Rationale for Triple-Drug Therapy for HIV Treatment Naïve and Maintenance after Suppression

Judith A. Aberg, MD
George Baehr Professor of Medicine
Chief Division of Infectious Diseases
Icahn School of Medicine at Mount Sinai and the Mount Sinai Health System
Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Employ strategies for optimizing antiretroviral treatment in treatment-naïve individuals
• Analyze emerging issues of two vs three drugs for treatment-naïve and treatment-experience (without prior virologic failure) PWH which may impact long-term virologic suppression and drug-associated toxicities
Faculty and Planning Committee Disclosures
Please consult your program book.

• Advisory Board for Gilead, Janssen, Merck, Viiv
• Multi-Center Trial Support: BMS, Gilead Sciences and Viiv Healthcare/GlaxoSmithKline, Shionogi
• Member, DHHS ARV guidelines panel. Views presented here do not reflect the views of the DHHS or members of the DHHS panel

Off-Label Disclosure

The following off-label/investigational uses will be discussed in this presentation:
Two drug therapies, cabotegravir and rilpivirine LA
Goals of HIV Therapy

- **Indefinitely maintain suppression** of plasma HIV RNA levels below the level of detection of sensitive of HIV RNA assays – FDA Guidance

- **Maximal and durable suppression** of plasma viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4 count, and confers substantial clinical benefits – DHHS Guidelines

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Evolution of HIV Treatment

- Shift from monotherapy to triple therapy based on more durable suppression with prevention of resistance development

HAART: Highly Active Antiretroviral Therapy
Paradigm Shift: Preventing Resistance

Double-blind, randomized trial in ART-naïve HIV-infected adults comparing NFV vs LPV/r both with NRTIs of d4T + 3TC at Week 108

- DHHS Guidelines recognize the importance of resistance barrier in justification of LPV/r’s preferred status
  - 2003: trial data for virologic potency, patient tolerance, and pill burden
  - 2004: trial data for virologic potency, barrier to virologic resistance, patient tolerance


Study M98-863: NFV vs LPV/r with d4T + 3TC (Treatment-Naïve)
Current Commonly Used Classes of ARVs

NRTIs
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir AF
- Tenofovir DF
- Zidovudine

NNRTIs
- Delavirdine
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

PIs
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

PK booster
- Cobicistat

INSTIs
- Raltegravir
- Elvitegravir
- Dolutegravir
- Bictegravir

Entry Inhibitors
- Maraviroc

Fusion Inhibitors
- Enfuvirtide

ARV: antiretroviral, NNRTI: non-nucleoside reverse transcriptase inhibitor, NRTI: nucleoside reverse transcriptase inhibitor, PI: protease inhibitor, INSTI: integrase strand transfer inhibitor
DHHS and IAS-USA Guidelines’ Position on 2-Drug Regimens

- All currently Recommended Initial Regimens consist of 2 NRTIs + 3rd ARV\(^1,2\)
- **Except** in rare situations when ABC, TAF, TDF, and NRTIs can not be used\(^1,2\)

<table>
<thead>
<tr>
<th>DHHS(^1)</th>
<th>Regimen Switching in the Setting of Virologic Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other ARV Regimens for Initial Therapy when ABC, TAF, and TDF Cannot Be Used</strong></td>
<td><strong>Good Supporting Evidence</strong></td>
</tr>
<tr>
<td>• DRV/r + RAL&lt;br&gt;<em>Only</em> with HIV RNA $&lt; 100,000$ c/uL, CD4 counts $&gt; 200$ cells/mm(^3), and not able to take ABC, TAF, or TDF</td>
<td>• Pl/r + FTC or 3TC&lt;br&gt;(i.e., ATV/r + 3TC, DRV/r + 3TC, or LPV/r + 3TC)&lt;br&gt;May be a reasonable when the use of TDF, TAF, or ABC is contraindicated or not desirable and no baseline resistance</td>
</tr>
<tr>
<td>• LPV/r + 3TC&lt;br&gt;<em>Only</em> when ABC, TAF, or TDF and other alternatives cannot be used.</td>
<td>• DTG + RPV&lt;br&gt;Can be a reasonable when the use of NRTIs is not desirable and when resistance to either DTG or RPV is not expected</td>
</tr>
<tr>
<td><strong>Under Evaluation and Not Yet Recommended</strong></td>
<td><strong>Some Supporting Evidence</strong></td>
</tr>
<tr>
<td>• DTG + 3TC (PADDLE study 20 pts VL&lt;100K and A5353)</td>
<td>Cannot yet be recommended under most circumstances, or at all, until further evidence is available</td>
</tr>
<tr>
<td>• DRV/r + 3TC (ANDES Trial)</td>
<td>• DRV/r + RAL</td>
</tr>
</tbody>
</table>

DHHS and IAS-USA Guidelines’ Position on 2-Drug Regimens

- All currently Recommended Initial Regimens consist of 2 NRTIs + 3rd ARV\textsuperscript{1,2}
- **Except** in rare situations when ABC, TAF, TDF, and NRTIs can not be used\textsuperscript{1,2}

- Initial 2DC are recommended only in rare situations when a patient cannot take ABC, TAF, or TDF.

- Induction maintenance strategies (switching from 3- to 2-drug regimens in patients with virologic suppression).
  - Although trials provide some support for this approach including FDA approved combination of DTG and RPV: “the use of a three-drug combination regimen is generally recommended when switching patients with suppressed viral loads to a new regimen”
  - It is critical to review a patient’s full ARV history, including virologic responses, past ARV-associated toxicities, and cumulative resistance test results (if available) before selecting a new antiretroviral therapy (ART) regimen
  - More intensive monitoring to assess tolerability, viral suppression, adherence, and laboratory changes is recommended during the first 3 months after a regimen switch

### Wholesaler Acquisition Cost (US $) 30 days as of Feb 2018

<table>
<thead>
<tr>
<th></th>
<th>Mono and 2DC Cost</th>
<th>Three Drug Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG all mg doses</td>
<td>1657.60</td>
<td></td>
</tr>
<tr>
<td>RPV 25 mg</td>
<td>1043.10</td>
<td></td>
</tr>
<tr>
<td>DTG/RPV 50/25 mg</td>
<td>2579.00</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>1204.50</td>
<td></td>
</tr>
<tr>
<td>Abacavir/dolutegravir/lamivudine</td>
<td>2294.30</td>
<td></td>
</tr>
<tr>
<td>Bictegravir/emtricitabine/TAF</td>
<td>2945.70</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/emtricitabine/TAF</td>
<td>2577.70</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/emtricitabine/TDF</td>
<td>2704.00</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine/rilpivirine/TAF</td>
<td>2,345.87</td>
<td></td>
</tr>
</tbody>
</table>
**Study Design**

**SINGLE**

- Treatment-Naïve HIV-1 RNA ≥ 1,000 c/mL HLA-B*5701 negative
- Stratified by baseline viral load and CD4 cell count

1:1

414

DTG QD + ABC/3TC QD + EFV/TDF/FTC Placebo

EFV/TDF/FTC QD + DTG QD + ABC/3TC QD Placebo

96 Weeks

**SPRING²**

- Treatment-Naïve HIV-1 RNA ≥ 1000 c/mL
- Stratified by baseline viral load and NRTI backbone

1:1

411

DTG QD + 2 NRTIs* QD + RAL BID Placebo

RAL BID + 2 NRTIs* QD + DTG QD Placebo

96 Weeks

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### Resistance Consequences of Virologic Failure

<table>
<thead>
<tr>
<th></th>
<th>SINGLE</th>
<th>SPRING²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG + ABC/3TC (n=414)</td>
<td>EFV/TDF/FTC (n=419)</td>
</tr>
<tr>
<td>Participants with PDVF, n</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>NRTI major mutations, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>NNRTI major mutations, n</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>INSTI major mutations, n</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>DTG QD + 2 NRTIs (n=411)</td>
<td>RAL BID + 2 NRTIs (n=419)</td>
</tr>
<tr>
<td>Participants with PDVF, n</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>NRTI major mutations, n</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>INSTI major mutations, n</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

No integrase mutations or major RT mutations detected on DTG + 2 NRTIs through Week 96

Does 3TC or FTC resistance matter?

Pro:
- M184V may be associated with hypersusceptibility to TDF
- Less fit Virus

Con:
- In a 2 drug INSTI plus 3TC or FTC; then person is on monotherapy
- Presence of M184V in chronic naïve PWH is 5-9%; treatment experienced is higher
DOLUMONO – DTG Monotherapy (Suppressed)

DTG as Maintenance Monotherapy For HIV-1

DOLUMONO is a multicenter randomized non-inferiority trial comparing 96 participants on DTG 50mg QD monotherapy vs cART

### Characteristics of Virologic Failures on DTG Monotherapy* †

<table>
<thead>
<tr>
<th>Pt</th>
<th>BL 3rd agent (with F/TDF)</th>
<th>Timing of Failure</th>
<th>HIV-RNA at Failure (c/ml)</th>
<th>Integrase Sequence at Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RPV</td>
<td>W4</td>
<td>71,600</td>
<td>No RAMs</td>
</tr>
<tr>
<td>2</td>
<td>EFV</td>
<td>W12</td>
<td>678</td>
<td>Not successful</td>
</tr>
<tr>
<td>3</td>
<td>RPV</td>
<td>W30</td>
<td>3,510</td>
<td>No RAMs</td>
</tr>
<tr>
<td>4</td>
<td>RPV</td>
<td>W30</td>
<td>1,570</td>
<td>S230R</td>
</tr>
<tr>
<td>5</td>
<td>DTG</td>
<td>W36</td>
<td>1,440</td>
<td>Not successful</td>
</tr>
<tr>
<td>6</td>
<td>RPV</td>
<td>W48</td>
<td>4,990</td>
<td>No RAMs</td>
</tr>
<tr>
<td>7</td>
<td>NVP</td>
<td>W60</td>
<td>3,470</td>
<td>R263K</td>
</tr>
<tr>
<td>8</td>
<td>NVP</td>
<td>W72</td>
<td>4,180</td>
<td>N155H</td>
</tr>
</tbody>
</table>

* All CD4 T-cell nadir ≥210 cells/mm³ and >95% adherence (according to clinician)
† 8% (8/96) of participants on DTG monotherapy experienced virologic failure at Week 48

- **Study prematurely discontinued due to predefined stopping rule (emergent INSTI resistance in 2 or more subjects)**
- **The genetic barrier is insufficient to allow for maintenance monotherapy**

Why the Debate about 2-Drug Combinations (2DC) in Tx Naïve and Tx experienced without prior VF

1. How durable is a 2DC in maintaining suppression?
2. What is the barrier to the development of resistance in patients who have incomplete suppression with 2DC?
3. What adverse events (AEs) are there in a 2DC?
4. Are there any AEs improved by switching to 2DC? Can we finally put a stop to the abacavir-tenofovir marketing wars?
5. Why are companies still developing 3 drug combination pills if 2 drug combination is so effective?
6. How should cost be weighted against tolerability, durability and resistance?
ARV Regimen Considerations as Initial Therapy

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Consideration(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease (defined as eGFR&lt;60 mL/min)</td>
<td>Avoid TDF&lt;br&gt;Use ABC or TAF</td>
</tr>
<tr>
<td>Kidney disease risk</td>
<td>TDF is not recommended</td>
</tr>
<tr>
<td>Osteopenia or osteoporosis risk or diagnosis</td>
<td>TDF is not recommended</td>
</tr>
<tr>
<td>High cardiac risk</td>
<td>ABC should be used with caution in patients who have or who are at high risk of cardiovascular disease.</td>
</tr>
</tbody>
</table>
And for the record, here’s a list of NRTI-sparing studies that gave “meh” results at best:

- **ACTG 5142 — LPV/r + EFV vs NRTIs + EFV vs NRTIs vs LPV/r.**
  LPV/r + EFV had high rates of hyperlipidemia; regimen was also cumbersome with lots of GI side effects.

- **SPARTAN — ATV + RAL vs ATV/r + TDF/FTC.**
  More treatment failure, more jaundice in the ATV + RAL arm.

- **PROGRESS — LPV/r + RAL vs. LPV/r + TDF/FTC.**
  Comparable success rates, but baseline HIV RNA low in the study population; 3 pill, twice-daily regimen.

- **ACTG 5262 — Single-arm study of DRV/r + RAL.**
  Unexpectedly high rates of virologic failure (with resistance), especially among those with HIV RNA > 100k at baseline.

- **A4001078 — ATV/r + MVC vs ATV/r + TDF/FTC**
  Only 75% virologic suppression rate in ATV/r + MVC arm, with more hyperbilirubinemia than the control group; study not fully powered.

- **RADAR — DRV/r + RAL vs. DRV/r + TDF/FTC.**
  63% suppression rate in the RAL arm, vs 84% for TDF/FTC; study not fully powered.
MODERN Study
DRV/r + MVC vs. DRV/r + FTC/TDF

STUDY STOPPED DUE to increase VF in dual therapy. No safety advantage
### Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r

**NEAT 001 DRV/r + RAL vs DRV/r + TDF/FTC**  
96-Week Results; Primary Endpoint

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall n = 805</th>
<th>Baseline HIV-1 RNA</th>
<th>Baseline CD4+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAL + DRV/r</td>
<td>TDF/FTC + DRV/r</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-1.1 (8.6)</td>
<td>17.4 %</td>
<td>13.7 %</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100,000 c/mL</td>
<td>-3.9 (3.5)</td>
<td>7 %</td>
<td>7 %</td>
</tr>
<tr>
<td>≥ 100,000 c/mL</td>
<td>-0.05 (19.3)</td>
<td>36 %</td>
<td>27 %</td>
</tr>
<tr>
<td>Baseline CD4+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200/mm³</td>
<td>-3.4 (6.3)</td>
<td>39.0 %</td>
<td>21.3 %</td>
</tr>
<tr>
<td>≥ 200/mm³</td>
<td>4.7 (30.8)</td>
<td>13.6 %</td>
<td>12.2 %</td>
</tr>
</tbody>
</table>

Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

- **p = 0.09***
- **p = 0.02***

*Lancet 2014;384:1942-51*
NEAT 001: PI regimen vs DRV + RTV + RAL (Treatment-Naïve)

Treatment Failure & Resistance Outcomes at Week 96

- Treatment failure was higher with 2DC vs Triple Therapy: 19% vs 15%

- Resistance: 21% 2DC vs 0% Triple Therapy
  - 2DC group had integrase (5/29) and RT mutations (1/29) present

![Treatment Failure Rate by CD4 Strata](image)
Virologic failure during follow-up, and resistance data

<table>
<thead>
<tr>
<th></th>
<th>RAL + DRV/r n=401</th>
<th>TDF/FTC + DRV/r n=404</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-defined virological failure (PDVF), n</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>Number of PDVFs who met criteria for genotype testing (HIV RNA &gt; 500 copies/mL at or after W32)</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>Number of patients with single unconfirmed value of HIV RNA &gt; 500 copies/mL at or after W32 (meeting criteria for genotype testing)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Genotype done, n</td>
<td>28/36</td>
<td>13/15</td>
</tr>
<tr>
<td>Major resistance mutations, n</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NRTI</td>
<td>1 (K65R)</td>
<td>0</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>INI</td>
<td>5 (N155H)*</td>
<td>-</td>
</tr>
</tbody>
</table>

* 1 additional patient with T97A

According to the protocol, genotypic testing was carried out by local laboratories when patients had a single VL > 500 copies/mL at or after W32.

Protocol-defined virological failure change of any component of the initial randomised regimen before W32 because of confirmed insufficient virological response, defined as HIV-1 RNA reduction < 1 log10 copies/mL by W18 or HIV-1 RNA ≥ 400 copies/mL at W24; failure to achieve virological response by W32 (confirmed HIV-1 RNA ≥ 50 copies/mL at W32); confirmed HIV-1 RNA ≥ 50 copies/mL at any time after W32.
In the NEAT001/ANRS143 trial, there was no RAM at virological failure in the standard tenofovir/emtricitabine plus darunavir/ritonavir regimen, contrasting with a rate of 29.5% (mostly IN mutations) in the raltegravir plus darunavir/ritonavir NRTI-sparing regimen. The cumulative risk of IN RAM after 96 weeks of follow-up in participants initiating ART with raltegravir plus darunavir/ritonavir was 3.9%.
DRV/R FDC plus 3TC for HIV-1 treatment naive patients: Week 48 results of the ANDES study

- 1). Small numbers over 48 weeks
- 2). No difference in VL outcome
- 3). No improvement in toxicity

Figueroa MI, et al. CROI 2018 ABST#489

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 50 copies/mL at Wk 48, n (%)</th>
<th>All Patients</th>
<th>DRV/RTV + 3TC/TDF</th>
<th>DRV/RTV + 3TC</th>
<th>Treatment Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (ITT snapshot analysis) (n = 145)</td>
<td>136 (94)</td>
<td>66 (94)</td>
<td>70 (93)</td>
<td>-1.0 (-7.5 to 5.6)</td>
</tr>
<tr>
<td>Patients with baseline HIV-1 RNA &gt; 100,000 copies/mL (ITT snapshot analysis) (n = 35)</td>
<td>32 (91)</td>
<td>12 (92)</td>
<td>20 (91)</td>
<td>-1.4 (-17.2 to 14.4)</td>
</tr>
</tbody>
</table>

- Overall safety similar between arms
  - No significant difference in AEs leading to discontinuation, serious AEs, or deaths
  - Grade 2-4 AEs possibly or probably related to treatment occurred in 17 patients receiving triple therapy vs 11 receiving dual therapy
    - Most AEs gastrointestinal
  - Similar rate of laboratory abnormalities between arms, except elevations in total cholesterol, which were more common with dual therapy (19% vs 4%; \( P = .01 \))
Study Design

Phase II, single-arm, 52-week, study of DTG 50 mg + 3TC 300 mg in treatment-naïve participants

Primary Objective
- To estimate the virologic success rate at **week 24**, defined as on-treatment VL < 50 c/mL, using the FDA Snapshot definition

Key Secondary Objectives
- Compare efficacy with baseline VL ≤100,000 (n=37) vs >100,000 (n=83) c/mL
- Describe emergent integrase and RT resistance during virologic failure
- Evaluate safety and tolerability
- Explore impact of minority drug-resistant variants and drug exposure/adherence on observed outcomes


* No active nor planned HCV within the study, HCV coinfection was not exclusionary
Virologic Outcomes at **Week 24**: FDA Snapshot

**Virologic Outcome at Week 24 by Baseline Viral Load (VL)**

- **HIV-1 RNA < 50 c/mL**: 90%
- **HIV-1 RNA ≥50 c/mL**: 8%
- **No Virologic Data**: 2%

<table>
<thead>
<tr>
<th>Baseline VL</th>
<th>HIV-1 RNA ≥50 cpm* (n=5)</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100,000</td>
<td></td>
<td>INSTI</td>
</tr>
<tr>
<td>≤100,000</td>
<td></td>
<td>R263R/K</td>
</tr>
<tr>
<td>≤100,000</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

*Includes Protocol Defined Virologic Failures, n=3 (confirmed VL>400 cpm at Week 16 or 20 or confirmed VL>200 cpm at/after Week 24) and lack of virologic success, n=2 (VL≥50 cpm at Week 24)

At **Week 24**, 5 participants had early virologic failure and one patient had mutations against DTG and 3TC: \(\text{?}\) **LONG TERM DURABILITY**

Virologic Non-Success: FDA Snapshot Analysis

ACTG 5353: DTG + 3TC (Treatment-Naïve)

2 out of 5 virological failures were virological rebound*

*Did not meet the protocol-defined virologic failure criteria

Virologic Failure with 2-Class Resistance

ACTG 5353: DTG + 3TC (Treatment-Naïve)


PDVF, Protocol-Defined Virologic Failure
LLOQ; Lower Limit of Quantification

DTG + 3TC

HIV-1 RNA (c/mL)

M184V
R263R/K
None

DTG concentration (ng/mL)

0 2 4 8 12 16 20 24 32

0 1000 2000 3000 4000

LLOQ
**Induction Maintenance Naive Switch (201584)**

Randomized, open-label, multicenter, parallel-group, non-inferiority study

- **Primary Objective:** To demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks compared to continuation of a single tablet integrase regimen over 48 weeks in HIV-1 antiretroviral naïve subjects.

- **Primary endpoint:** Proportion of subjects with a virologic failure endpoint as per FDA Snapshot algorithm at Week 48 for the Intent-to-treat exposed (ITT-E) population.

- **NI Margin:** 5% individual study NI margin based on virologic failure rate.

**Clinical Trials.gov NCT02938520**
Randomized, open-label, multicenter, parallel-group, non-inferiority study

- **Primary Objective:** Demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA every 4 weeks compared to continuation of current first line antiretroviral regimen (ART) over 48 weeks in HIV-1 infected ART-experienced subjects

- **Primary endpoint:** Proportion of subjects with a virologic failure endpoint as per FDA Snapshot algorithm at Week 48 for the Intent-to-treat exposed (ITT-E) population

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### Study Design

**Screening Phase**
- PI, NNRTI or INI Based Regimen with 2 NRTI Backbone
- Randomization 1:1
- N= 570

**Maintenance Phase**
- Oral CAB + RPV
- PI, NNRTI or INI
- Current ART

**Extension Phase**
- Oral CAB + RPV
- PI, NNRTI or INI
- Current ART

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**Uninterrupted ART 6 months, VL<50 c/mL at Screening, 2 VL<50 c/mL in previous 12 months**

**INI based regimen will be capped at 40% of study enrolment, excludes abacavir/dolutegravir/lamivudine**

**Optional Late Switch to CAB LA + RPV LA at Wk 52 for subjects randomized to continue current ART**

**Subjects who withdraw from or complete IM CAB LA + RPV LA treatment must enter 52 week long term follow up phase**

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clinicaltrials.gov NCT02951052
No question we need to continue our quest for well tolerated, simple, less toxic ART that will result in sustained virologic suppression

The data are inconclusive that 2 Drug Combination in Treatment Naïve PWH is non-inferior or more cost effective than the current preferred first line regimens

- **GEMINI 1 and 2** (NCT02831673 and NCT02831764) – Two identical studies comparing a two-drug regimen of dolutegravir plus lamivudine with a three-drug regimen of dolutegravir plus the fixed-dose tablet tenofovir/emtricitabine in treatment-naïve adults living with HIV results anticipated July 2018

Current 2DC long acting injectable studies in naïve still require an induction 3DC

Switch studies always have potential risk of failure given potential for archived resistance. Questions remain if participant would have failed if they stayed on their suppressive regimen.

Future studies are warranted.

Vote for the old and the weary; oh, this is not about me…Vote for 3 drugs as first line now.