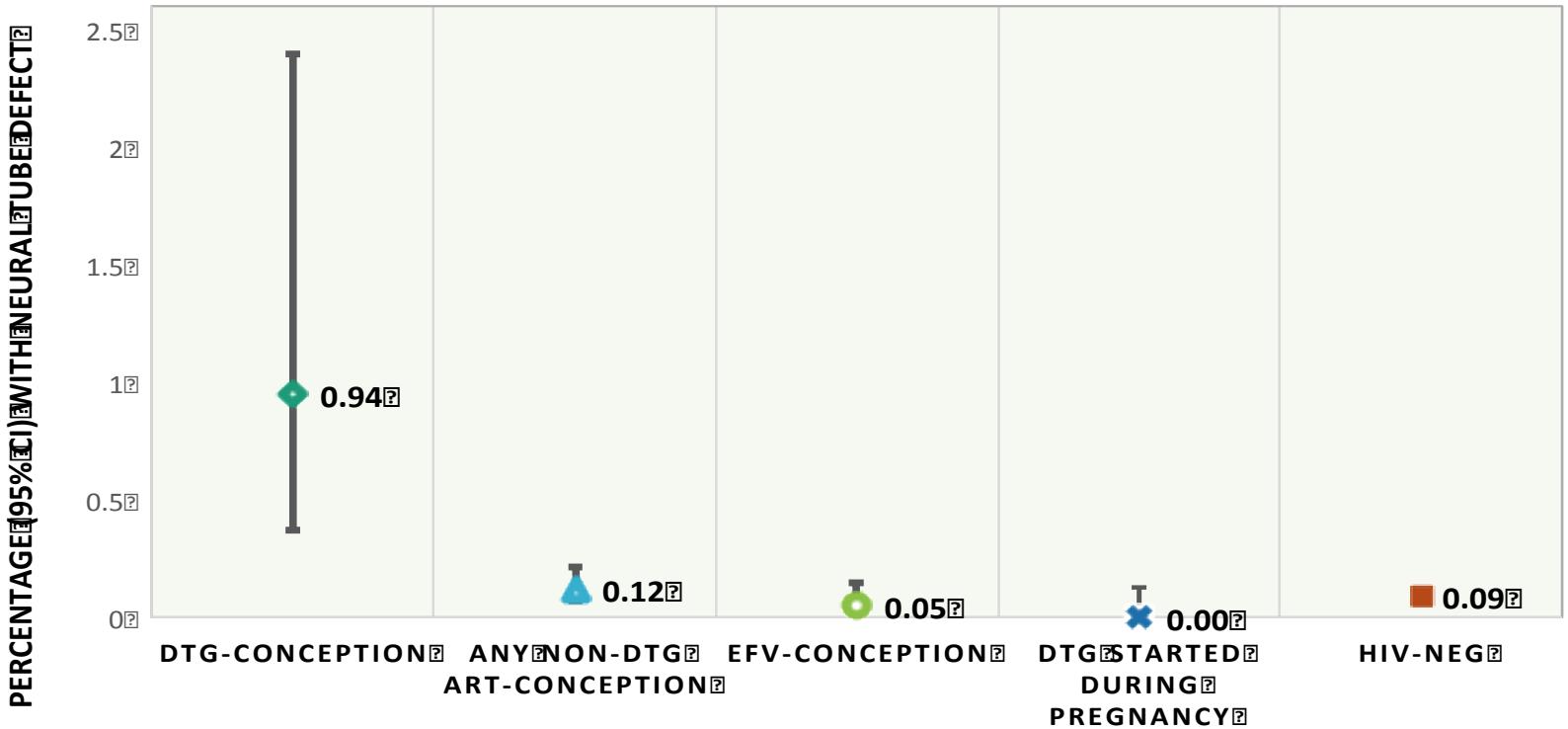


	Dolutegravir/ TDF/FTC (N=1729)	Efavirenz/ TDF/FTC (N=4593)
Any Adverse Birth Outcome		
Unadjusted RR (95% CI)	0·95 (0·88,1·03)	ref
Adjusted RR (95% CI)	0·95 (0·88,1·03)	ref
Severe Birth Outcome		
Unadjusted RR (95% CI)	0·95 (0·81,1·11)	ref
Adjusted RR (95% CI)	0·94 (0·81,1·11)	ref

Zash et al. *Lancet GH*, 2018

Tsepamo Study Preliminary Neural Tube Defect (NTD) Results (May 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*



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

Zash R et al. N Engl J Med 2018

May 2018: Possible DTG Safety Signal Reported

AIDSinfo | OFFERING INFORMATION ON HIV/AIDS TREATMENT, PREVENTION, AND RESEARCH

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HIV/AIDS News

Home > HIV/AIDS News > Statement on Potential Safety Signal in Infants Born to Women Taking Dolutegravir from the HHS Antiretroviral Guideline Panels

Statement on Potential Safety Signal in Infants Born to Women Taking Dolutegravir from the HHS Antiretroviral Guideline Panels

Date: May 18, 2018
Source: AIDS*info*

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New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir

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Safety Alerts for Human Medical Products

2018 Safety Alerts for Human Medical Products

Juluca, Tivicay, Triumeq (dolutegravir): FDA to Evaluate - Potential Risk of Neural Tube Birth Defects

HIV/AIDS

WHO statement and Q&A on potential safety issue related with DTG

23 May 2018 – On 18 May 2018, WHO has issued a web statement signalling a potential risk of neural tube defects in infants born to women who were taking dolutegravir (DTG) at the time of conception.

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

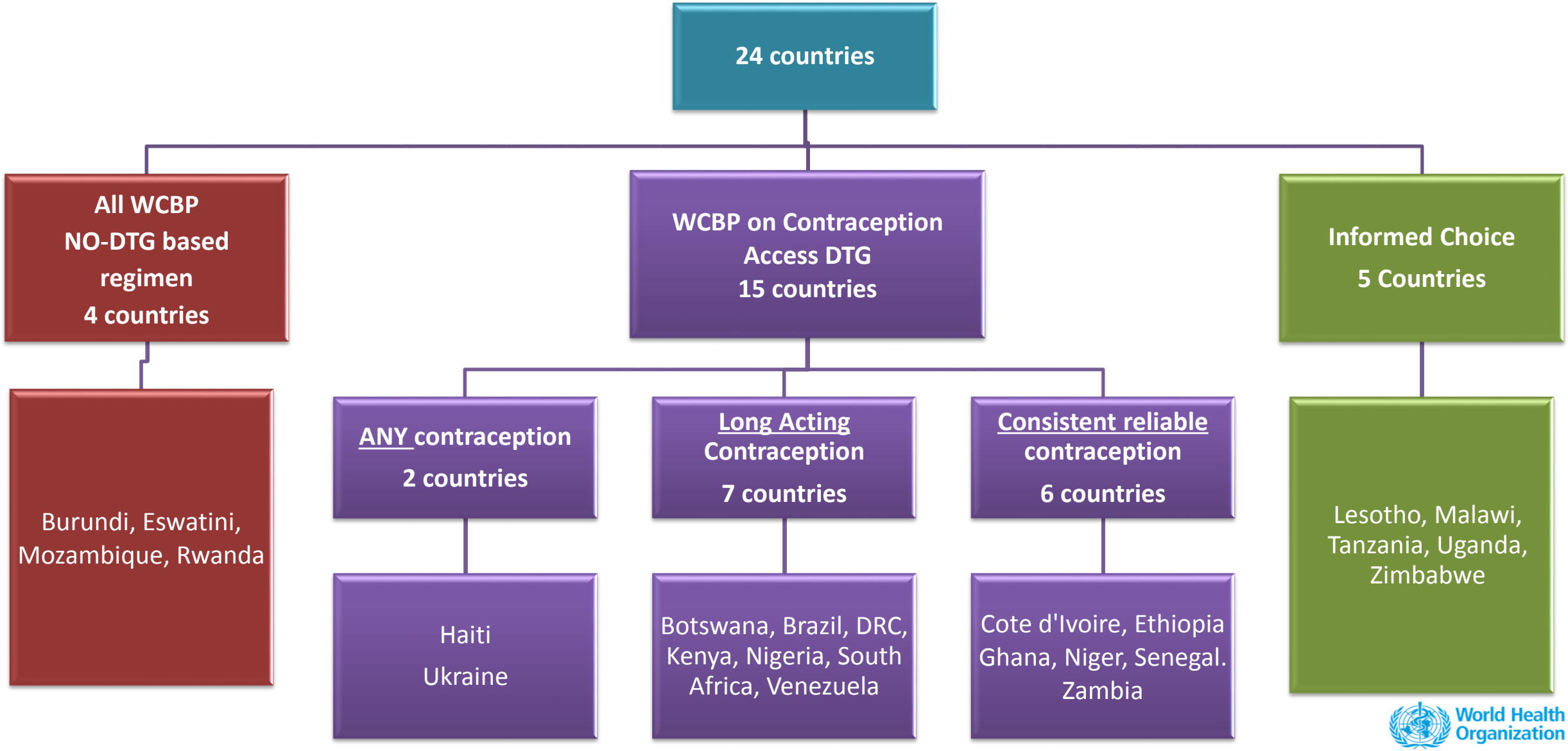
BOX 3. A WOMAN-CENTRED APPROACH

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).*

- 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).

Access to DTG as preferred 1st line among WCBP, April 2019



World Health Organization

PICO questions for 2019 update

DTG in 1st 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**? NEW

DTG in 2nd 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? NEW

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 1st line ART
(summary 2019 WHO Sys Review & NMA)

	major outcomes	DTG vs EFV_{600}	quality of evidence
Efficacy outcomes	Treatment discontinuation (any or due AEs)	DTG better	high
	Viral suppression (4-96 weeks), viral suppression at delivery (PW), transmission (PW)	DTG probably better	high to moderate
	CD4 recovery (24-144 weeks)	DTG probably better	high to moderate
	Mortality	comparable	low
Tolerability, safety & resistance outcomes	Neuropsychiatric AEs (any grade), depression (grade 3 or 4), dizziness (any grade)	DTG probably better	moderate to low
	Sleep disorders (any grade)	comparable	very low
	Body weight gain	EFV probably better	moderate
	NTD	EFV may be better	low
	HIVDR (overall, NRTI or anchor drug)	DTG probably better	high to moderate

Reference: Steve Kanters, For WHO ARV GDG, 5-7 June 2019

World Health Organization

Safety and Efficacy of EFV_{400} and EFV_{600} in 1st line ART (PICO 3)

(summary 2019 WHO Sys Review & NMA)

	major outcomes	EFV_{400} vs EFV_{600}	quality of evidence
Efficacy outcomes	Treatment discontinuation (due AEs)	EFV400 better	high to moderate
Efficacy outcomes	Viral suppression (48-96 weeks), VL suppression if baseline > 100,000 (48 weeks)	comparable	moderate
Efficacy outcomes	CD4 recovery (24-96 weeks)	comparable	moderate
Efficacy outcomes	Mortality	comparable	low
Tolerability, safety & resistance outcomes	Neuropsychiatric AEs (any grade), depression (grade 3 or 4), dizziness (any grade), sleep disorders (any grade)	comparable	low to very low
Tolerability, safety & resistance outcomes	Body weight gain	comparable	low
Tolerability, safety & resistance outcomes	Treatment related adverse events	EFV400 better	moderate
Tolerability, safety & resistance outcomes	HIVDR (overall, NRTI or anchor drug)	comparable	very low

Reference: Steve Kanters, For WHO ARV GDG, 5-7 June 2019

World Health Organization

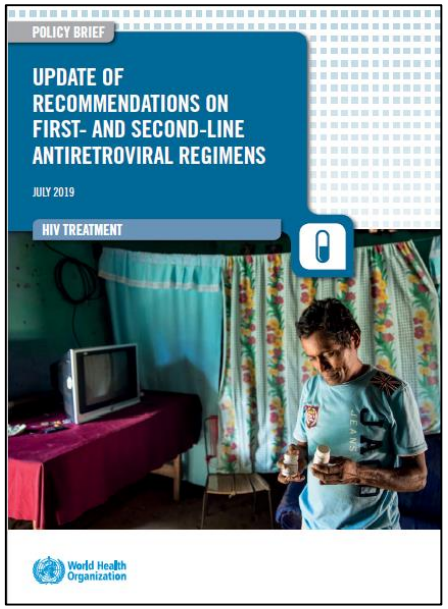
Current optimization profiles of new ARV drugs comparative analysis

Optimization criteria		DTG	EFV_{400}	TAF	DRV
Efficacy and safety	Virologic potency				
	Lower toxicity				
	High genetic barrier to resistance				
Simplification	Available as generic FDC				
	Low pill burden/pill size				
Harmonization	Use in pregnant women				
	Use in childbearing age women				
	Use in children				
	Use in HIV-associated TB				
	Few drug interactions				
Cost	Low price				

yes no ongoing studies

World Health Organization

2019 WHO recommendations: First-line ART regimens



First-line ART regimens[a]

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[b] *(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[c] *(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)*

[a] See Table 1 for ARV drug selection.
[b] See Box 2 on women and adolescent girls of childbearing potential using DTG.
[c] Except in settings with pretreatment HIV drug resistance to EFV/nevirapine (NVP) exceeding 10%.

World Health Organization

2019 WHO recommendations: First-line ART regimens

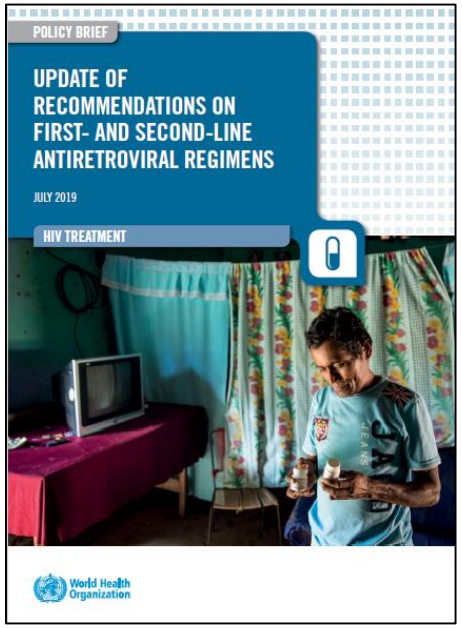


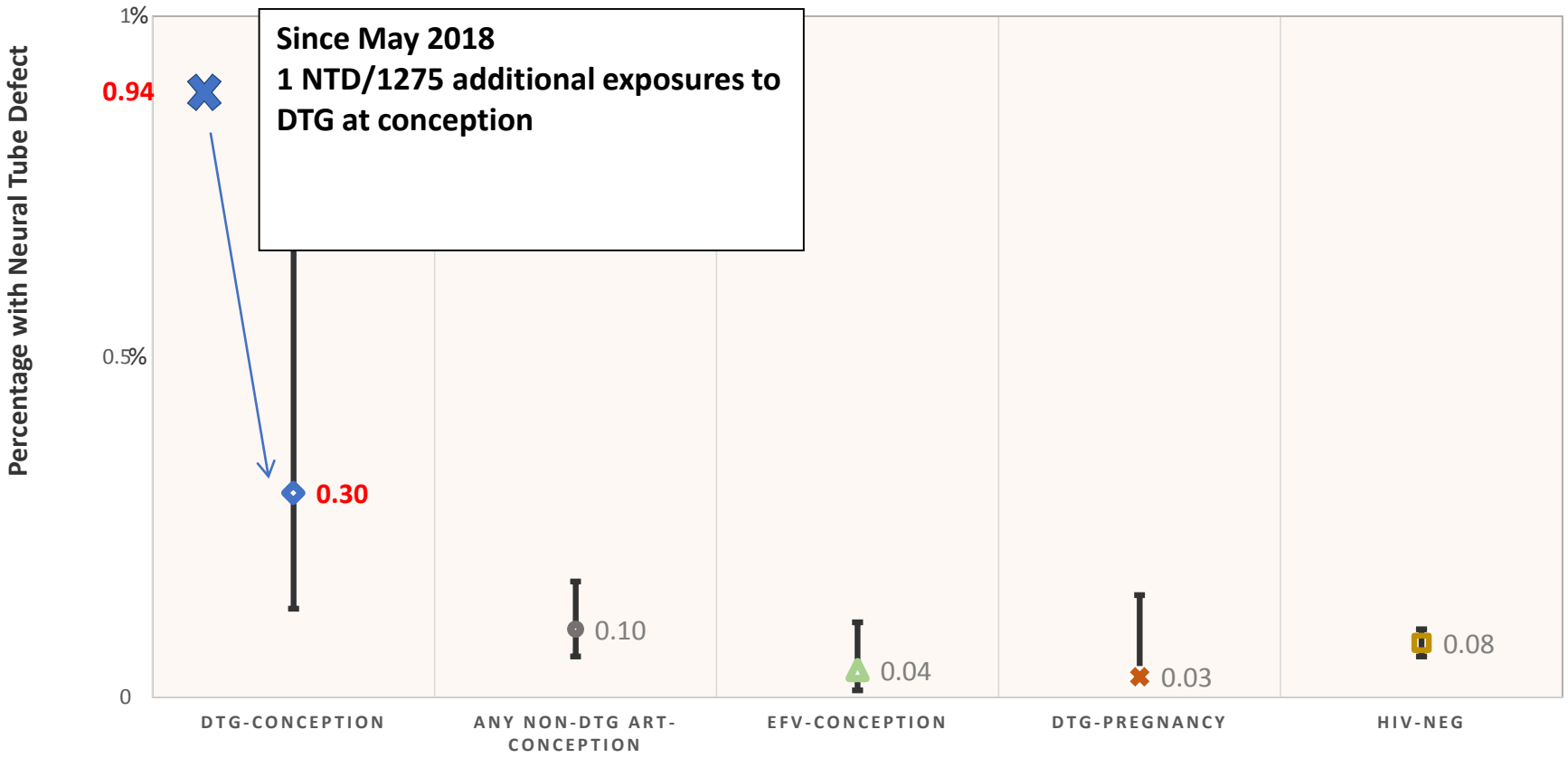
Table 1. Preferred and alternative first-line ART regimens

Population	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults and adolescents	TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b]	TDF + 3TC (or FTC) + EFV 600 mg[b] AZT + 3TC + EFV 600 mg[b] TDF + 3TC (or FTC) + PI/r[b] TDF + 3TC (or FTC) + RAL TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG[a]
Children	ABC + 3TC + DTG[d]	ABC + 3TC + LPV/r ABC + 3TC + RAL[e] TAF + 3TC (or FTC) + DTG[f]	ABC + 3TC + EFV (or NVP) AZT + 3TC + EFV[g] (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates	AZT + 3TC + RAL[h]	AZT + 3TC + NVP	AZT + 3TC + LPV/r[i]

- 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

World Health Organization

Tsepamo update: NTD Prevalence by Exposure (March 2019)



NTDs/Exposures	5/1683	15/14792	3/7959	1/3840	70/89372
% with NTD (95% CI)	0.30% (0.13, 0.69)	0.10% (0.06, 0.17)	0.04% (0.01, 0.11)	0.03% (0.0, 0.15)	0.08% (0.06, 0.10)
Prevalence Difference (95% CI)	ref	0.20% (0.01, 0.59)	0.26% (0.07, 0.66)	0.27% (0.06, 0.67)	0.22% (0.05, 0.62)

Adverse Birth Outcomes: Conception EFV vs. DTG*

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

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

ORIGINAL RESEARCH

CEPAC

Annals of Internal Medicine

Risks and Benefits of Dolutegravir- and Efavirenz-Based Strategies for South African Women With HIV of Child-Bearing Potential

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

Articles

HIV SYNTHESIS

Lancet HIV 2019; 6: e116–27

Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study

Andrew N Phillips, Francois Venter, Diane Havlir, Anton Pozniak, Daniel Kuritzkes, Annemarie Wensing, Jens D Lundgren, Andrea De Luca, Deenan Pillay, John Mellors, Valentina Cambiano, Loveleen Bansi-Matharu, Fumiyo Nakagawa, Thokozani Kalua, Andreas Jahn, Tsitsi Apollo, Owen Mugurungi, Polly Clayden, Ravindra K Gupta, Ruanne Barnabas, Paul Revill, Jennifer Cohn, Silvia Bertagnolio, Alexandra Calmy

CEPAC

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

Treatment efficacy & adverse event assumptions	EFV	DTG
48 week virologic suppression to <50 c/mL for new ART starts without NNRTI PDR, %	91	94
Adverse events leading to switch to PI-based ART, %	9	3

- VL monitoring: SA guidelines
- NTD risk per **Tsepamo 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 **Tsepamo 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

What would be the negative outcomes of avoiding <u>any</u> excess NTDs by using EFV?

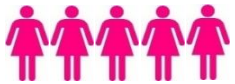
With Tsepamo May 2019 assumptions, there would be **0.3 more child deaths per NTD averted with use of EFV**, due to the additional HIV-infected children with EFV vs DTG.

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

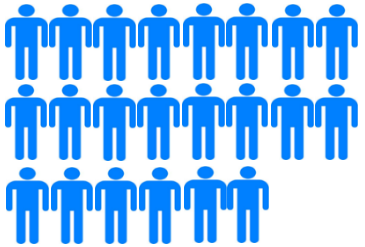
For every 1 NTD averted with use of *EFV* compared to *DTG*, it is predicted that there will be this many additional outcomes:

EFV vs DTG

5 Deaths among women



22 Sexual transmissions



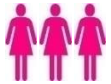
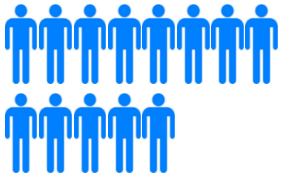
4 MTCT transmissions

<1 more child deaths*

0.3 more child deaths

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)**:

	DTG	***DTG-C***
	1 more NTDs 	0 more NTDs#
	<1 fewer child deaths* ***Fewer child deaths with DTG vs EFV***	0 more child deaths#
	3 more women alive 	1 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

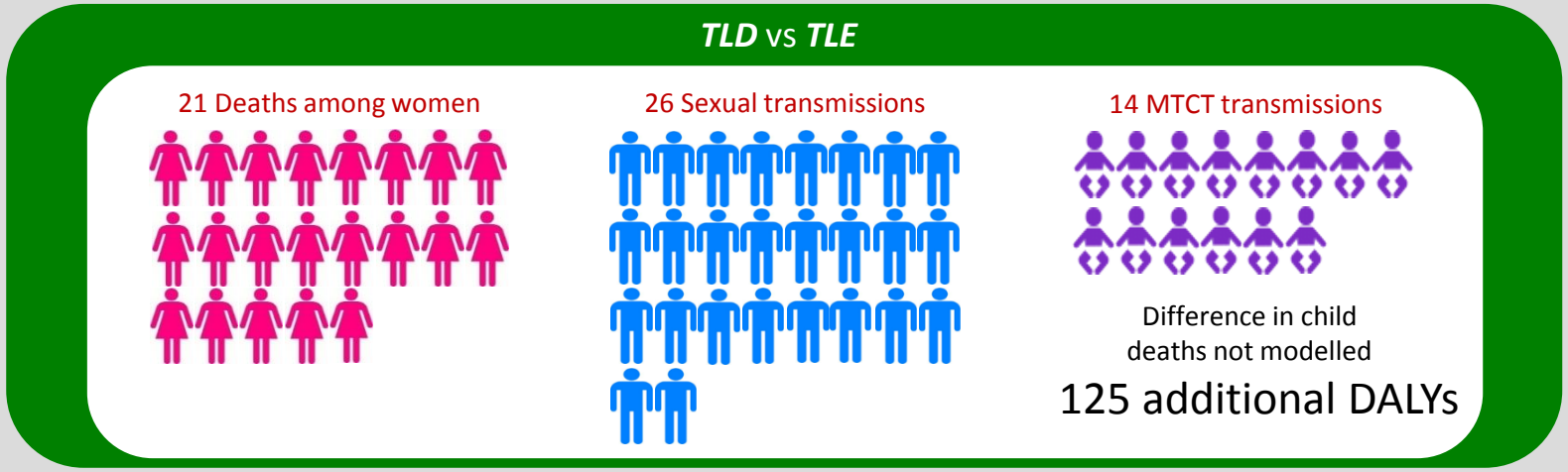
HIV SYNTHESIS

What would be the negative outcomes of avoiding <u>any</u> 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%

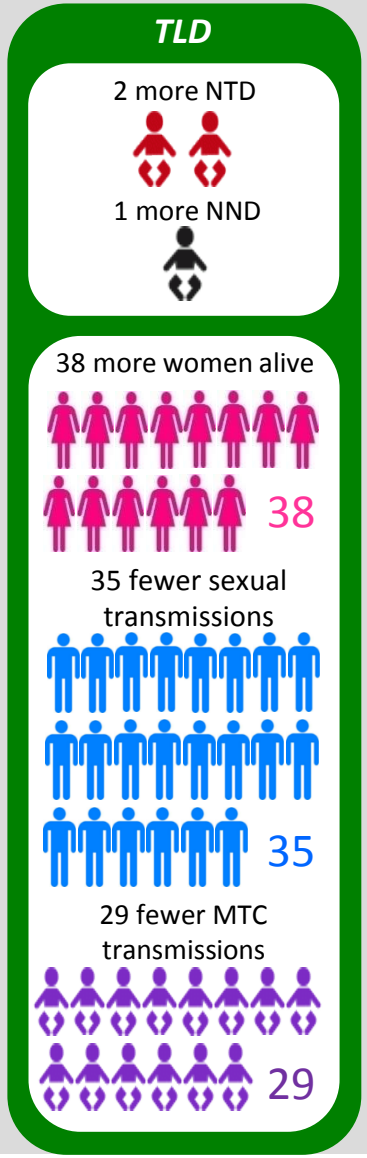
For every 1 adverse infant outcome (NTD+NND) averted with use of *TLE* compared to *TLD*, it is predicted that there will be this many additional outcomes:



numbers ≥0.5 rounded up

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)**:



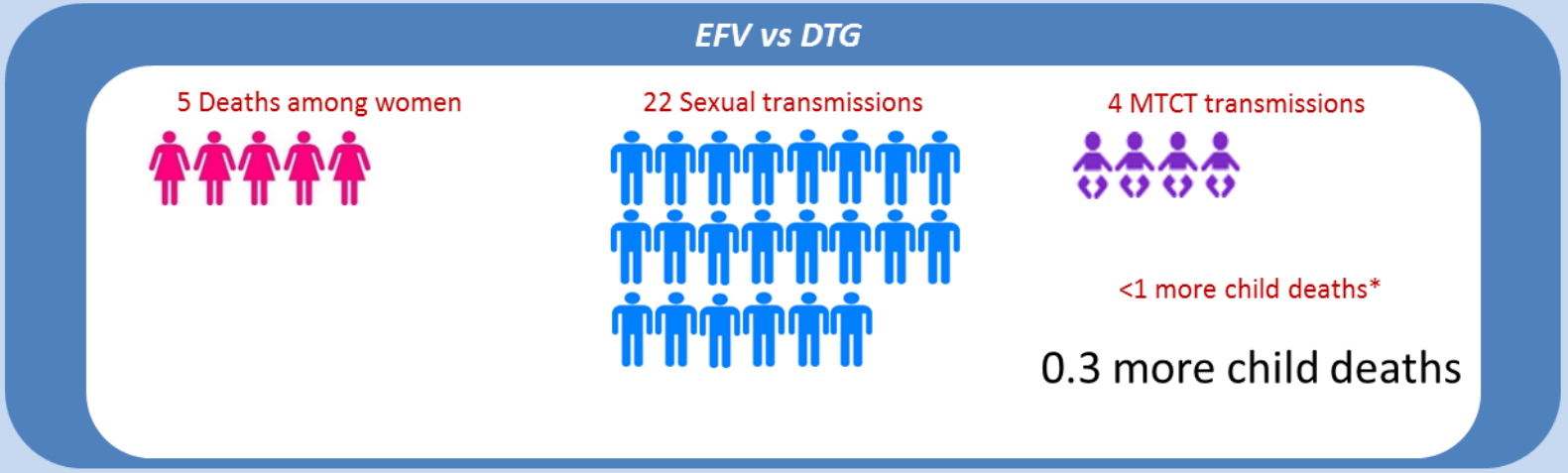
*n<0.5; #n=0; numbers ≥0.5 rounded up

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**

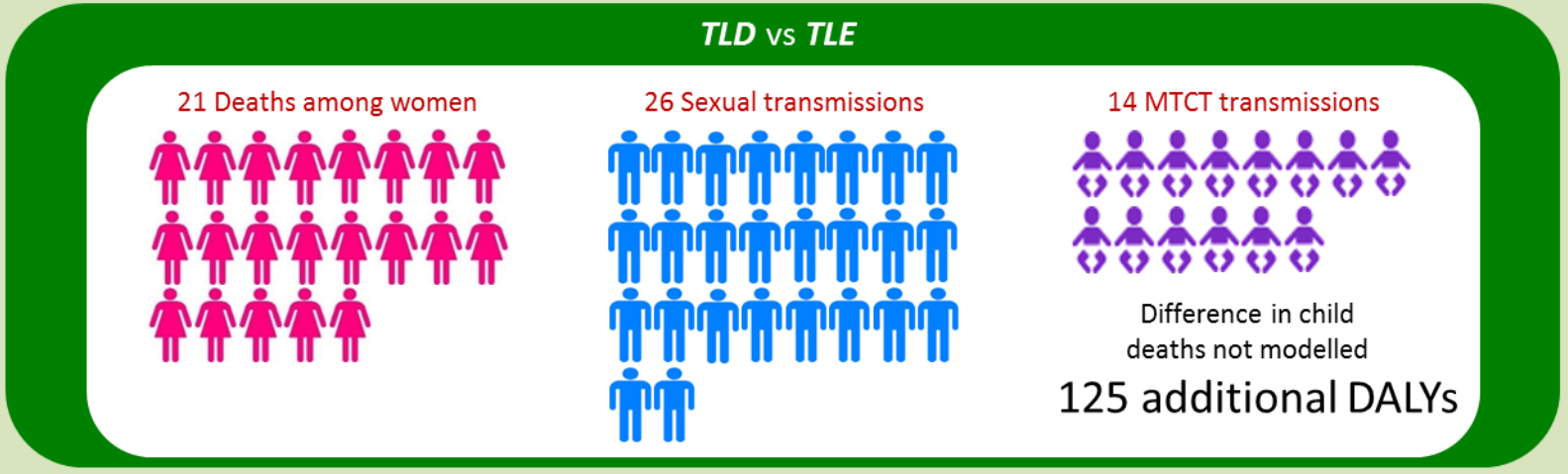
CEPAC: Tsepamo May 2019 NTD risk, NMA ARV efficacy, PDR 10.7%

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

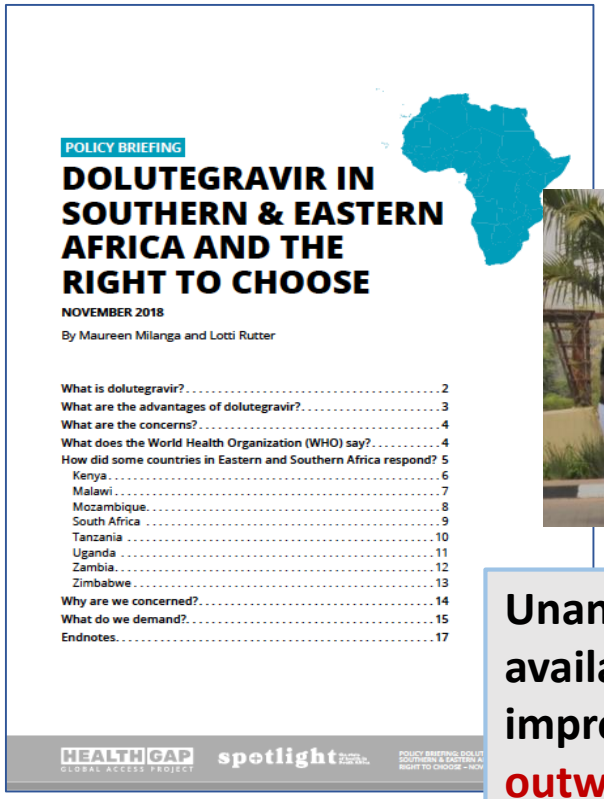


SYNTHESIS: Tsepamo May 2019 NTD risk, incl. ADVANCE/NAMSAL, PDR 9%

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:



Community Voices Clear


POLICY BRIEFING

DOLUTEGRAVIR IN SOUTHERN & EASTERN AFRICA AND THE RIGHT TO CHOOSE

NOVEMBER 2018

By Maureen Milanga and Lotti Rutter

HEALTHGAP GLOBAL ACCESS PROJECT spotlight

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)

	major outcomes	DTG vs LPVr	quality of evidence
Efficacy outcomes	Viral suppression (4-96 weeks)	DTG better	high
	Viral suppression baseline VL > 100,000 (48 weeks)	comparable	moderate
	CD4 recovery (24-48 weeks)	comparable	moderate
	Mortality	comparable	low
Tolerability, safety & resistance outcomes	Neuropsychiatric AEs (any grade)	comparable	low
	Treatment related SAE	comparable	low
	Treatment emergent AE, related AEs	DTG probably better	high
	Treatment discontinuation (any or due AEs)	DTG probably better	high
	HIVDR (overall)	comparable	very low

Reference: Steve Kanters, For WHO ARV GDG, 5-7 June 2019

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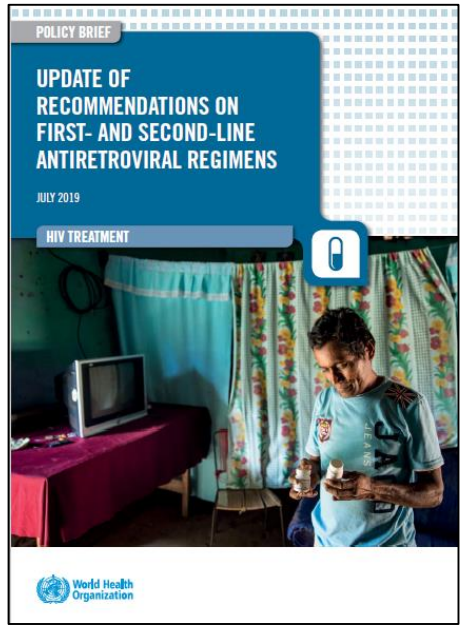
2019 WHO recommendations: Second-line ART regimens



Second-line ART regimens[a]

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[b] *(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.

World Health Organization

2019 WHO recommendations: Second-line ART regimens

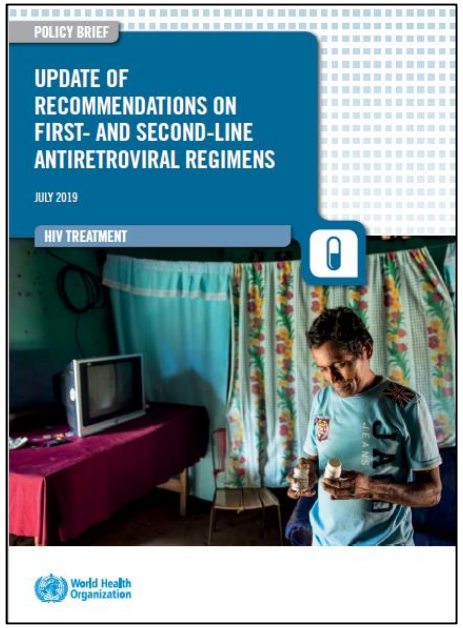


Table 2. Preferred and alternative second-line ART regimens

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents[a]	TDF[b] + 3TC (or FTC) + DTG[c]	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r[d]
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG[c]	AZT + 3TC + ATV/r (or LPV/r or DRV/r)[d]
	AZT + 3TC + EFV (or NVP)	TDF[b] + 3TC (or FTC) + DTG[c]	TDF[b] + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)[d]
Children and infants	ABC + 3TC + DTG[e]	AZT+ 3TC + LPV/r (or ATV/r[f])	AZT + 3TC + DRV/r[g]
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) + 3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f] or DRV/r[g])

World Health Organization

INSTI and new story of weight gain among PLHIV

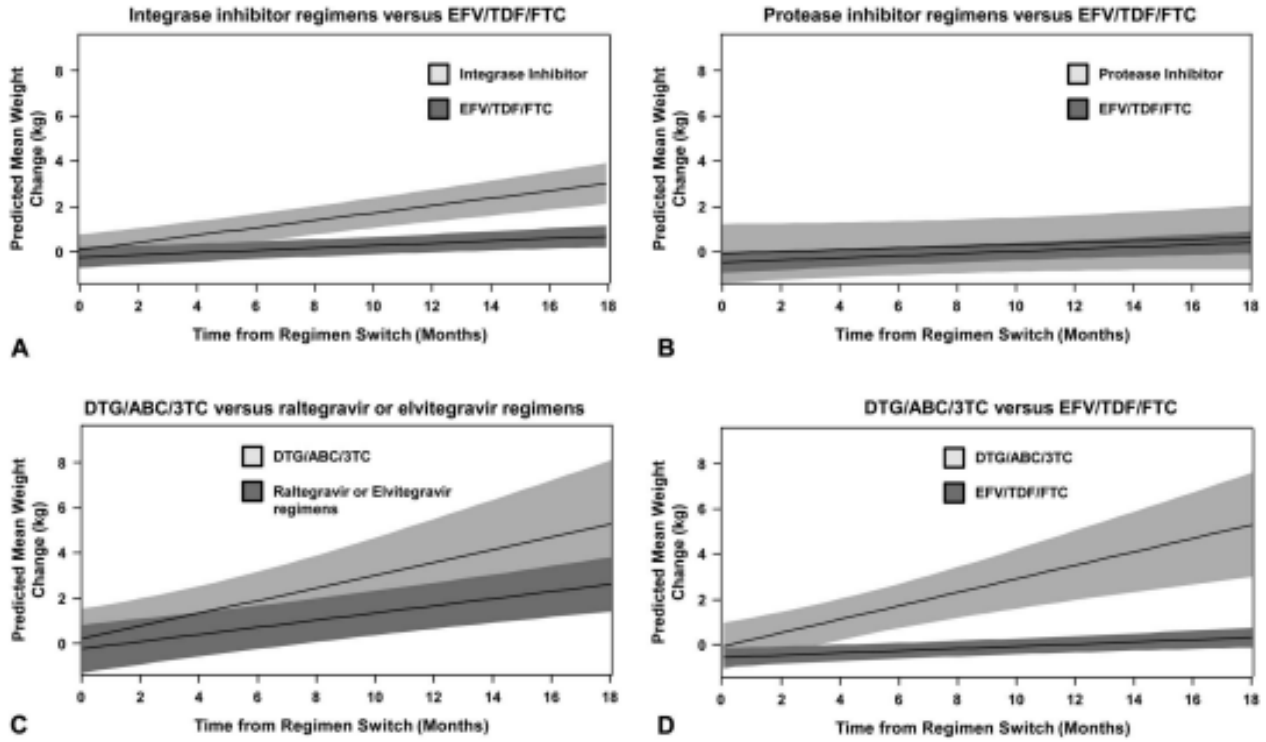
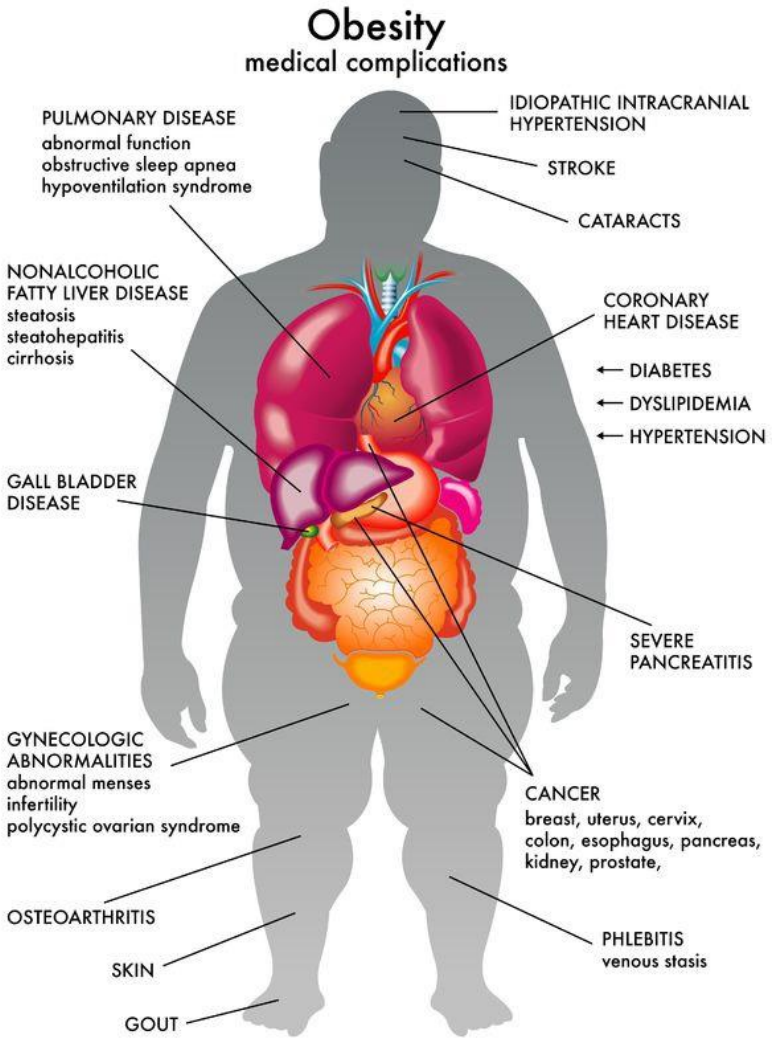


FIGURE 1. Weight change at 18 months among patients switching to an integrase inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel A), switching to a protease inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel B), switching to DTG/ABC/3TC versus a raltegravir or elvitegravir-based 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

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

* 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.

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2019 WHO ART Guidelines: What has been changed?

Topic	2018 interim guidelines	2019 updates
Use of DTG in 1st 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 1st 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 2nd line	**DTG as preferred option if not used in 1st 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 1st 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 1st line** • Strong recommendation • Moderate certainty of evidence

World Health Organization

HIV treatment and Contraceptive Services Integration Implementation Tool

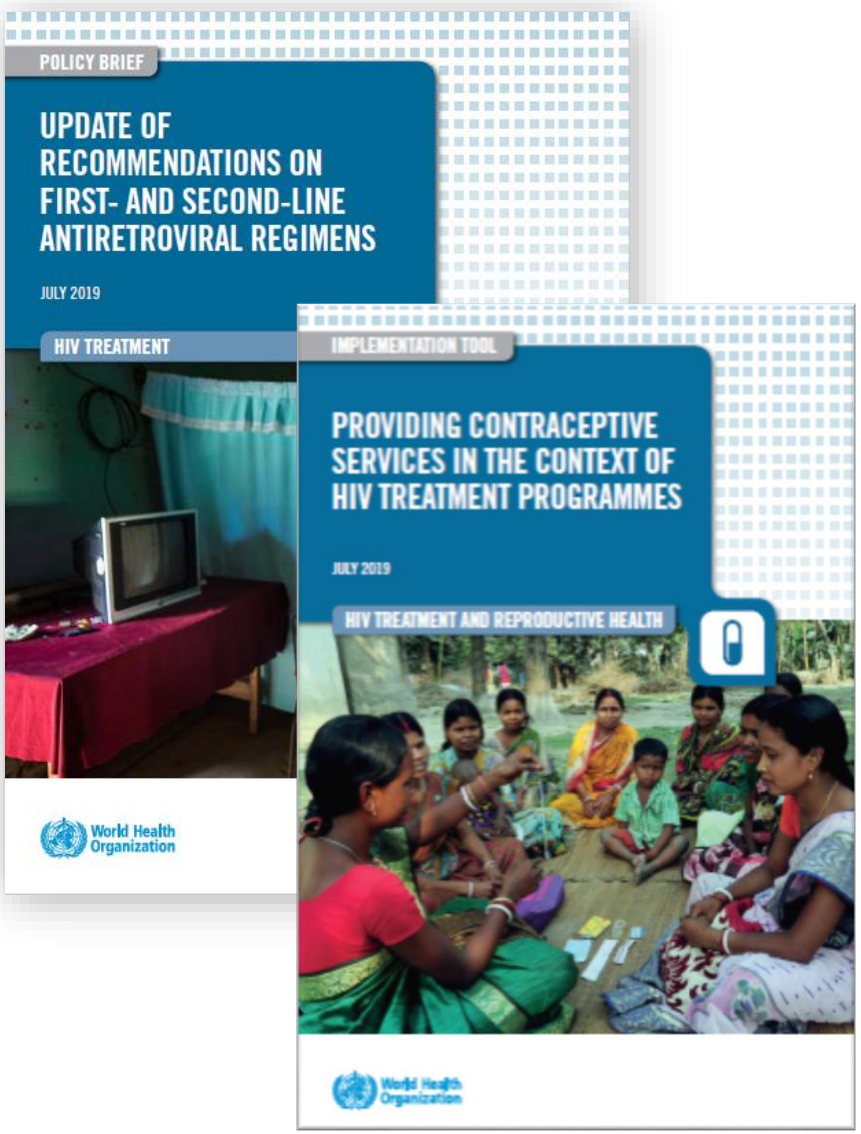
1. ENSURING **ACCESS** TO INTEGRATED, RIGHTS-BASED, CLIENT-CENTRED, HIGH-QUALITY CONTRACEPTIVE CARE
2. ENSURING CONTRACEPTIVE **OPTIONS** AND EFFECTIVENESS FOR WOMEN AND ADOLESCENT GIRLS LIVING WITH HIV
3. CONTRACEPTIVE CONSIDERATIONS FOR WOMEN AND ADOLESCENT GIRLS RECEIVING **ART**
4. CONTRACEPTIVE CONSIDERATIONS ACROSS THE **LIFE-COURSE** IN HIV TREATMENT PROGRAMMES

https://www.who.int/hiv/pub/arv/tool-contraceptive-hiv-treatment/en/

New WHO HIV Tx App
Get online with WHO ARV and Treatment Guidelines - 2019

- https://hivtx.org
- 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/

World Health Organization