Transition to new antiretrovirals in low-income and middle-income countries

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Investing In The Future – Impacting Real Lives

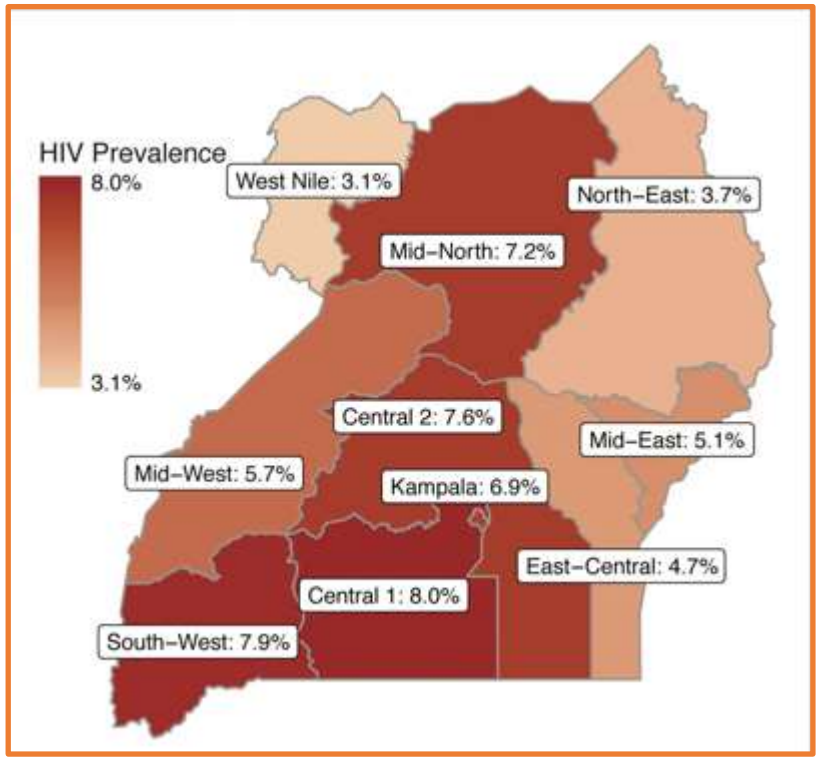
Ending the AIDS epidemic as a public health threat

UNAIDS

Fast-Track Targets

by 2020	by 2030
90-90-90 HIV treatment	95-95-95 HIV treatment
500 000 New HIV infections or fewer	200 000 New HIV infections or fewer
ZERO Discrimination	ZERO Discrimination

Uganda



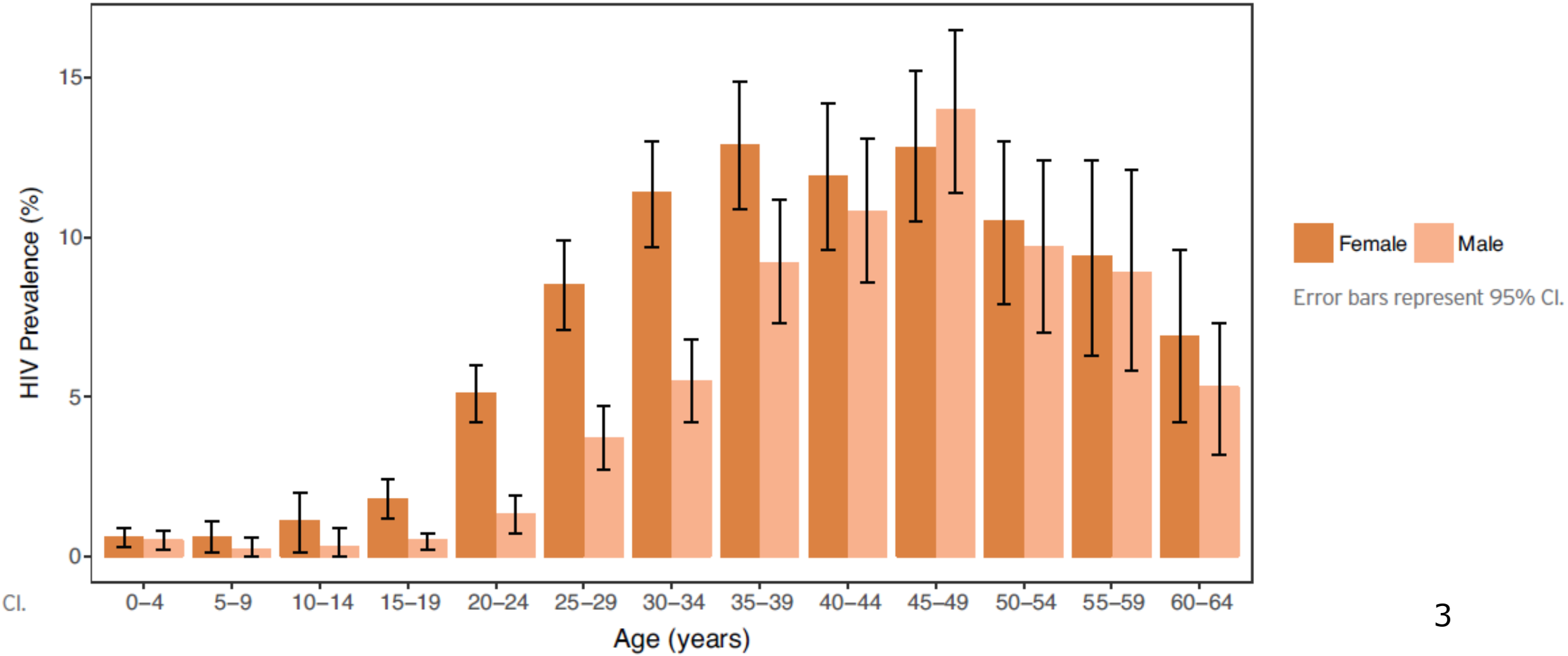
- **2018 Estimates**
- 1.3 million PLWH (1 million on ART)
- 50,000 new infections

HIV prevalence 6.2%

PEPFAR COP Uganda 2019

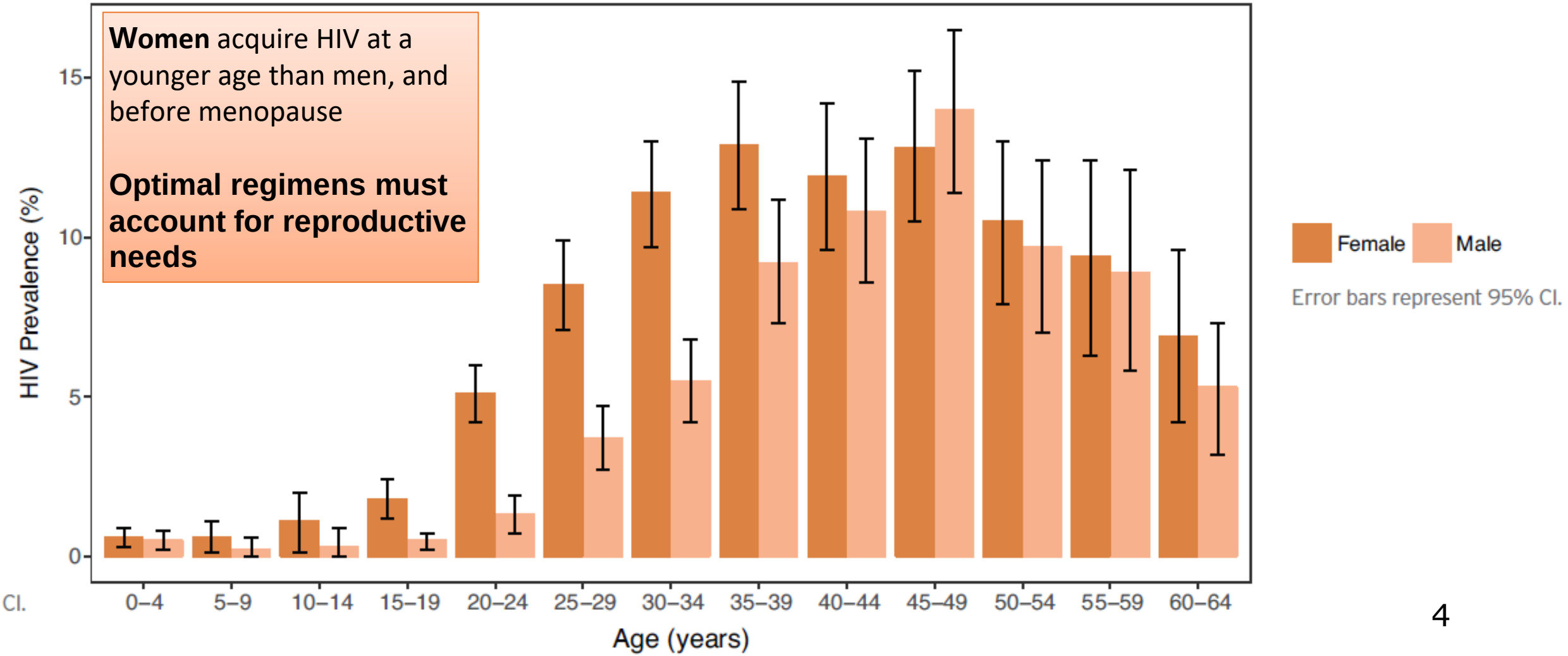
Who are we treating today?

Uganda Population-Based HIV Impact Assessment



Who are we treating today?

Uganda Population-Based HIV Impact Assessment

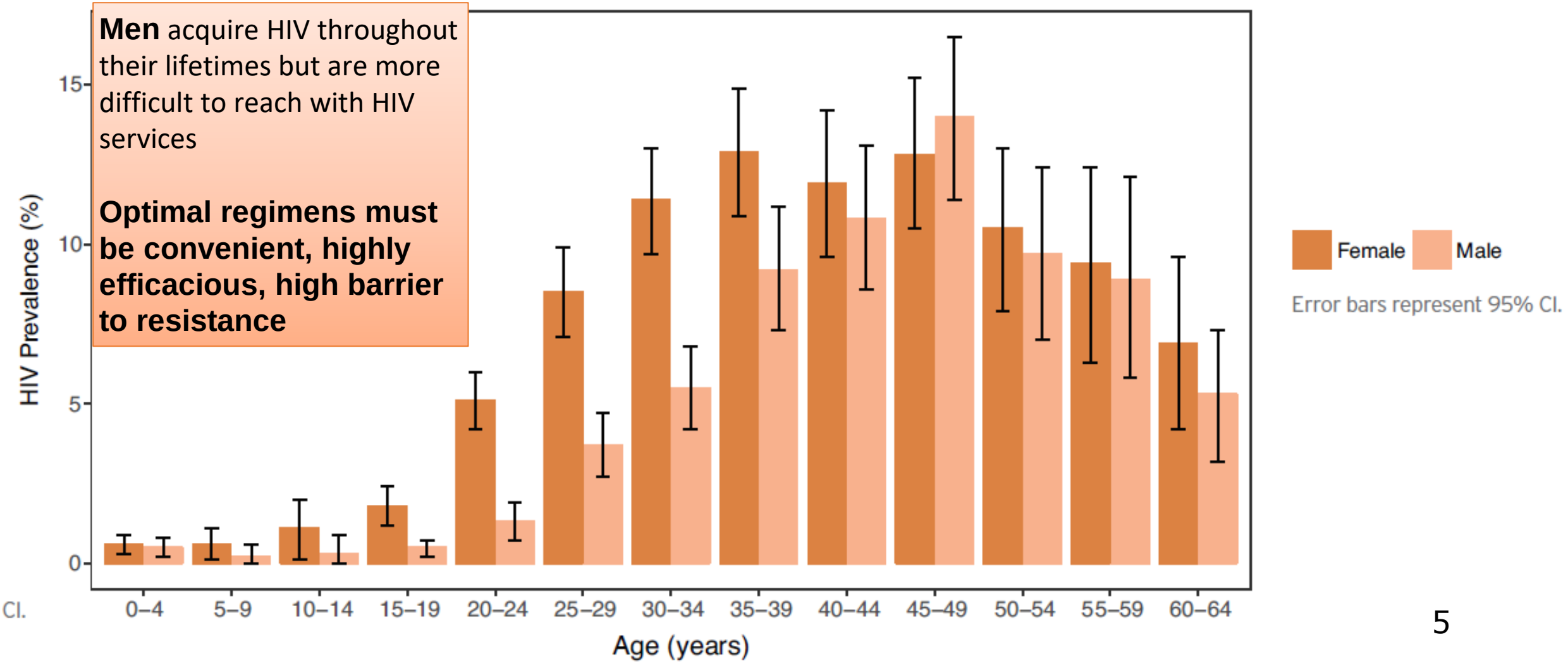


Who are we treating today?

Uganda Population-Based HIV Impact Assessment

Men acquire HIV throughout their lifetimes but are more difficult to reach with HIV services

Optimal regimens must be convenient, highly efficacious, high barrier to resistance



Dolutegravir-based regimens

TREATMENT 2.0

Optimize Drug Regimens
2020 Goal: available in low and middle income countries (LMICs) ART that is:

1. **Effective**
2. **Affordable**
3. **One pill, once-daily** to improve adherence
4. Suitable for most populations (including pregnancy, children, concomitant TB treatment)
5. **Minimal toxicities or drug interactions**
6. High **barrier to resistance**

WHO recommends dolutegravir containing regimens for all adults (including pregnant women) first and second line regimens*

Tenofovir lamivudine dolutegravir (TLD) – One pill once a day prioritized by 91 countries for scale up

Uganda is an early adopter country commenced roll-out in AUG 2017

By 2019 November >500,000 PLWH had been transitioned to TLD

WHO/CDS/HIV/19.15 2019

Public health approach to HIV treatment

- **Test and treat**, focus on identifying, starting and retaining clients on ART

- **Differentiated service delivery models**
  - Less frequent visits for stable patients,
  - Fast track pharmacy refills, peer HIV support including community drug distributions

- **Minimal laboratory monitoring**
  - Viral load prioritized over CD4 counts for ongoing monitoring, limited role for resistance testing
  - Limited or no funding for other support lab tests

Ethnic Factors and Impact on Drug Therapy

Intrinsic factors

- **Gender**
- Age
- Race
- Polymorphism
- Height
- Body weight
- **Diseases**
- Food habits

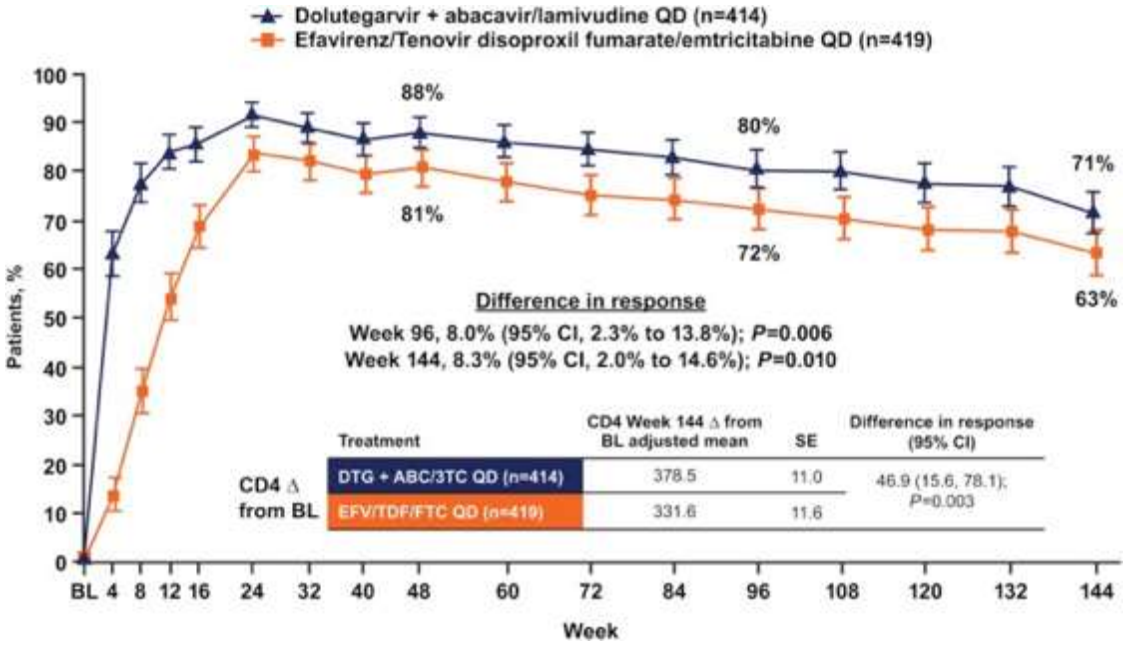
Extrinsic factors

- Culture
- Socioeconomic factors
- Medical practice
- Drug compliance

ICH E5

Why transition from efavirenz to DTG?

Virolgoic efficacy: statistical superiority of DTG-based regimen over an efavirenz-based regimen through 144 weeks



SINGLE Trial

Walmsley S et al, JAIDS 2015

Adverse Events: High prevalence of persistent CNS side effects in Ugandans receiving

43% patients on EFV reported a nervous system or psychiatric disorder side effect

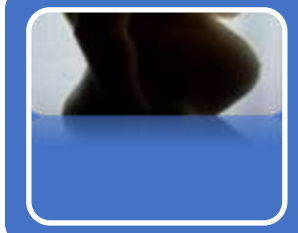
61% patients rated symptoms as severe ≥5/10

22 months median duration of symptoms experienced

SAPU Study

Seden et al. J. Antimicrob. Chemother, 2018

Dolutegravir use in women of childbearing age



Pregnancy/PMTCT

- Dose adjustments in pregnancy?

Post-partum/Breastfeeding

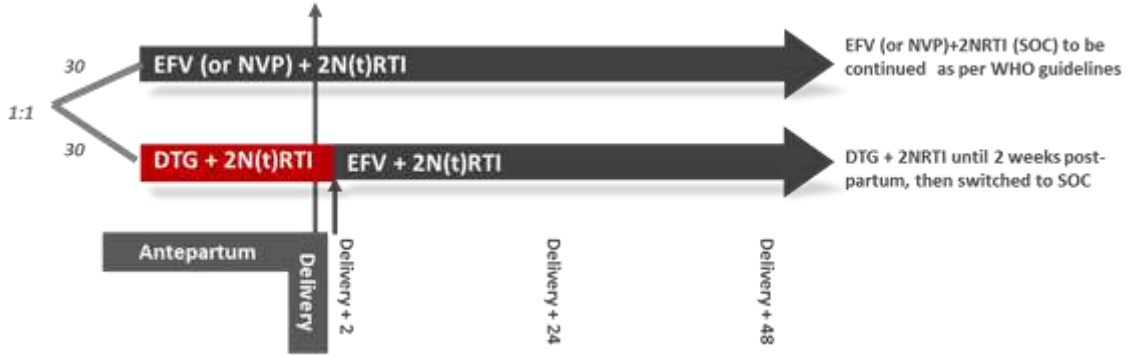
- How much drug gets to the baby?

Non-pregnant

- Contraception plus ART?

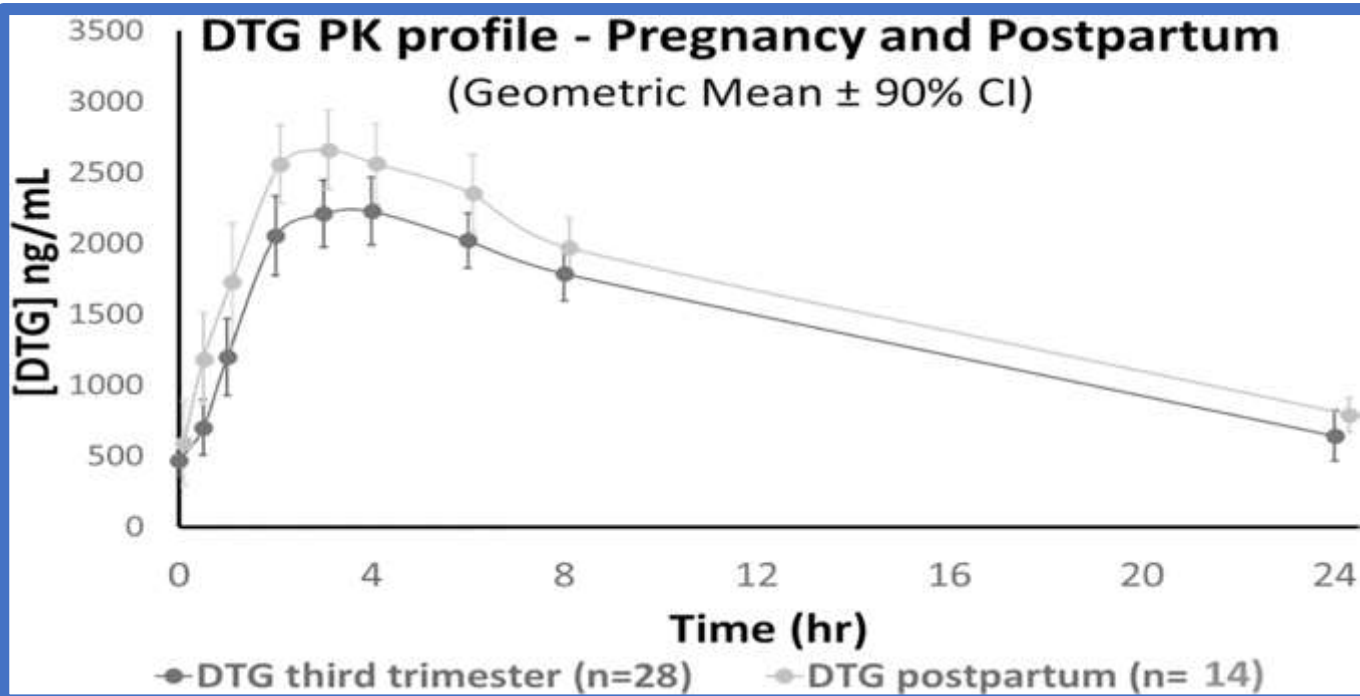
DolPHIN-1 Study

DolPHIN-1 Objective: Investigate the steady-state PK of DTG in HIV-infected women during the third trimester of pregnancy and after two weeks postpartum (AUC_{0-24})



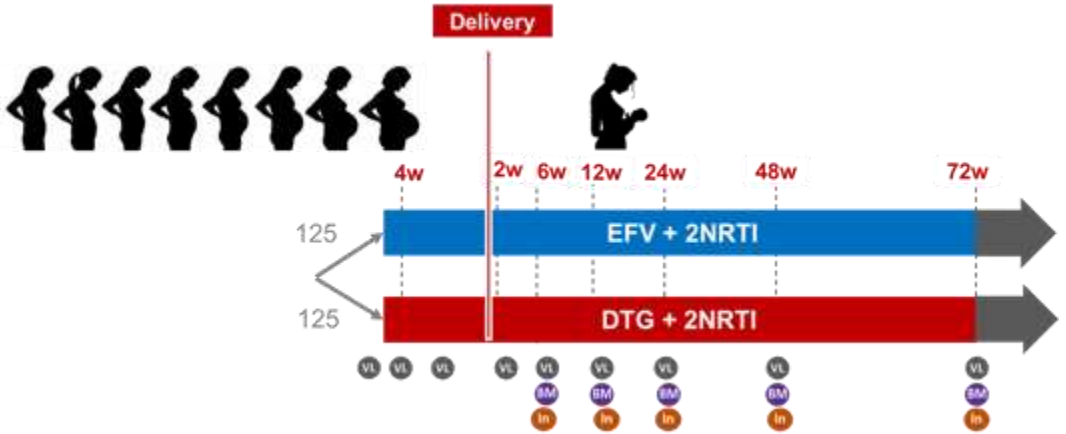
- 32% of women had low concentrations of DTG in T3
- DTG transferred across the placenta (121%)
- Infant exposures 6 – 8 % of maternal exposures
- Superior virologic suppression in DTG arm (p=0.001)

Waitt C, et al. Plos Med 2019



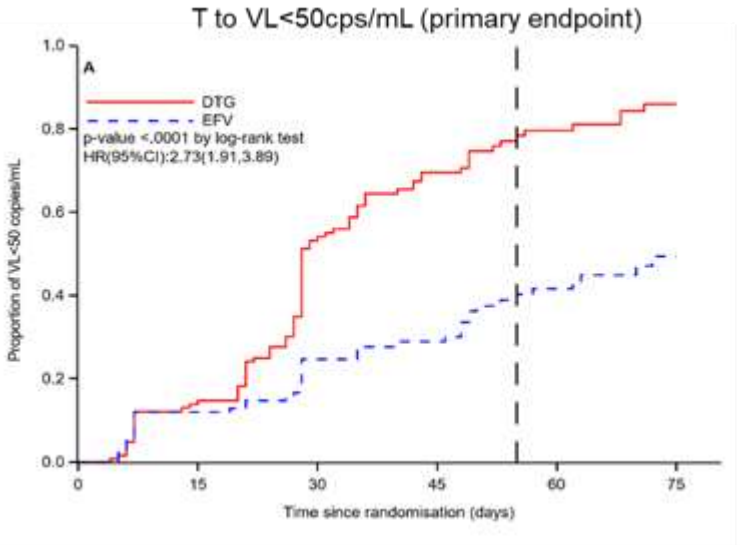
DolPHIN-2 Trial

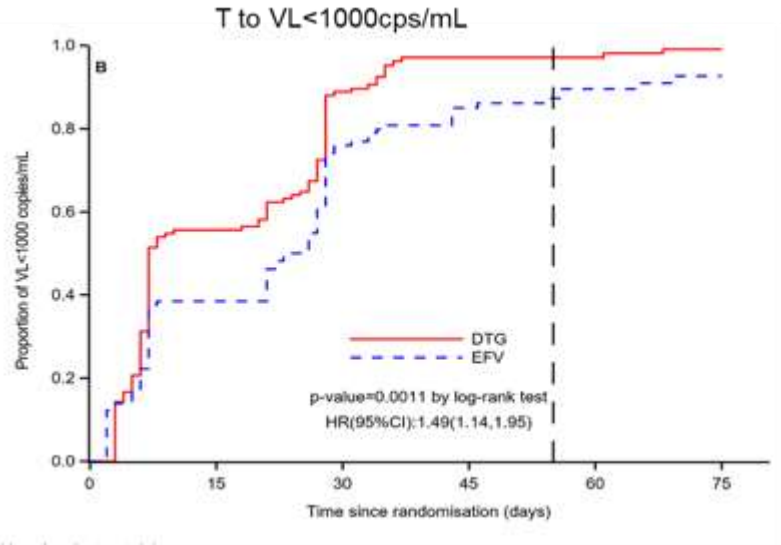
DolPHIN-2 Hypothesis: Faster VL declines with DTG may reduce MTCT at birth & during breastfeeding (BF) in HIV+ mothers initiating DTG or efavirenz-based ART in the third trimester



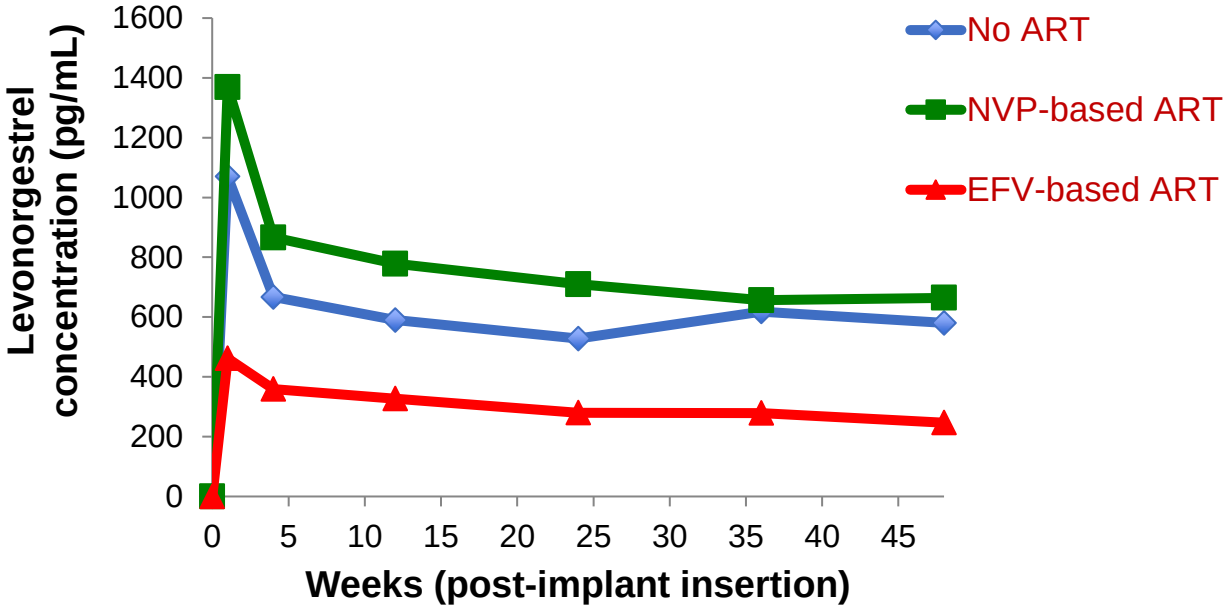
DTG achieves more rapid virological suppression before delivery compared to EFV when initiated in late pregnancy

Kintu K. et al. CROI 2019



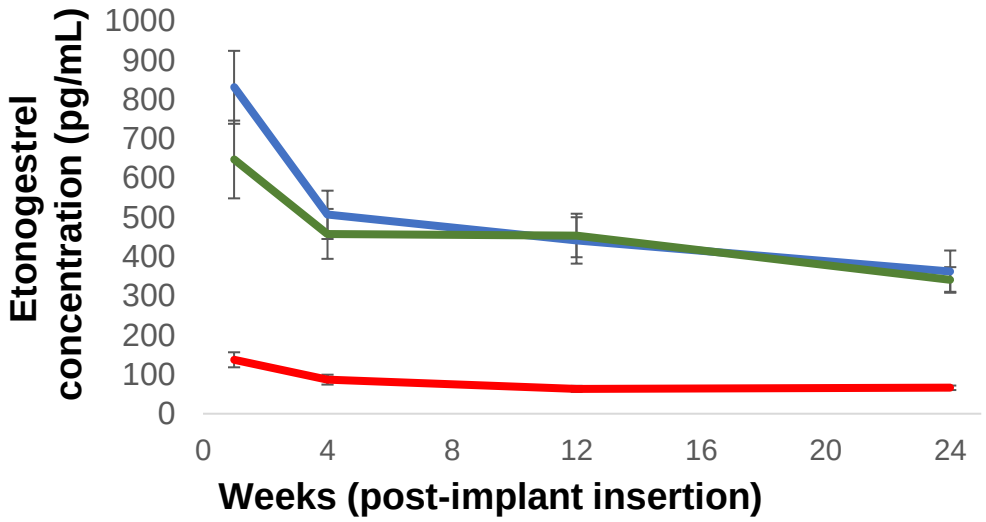


Contraceptive implants versus ART



levonorgestrel concentrations reduced by >45% by efavirenz

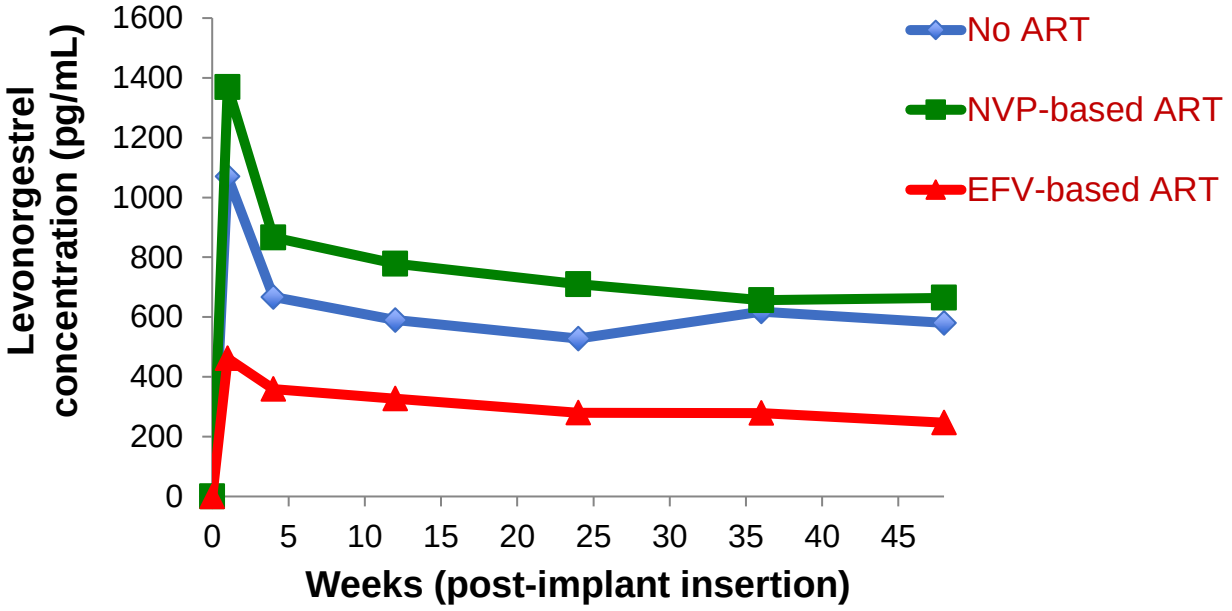
Scarsi et al. Clin Infect Dis. 2016



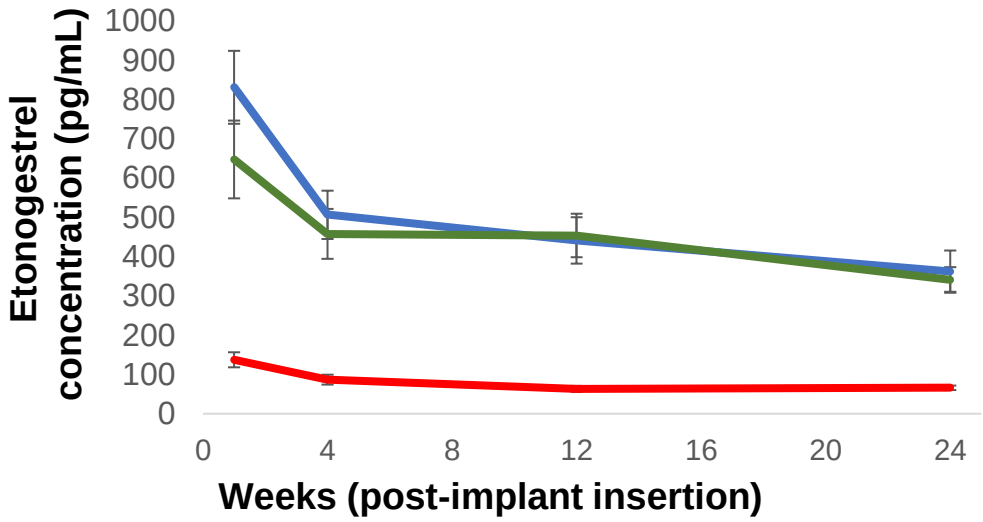
etonogestrel concentrations reduced by >80% by efavirenz

Chappell CA et al, AIDS 2017

Contraceptive implants versus ART



Scarsi et al. Clin Infect Dis. 2016

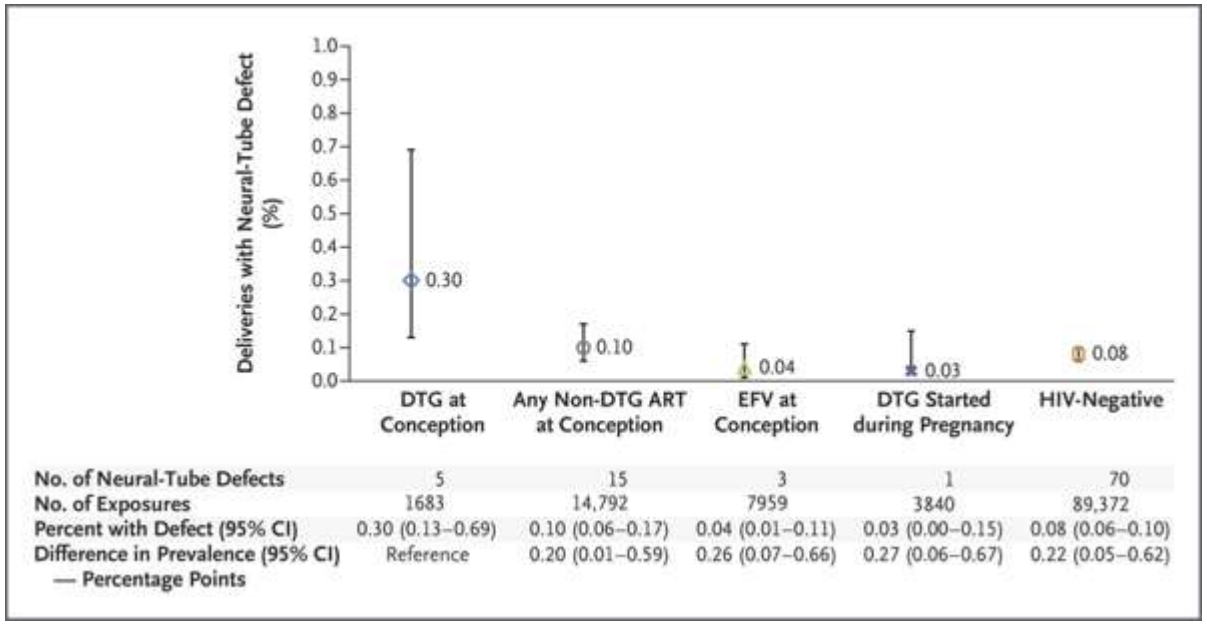


Chappell CA et al, AIDS 2017

HIV Drug Interactions
www.hiv-druginteractions.org

DTG Teratogenicity Alert

- Women of childbearing potential – 2018 teratogenicity alert for DTG – neural tube defects in Botswana cohort
- Subsequent follow-up data showed declining prevalence of neural tube defects but still slightly increased risk compared to other regimens



	DTG at Conception	Any Non-DTG ART at Conception	EFV at Conception	DTG Started during Pregnancy	HIV-Negative
No. of Neural-Tube Defects	5	15	3	1	70
No. of Exposures	1683	14,792	7959	3840	89,372
Percent with Defect (95% CI)	0.30 (0.13–0.69)	0.10 (0.06–0.17)	0.04 (0.01–0.11)	0.03 (0.00–0.15)	0.08 (0.06–0.10)
Difference in Prevalence (95% CI) — Percentage Points	Reference	0.20 (0.01–0.59)	0.26 (0.07–0.66)	0.27 (0.06–0.67)	0.22 (0.05–0.62)

WHO lifted recommendation to restrict in use among WOCBP

Critical – informed choice of the woman with risks and benefits discussed prior to initiating DTG

Consider alternatives where resources permit

Zash et al . N Engl J Med 2019; 381:827-840
Laker et al. Drug Safety2020 43,1133–1140(2020)

Alhassan Y. BMC Health Serv Res. 2020 Aug 1;20(1):705

Hyperglycemia in adults receiving DTG in Uganda

First-line ART

Started on DTG
3401

Did not switch
3230

16 cases
0.47%

1 case
0.03%

p=0·0004, Fisher's exact

Positive de-challenge
2/16 at 6 months

Analysis of 16 patients

- Age **> 40 years,**
- Severe elevation of glucose in 15/16.
- Median **duration on DTG was 4 months (IQR: 2.5 – 4.5)**
- **Common**: All ART experienced at initiation. Weight loss from DTG initiation to presentation. Comorbidities prior to hyperglycemia (eg, hypertension).

Lamorde M, et al. Dolutegravir-associated hyperglycaemia in patients with HIV. Lancet HIV. 2020 Feb 24. pii: S2352-3018(20)30042-4. doi: 10.1016/S2352-3018(20)30042-4.

Comparison – characteristics of patients with hyperglycemia versus those that did not develop hyperglycemia

- Older age
- Being male
- Hypertension
- Stavudine use in past regimens
- Longer duration on ART

	No hyperglycaemia (n=6631)	Hyperglycaemia (n=16)	p value
Age ≥50 completed years	1670/6629 (25·2%)	8/16 (50·0%)	0·023
Male sex	2378/6630 (35·9%)	13/16 (81·3%)	<0·0001
Body-mass index at baseline ≥25 kg/m²	2736/6437 (42·5%)	7/15* (50·47%)	0·948
Weight change from dolutegravir initiation to hyperglycaemia diagnosis			
Weight loss	NA	12/15* (80·0%)	..
Weight gain	NA	2/15* (20·0%)	..
Hypertension†	956/6631 (14·4%)	8/16 (50·0%)	<0·0001
Initial nucleoside reverse transcriptase regimen			
Stavudine	1107/6589 (16·8%)	9/16 (56·3%)	<0·0001‡
Zidovudine	2125/6589 (32·2%)	6/16 (37·5%)	..
Tenofovir disoproxil fumarate	3357/6589 (51·0%)	1/16 (6·2%)	..
ART duration before onset of hyperglycaemia			
<5 years	2398/6578 (36·4%)	2/16 (12·5%)	0·016‡
5–10 years	2478/6578 (37·6%)	5/16 (31·2%)	..
>10 years	1712/6578 (26·0%)	9/16 (56·3%)	..

ART=antiretroviral therapy. NA=not applicable. *Data missing for one patient. †Patient was prescribed antihypertensive drugs before the roll-out of dolutegravir in the clinic, or documentation of self-reported hypertension in the clinic database before the roll-out of dolutegravir. ‡From χ^2 tests used to test for differences between three-level categorical variables of ART type and ART duration, each with the presence or absence of hyperglycaemia.

***Table*: Characteristics of patients presenting with hyperglycaemia following dolutegravir initiation versus patients on first-line antiretroviral therapy who did not present with hyperglycaemia**

Lamorde M, et al. Dolutegravir-associated hyperglycaemia in patients with HIV. Lancet HIV. 2020 Feb 24. pii: S2352-3018(20)30042-4. doi: 10.1016/S2352-3018(20)30042-4.

Evidence base DTG and hyperglycemia

Case 1: DTG-induced hyperglycemia

- African-American male HIV positive, 16 years on ART known Type II DM on multiple co-meds for 5 years.
- Symptomatic hyperglycemia 3 weeks after DTG start.
  - plasma glucose level, 52.7 mmol/L; creatinine 5.26mg/dL; and HbA1C, 14.9%.).
- DTG discontinuation lead to improved glucose control

Case 2: 48 year old HIV positive patient, self-discontinued TDF/FTC/EFV
Started TDF/FTC/DTG (HbA1c – 5.9%)
Month 1: Hyperglycemia (27 mmol/L)
- treated with metformin 500 but DTG continued
Month 2: Hyperosmolar hyperglycemic state (>90 mmol/L), Hb A1C 12.9%, trace ketones

N-ACCORD cohort: Integrase inhibitors had an increased risk for incident diabetes 1.22 (95% CI, 0.95-1.57) versus NNRTI

- **PRODUCT INFORMATION**
- **Treatment naïve studies**
  - **SPRING-2: Grade III <1% at 24 months**
  - **SINGLE study: Grade III 2% at 36 months**
- **Treatment experienced**
  - **SAILING Study - Integrase naïve patients**
  - At 24 months, hyperglycemia (Grade III or IV) is expected to occur in **1%.**
  - **VIKING-3: Integrase experienced patients - DTG given at 50 mg twice daily**
  - **Grade II-IV – 14%** at 12 months,

NB: hyperglycemia not reported at 6 months in publication.

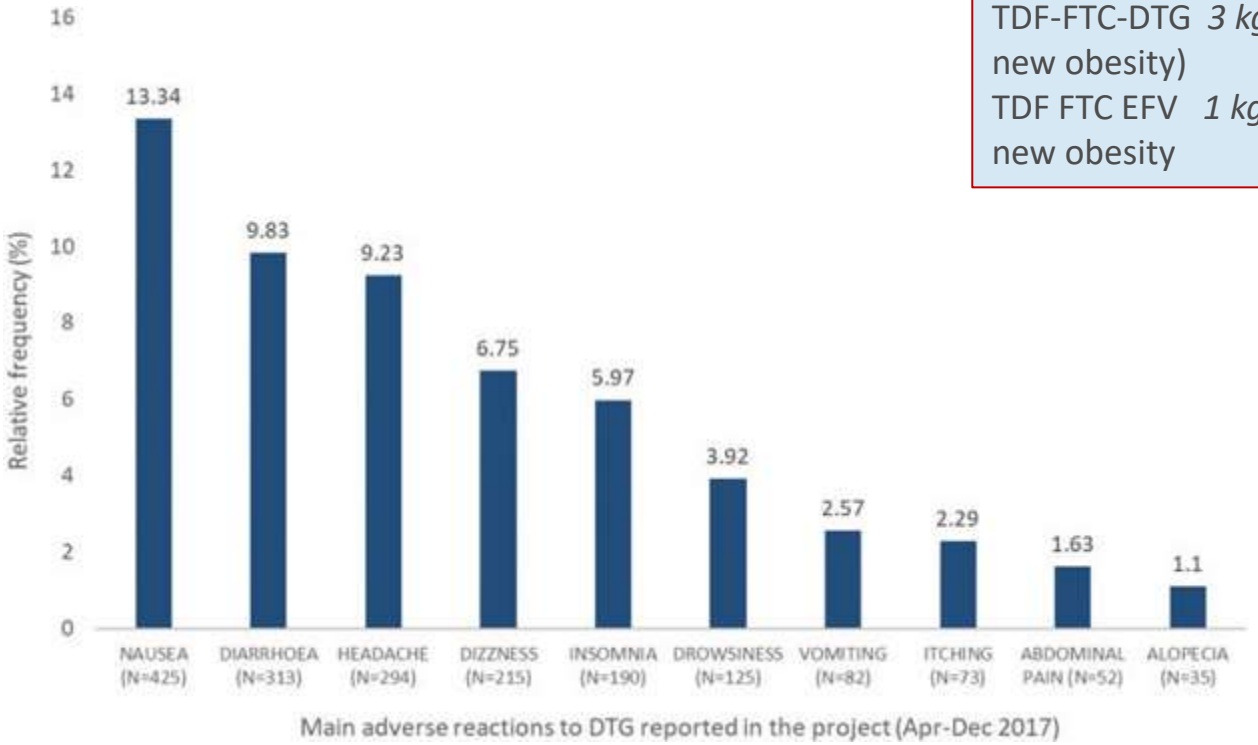
McLaughlin et al JAC 2018
Kamal et al. Journal of the Endocrinology Society 3 supplement_1
Rebeiro et al. ID Week. Abstract LB9.2019

(https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL.PDF).

Dolutegravir toxicities

Brazilian pharmacovigilance data following DTG roll out

72,032 patients participated in the program - 3185 adverse reactions

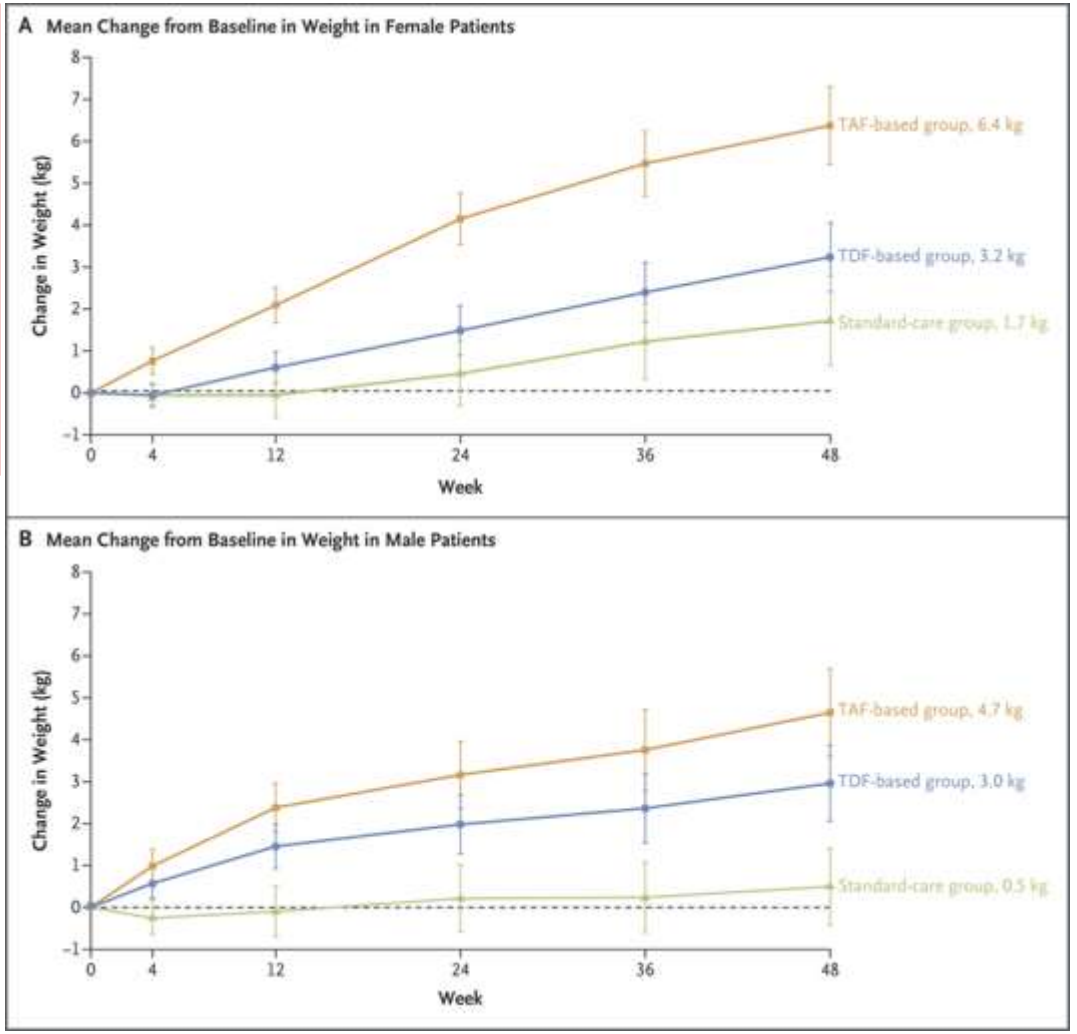


Batista et al Medicine: 2019, 98 10 - p e14828

At week 48,

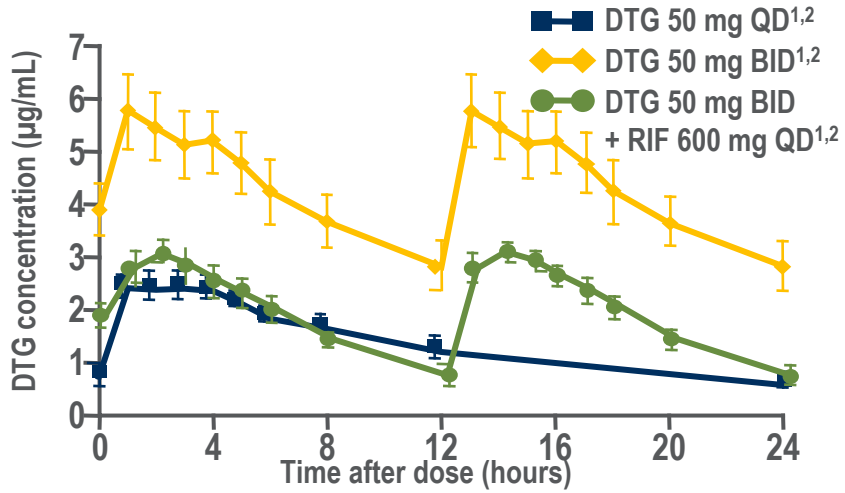
absolute weight gain, **%**
new obesity
TAF-FTC-DTG *6 kg*, **14%** new obesity
TDF-FTC-DTG *3 kg*, **7%** new obesity)
TDF FTC EFV *1 kg*, **6%** new obesity

Weight gain – ADVANCE Trial



Venter FC, et al. N Engl J Med 2019; 381:803-815

DTG and Rifampicin



RIF + DTG 50 bd

- **AUC ↓54% Cmin ↓72%**
- **DTG 50 bd + rif comparable Cmin**

INSPIRING– 24w and 48w outcomes in co-infected patients, favorable HIV, TB outcomes

Dooley et al. J Acquir Immune Defic Syndr 2013; 62:21–7
Dooley et al. Clin Infect Dis 2020 Feb 3;70(4):549-556.

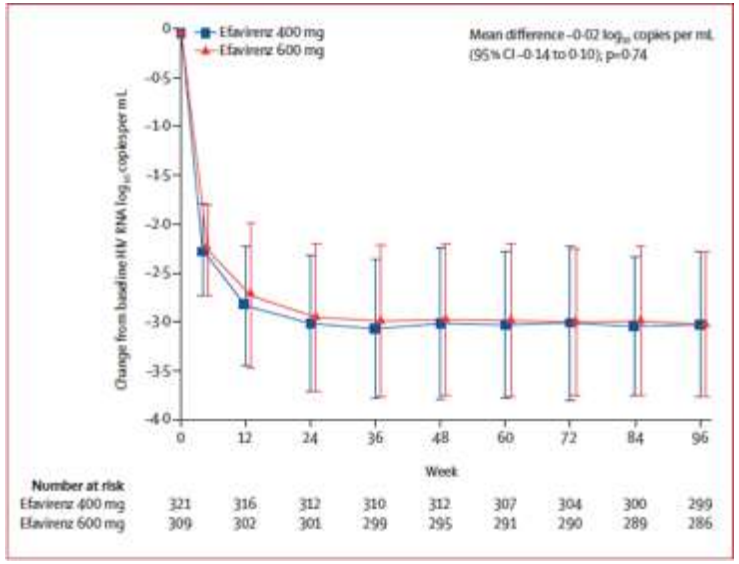
Options:

DTG to be used at 50 mg twice daily with rifampicin – WHO recommendation

Efavirenz based regimens preferred - EACS

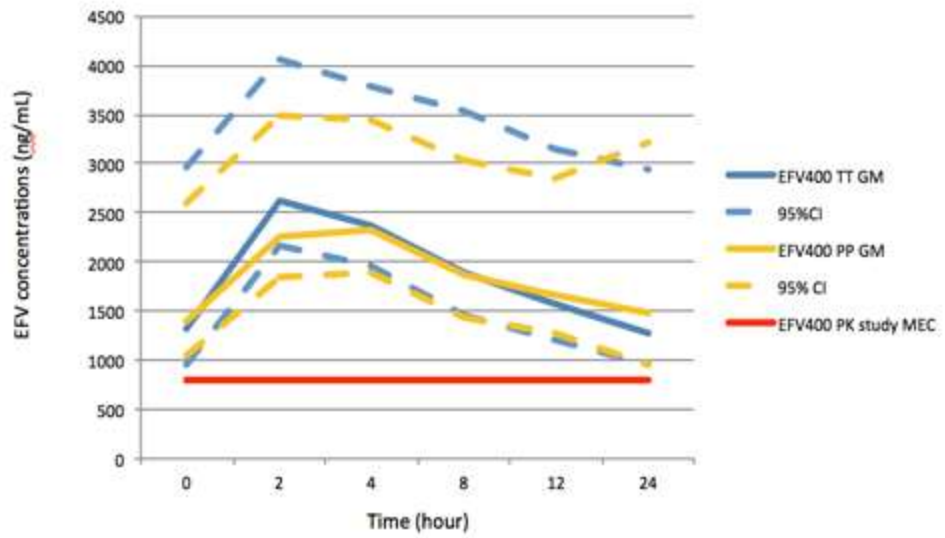
Efavirenz 400mg

- **The ENCORE-1 (*N*= 636) demonstrated non-inferiority between efavirenz 400 mg (EFV400) once daily (OD) and standard dose (efavirenz 600 mg OD)**



Mean change in HIV-RNA from baseline to week 96

Pregnant women, tuberculosis co-infection excluded



SSAT 063: EFV400 pharmacokinetic parameters were lower in 3rd trimester compared with PP($AUC_{13\%}$ and C_{24} 23% lower) but were in range for ENCORE1 patients. [2]

SSAT 062: isoniazid plus rifampicin associated with limited changes in EFV400 exposure (<23%) and EFV400 concentrations were maintained within ranges of those measured in PLWH in ENCORE-1. [3,4]

[1]Puls et al Lancet 2014 [2]Lamorde et al. Clin Infect Dis, 2018 [3]Cerrone et al. Clin Infect Dis, 2018 4Kaboggoza JP et al. Open Forum Infect Dis. 2019

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