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

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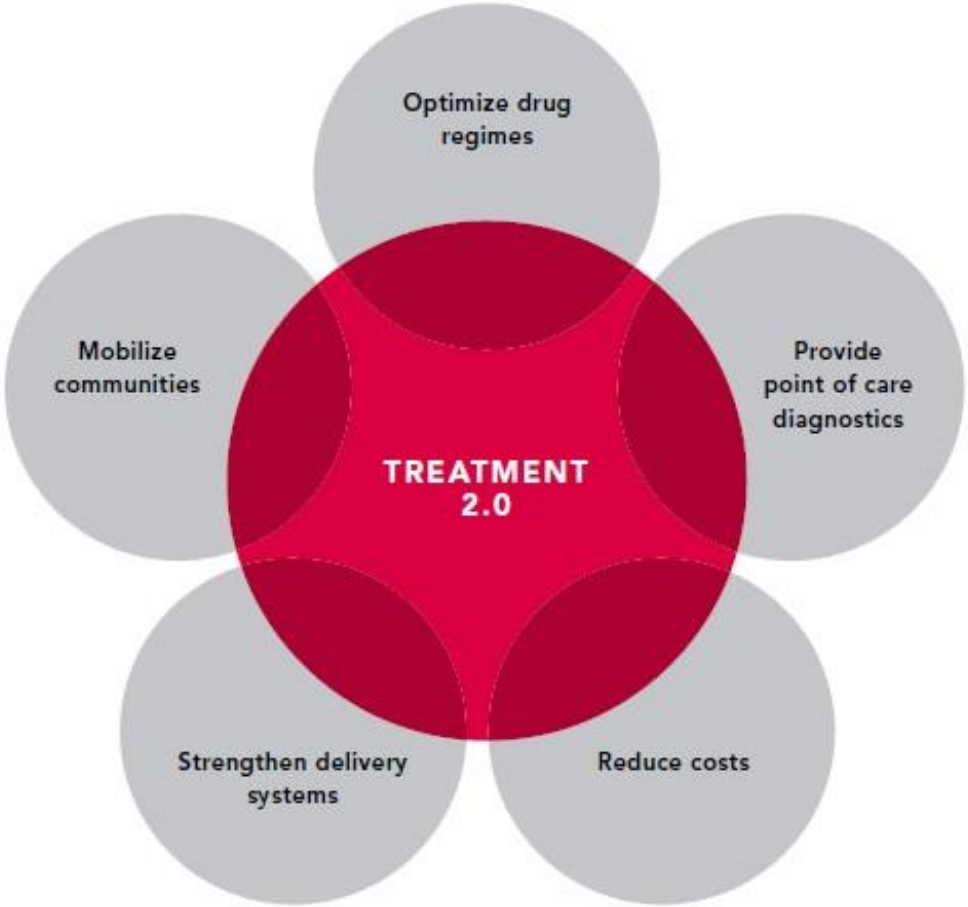
Investing In The Future – Impacting Real Lives

**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**



# Generic regimens

| ARV, co-formulation or FDC | Generic Filing Year | Cost (pppy) |
|---|---|---|
| DTG | 2015 | $44 |
| DTG/TDF/3TC | 2016 | $75 |
| EFV400/TDF/3TC | 2016 | $99 |
| DRV/r | 2016 | $413 |

| Optimization criteria | | DTG | EFV400 | DRV/r |
|---|---|---|---|---|
| Efficacy and safety | High antiretroviral potency | ✓ | ✓ | ✓ |
| | Low toxicity | ✓ | ✓ | ✓ |
| | High genetic barrier to resistance | ✓ | ✗ | ✓ |
| Simplification | Available as generic fixed-dose combination | ✓ | ✓ | ✗ |
| | Low pill burden | ✓ | ✓ | ✗ |
| Harmonization | Use for pregnant women | ? | ? | ✓ |
| | Use for children | ? | ✗ | ✓ |
| | Use in HIV-associated TB | ? | ? | ✗ |
| | Few drug interactions | ✓ | ✗ | ✗ |
| Cost | Low price | ✓ | ✓ | ✗ |

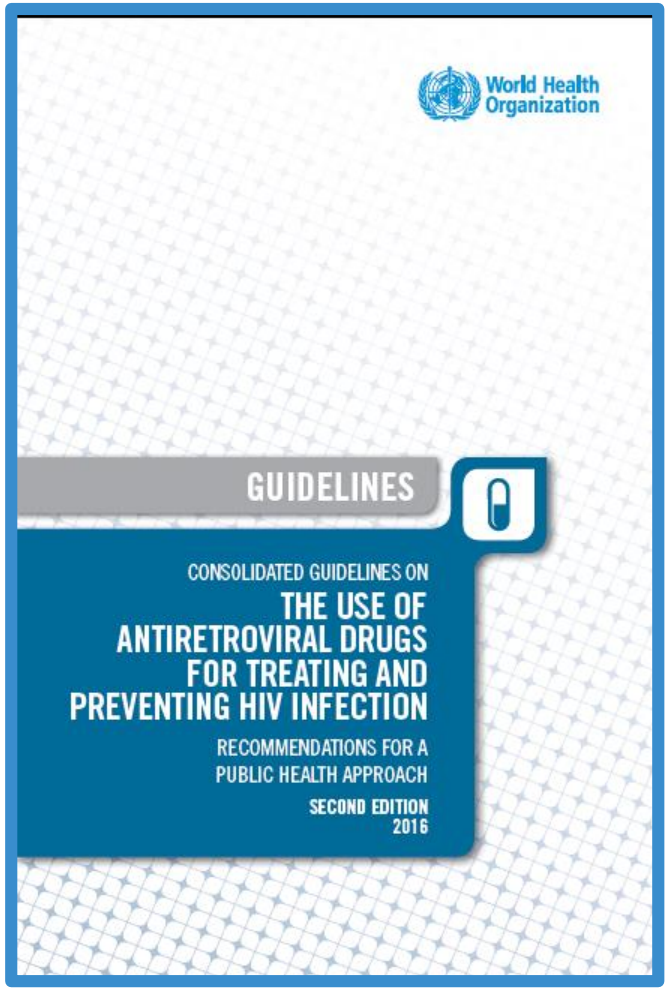
# Treatment 2.0 Ideal treatment guideline

| Adults and adolescents (including TB, pregnant women) | |
|---|---|
| First-line | Regimen 1<br>FDC, once daily |
| Second-line | Regimen 2<br>FDC, once daily |

# WHO guidance…first-line antiretroviral therapy 2016

| PREFERRED REGIMEN | TDF + 3TC (or FTC) + EFV |
|---|---|
| **ALTERNATIVE REGIMENS** | AZT + 3TC + EFV (NVP)<br>TDF + 3TC + DTG*<br>TDF + 3TC + EFV400*<br>TDF + 3TC + NVP |

** Caveat: Inadequate data in pregnancy for DTG, inadequate data in pregnancy and TB for EFV400*



# WHO December 2018 addendum to 2016 guidelines

| Populations | | | | Preferred first line regimen | Alternative first line regimen(s) | Special situations |
|---|---|---|---|---|---|---|
| Adult men and adolescent boys | | | | TDF + 3TC (or FTC) + DTG | TDF + 3TC (or FTC) + EFV 600mg | AZT + 3TC + EFV 600mg |
| Adult women and adolescent girls | Pregnant or breastfeeding[a] | | | | TDF + 3TC (or FTC) + EFV 400mg | TDF + 3TC (or FTC) + PI/r[b] |
| | Not of childbearing potential | | | | | |
| | of child-bearing potential | Offered and using effective contraception | | | | |
| | | Offered but not using effective contraception or without access to contraception or want to become pregnant[g] | Choose to use DTG after informed choice | | | |
| | | | Choose to use EFV after informed choice | TDF + 3TC (or FTC) + EFV 600mg | TDF + 3TC(or FTC) + EFV 400mg<br>TDF + 3TC (or FTC) + ATV/r[b] | AZT + 3TC + EFV 600mg<br>TDF + 3TC (or FTC) + RAL |

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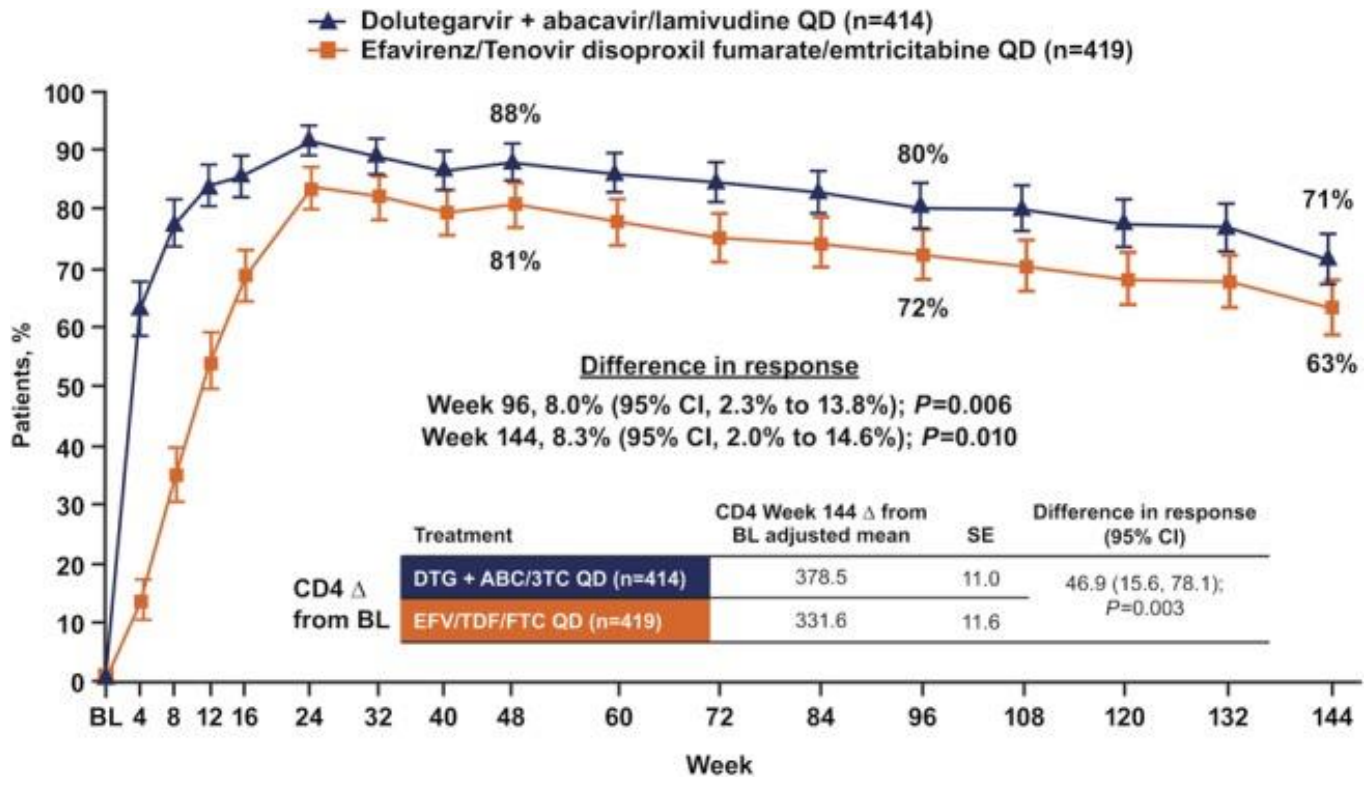
| | | without access to contraception or want to become pregnant[g] | Choose to use EFV after informed choice | TDF + 3TC (or FTC) + EFV 600mg | TDF + 3TC(or FTC) + EFV 400mg<br>TDF + 3TC (or FTC) + ATV/r[b] | 3TC + EFV 600mg<br>TDF + 3TC (or FTC) + RAL |

# Why transition from efavirenz?

- SINGLE trial demonstrated statistical superiority of DTG-based regimen over an efavirenz-based regimen through 144 weeks
- Efficacy: Increasing reports of transmitted NNRTI resistance
- Safety: Persistent central nervous system side effects
  - In Uganda, 33% of patients had side effects (median duration on efavirenz, 22 months)



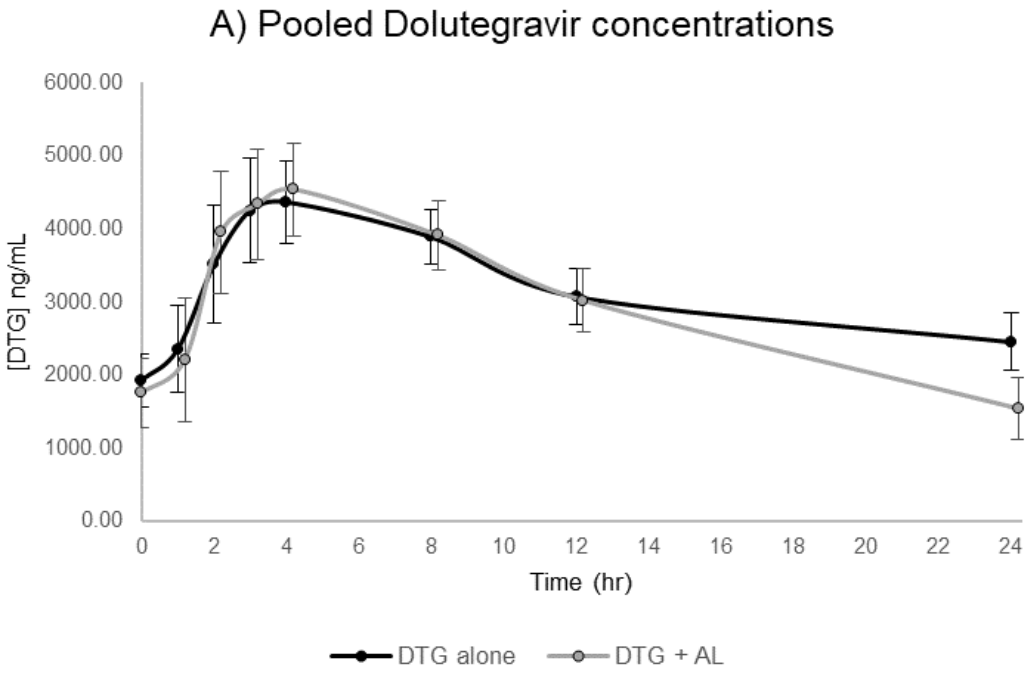

Walmsley S et al, JAIDS 2015; Seden K et al, J Antimicrob Chemother. 2018 Nov 1;73;

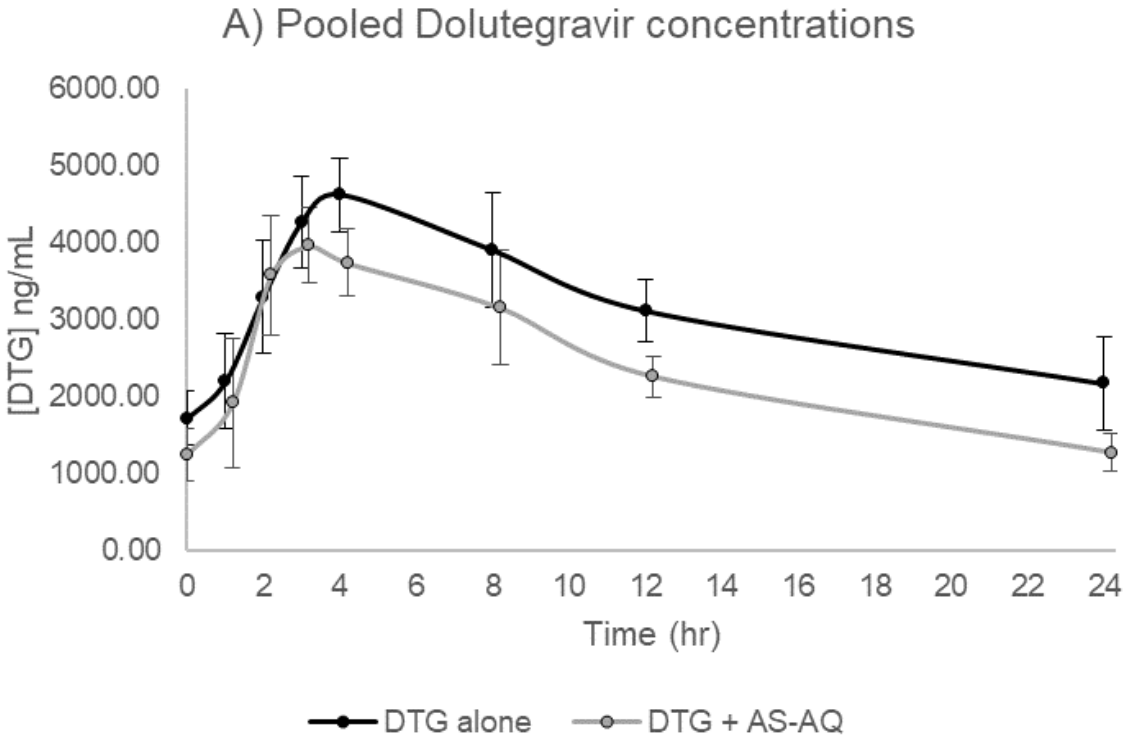
# Malaria

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

[1]Lamorde et al AIDS 2013 [2]Byakika-Kibwika et al JAC 2012

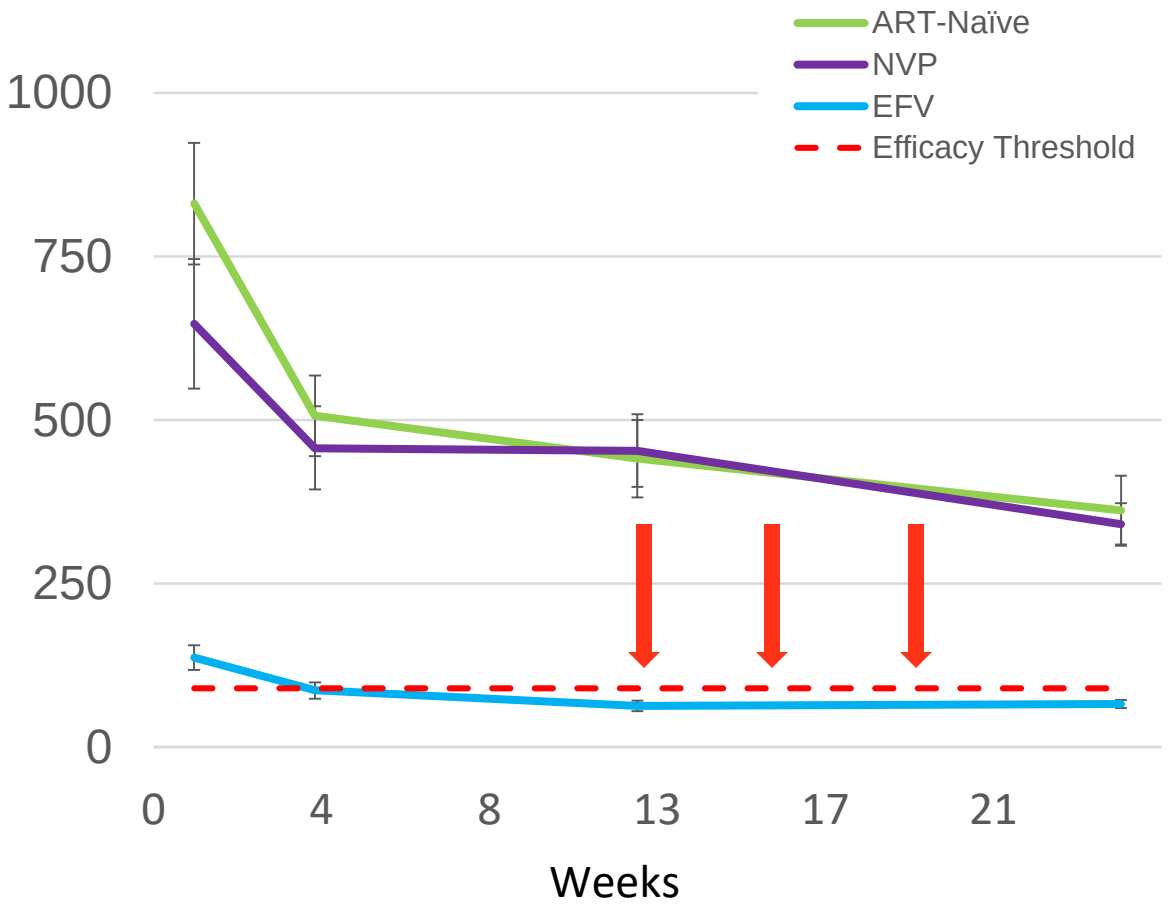
# Dolutegravir plus antimalarials




- Dolutegravir can be used at standard doses with artemether lumefantrine (AL) and artesunate amodiaquine (AS-AQ)

# Etonogestrel contraceptive implant + ART



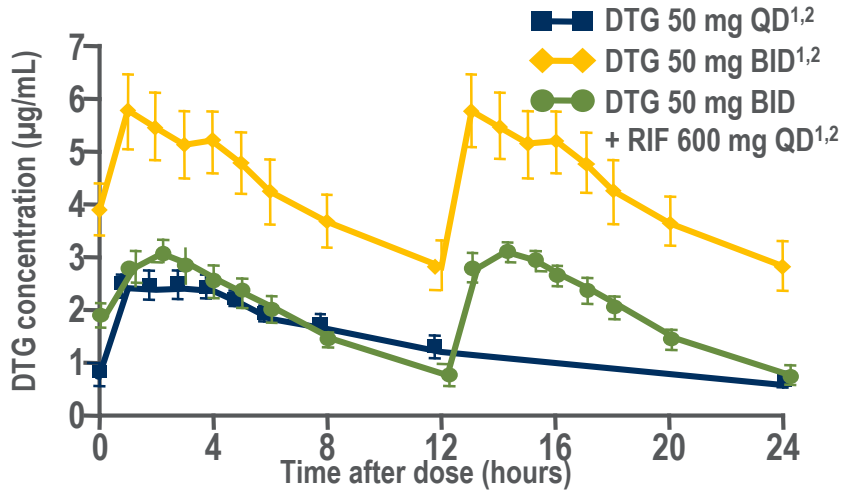

| Study week | NVP: ART-Naïve[1] | EFV: ART-Naïve[1] |
|---|---|---|
| 1 | 0.78 (0.74-0.81) | 0.16 (0.16-0.17) |
| 4 | 0.90 (0.88-0.91) | 0.17 (0.17-0.17) |
| 12 | 1.03 (1.02-1.04) | 0.14 (0.14-0.14) |
| 24 | 0.94 (0.90-1.01) | 0.18 (0.17-0.20) |
| $AUC_{0-24}$ | 0.94 (0.94-0.94) | 0.16 (0.16-0.16) |

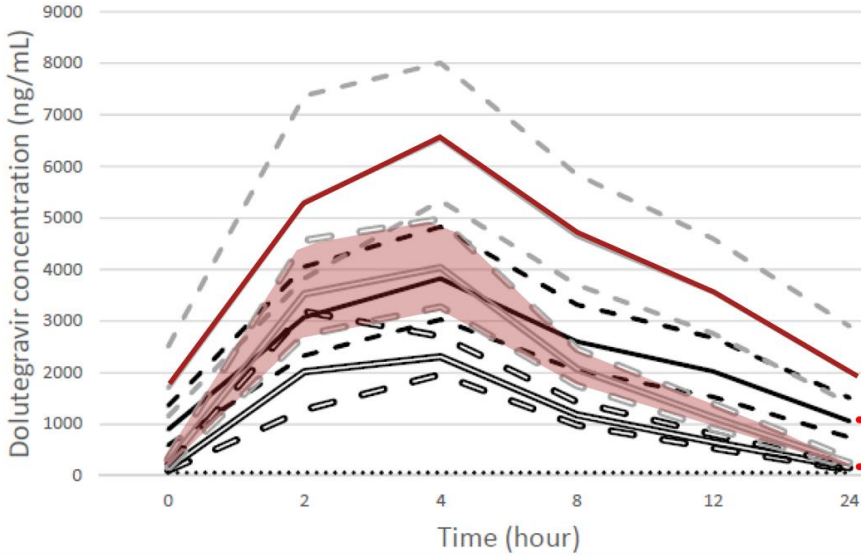
*[1]Geometric mean ratio (GMR), with 90% CI*

**[ENG] >80% lower in women using efavirenz-based ART compared to no ART**

Chappell CA et al, AIDS 2017

# 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

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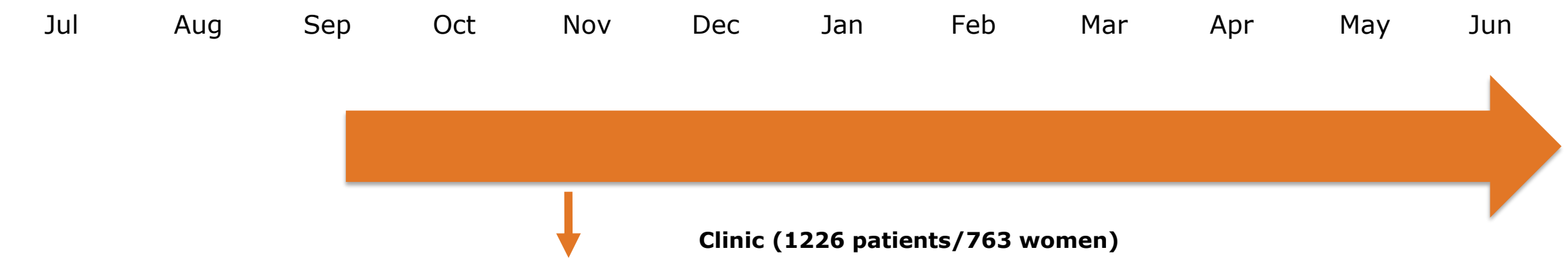
| | | | choice | TDF + 3TC (or FTC) + EFV 600mg | TDF + 3TC(or FTC) + EFV 400mg | AZT + 3TC + EFV 600mg |
| | | | | | TDF + 3TC (or FTC) + ATV/r[b] | TDF + 3TC (or FTC) + RAL |

**In a Botwsana study, 4 out of 426 women developed neural tube defects**

# Managing a potential NTD safety alert




Jun 17: Planning for DTG country roll out

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

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

Apr 18: MOH press release on transition to DTG

May 18: 41 countries inform WHO of decision to switch to DTG as preferred first line

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

July 18: WHO Policy Brief

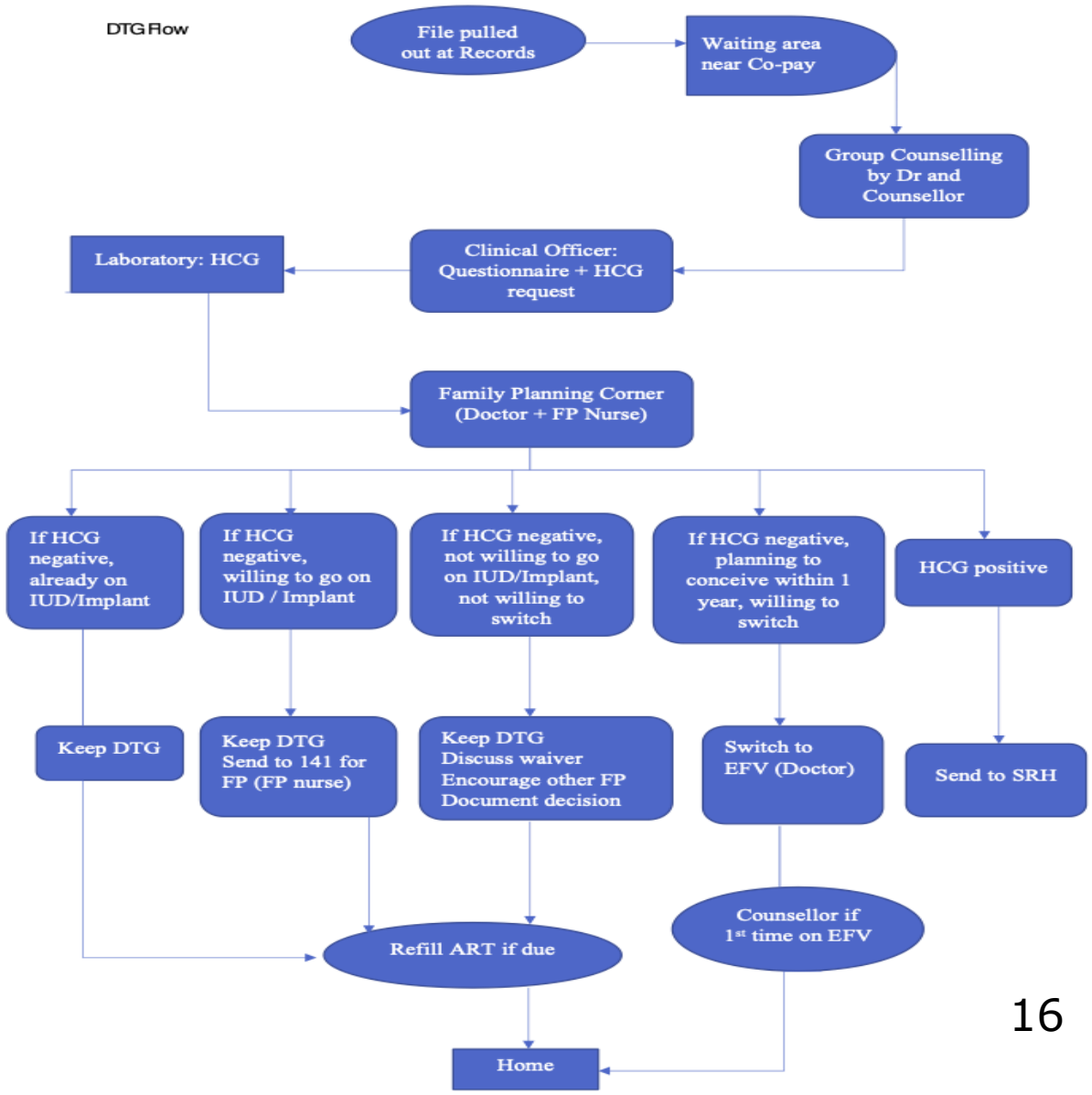
Sep 18: New Uganda Guidelines

Dec 18: New WHO Guidelines

# Managing a potential NTD safety alert

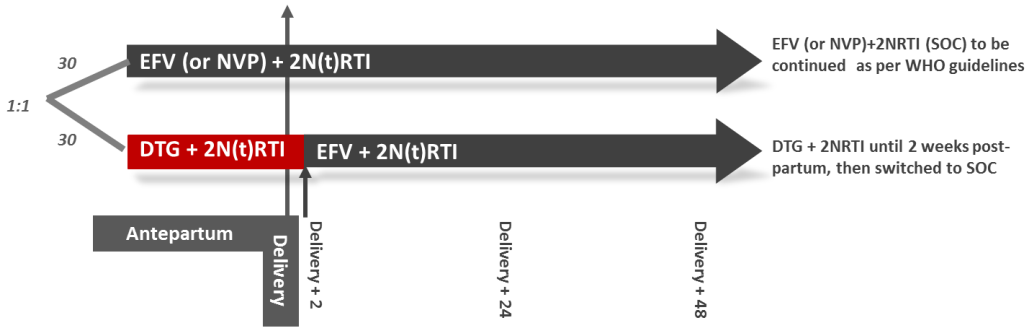
## Clinic Response

- **Week 1**: Clinic plan consultations: MOH, CHAI; patient notification starts
- **Week 2**: Clinic plan finalized, all PCT staff trained, mass rescheduling
- **Week 3**: Surge in patient notification, incident system in place, new clinic flow
- Pregnancy exposure reporting…



# DolPHIN Studies

## DolPHIN-1 pilot



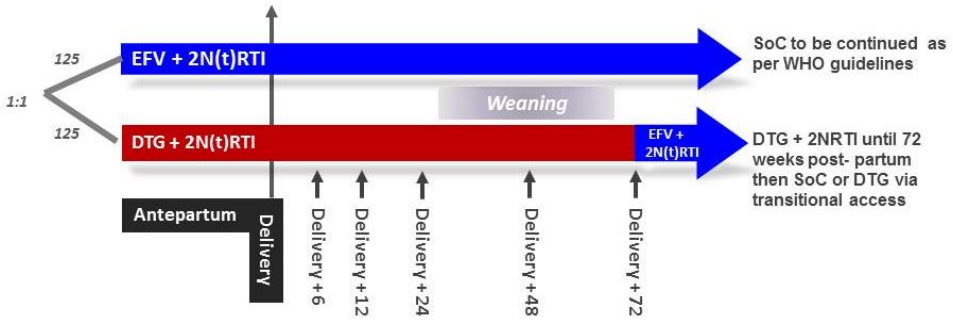

**ViiV funded**

**AIM**

- PK of DTG in T3, BM and infants
- Define optimal dose of DTG in T3
- Safety data
- Preliminary data on VL compared with EFV
- 28-34w gestation
- DTG continued for 2w PP

**Optimal Dosing in T3 and PP**
**Infant exposures (IP and BF)**
**Preliminary efficacy data (mother)**
**Preliminary safety data (mother, infant)**

## DolPHIN-2




**UNITAID funded**

**AIM**

- RCT, maternal VL is primary endpoint
- Safety data
- 28w – labour
- DTG continued until 72 weeks post-partum

DolPHIN2

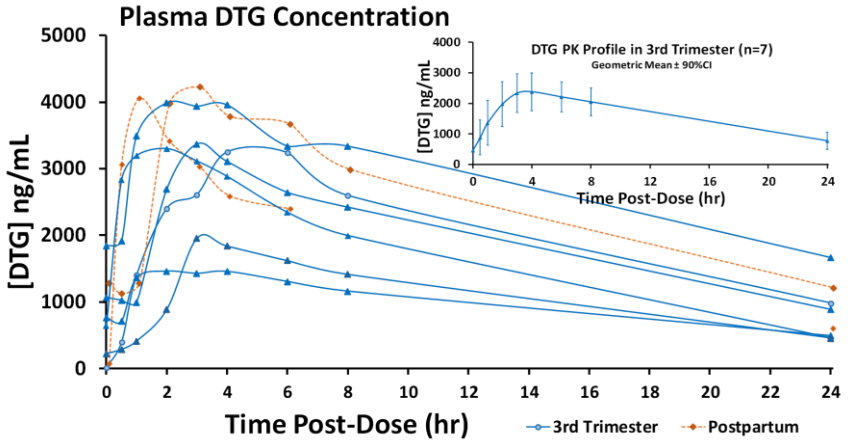
# DolPHIN-1 Study

**Hypothesis: In women newly presenting with HIV in late pregnancy, DTG is safe and effective for suppressing viral load at delivery**

32% of women had low concentrations of DTG in T3

DTG well transferred across the placenta 122%

Superior virologic suppression at the 2 week post-partum visit in DTG arm (p=0.001)



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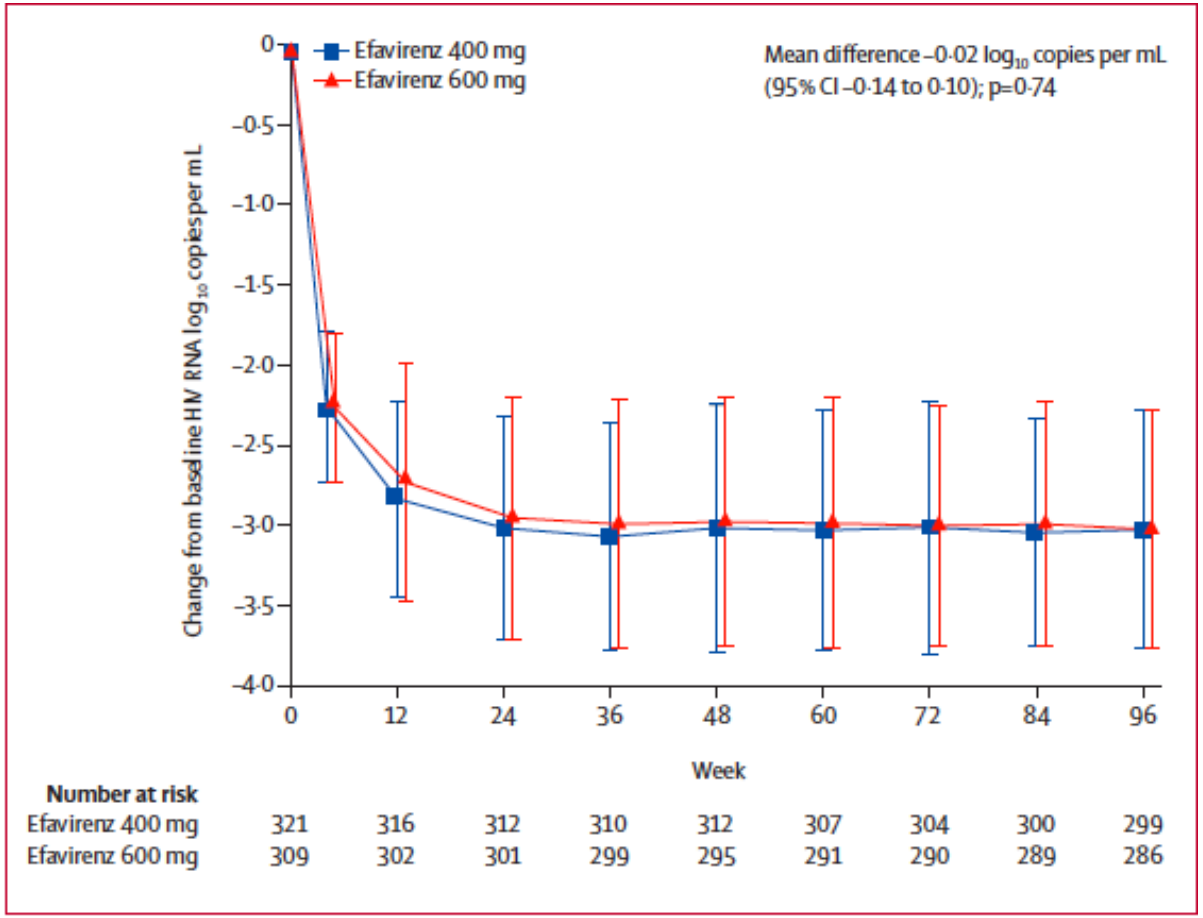
# ENCORE-1 Study Results

The ENCORE-1 (*N*= 636) study showed that treatment outcomes with a regimen containing efavirenz 400 mg (EFV400) once daily (OD) were non-inferior to outcomes with regimens containing the standard dose (efavirenz 600 mg OD).[1]

Two populations excluded from the trial

1. Pregnancy
2. Tuberculosis co-infection




Mean change in HIV-RNA from baseline to week 96

Puls et al Lancet 2014

# Pharmacokinetics, pharmacodynamics and pharmacogenomics of efavirenz 400mg once-daily during pregnancy and postpartum

Mohammed Lamorde, Xinzhu Wang, Megan Neary, Elisa Bisdomini, Shadia Nakalema,
Pauline Byakika, Jackson Mukonzo, Waheed Khan, Andrew Owen, Myra McClure, Marta Boffito

*Primary*

- To investigate the PK of EFV400 mg during pregnancy (TT) and PP

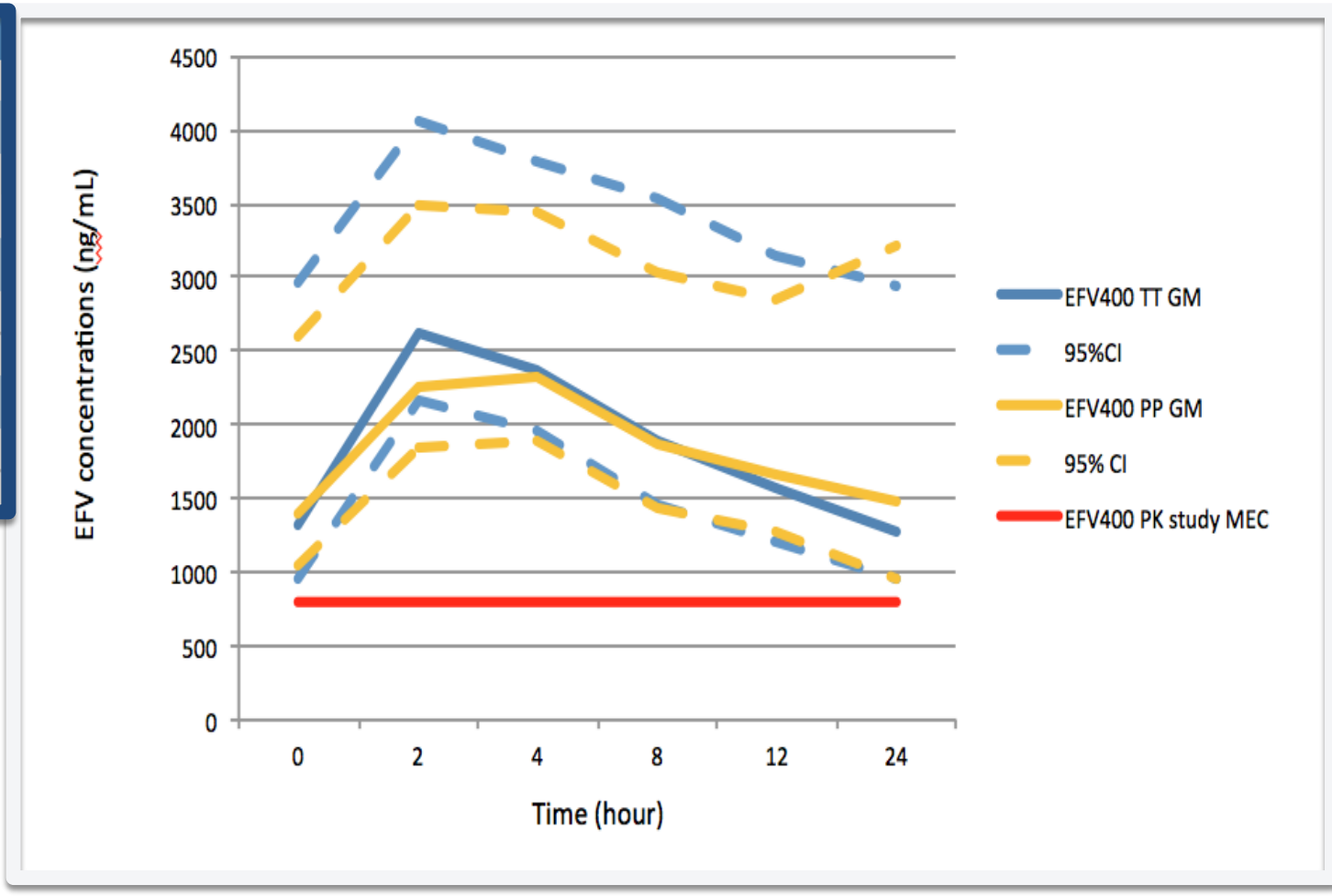
*Secondary*

- To investigate the safety and tolerability of EFV400 mg during pregnancy

*Clinical Infectious Diseases*,
February 2018 ciy161, https://doi.org/10.1093/cid/ciy161

# Results (2) Pharmacokinetic Parameters

| | EFV GM (95% CI) | | GM (90% CI) |
|---|---|---|---|
| *PK parameter* | TT | PP | TT/PP |
| $C_{max}$ | 2751 (2301-4043) | 2790 (2222-4170) | 0.93 (0.80-1.08) |
| ng/mL | | | |
| CV% | 142 | 147 | |
| $C_{trough}$ | 1205 (897-2681) | 1469 (973-3121) | 0.73 (0.60-0.89) |
| ng/mL | | | |
| CV% | 78 | 85 | |
| $AUC_{0-24}$ | 39941 (31082-72568) | 43168 (33012-72028) | 0.84 (0.72-0.99) |
| ng.h/mL | | | |
| CV% | 97 | 121 | |



# NAMSAL trial

**Dolutegravir versus an efavirenz 400 mg-based regimen for the initial treatment of HIV-infected patients in Cameroon: 48-week efficacy results of the NAMSAL ANRS 12313 trial.**

Randomised, open label, multicentre trial: HIV positive, ART-naive adults with viral load >1000 copies/mL were assigned (1:1) to TLD or TLE400

**Viral load <50 copies/mL at Week 48**

TLD (N=310) 74.5%

TLE400 (N=303) 69.0% *difference +5.5% (95% CI –1.6 to +12.7); p=0.13 for the superiority test.*

Virological failure >1000 copies/mL = 19 (3 with TLD, 16 with TLE400, with 6 of the TLE400 arm patients with baseline resistance)

Cournil A et al. NAMSAL ANRS 12313 trial. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Oral abstract O342.

# Pharmacokinetics of Efavirenz 400mg with Isoniazid/Rifampicin in People with HIV

Maddalena Cerrone , Xinzhu Wang , Megan Neary , Christine Weaver , Serge Fedele , Isaac Day-Weber , Andrew Owen , Andrew Hill , Myra McClure , Marta Boffito

*Primary*

- To evaluate the steady-state pharmacokinetics of efavirenz 400 mg once daily during co-administration with rifampicin and isoniazid

*Secondary*

- To assess the safety and tolerability of efavirenz 400 mg once daily during co-administration with rifampicin and isoniazid

*CROI Conference Boston (Abstract 457) March 2018*

# Results (2)

| | PK2/PK1 | PK3/PK2 | PK3/PK1 |
|---|---|---|---|
| **Cmax** | 0.91 (0.83-0.99) | 0.97 (0.88-1.06) | 0.85 (0.78-0.94) |
| **AUC** | 0.91 (0.86-1.13) | 0.94 (0.88-1.06) | 0.86 (0.80-1.09) |
| **C24** | 0.85 (0.72-0.99) | 0.91 (0.78-1.05) | 0.77 (0.64-0.94) |

*PK parameter results are presented Geometric Mean Ratios and (90%Confidence Intervals).*

- INH/RIF co-administration in TB-PLWH with a VL⟨50 was associated with limited changes in EFV400 exposure (<23%) and EFV400 concentrations were maintained within ranges of those measured in PLWH in ENCORE-1 [1].

- Results from this cohort conclude that EFV400 can be co-administered with anti-TB treatment.

# Acknowledgements


- National AIDS Control Program
- Kim Scarsi, University of Nebraska Medical Center
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- Kay Seden, University of Liverpool
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- Ceppie Merry,  Trinity College Dublin