Optimizing ART for Long-Term HIV Care

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Professor of Medicine
Chulalongkorn University; and
HIV-NAT, TRC-ARC
Disclosure

• KR has received honoraria for advisory, speaker from MSD, Janssen-Cilag, Roche diagnostic, Viiv, Mylan and GPO.

• KR has also been an investigator of clinical trials funded by Viiv, Gilead, BMS, Mylan and GPO.
“Start ART at any CD4 count”

Strong evidences supporting “Early ART”

**START trial**

↓ 57% *Serious events & death*

(TB, KS, Lymphoma) (4.1% vs 1.8%) *(N=4685)*

HR: 0.43; 95% CI: 0.30-0.62; *P < .001*

**TEMPRANO trial**

↓ 44% *death /severe illness*

HR: 0.56; 95% CI, 0.33 to 0.94

*(N= 2056, 41% CD4 count ≥500 )*

**HPTN 052 trial**

↓ 96% *in transmission*

HR 0.04; 95% CI, 0.01–0.27; *P < 0.001*
Average Life-expectancy
National AIDS Program, Thailand
*Data after survived beyond 6 months of treatment*

**ARV started from age 20**

- **Life-expectancy**
  - 20 + 61 = 81 yo

**Baseline CD4 counts**

<table>
<thead>
<tr>
<th>Baseline CD4 counts</th>
<th>Additional year of Life (yrs)</th>
<th>Less</th>
<th>Equal/more</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>29</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>31</td>
<td>46</td>
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<td>200</td>
<td>32</td>
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<td>250</td>
<td>33</td>
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</tr>
<tr>
<td>350</td>
<td>34</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

Sirinya Teeraananchai et al. Antiviral Therapy 2016
U.S. DHHS 2018
Guidelines: preferred regimens

NRTI-1 + NRTI-2 + Integrase Inhibitor

- TAF
- TDF
- ABC

- FTC
- 3TC

DTG
- BIC
- EVG
- RAL

InSTI-based ART regimen only

1 HLA-B*5701 negative, and 2 ABC/3TC/D TG as a STR, 3 STR : BIC/TAF/FTC
EACS Guidelines 2017

NRTI-1 + NRTI-2 + Integrase Inhibitor

- TAF
- TDF
- ABC*
- FTC
- 3TC*
- DTG*
- EVG
- RAL
- DRV/c
- DRV/r
- RPV
- NNRTI

*ABC only for HLA-B*5701 negative person,
*ABC+3CT combined with DTG as a STR
Recommended First-line ART in **RLS**

- **WHO 2016**
  - TDF + xTC + **EFV**
  - TDF + xTC + DTG *(alternative)*

- **SA 2017**
  - TDF + xTC + **EFV**
  - TDF + xTC + DTG *(only in private setting)*
  - TDF + xTC + **RPV**

- **Thailand 2017**
  - TDF + xTC + **EFV**
  - TDF + xTC + **RPV**
How to win the battle? *Ending AIDS*

**Treatment coverage**
- Viral suppressed cases
- High Retention

**Prevention Coverage**
- Early Test-and-treat
- PrEP
- STI treatment

**New infection**
- Undiagnosed cases
- Poor-adhered cases
- Drug-resistance Cases
Cost vs Long-term Side Effects

ARV and Risk of Specific Toxicities

TDF
Atazanavir/r
(renal stone)
EVG/cobi³
DTG³

Efavirenz

TDF

LPV/r
ABC*
Accelerating Access to Simpler, Safer, and More Affordable HIV Treatment Through ART Optimization

What is antiretroviral treatment (ART) optimization?

At its core, ART optimization is about ensuring that people living with HIV receive the best-available ART in the most efficient and cost-effective manner possible. In low- and middle-income countries (LMIC) – where the HIV-positive population includes significant proportions of women of childbearing age, children, and people living with TB, malaria, and other co-infections – optimization requires drugs that are: (1) effective, safe, well-tolerated, and easy to use for people in these demographic groups and (2) adapted to resource and infrastructure constraints (i.e. affordable, heat-stable, and available in fixed-dose combinations, or FDCs). Optimization is achieved by continuous and coordinated efforts by global and country-level stakeholders to simplify, standardize, and harmonize all categories of antiretroviral (ARV) drugs, including first-, second-, and third-line treatments for infants, children, adolescents, and adults (including pregnant and breastfeeding women, and TB patients).
Optimizing ART

Optimized Triple ART
Optimized Dose ART
Optimized Dual ART

Study Populations
ART Naive
ART Experienced
Can **Dolutegravir** be recommended as a First-line ART in LMICs

“An Universal ART Regimen”
TLD = TDF/3TC/DTG : one pill a day

• Pricing Agreement done: 75 USD/y for the LMIC public sectors 90 eligible countries !!
• U.S. FDA gave a tentative approval for PEPFAR
• aiming to launch in April 2018
OPTIMIZE, Global Partnership

Trials underway for additional sub-populations

**TLD**
Tenofovir disoproxil fumarate (TDF)/emtricitabine or lamivudine (XTC)/dolutegravir (DTG)

**TAFxD**
Tenofovir alafenamide fumarate (TAF) emtricitabine or lamivudine (XTC)/dolutegravir (DTG)

**Heat-stable DRV/r co-formulation**
Darunavir/ritonavir

**TLE400**
Tenofovir disoproxil fumarate (TDF)/emtricitabine or lamivudine (XTC)/efavirenz 400 (EFV400)

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**DolPHIN1:** Safety in pregnant women in 3rd trimester. Results expected Q3/2017.\(^{ix}\)

**DolPHIN2:** Efficacy in pregnant women in 3rd trimester. Results expected 2021.\(^{ix}\)

**ViiV:** Safety and efficacy of DTG vs EFV in TB patients. Results expected Q4/2017.\(^{xi}\)

**IMPAACT P2010:** Efficacy during pregnancy and up to 48 weeks post-partum, compared to TLE, TLD.\(^{xv}\) Results expected Q3/2018.\(^{xvi}\)

**ADVANCE:** Safety, efficacy in adults and adolescent (including women who become pregnant), compared to TLE, TLD. Results expected Q4/2018.\(^{xvii}\)

**Wits RHI:** Switch study of DRV/r400/100mg v. LPV/r. Results expected Q1/2018.\(^{xviii}\)

**SSAT:** Efficacy of DRV/r 400/100 v. DRV/r 600/100 v. DRV/r 800/100.\(^{xix}\) Not yet funded.

**Mylan:** TB and pregnancy PK study. Pregnancy results expected Q3/2017. TB results expected Q1/2018.\(^{xx}\)

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Clinical Evidences on Safety, Efficacy and Appropriate Dose in 3 major populations are needed:

- Late Pregnancy
- TB/HIV patients
- Children, adolescent
FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

AIDSinfo

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

Date: May 18, 2018
Source: AIDSinfo
Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study

Rebecca Zash, Denise L Jacobson, Madiegri Diseko, Gloria Mayordi, Mompati Mmalane, Max Essex, Tendani Galetle, Chipo Petlo, Shahin Lockman, Lewis B Holmes, Joseph Makhema, Roger L Shapiro

Summary
Background Global rollout of dolutegravir-based antiretroviral therapy (ART) has been hampered in part by insufficient safety data in pregnancy. We compared birth outcomes among women initiating dolutegravir-based ART with those among women initiating efavirenz-based ART in pregnancy in Botswana.

Methods In this observational study, we included all women who initiated firstline ART from 1 February 2016 to 31 December 2016. Women were classified into three groups: ART started from 1 February to 31 March 2016; ART started from 1 April to 30 June 2016; or ART started from 1 July to 31 December 2016. Women started ART with either dolutegravir (DTG) 1729, or efavirenz (EFV) 4593, or zidovudine-based regimens with or without ritonavir-boosted lopinavir (alogs).

Findings We compared birth outcomes among women initiating efavirenz-based ART. The risk for any adverse birth outcome among women on dolutegravir versus efavirenz was similar (33.2% vs 35.0%; aRR 0.95, 95% CI 0.88–1.03), as was the risk of any severe birth outcome (10.7% vs 11.3%; 0.94, 0.81–1.11). We found no significant differences by regimen in the individual outcomes of stillbirth, neonatal death, preterm birth, very preterm birth, SGA, or very SGA.

Interpretation Adverse birth outcomes were similar among pregnant women who initiated dolutegravir-based and efavirenz-based ART. Dolutegravir-based ART can be safely initiated in pregnancy.

Funding National Institutes of Health.

DTG 1729 vs EFV 4593
Severe birth outcome
10.8% vs 11.3 5%
aRR = 0.94 (0.1-1.1)
DolPHIN-1: Dolutegravir VS Efavirenz When Initiating Treatment in Late Pregnancy

• The planned interim analysis suggests **DTG appears to be well-tolerated and effective** when initiated in late pregnancy.

• PK findings suggest that **dosing of DTG at 50mg once-daily appears appropriate** in third trimester.

Abstract Number: 807; CROI 2018, Boston, Massachusetts
DolPHIN-2
Dolutegravir in Pregnant HIV Mothers and Their Neonates

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**Estimated Enrollment:** 250 participants

**Intervention Model Description:** An open-label, multicentre randomized controlled trial

**Actual Study Start Date:** January 22, 2018

**Estimated Primary Completion:** Sep 2020

**Estimated Study Completion:** March 2021

**Sponsor:** University of Liverpool

**Collaborators:**
- UNITAID
- University of Cape Town
- Liverpool School of Tropical Medicine
- Infectious Diseases Institute, Uganda
- Radboud University

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The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.
INSPIRING: Phase IIIb Study Design

Phase IIIb, randomized, multicenter, open-label, non-comparative, active-control parallel-group study

**TB therapy**
- **HRZE (2 months)**
- **HR (4 months)**
- **DTG dose switch 2 weeks post-completion of TB treatment**

**HIV/TB coinfect ed ART-naive adults**
- **DTG (50 mg BID) + 2 NRTIs (n = 69)**
- **DTG (50 mg QD) + 2 NRTIs**
- **EFV (600 mg QD) + 2 NRTIs (n = 44)**

**Inclusion criteria**
- HIV-1 RNA ≥1000 copies/mL and CD4+ ≥50 cells/mm³
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomization and no later than the screening date

**DTG:EFV 3:2 randomization stratified by**
- Screening plasma HIV-1 RNA ≤100,000 or >100,000 copies/mL
- Screening CD4+ ≤100 cells/mm³ or >100 cells/mm³

**Screening** −28 to −14 days
**Day 1**
**24 weeks**
**52 weeks End of randomized phase**

**Interim analysis:** % <50 c/mL (Snapshot)
**Primary endpoint at Week 48:** % <50 c/mL (Snapshot)

**ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; HR, isoniazid, rifampin; HRZE, isoniazid, rifampin, pyrazinamide, ethambutol; NRTI, nucleoside reverse transcriptase inhibitor; RIF, rifampin; TB, tuberculosis.**

*Duration of continuation phase of TB treatment according to local guidelines (continuation phase up to 7 months in some countries).*  
ClinTrials.gov NCT02178592

Dooley et al. CROI 2018; Boston, MA.
INSPIRING Pharmacokinetic Data

Pre-dose concentration: DTG 50 mg BID with RIF

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>DTG Conc (ng/mL)</th>
<th>Geomean (90% CI)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 8</td>
<td>41</td>
<td>852</td>
<td>(208-2340)</td>
<td>118</td>
</tr>
<tr>
<td>Wk 24</td>
<td>22</td>
<td>942</td>
<td>(19-3380)</td>
<td>276</td>
</tr>
</tbody>
</table>

Pre-dose concentration: DTG 50 mg QD without RIF (post-TB treatment phase)

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>DTG Conc (ng/mL)</th>
<th>Geomean (90% CI)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 36</td>
<td>16</td>
<td>1143</td>
<td>(80-4370)</td>
<td>151</td>
</tr>
<tr>
<td>Wk 48</td>
<td>12</td>
<td>591</td>
<td>(19-3310)</td>
<td>359</td>
</tr>
</tbody>
</table>

INSPIRING DTG \(C_{\text{tau}}\) when administered twice daily with RIF were similar to DTG 50 mg once daily without RIF and to previously reported data for DTG 50 mg once daily in Phase 2/3 HIV trials.

- Median change from Baseline CD4+ cell count (Q1, Q3) at Week 24: DTG, 146 cells/mm\(^3\) (71, 214); EFV 93 cells/mm\(^3\) (47, 178)
Conclusions:

• Interim Week 24 results: **DTG 50 mg twice daily appears** to be effective and well-tolerated in HIV/TB co-infected adults **receiving RIF-based TB therapy**.

• **Rates of IRIS were low**.

• There were no new toxicity signals for DTG and no discontinuations due to liver events.

• These data support the use of DTG based regimen in HIV/TB co-infection.

Dooley K, et al. CROI 2018, abstract #33
ADVANCE Study

- Non-inferiority of 2 new combinations to current treatment (Efavirenz-based)
- Open label, randomized study over 96 weeks
- Primary endpoints is at 48 weeks
- Pharmacokinetic sampling of both DTG/TAF in those who contract TB or become pregnant

N= 1110
≥12 yo, ≥ 40 Kg

N= 90-120 in age group 12-18 years

DTG+TAF + FTC

DTG+TDF + FTC

EFV+TDF + FTC

48 weeks results available in early 2019

Does dosage matter?

*Can we lower the dose to minimize cost and toxicities?*

Candidate ARVs for Dose Optimization Trials:
- Efavirenz
- Lopinavir
- Atazanavir
Dose Optimization

Efavirenz
Standard doses of **Efavirenz** associated with a higher exposure in Thais/Asians

<table>
<thead>
<tr>
<th>Ethnic and dosing</th>
<th>Caucasian Std dose</th>
<th>Asian Std dose</th>
<th>Asian Lower Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std dose</td>
<td>600 mg OD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower dose</td>
<td>400 mg OD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median AUC (h*mg/L)

van der Lugt J, and Avinhingsanon A. Asian Biomedicine Feb 2009
DMP-006 trial: EFV Phase II (1996-97)

16 weeks data

Hill et al. *The Open Infectious Dis J* 2010, 4, 85-91
Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial

ENCORE1 Study Group*

Lancet 2014; 383: 1474–82

Conducted by Kirby Institute, Sydney, Australia
ENCORE1 Study: 48 Weeks

EFV 400 mg was non-inferior to EFV 600 mg

Encore study group. Lancet 2014; 383: 1474–82
ENCORE1: 96 weeks results
Non-inferiority findings = confirmed

The Lancet Infectious Diseases 2015

Figure 3: Mean change in HIV RNA viral load from baseline to week 96 for the modified intention-to-treat population
Plotted points are mean log_{10} copies per mL; error bars are SDs.
ENCORE1: 96 weeks results on AEs

EFV-related AEs (%)

- **EFV 400**: 39%
- **EFV 600**: 48%

Stopping due to EFV-related AEs

- **EFV 400**: 13%
- **EFV 600**: 28%

P = 0.03

The Lancet Infectious Diseases 2015
Conclusions:
With both doses of efavirenz studied, CSF concentrations were considered adequate to inhibit HIV replication.
Efficacy of Once-daily Regimens based on controlled trials (48 weeks results, NS=F)

Efavirenz 400 – STR

STR EFV 600 mg → STR with EFV 400 mg

Mylan Pharm

TDF/FTC + EFV 400

U.S. FDA Tentative Approval 03/10/2017

600 mg EFV may be needed for

1. Pregnancy
2. Tuberculosis - with Rifmapicin
Dose Optimization
Atazanavir/ritonavir
Standard dose of **Atazanavir (ATV)** was associated with a high exposure in Asians

ATV was boosted with ritonavir 100 mg OD

**LASA study**

Non-inferiority tiral ATV 300 vs 200 boosted with rtv 100

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van der Lugt J, and Avinhingsanon A. Asian Biomedicine Feb 2009
Low-dose versus standard-dose ritonavir-boosted atazanavir in virologically suppressed Thai adults with HIV (LASA): a randomised, open-label, non-inferiority trial

Torsak Bunupuradah, Sasisopin Kiertiburanakul, Anchalee Avihingsanon, Ploenchan Chetchotisakd, Malee Techapornroong, Niramon Leerattanapetch, Pacharee Kantipong, Chureeratana Bowonwatanuwong, Sukit Banchongkit, Virat Klinbuayaem, Sripetcharat Mekvivattanawong, Sireethorn Nimitvilai, Supunnee Jirajariyavej, Wisit Prasithsirikul, Warangkana Munsakul, Sorakij Bhakeecheep, Suchada Chaivoot, Praphan Phanuphop, David A Cooper, Tanakorn Apornpong, Stephen J Kerr, Sean Emery, Kiat Ruxrungtham, for the LASA Study Group*
LASA Study: Design and Endpoints

N=560

• Adults age >18 Yr
• On boosted PI regimens for ≥ 3 mo
• Plasma HIV-RNA <50 c/ml for ≥12 mo

Atazanavir/r
200 /100 mg OD

Randomized 1:1
With 2 NRTIs

Atazanavir/r
300 /100 mg OD

Primary endpoint
proportion of patients whose HIV-RNA <200 c/mL after 48 weeks of treatment

Non-inferiority
if the lower limit of the 95% CI for the difference in proportion with VF was above -10% in an ITT analysis at 48 weeks

Assessments: 0, 12, 24, 36, and 48 weeks blinded bilirubin results

Type analyses:
intention to treat (ITT), per protocol (PP),
snapshot (non-completer=failure) analysis

Stratification by
sites, and use of tenofovir, indinavir

PI: protease inhibitor, r: ritonavir, OD: once daily
LASA Study Results at Week 48

N=560 with 2nd-lne LPV/r-based viral suppression ≥3 months

**Dose Optimization**

- **ATV/r 200**
- **ATV/r 300**

**% Patients with HIV-RNA <50 c/ml**

<table>
<thead>
<tr>
<th></th>
<th>ATV/r 200</th>
<th>ATV/r 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>NC=F</td>
<td>92</td>
<td>86</td>
</tr>
</tbody>
</table>

\(P = 0.03\)

**% Patients Discontinuation**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Clinical jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r 200</td>
<td>2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>ATV/r 300</td>
<td>7.6</td>
<td>2.2</td>
</tr>
</tbody>
</table>

\(P = 0.01\), \(P = 0.06\)

Implementation
from research findings into the health care system

PK study and pilot study

Efficacy study

Guidelines implementation

Randomized control trial with adequate sample size
“LASA study”
Non-inferiority design, N=560
Cost Saving When Using Lower Dose

Atazanavir (from 300 to 200 mg)

5 year savings
Up to 1000 million Baht
To treat 5000 cases with a 10% increase/year

Cost Saving (million Baht)

2015 2016 2017 2018 2019

160 171 190 205 226

300 mg 200 mg

30 tab/bottle 60 tab/bottle
DTG-based Dual ART (2DR)

For Naïve and for Switching in viral suppressed individuals
ACTG A5353: Pilot Study of Dual ART (DTG/3TC) Dolutegravir + Lamivudine in Treatment-Naive Patients

- **Single-arm**, 52-wk phase II study (N = 120)[1]
  - HIV-1 RNA ≥ 1000 to < 500,000 c/mL; no PI, INSTI, or reverse transcriptase resistance; no active HBV infection
  - Median age, 30 yrs; male, 87%; median CD4+ cell count, 387 cells/mm³; median HIV-1 RNA, 4.61 log₁₀ copies/mL
- **Primary efficacy outcome**
  - 90% achieved HIV RNA-1 < 50 copies/mL at Wk 24 (FDA Snapshot)
- No discontinuations due to AEs

### Virologic Outcomes at Wk 24[1]

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>BL HIV-1 RNA, c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 100,000 (n = 37)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 c/mL</td>
<td>89</td>
</tr>
<tr>
<td>Virologic nonsuccess</td>
<td>8</td>
</tr>
<tr>
<td>▪ HIV-1 RNA ≥ 50 c/mL</td>
<td>0</td>
</tr>
<tr>
<td>▪ D/c for other reasons* while HIV-1 RNA ≥ 50 c/mL</td>
<td>0</td>
</tr>
</tbody>
</table>


**Fully powered phase III GEMINI-1**[2] and -2[3] under way

Slide credit: clinicaloptions.com
GEMINI 1 & 2: DTG/3TC vs DTG/TDF/FTC

ViiV on June 14, 2018 has announced the 48 weeks endpoints

- Total N approximately = 1,400 men and women living with HIV.
- At Week 48, the studies met the primary endpoint for non-inferiority based on plasma HIV-1 RNA <50 copies per milliliter (c/mL)
- No patient who experienced virologic failure in either treatment arm developed treatment-emergent resistance.
**SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV in Patients With No Previous VF**

- Randomized, open-label phase III trials of virologically suppressed patients with no previous virologic failure switched to DTG + RPV or continued baseline ART (N = 1024; 70% to 73% of patients receiving TDF at baseline)


![Bar chart showing virologic efficacy at week 48](attachment:image.png)

**Treatment Difference (95% CI)**

- Favors Baseline ART: -0.2
- Favors DTG + RPV: 2.5

Slide credit: clinicaloptions.com
DTG/RPV STR (Juluca®)
FDA Approved for **Maintenance Therapy**: November 2017
• Once-daily single-tablet regimen
• For patients who have been **virologically suppressed for ≥ 6 mos**
• Patients must have **no history of treatment failure and no resistance** to DTG or RPV
• **Must be taken with a meal**
• **DDIs**: Separate dose of DTG/RPV and antacid/polyvalent cation–containing medications. Avoid PPIs (eg, omeprazole, pantoprazole)
Position’s on the use of EFV400 and DTG

Baseline pre-treatment

**NNRTI HIV DR %**

- **< 10%**
  - EFV 600
  - EFV 400*
  - *Low cost DTG is not available*

- **≥ 10%**
  - EFV 600
  - DTG 50 mg
  - *Low cost DTG is available*

*Remark: In Thailand, while EFV400 STR is not yet available, RPV is preferred when CD4 >350
Summary
## Optimizing First-line ART: Pros and Cons

<table>
<thead>
<tr>
<th>ART</th>
<th>TB + Rifampicin</th>
<th>Early Pregnancy</th>
<th>Late Pregnancy</th>
<th>HBV</th>
<th>DDIs</th>
<th>STR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple-DTG TLD, TAFxD</td>
<td>Double DTG dose: 100 mg/day</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>Al-Mg Hydroxide Antacid</td>
<td>✓</td>
</tr>
<tr>
<td>Dual-DTG: DTG/3TC</td>
<td>Double DTG dose to 100 mg/day</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>Al-Mg Hydroxide Antacid</td>
<td>X</td>
</tr>
<tr>
<td>EFV400: TLE400</td>
<td>EFV 600</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Methadone</td>
<td>✓</td>
</tr>
<tr>
<td>RPV-based</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Rifampicin</td>
<td>✓</td>
</tr>
</tbody>
</table>
ART Experienced individuals

**NNRTI-based failure**
- 2NTRIs+ DTG
- 2NTRIs+ bPI

**Viral suppressive ART**
- DTG/RPV
- ATV/r 200/100 + 2 NRTIs

**DTG-based failure**
- No DR detected?
  - Improve adherence
- DR detected
  - 2NTRIs+ bPI
  - NNRTI + bPI

No Hx of previous DR to these ARVs
For the LASA and ENCORE-1 studies

We are very grateful to all the study participants; and all of the HIV-NAT, TRC-ARC staffs, the IRBs, DSMBs, collaborators, and the funding organizations.

Funding:
Thank You