PREGART: Overview

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Addis Ababa, Ethiopia

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The PREGART Consortium

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PREGART

Protecting mother and baby

Safety and efficacy of dolutegravir and EFV 400 for pregnant and breast feeding women: a Randomized Non-inferiority Clinical Trial

- **Acronym: PREGART**
- **COORDINATOR**

  → Hawassa University (HU), Ethiopia, Dr Birkneh Tadesse,
- **PARTICIPANTS**

  → Professor Eleni Aklillu, Karolinska Institutet, Sweden

  → Dr Jackson K Mukonzo, Makerere University, Uganda

  → Dr Marco Simonelli, Istituto Superiore Di Sanita, Italy
- **EDCTP2 CONTRIBUTION (€)**

  → 3,902,468.75

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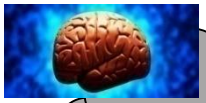
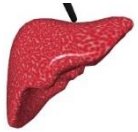


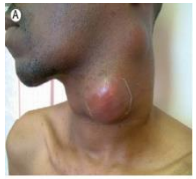


Toxicities

When to start ART ??

Adherence

IRIS



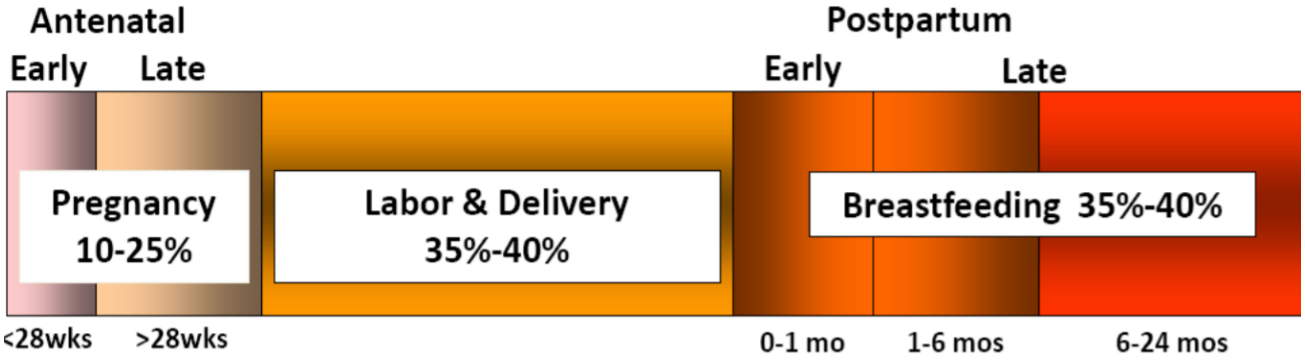
Efavirenz **600mg or 800mg**

HIV in Pregnancy

- MTCT accounts for 90% of HIV infections in children
- Cumulative risk of MTCT

  → Without ART 15% to 45%.

  → With ART < 5%.



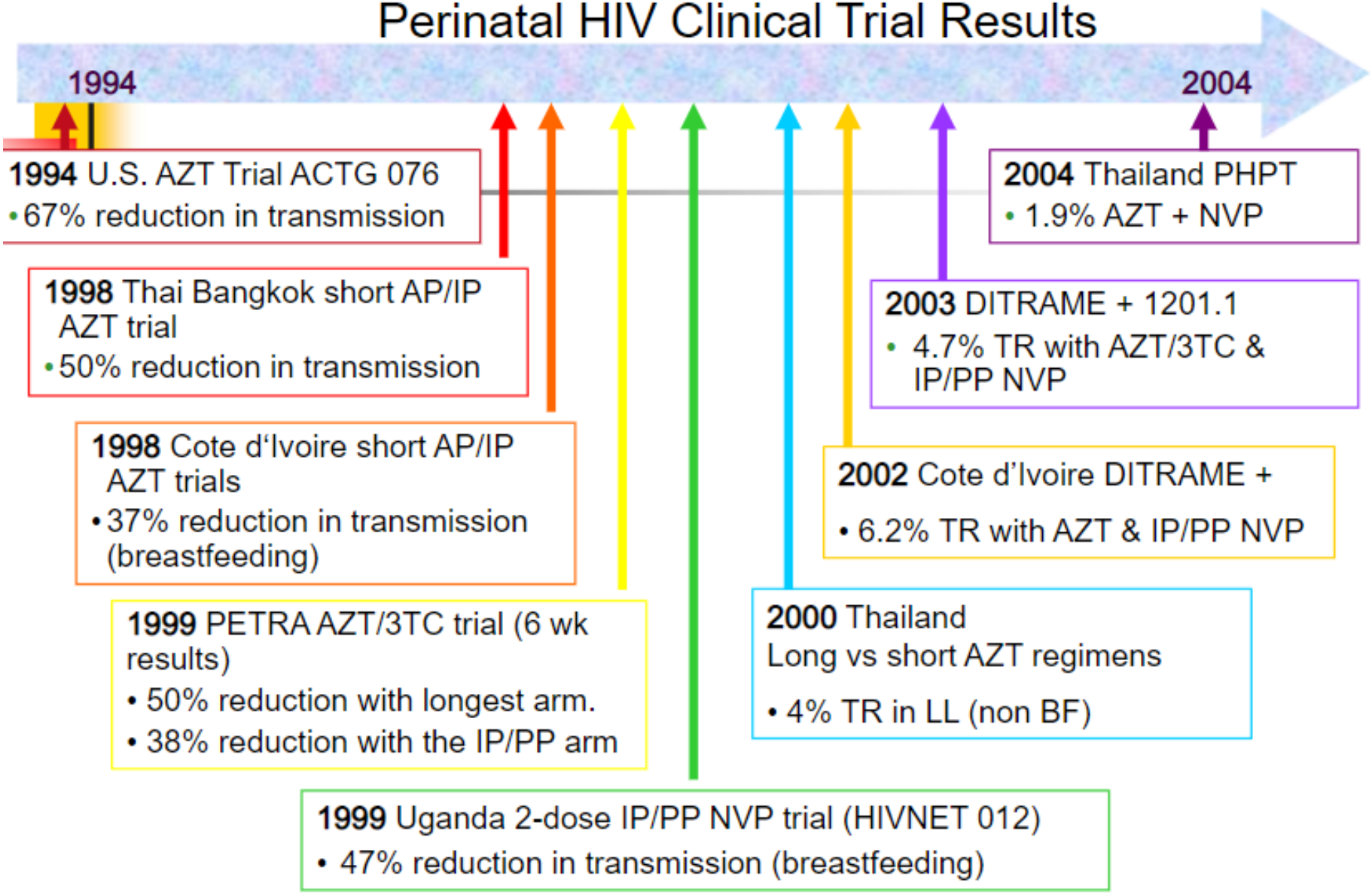
- **Access to ART**

  → 2010 - 51% pregnant women living with HIV had access to ART

  → 2017 - about 80%

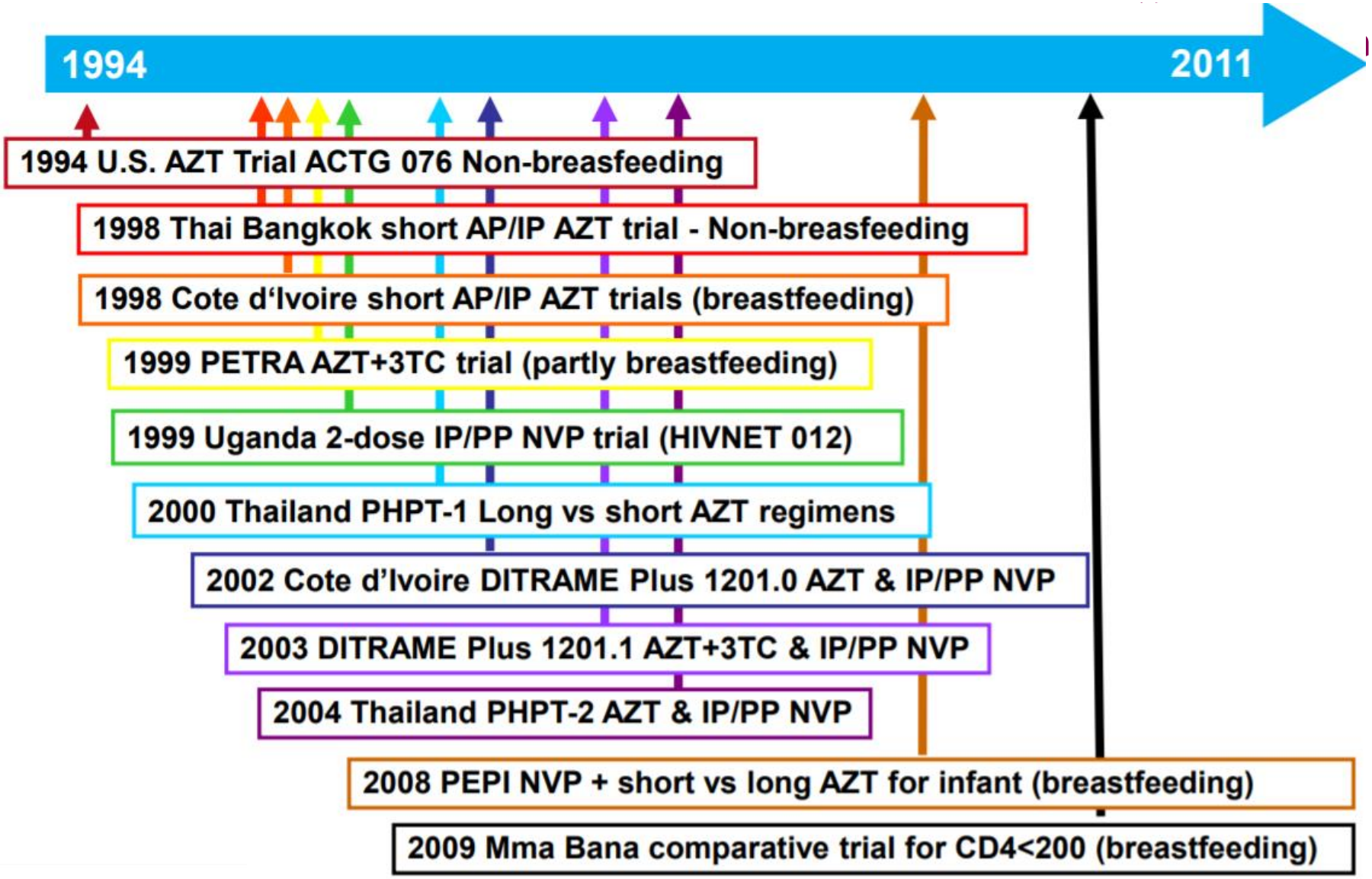
  → Around **1.4 million HIV infections among children were prevented** between 2010 and 2018 due to the implementation of PMTCT services

What did we know and when did we know it?
Perinatal HIV Clinical Trial Results



Postpartum infant nevirapine for 6wks; 14 wks and 6 months and breastfeeding transmission (2008-2010)

Study	Intervention arms	Postpartum MTCT	% reduction (efficacy)
SWEN, Ethiopia, India, Uganda. Lancet: Study team 2008	sdNVP vs 6 wks NVP	5.3% vs 2.5%	53% efficacy
PEPI, Malawi. NEMJ: Kumwenda N et al. 2008	sdNVP/1 wk AZT vs 14 wks NVP	8.4% vs 2.8%	67% efficacy
BAN, Malawi. NEMJ: Chasela C at al. 2010	sdNV6 mos NVP P/1 wk AZT-3TC vs	5.7% vs 1.7%	70% efficacy



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Key recommendation

- *EFV is not recommended for ART-eligible women with childbearing potential unless effective contraception can be assured* ***(Level A-IV recommendation)****.*
- *EFV remains a viable option as a NNRTI component of a first-line regimen in pregnant women in the second or third trimester who cannot receive NVP* ***(Level A-III recommendation)****.*
- *Women receiving EFV-based ART regimen who desire to become pregnant should switch to a NVP containing, triple NRTI-, or a PI-based regimen* ***(Level A-IV recommendation)****.*
- *The dual NRTI combination d4T + ddI should be avoided in pregnancy because*

2006 version

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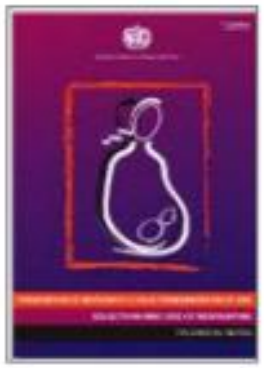
From Evidence to Policy: Evolution of WHO PMTCT ARV Recommendations



2001

2004

2006

2010

2013

PMTCT	4 weeks AZT; AZT+ 3TC, or SD NVP	AZT from 28 wks + SD NVP	AZT from 28wks + sdNVP +AZT/3TC 7days	Option A (AZT +infant NVP) Option B (triple ARVs)	Option B or B+ ART for all PW/BF women regardless of CD4
ART	No recommendation	CD4 <200	CD4 <200	CD4 ≤350	For B - CD4 ≤500

Move towards: more effective ARV drugs, extending coverage throughout MTCT risk period, and ART for the mother's health

unicef

WHO Guidelines for pregnant women living with HIV – Sep 2015

- In September 2015 WHO released guidelines recommending that all pregnant women living with HIV be immediately provided with lifelong treatment, regardless of CD4 count (Option B+)

→ **EFV** + TDF + 3TC (or FTC) as a once-daily fixed-dose combination

Safety and Efficacy of DTG and EFV600 in 1st line ART
(summary 2018 WHO Sys Review & NMA)

major outcomes	DTG vs EFV_{600}	QUALITY OF EVIDENCE
Viral suppression (96 weeks)	DTG better	moderate
Treatment discontinuation	DTG better	high
CD4 recovery (96 weeks)	DTG better	moderate
Mortality	comparable	low
AIDS progression	comparable	low
SAE	comparable	low

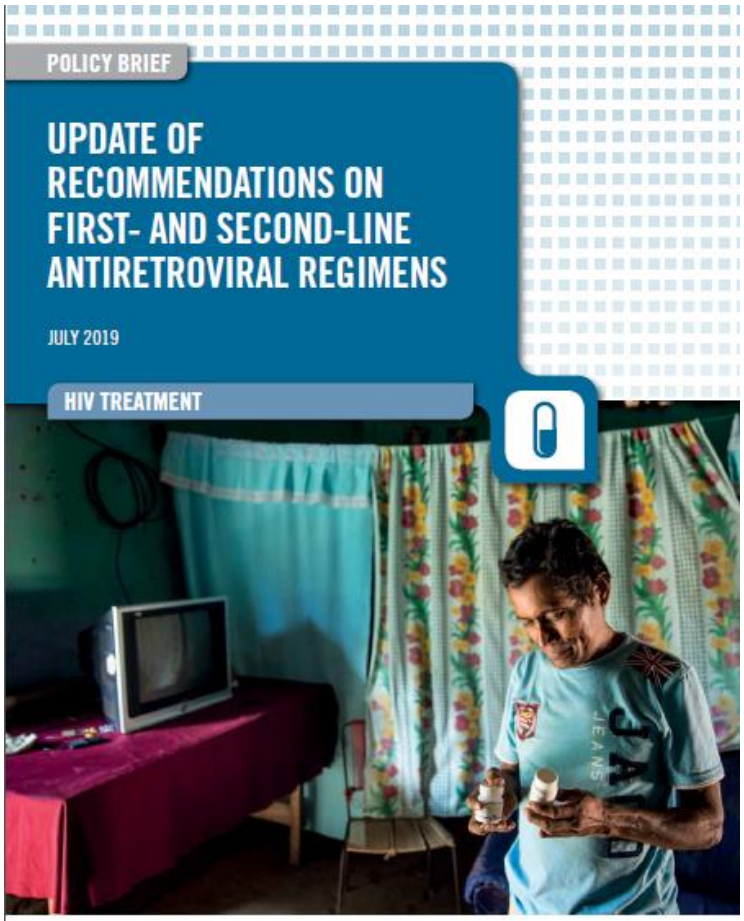
Reference: Steve Kanters, For WHO ARV GDG, 16-18 May 2018

WHO, 2018

Background and Rationale of PREGART

- EFV400 and DTG were found to be compelling alternatives to EFV600
  - Lower cost (both DTG and EFV400)
  - Fewer drug adverse events (both DTG and EFV400)
  - High resistance barrier and lower risk of treatment failure (DTG)
  - Higher virological suppression at delivery (DTG)
  - Better tolerated (both DTG and EFV400)

Dickson L, 2015; McCormack PL, 2014



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

FOR IMMEDIATE RELEASE
10:00 CDT / 11:00 EDT
Monday, 22 July 2019

New studies and WHO guidance clarify the way forward for use of dolutegravir in women of childbearing age

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Box 1. Recommendations: first- and second-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)*

NEW

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)*

NEW

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%.

WHO - UPDATE OF RECOMMENDATIONS ONFIRST- AND SECOND-LINE ANTIRETROVIRAL REGIMENS- JULY 2019

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]

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted

Research Gap

- Safety and efficacy of DTG and EFV400 have not been conclusively studied to allow policy makers to revise guidelines for pregnant women
- Data from resource limited settings are especially lacking.

WHO Consolidated Guidelines 2018; Dickson L, 2015; McCormack PL, 2014

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Objectives of PREGART

- Provide evidence based recommendations for safe and effective first line ART regimens for PMTCT and treatment of HIV infected pregnant and breast feeding women living in resource limited settings.
  - The study will contribute towards optimization of existing WHO and regional guidelines of ART for HIV infected pregnant and breast feeding women.

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Objectives of PREGART

- To compare the safety and efficacy of three ART regimen recommended by the WHO as **preferred or alternate** first line regimens for **HIV infected adults** in pregnant and breastfeeding women

Control group

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Specific Objective 1

- To show that **DTG containing regimen** (Comb-2) for HIV infected pregnant and breast feeding women (**started after the first trimester of pregnancy**) is **non-inferior** to the standard EFV600 dose regimen (Comb-1) for
  - → effective virological suppression at delivery and
  - → prevention of MTCT (PMTCT) of HIV at birth, 6 weeks, 6 months and 12, 18 months of infant age.

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Specific Objective 2

- To show that **EFV400 based regimen** (Comb-3) is **non-inferior** to standard EFV600 dose regimen (Comb-1) for HIV infected pregnant and breast feeding women in terms of virological suppression at delivery and PMTCT at birth, 6 weeks, 6 and 12 months of infant age.

  → effective virological suppression at delivery and

  → prevention of MTCT (PMTCT) of HIV at birth, 6 weeks, 6 months and 12, 18 months of infant age.

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Specific Objective 3

- To compare safety and efficacy of DTG containing ART regimen (Comb-2) versus EFV400 containing regimen (Comb-3) among pregnant and breast feeding women for virological suppression at delivery and PMTCT.
- We will test the hypothesis that ART regimen Comb-2 **is equivalent** to Comb-3 as first line ART regimen for pregnant and breast feeding women in terms of **virological suppression at delivery and PMTCT** at birth, 6 weeks, 6 months and 12 months, 18 months of infant age.

Trial Design

- Multicenter, interventional, open label, parallel assignment, and controlled three-arm non-inferiority randomized clinical trial.
- The current standard ART regimen (EFV600 – Comb-1) will serve as a control to compare safety and efficacy of DTG - Comb-2 and EFV400 – Comb-3 ART regimens for pregnant and breast feeding HIV infected women.
- Study arms:
  - **Arm 1**: TDF + 3TC with the standard dose of Efavirenz (EFV600) (Comb-1) (the active control) ;
  - **Arm 2**: TDF + 3TC with DTG (Comb-2);
  - **Arm 3**: TDF + 3TC with EFV400 (Comb-3)

Study Sites & Participants

- HIV infected pregnant women who present during their second **trimester of pregnancy.**
- Enrolment sites:
  - → Ethiopia – 10 referral hospitals
  - → Uganda – 3 sites

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Study outcome

- **Primary Endpoints:**

  → i) Virological suppression at delivery:

  → ii) Mother to child transmission of HIV:

- **Secondary Endpoints:**

  →Type, frequency and severity of Adverse events

Capacity Building Activities

- **Long term training**
  - A total of **6 PhD students**
  - 2 Post doc students Short term trainings:
- **Short term training**
  - Trial design and implementation trainings
  - GCP and GCLP trainings
  - Data collection, security and analysis
- **Networking and collaboration**
  - South- South and South-North collaboration
  - A working and active consortium including

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Impact

- Reduction of the burden of HIV on the health system in low and middle-income countries:
- Improving HIV/AIDS treatment strategy for pregnant and breastfeeding women:
- Improved prevention of Mother-to-Child Transmission of HIV during pregnancy and breastfeeding
- Academic and Scientific impact:
- Clinical trial capacity building in Africa

Impact of PREGART for guideline revision and optimization

- **Safe and effective cART regimens** for HIV infected pregnant women living in resource constrained settings will be identified.
- Better care and follow up for HIV infected pregnant women living in resource limited settings.

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With safe and effective cART we will ensure better health for women and ensure zero transmission of HIV infection to their babies!!

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Acknowledgment

This project is part of the EDCTP2 programme supported by the European Union

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Thank You!