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

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Investing In The Future – Impacting Real Lives

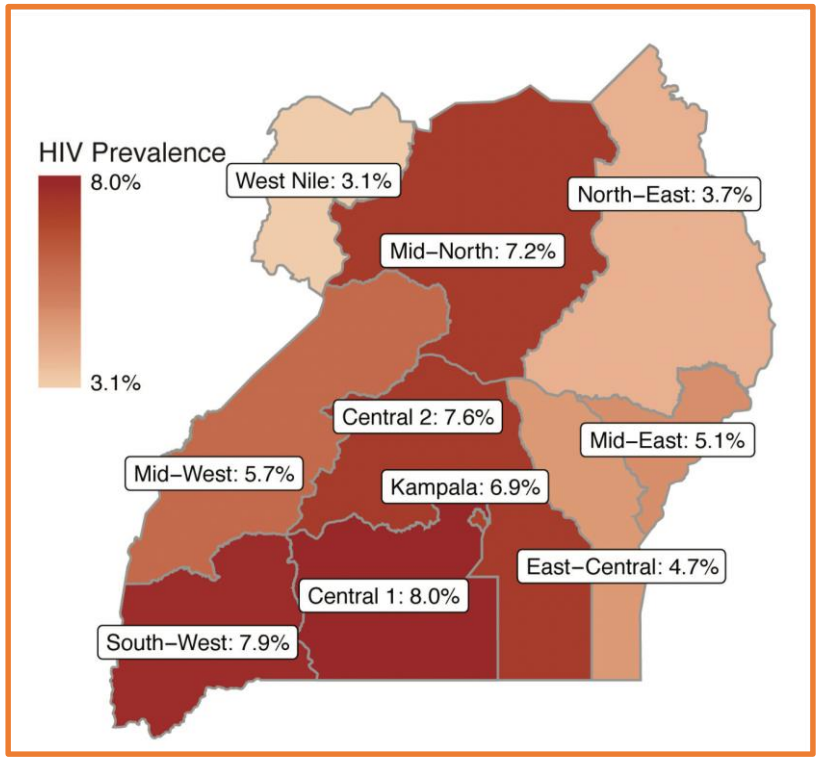
Ending the AIDS epidemic as a public health threat

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



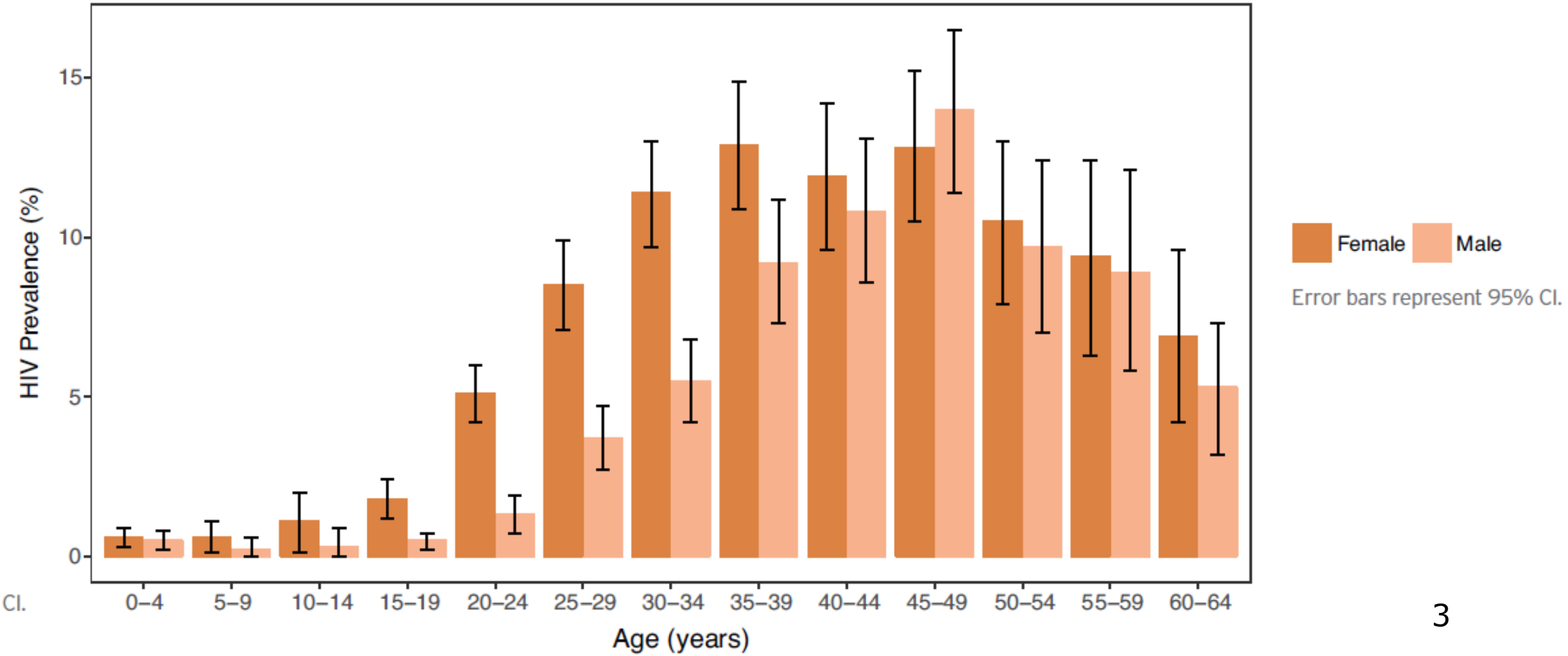
HIV prevalence 6.2%

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

PEPFAR COP Uganda 2019

Who are we treating today?

Uganda Population-Based HIV Impact Assessment



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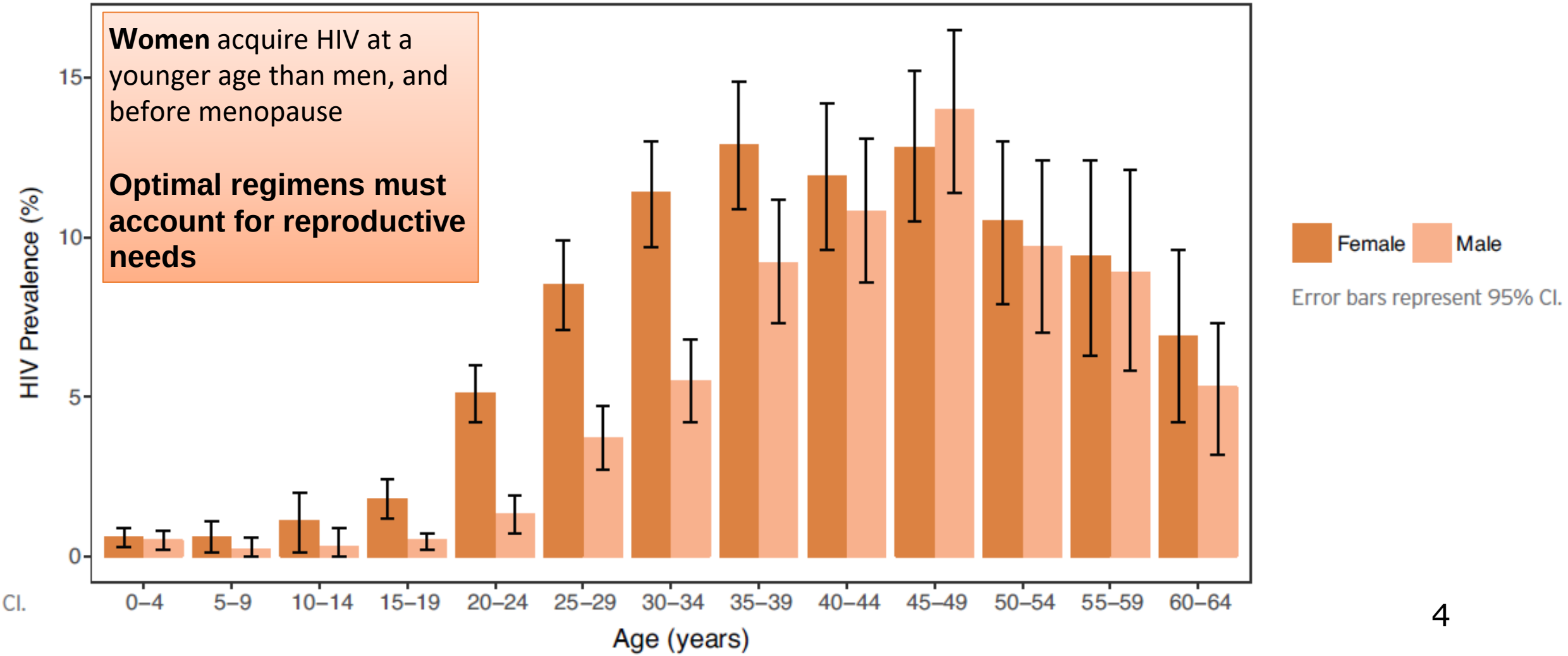
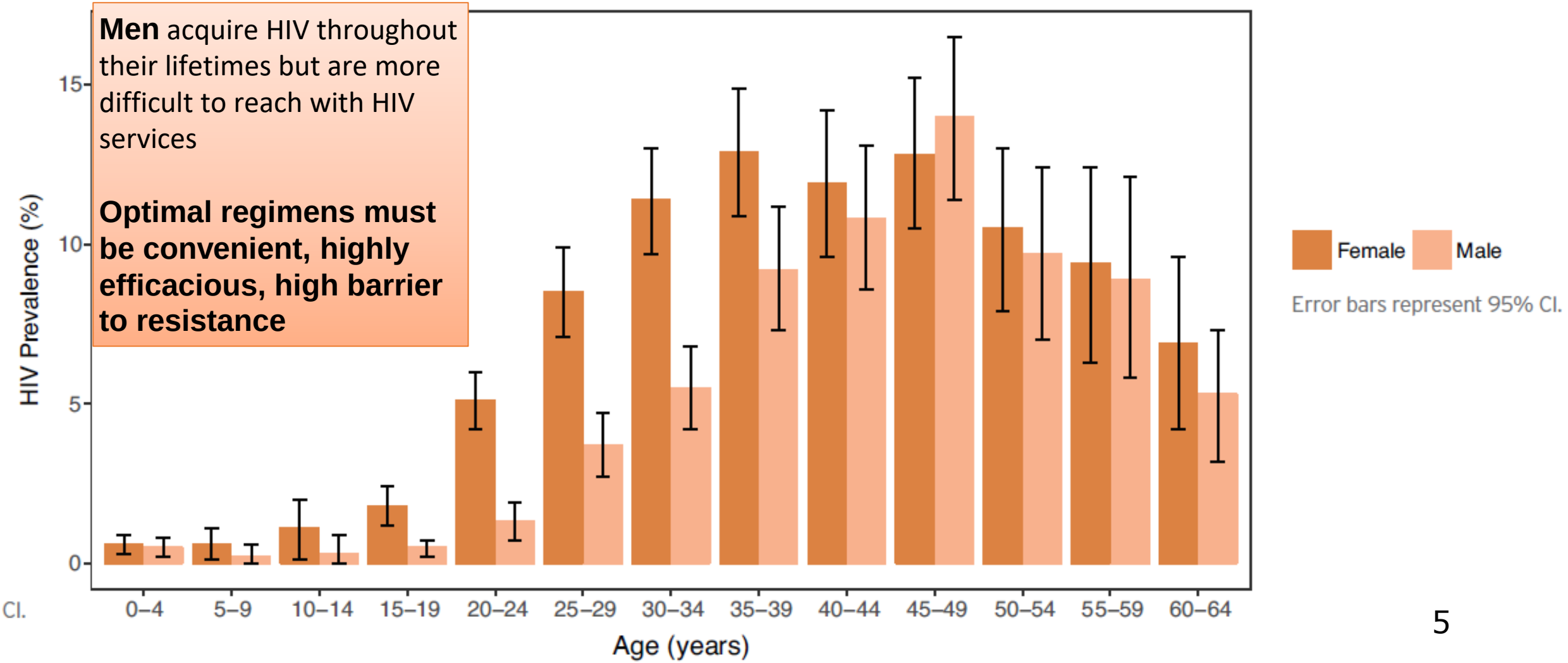


Who are we treating today?

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

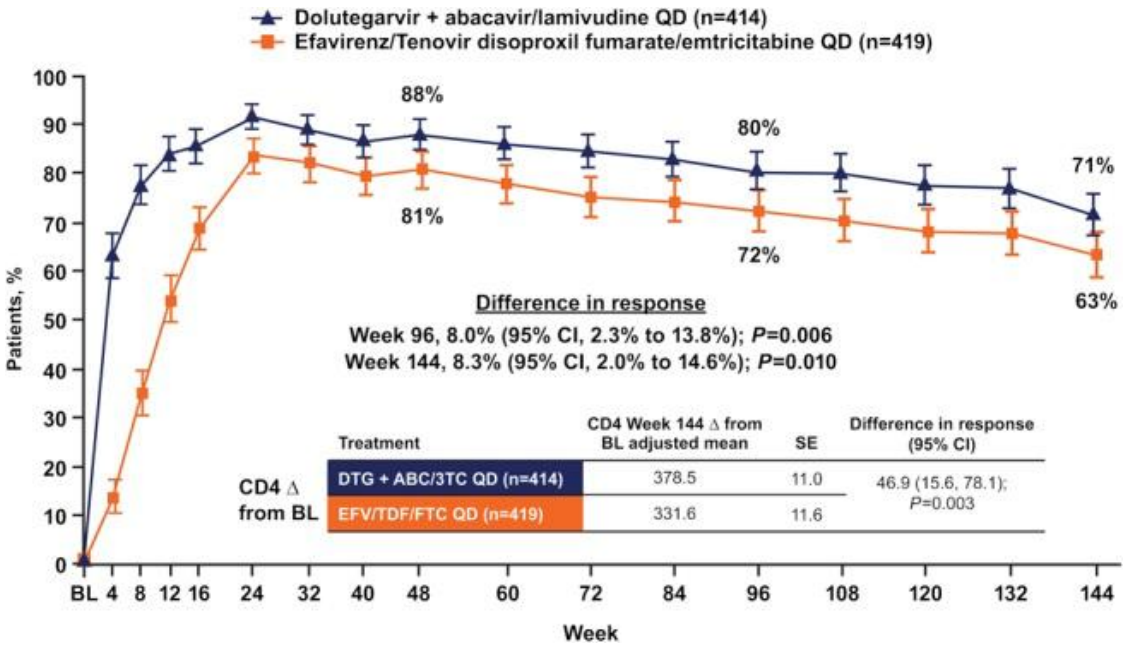
Extrinsic factors

- 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

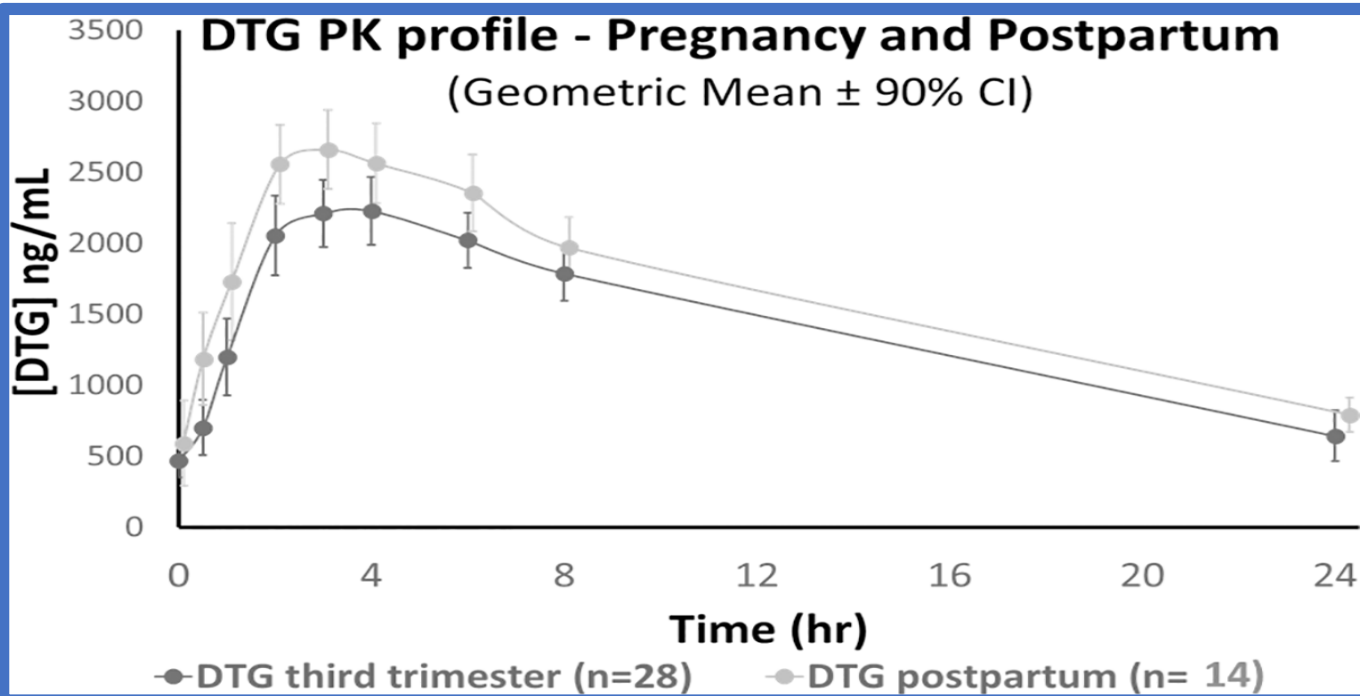
- Contraception plus ART?

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})

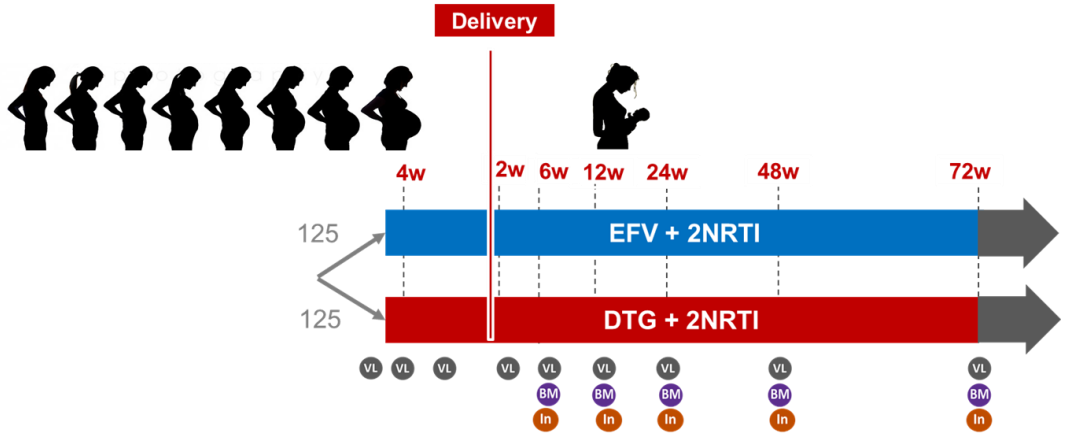
- 32% of women had low concentrations of DTG in T3
- DTG transferred across the placenta (121%)
- Infant exposures 6 – 8 % of maternal exposures
- Superior virologic suppression in DTG arm (p=0.001)

Waitt C, et al. Plos Med 2019



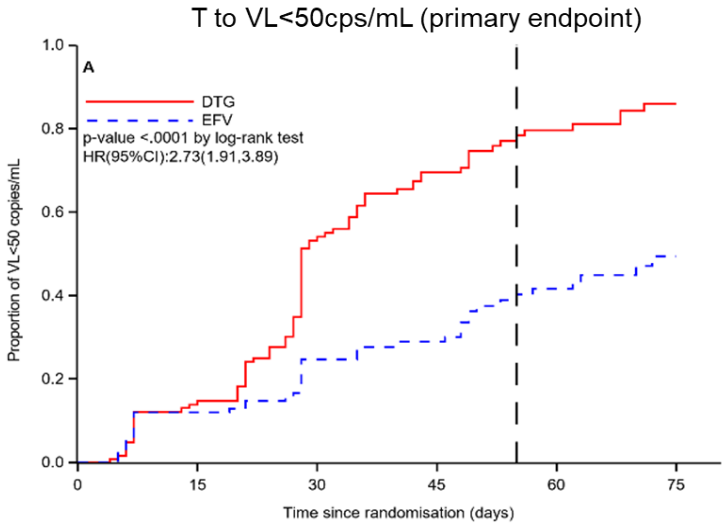
DolPHIN-2 Trial

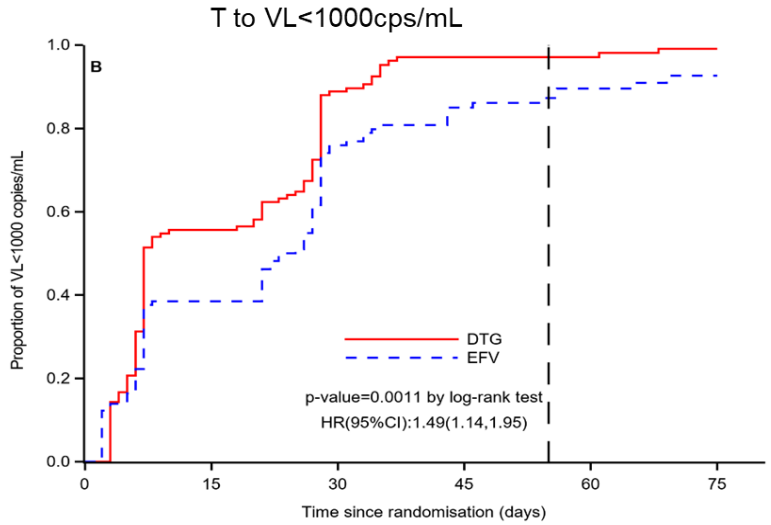
DolPHIN-2 Hypothesis: Faster VL declines with DTG may reduce MTCT at birth & during breastfeeding (BF) in HIV+ mothers initiating DTG or efavirenz-based ART in the third trimester



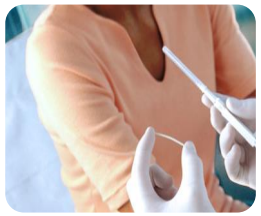
DTG achieves more rapid virological suppression before delivery compared to EFV when initiated in late pregnancy

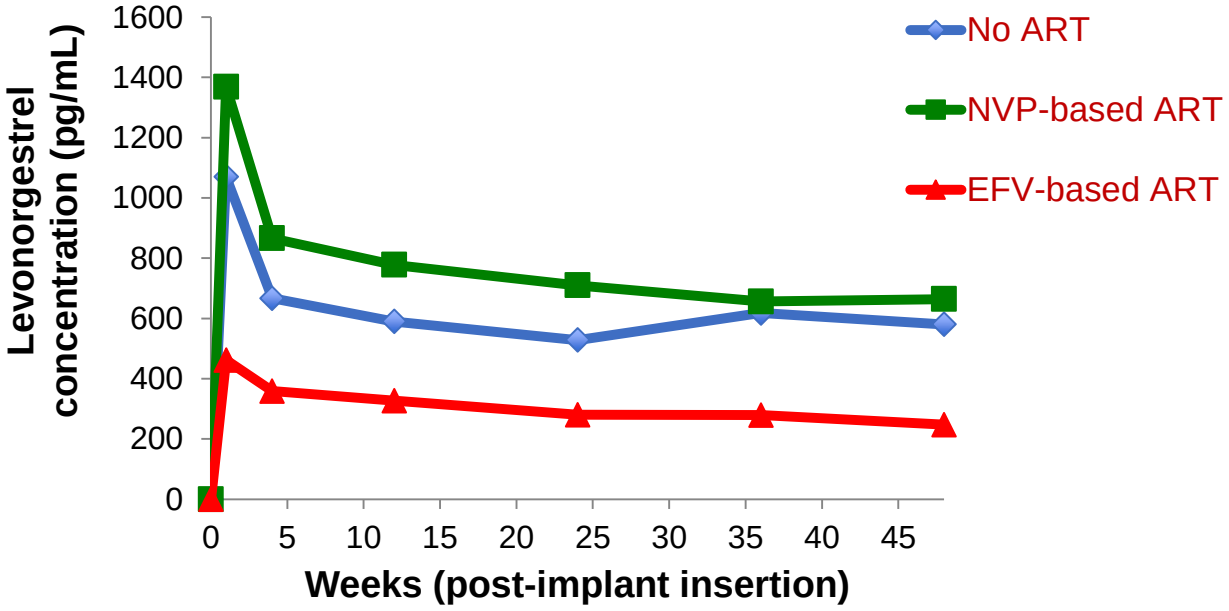
Kintu K. et al. CROI 2019





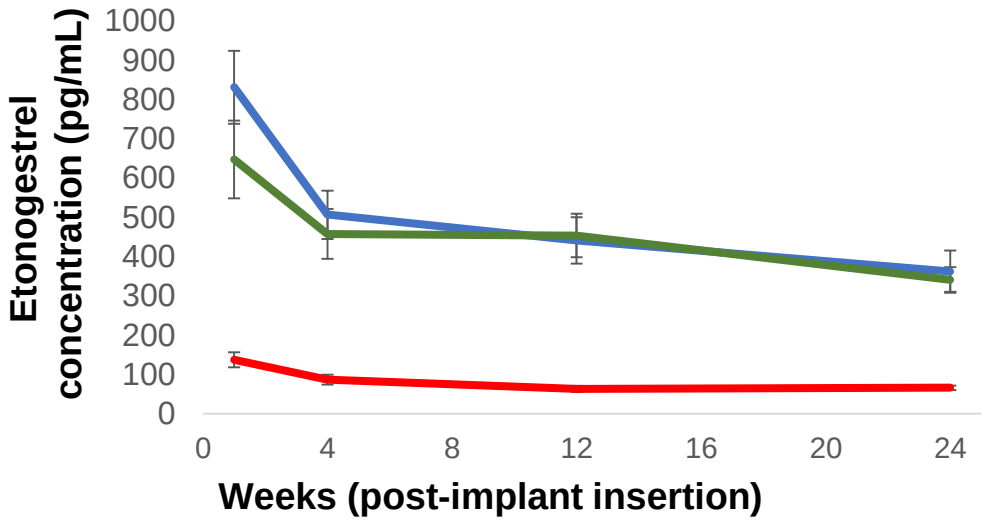
Contraceptive implants versus ART





levonorgestrel concentrations reduced by >45% by efavirenz

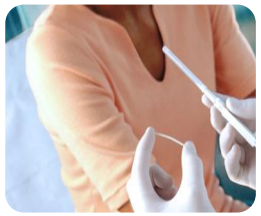
Scarsi et al. Clin Infect Dis. 2016

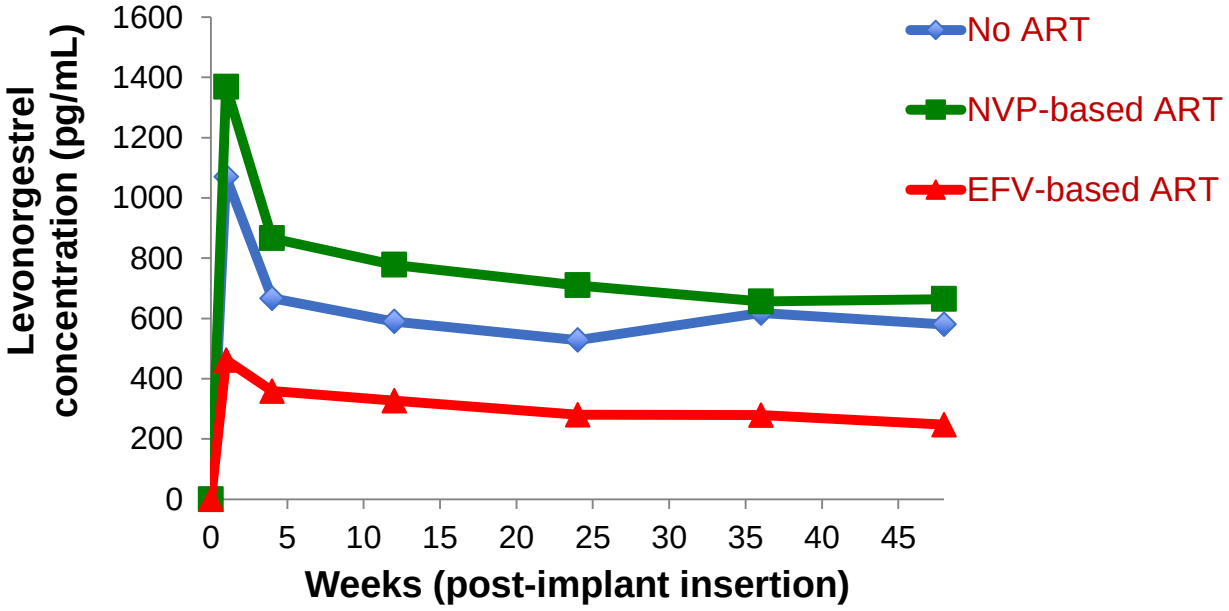


etonogestrel concentrations reduced by >80% by efavirenz

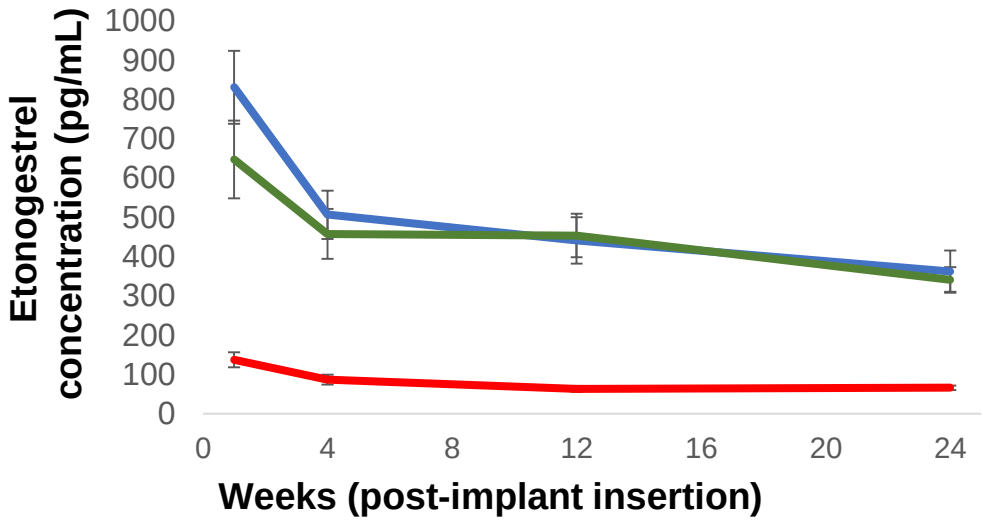
Chappell CA et al, AIDS 2017

Contraceptive implants versus ART



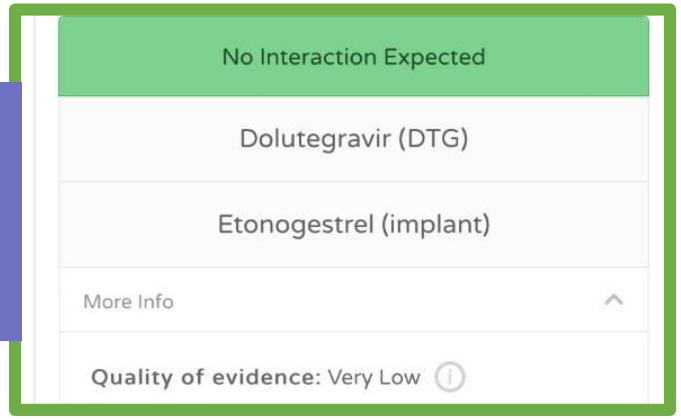


Scarsi et al. Clin Infect Dis. 2016



Chappell CA et al, AIDS 2017

HIV Drug Interactions
www.hiv-druginteractions.org



Dolutegravir: Managing a potential NTD safety alert

Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun

Clinic (1226 patients/763 women)

Sep 17: MOH Pilot EFV DTG for toxicity (200 people)

Feb 18: MOH Pilot first line NNRTIs DTG (>1000 people)

May 18: Warnings: *Potential* risk of *neural tube defects* (FDA, EMA, and WHO)

June 2019 WHO lifts restriction based on new evidence[2]

Women called back for information and provision of contraception
79% (402/510) opted to stay on DTG.
Only, 40% (160/402) chose effective contraceptives[1]

[1]Arinaitwe et al CROI 2019. Zash et al. NEJM 2019

Case reports of hyperglycemia following transition to DTG

First-line ART

Started on DTG
3401

16 cases

Did not switch
3230

1 case

Reports of symptomatic patients with severely elevated blood glucose

Analysis of 16 patients

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

Positive de-challenge
3/16 at 6 months

Submitted

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).

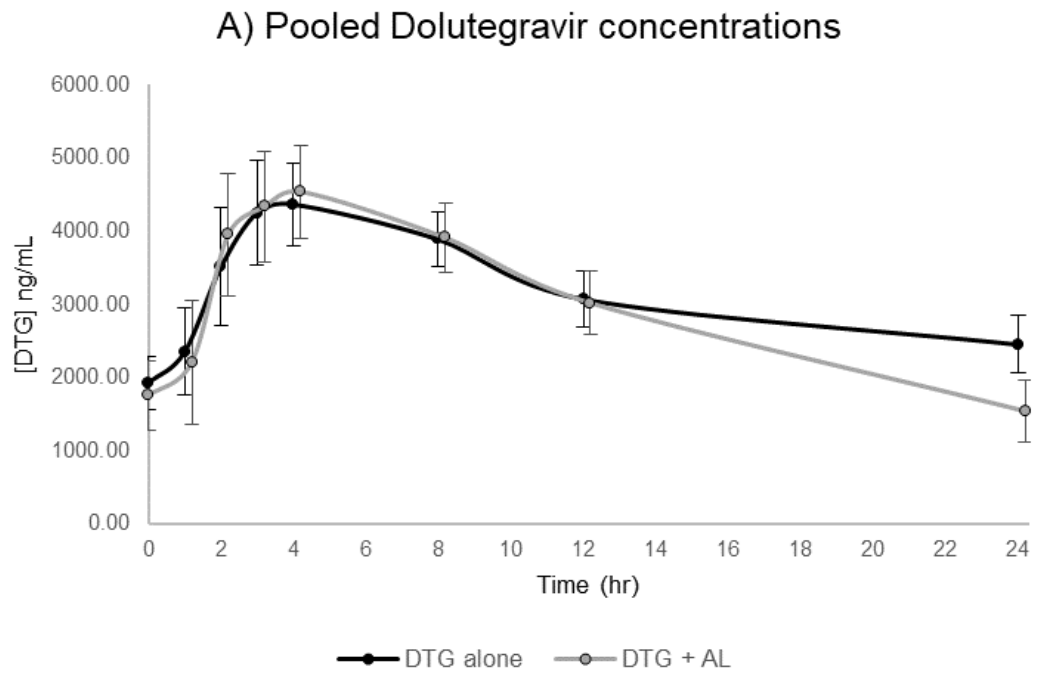
Dolutegravir use with co-endemic diseases

- Tuberculosis
- Malaria

Malaria

First-line antimalarial drug artemether-lumefantrine prone to drug interactions with efavirenz, contraindicated with rifampicin

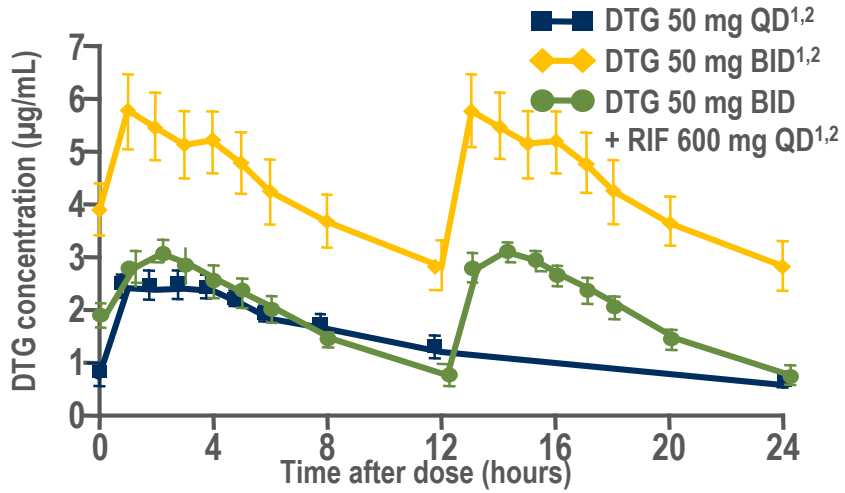
Co-administered drug	Effect on artemether-lumefantrine exposure		
	artemether	DHA	lumefantrine
rifampicin[1]	89%	85%	68%
efavirenz[2]	77%	75%	55%



No clinically significant interactions between DTG and artemether lumefantrine or artesunate amodiaquine[3]

[1]Lamorde et al AIDS 2013 [2]Byakika-Kibwika et al JAC 2012 [3] Walimbwa et al, AAC 2019

Tuberculosis (DTG and rifampicin)

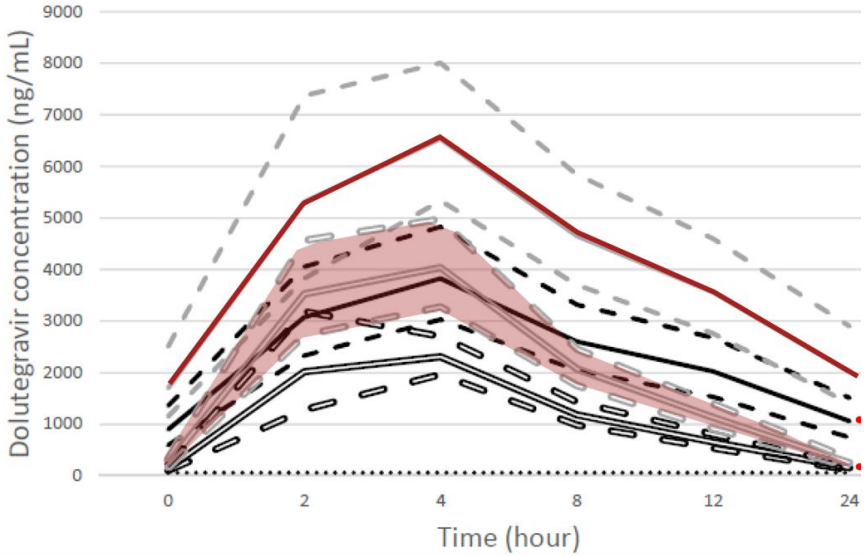


RIF + DTG 50 bd

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

INSPIRING (CROI 2018, IAS 2018) – 24w and 48w outcomes in co-infected patients

Dooley et al. J Acquir Immune Defic Syndr 2013; 62:21–7
Dooley et al. CROI 2018



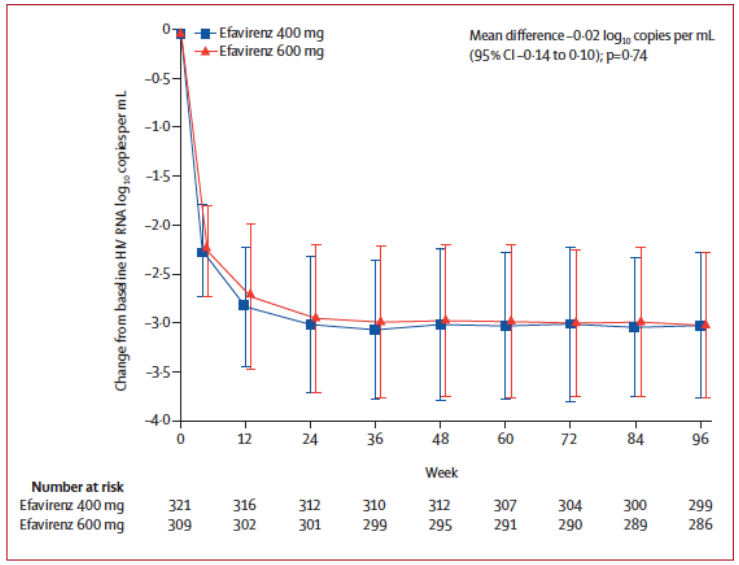
RIF v+ DTG 100mg od

- DTG 100mg od: Cmin ↓76% with Rif
- DTG absorption saturates between 50 - 100mg
- Cmin >PA-IC_{90} in all, but below MEC of 300mg/mL in most cases

Boffito et al 2018 PK workshop Baltimore

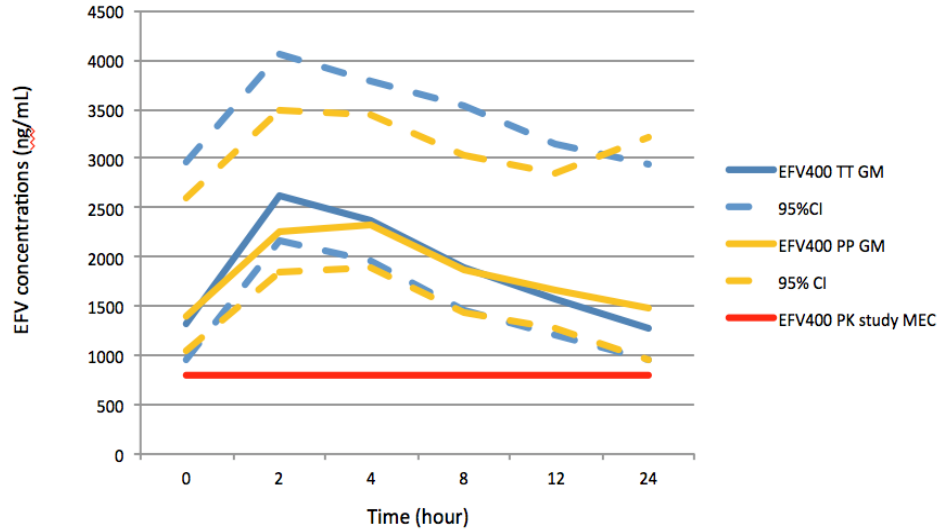
Efavirenz 400mg

- **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

Acknowledgements

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