Starting and Sequencing ART in Resource Limited Settings

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## Antiretroviral Agents Approved by US FDA (Aug 2012)

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine (AZT)</td>
<td>nevirapine (NVP), efavirenz (EFV)</td>
<td>saquinavir (SQV)</td>
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<tr>
<td>didanosine (ddl)</td>
<td>Rilvipirine (RLP)</td>
<td>indinavir (IDV)</td>
</tr>
<tr>
<td>zalcitabine (ddC)</td>
<td>etravirine (ETV)</td>
<td>ritonavir (RTV)</td>
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<tr>
<td>stavudine (d4T)</td>
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<td></td>
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<tr>
<td>lamivudine (3TC)</td>
<td>tenofovir DF (TDF)</td>
<td>lopinavir/ritonavir (LPV/r)</td>
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<tr>
<td>abacavir (ABC)</td>
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<tr>
<td>emtricitabine (FTC)</td>
<td>enfuvirtide (ENF, T20)</td>
<td>fosamprenavir (FPV)</td>
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<tr>
<td></td>
<td>Maraviroc (CCR5)</td>
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### Nucleotide RTIs

### Entry Inhibitors

### Integrase Inhibitors

<p>| | | |</p>
<table>
<thead>
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<tr>
<td></td>
<td>Raltegravir, Elvitegravir</td>
<td>tipranavir (TPV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darunavir (DRV)</td>
</tr>
</tbody>
</table>
Research Questions in Antiretroviral Therapy

- When to start ART?
- What to start with?
- When to switch?
- What to switch to?
When to initiate Antiretroviral Therapy?

- Risk of progression
- Risk of AE
- Adherence commitment
- Resistance development
- Cost and readiness

HPTN052/ACTG5245
Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm³

Primary Transmission Endpoint
Virologically-linked transmission events

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

HPTN 052 Study Design

Immediate ART
CD4 350-550

Delayed ART
CD4 ≤250
# HPTN 052 Enrollment

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<tr>
<th>Region</th>
<th>Site</th>
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<td>Americas</td>
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<td></td>
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<td></td>
<td>Harare, Zimbabwe</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>1763</strong></td>
</tr>
</tbody>
</table>

"HPTN 052 Enrollment"
HPTN 052: HIV-1 Transmission

Total HIV-1 Transmission Events: 39

Linked Transmissions: 28
- Immediate Arm: 1
- Delayed Arm: 27

Unlinked or TBD Transmissions: 11

• 96% reduction in the risk of transmission following ART

p < 0.001

IAS 2011; NEJM 2011
HPTN 052: Early versus Delayed ART and Clinical Events

Death, WHO stage 4 clinical event, pulmonary TB or severe bacterial infection

1763 HIV+ randomized to ART:

CD4 350-550 (immediate) vs. confirmed CD4 < 250 (delayed)

HR: 0.6 [0.4, 0.9], P=0.01

65 events delayed
40 events immediate

IAS 2011
#MOAX0105

IAS 2012
#THLBB05
# Tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>17  [ 1/100PY ]</td>
<td>518</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>14  [ 0.8/100PY ]</td>
<td>521</td>
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<tr>
<td>Extrapulmonary TB</td>
<td>3  [0.2/100PY]</td>
<td>443</td>
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<tr>
<td>Peripheral Lymph Nodes</td>
<td>2</td>
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<td>Pleural</td>
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<tr>
<td>Skeletal</td>
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<td>--</td>
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<tr>
<td>Meningeal</td>
<td>0</td>
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</tbody>
</table>
HPTN 052

- 1,750 heterosexual serodiscordant couples in resource-constrained countries randomized to receive ART early (CD4 350-550 cells/µL) or defer until CD4 < 250 cells/µL

<table>
<thead>
<tr>
<th>Event Rates</th>
<th>Early ART</th>
<th>Deferred ART</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission Rate per 100 pt-years (95% CI)</td>
<td>0.3 (0.1-0.6)</td>
<td>2.2 (1.6-3.1)</td>
<td>0.11 (0.04-0.32)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Clinical Event Rate per 100 pt-years (95% CI)</td>
<td>2.4 (1.7-3.3)</td>
<td>4.0 (3.5-5.0)</td>
<td>0.59 (0.40-0.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

When to initiate Antiretroviral Therapy?

- Risk of progression
- Risk of AE
- Adherence commitment
- Resistance development
- Cost and readiness

HPTN052/ACTG5245
When to initiate Antiretroviral Therapy?

Risk of progression

Risk of AE

Adherence commitment

Resistance development

Cost and readiness

<200

<250

<350

350-500

?>500
Early initiation “CD4 > 500” NA ACCORD

The first analysis involved 8362 patients; 2084 (25%) initiated therapy at a CD4 count of 351 to 500 cells/mm³, while 6278 (75%) deferred therapy.

- Deferred-therapy group, there was increase of 69% in the risk of death, as compared with that in the early-therapy group (P < 0.001).

- In the second analysis involving 9155 patients, 2220 (24%) initiated therapy at a CD4 count above 500 cells/mm³ and 6935 (76%) deferred therapy.
  - Among patients in this deferred-therapy group, the risk of death increased by 94% (P < 0.001).

- HIV infection and decreasing CD4+ counts are associated with a higher risk of cardiovascular, liver, and renal diseases and non-AIDS-defining cancers, and treatment with antiretroviral therapy appears to reduce the risk of these conditions.
START design

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm³

Early ART Group
Initiate ART immediately following randomization
N=2,000

Deferred ART Group
Defer ART until the CD4+ count declines to < 350 cells/mm³ or AIDS develops
N=2,000
OUTCOME: When to initiate Antiretroviral Therapy?

Risk of progression vs. Risk of AE

- Adherence commitment
- Development of resistance

HPTN052, START
When to Start ART During Acute Opportunistic Infections: IAS–USA Recommendations 2012

• Start ART as soon as possible, preferably within the first two weeks (Ala) except for TB and cryptococcal meningitis as indicated below:
  – Patients with cryptococcal meningitis should be managed in consultation with experts (BIII)
  – Patients with TB should start TB treatment first; start ART as soon as possible but within the first 2 weeks for those with CD4 < 50 cells/µL
  – Within the first 2-8 weeks of TB treatment for those with TB meningitis
  – Within the first 8-12 weeks of TB treatment for others
<table>
<thead>
<tr>
<th>Guidelines for Initiation of ART</th>
<th>AIDS/sympts.</th>
<th>CD4 &lt;200</th>
<th>CD4 200-350</th>
<th>CD4 350-500</th>
<th>CD4 &gt;500</th>
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<tbody>
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<td>YES</td>
<td>YES</td>
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<td><a href="http://www.aidsinfo.nih.gov">www.aidsinfo.nih.gov</a></td>
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<tr>
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<td>YES</td>
<td>YES</td>
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<td>Thompson JAMA 2012;308:387</td>
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<tr>
<td>UK ’12</td>
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<td><a href="http://www.who.int/hiv/pub/arv/adult2010/en">http://www.who.int/hiv/pub/arv/adult2010/en</a></td>
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Antiretroviral Drug Approval:
1987 - 2012
Goal of antiretroviral therapy
Ideal combination to start

- Potent
- Available
- Convenient dosing (qd, FDC)
- Less toxic, comorbid(TB, Cardiac, Renal, Liver), Pregnancy
Antiretroviral Agents Approved by US FDA  
(Aug 2012)

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<td></td>
<td>Raltegravir (MK0518) Elvitegravir (ELV)</td>
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## Options for antiretroviral therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Combination</th>
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<tbody>
<tr>
<td><strong>Standard</strong></td>
<td>NRTI + NRTI + NNRTI</td>
</tr>
<tr>
<td><strong>PI-based</strong></td>
<td>NRTI + NRTI + PI/r</td>
</tr>
<tr>
<td><strong>NRTI-sparing</strong></td>
<td>NNRTI + PI/r</td>
</tr>
<tr>
<td><strong>PI and NNRTI-sparing</strong></td>
<td>NRTI + NRTI + NRTI</td>
</tr>
<tr>
<td><strong>NRTIs+INSTI</strong></td>
<td>NRTI + NRTI + INSTI</td>
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</tbody>
</table>
ACTG A5095

Study population: Antiretroviral naïve subjects with HIV RNA ≥400 c/ml (N=1125)

Study regimens:
- ZDV/3TC + EFV
- ZDV/3TC/ABC
- ZDV/3TC/ABC + EFV

Primary endpoint: time to virologic failure
Duration: 120 wks after last patient enrolled

Gulick NEJM 2004;350:1850
Options for antiretroviral therapy

- **Standard**: NRTI + NRTI + NNRTI
- **PI-based**: NRTI + NRTI + PI/r
- **NA-sparing**: NNRTI + PI/r
- **PI and NNRTI-sparing**: NRTI + NRTI + NRTI
- **NRTIs+INSTI**: NRTI + NRTI + INSTI
ACTG A5142

Study population: Antiretroviral naïve subjects with HIV RNA ≥2000 c/ml (N=660)

Study regimens:

- (ZDV, d4T, TDF) + 3TC + EFV
- (ZDV, d4T, TDF) + 3TC + LPV/r
- EFV + LPV/r

Primary endpoint: time to virologic failure

Duration: 96 wks after last patient enrolled

Riddler NEJM 2008;358:2095
Options for antiretroviral therapy

Standard
- NRTI + NRTI + NNRTI

PI-based
- NRTI + NRTI + PI/r

NA-sparing
- NNRTI + PI/r

NRTIs+INSTI
- NRTI + NRTI + INSTI
What to start?: Preferred Strategies

U.S. DHHS, IAS-USA, BHIVA, EACS

- 2 NRTI + NNRTI
- 2 NRTI + PI/r
- 2 NRTI + INSTI

WHO

- 2 NRTI + NNRTI
What to start?

NRTI
Recommended
Tenofovir
Zidovudine

Alternative
Stavudine
Abacavir
Didanosine

NRTI
• Lamivudine
• Emtricitabine

NNRTI/PI/In
• Nevirapine
• Efavirenz
• Atazanavir/r
• Darunavir/r
• Raltegravir
ACTG 5175 (PEARLS study)

A Phase-3, Randomized, open-label evaluation of the efficacy of once daily protease inhibitor and once daily NNRTI containing combinations for initial treatment of HIV-1 infected subjects from diverse areas of the world

Co-Chairs: Thomas Campbel, N. Kumarasamy, Timothy Flanigan, James Hakim

Study regimens: n=1571

Arm 1A: ZDV + 3TC + EFV- (Bid)
Arm 1B: ddI + FTC + ATZ- (Qd)
Arm 1C: TDF + FTC + EFV-(Qd)

What Antiretrovirals to with start?


**Favors Arm 1B**  
ddl + FTC + ATV

**Favors Arm 1A**  
ZDV/3TC + EFV

**Primary Endpoint**

- Virologic Failure
- AIDS Progression
- Death

Hazard Ratio (+/- 99.8% CI)

IAC-2008, Mexico
Study Regimens

Arm 1A: ZDV + 3TC + EFV- (Bid)
Arm 1B: ddI+ FTC + ATZ- (Qd)
Arm 1C: TDF + FTC + EFV-(Qd)
• No differences in risk of regimen failure or any of the primary efficacy endpoint components between arms
• Similar low cumulative probabilities of regimen failure over time
• No significant statistical interactions between treatment effect and gender, race and ethnicity, country or viral load stratum
Primary Safety Findings

- Lower risk of Safety Endpoints for FTC/TDF vs 3TC/ZDV
  - ARV dose modification difference driven by neutropenia and anemia (0 vs 59 cases)
  - Lab abnormalities difference driven by neutropenia, anemia, AST/ALT (67 vs 135 cases)
  - Grade 3/4 creatinine 5 vs 2 cases
  - Fewer serious metabolic dx in FTC/TDF arm (3 vs 19 cases; P < 0.001; lipodystrophy, pancreatitis, lactic acidosis)

- Interaction between sex and treatment arm for primary safety endpoint (P = 0.005):
  - HR for Women 0.48 (0.37-0.63)
  - HR for Men 0.83 (0.64-1.08)

- No significant interaction with race and ethnicity, country or viral load stratum

- Difference in probabilities of safety events similar over time

<table>
<thead>
<tr>
<th>Number of Events</th>
<th>Total Safety Endpoints</th>
<th>All Initial ARV Dose Modification</th>
<th>All Initial Grade 3 / 4 Signs and Sxs</th>
<th>All Initial Grade 3 / 4 Lab Abnormalities</th>
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<tbody>
<tr>
<td>50</td>
<td>243</td>
<td>140</td>
<td>115</td>
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</table>

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>3TC/ZDV + EFV</td>
<td>FTC/TDF + EFV</td>
</tr>
<tr>
<td>0.64 (0.54, 0.76)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>0.54 (0.44, 0.67)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>0.96 (0.74, 1.24)</td>
<td>0.73</td>
</tr>
<tr>
<td>0.55 (0.43, 0.71)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Cumulative Probability of Safety Event (%) over time:

- No significant interaction with race and ethnicity, country or viral load stratum
- Difference in probabilities of safety events similar over time
The regimens EFV with either FTC/TDF or 3TC/ZDV had similar high levels of efficacy.

Treatment effect did not vary by QD vs BID co-formulated NRTI, race, ethnicity, gender or geography.

Supports current WHO recommendations.

Significant safety advantage to EFV + FTC/TDF:
- Lower risk of potentially serious or life-threatening laboratory abnormalities and related dose modifications/substitutions.
- Lower risk of serious metabolic diagnoses.
- Overall safety benefit most pronounced in women.

**FTC/TDF** should be preferred over **3TC/ZDV** for initial treatment of patients at high risk of adverse events, particularly HIV-infected women.

IAS 2011; Plos Medicine 2012.
We evaluated the clinical outcomes and cost-effectiveness of first-line ART using tenofovir in India, compared with current practice using stavudine or zidovudine.

We used a state-transition model of HIV disease to examine strategies using different NRTs, combined with lamivudine and nevirapine.

Conclusions. Using tenofovir as part of first-line ART in India will improve survival, is cost-effective by international standards, and should be considered for initial therapy for HIV-infected patients in India.
79% of them had M184V, 71% had NNRTI mutations, (K103N,Y181C,G190A) 60% had TAMS, (M41L,T215Y/F,K70R,L210W,K219E/Q) 11% had Q151M 5% had K65R and 5% had L74V.

26% had 3 or more NNRTI mutations

This data clearly warns that patients with immunological failure with standard WHO criteria have severe mutations and which can jeopardize future 2nd line NRTI options and newer drugs.
High-level NRTI resistance among Malawians failing 1st line HAART

d4T/AZT+3TC+NVP
CD4 and clinical monitoring
96 failed patients were genotyped
Median CD4: 68; PVL: 4.72log; Duration on ART: 36 months

93% - NNRTI mutations
81% - M184V
23% - K70E or K65R

Impact of 1st line NRTI mutations on 2nd line options

**AZT/d4T/3TC**
- Selection: M184V + TAMs
- Resistance: 3TC, FTC, ZDV, d4T ±ABC, ±ddl, ±TDF
- Option: ?ABC, ?ddl, ?TDF

**ABC/3TC**
- Selection: M184V + L74V
- Resistance: 3TC, FTC
- Option: ZDV, d4T, TDF, ABC ± ddl

**TDF/XTC**
- Selection: M184V + K65R
- Resistance: TDF, 3TC, FTC, RP ABC, RP ddl
- Option: ZDV, d4T
## Choice of Dual NRTIs

<table>
<thead>
<tr>
<th>Combo</th>
<th>DHHS</th>
<th>Dosing</th>
<th>Toxicities</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC or 3TC</td>
<td>preferred</td>
<td>1 tab qd</td>
<td>renal (rare)</td>
<td>TDF/FTC(3TC)/EFV available</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>alternate</td>
<td>1 tab qd</td>
<td>HSR (do HLA test), ?↑MI</td>
<td>less effective for VL &gt;100K</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>alternate</td>
<td>1 tab bid</td>
<td>GI, anemia, lipoatrophy</td>
<td>longest clinical experience; tox.</td>
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<tr>
<td>ddI + (FTC or 3TC)</td>
<td>alternate</td>
<td>2 tab qd fasting</td>
<td>PN, pancreatitis</td>
<td>least clinical experience</td>
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</table>
What to start?

NRTI
Recommended
Tenofovir

Alternative
Zidovudine
Abacavir
Didanosine

NRTI
• Lamivudine
• Emtricitabine

NNRTI/PI
• Nevirapine
• Efavirenz
• Atazanavir/r
• Darunavir/r
• Raltegravir
The 2NN study: Virologic response

# What to start?

<table>
<thead>
<tr>
<th>Nevirapine</th>
<th>Efavirenz</th>
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<tr>
<td>Cheap</td>
<td>Expensive</td>
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<tr>
<td><strong>Availability of FDCs</strong></td>
<td><strong>Once daily-FDC</strong></td>
</tr>
<tr>
<td>Rash, hepatitis</td>
<td>CNS disturbances</td>
</tr>
<tr>
<td>Contraindicated</td>
<td><strong>Contraindicated</strong></td>
</tr>
<tr>
<td>Men with CD4&gt;400</td>
<td>pregnancy (1&lt;sup&gt;st&lt;/sup&gt; Tri)</td>
</tr>
<tr>
<td>Women with CD4&gt;250</td>
<td></td>
</tr>
<tr>
<td>Cannot be used with RMP</td>
<td><strong>Used with RMP</strong></td>
</tr>
<tr>
<td>Careful with HBV/HCV co-infection</td>
<td>Careful with pre-existing psychiatric illness</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
</tr>
<tr>
<td>CASTLE</td>
<td>883</td>
</tr>
<tr>
<td>Molina</td>
<td></td>
</tr>
<tr>
<td>2008;372:646</td>
<td></td>
</tr>
<tr>
<td>Lancet</td>
<td></td>
</tr>
<tr>
<td>KLEAN</td>
<td>877</td>
</tr>
<tr>
<td>Eron</td>
<td></td>
</tr>
<tr>
<td>2006;368:476</td>
<td></td>
</tr>
<tr>
<td>Lancet</td>
<td></td>
</tr>
<tr>
<td>GEMINI</td>
<td>337</td>
</tr>
<tr>
<td>Walmsley</td>
<td></td>
</tr>
<tr>
<td>2007 abstract</td>
<td></td>
</tr>
<tr>
<td>EACS</td>
<td></td>
</tr>
<tr>
<td>ARTEMIS</td>
<td>689</td>
</tr>
<tr>
<td>Ortiz</td>
<td></td>
</tr>
<tr>
<td>2008;22;1389</td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td></td>
</tr>
</tbody>
</table>
What to start?

**NRTI**
- Recommended
  - Tenofovir
- Alternative
  - Zidovudine
  - Abacavir
  - Didanosine

**NRTI**
- Lamivudine
- Emtricitabine

**NNRTI/PI**
- Efavirenz
- Atazanavir/r
- Darunavir/r
- Raltegravir

YRG.CARE
Favors Arm 1B
ddI + FTC + ATV

Favors Arm 1A
ZDV/3TC + EFV

Primary Endpoint

Virologic Failure

AIDS Progression

Death

Hazard Ratio (+/- 99.8% CI)

ACTG 5175-IAC-2008, Mexico
Raltegravir (RAL)-based Therapy Demonstrates Superior Virologic Suppression and Immunologic Response Compared with Efavirenz (EFV)-based Therapy, with a Favorable Metabolic Profile, Through 4 Years in Treatment-naïve Patients: 192 Week Results from STARTMRK

Enrolled Patients Randomized 1:1 To RAL:EFV Arms

281 Patients Treated with RAL + TDF/FTC
- 58 Patients (20.6%) Discontinued
  - 5 – lack of efficacy
  - 13 – AEs
  - 8 – lost to follow-up
  - 32 – miscellaneous
- 223 Patients (79.4%) Completed 192 Weeks

282 Patients Treated with EFV + TDF/FTC
- 85 Patients (29.9%) Discontinued
  - 8 – lack of efficacy
  - 26 – AEs
  - 17 – lost to follow-up
  - 34 – miscellaneous
- 197 Patients (69.9%) Completed 192 Weeks
Proportion (%) of Patients (95% CI) with HIV RNA < 50 copies/mL (Non-Completer = Failure)

\[ \Delta (RAL-EFV) \ [95\%\ CI] = +9.0 \ [1.6, 16.4] \]

Non-Inferiority p-Value < 0.001
The change from baseline in the Total CHOL:HDL-C ratio was -0.17 for the RAL group and 0.02 for EFV group (p=0.177).

† Last Observation Carried Forward approach. If patients initiated lipid-lowering therapy, last available lipid values prior to the use of lipid-lowering therapy were used in the analysis.
What ART to start (Preferred/Recommended)?

<table>
<thead>
<tr>
<th>US DHHS ’12</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="http://www.aidsinfo.nih.gov">www.aidsinfo.nih.gov</a></td>
<td>TDF/FTC</td>
<td>EFV</td>
<td>ATV/r</td>
<td>RAL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DRV/r</td>
<td></td>
</tr>
<tr>
<td>IAS-USA ’12</td>
<td>TDF/FTC</td>
<td>ABC/3TC</td>
<td>EFV</td>
<td>RAL</td>
</tr>
<tr>
<td>Thompson JAMA 2012:308:387</td>
<td></td>
<td></td>
<td>ATV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DRV/r</td>
<td></td>
</tr>
<tr>
<td>UK ’12</td>
<td>TDF/FTC</td>
<td>EFV</td>
<td>ATV/r</td>
<td>RAL</td>
</tr>
<tr>
<td><a href="http://www.bhiva.org">www.bhiva.org</a></td>
<td></td>
<td></td>
<td>DRV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EACS ’11</td>
<td>TDF/FTC</td>
<td>EFV NVP</td>
<td>ATV/r</td>
<td>RAL</td>
</tr>
<tr>
<td><a href="http://www.eacs.eu">www.eacs.eu</a></td>
<td>ABC/3TC</td>
<td></td>
<td>DRV/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LPV/r</td>
<td></td>
</tr>
<tr>
<td>WHO ’10</td>
<td>TDF + 3TC (or FTC)</td>
<td>EFV NVP</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td><a href="http://www.who.int/hiv/pub/arv/adult2010/en">http://www.who.int/hiv/pub/arv/adult2010/en</a></td>
<td>ZDV + 3TC (or FTC)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rilpivirine (TMC 278): Phase II

TMC278-C204: 96-Week Results

Study population: Rx-naïve, VL >5K (N=268)

HIV-1 RNA <50 copies/mL to week 96 (ITT-TLOVR algorithm)

ZDV/3TC or TDF/FTC +

Virologic responders (%; 95% CI)

CI = confidence interval

CD4+ cell count increases were higher in patients receiving MVC vs EFV (+170 vs +144)
One Pill, Once Daily

• **TDF/FTC/EFV**  Gallant NEJM 2006; Mathias JAIDS 2007
• **TDF/FTC/RPV**  Cohen Lancet 2011; Molina Lancet 2011

• **TDF/FTC/EVG/cobicistat**
  – Sax Lancet 2012; DeJesus Lancet 2012

• **GS-7340 (TDF pro-drug)/FTC/EVG/cobicistat**
• **GS-7340 (TDF pro-drug)/FTC/DRV/cobicistat**
• **ABC/3TC/DTG**
HIV-2

TDF/AZT+3TC/FTC+LPVr/DRVr

NNRTI is not active against HIV-2

Atazanavir is essentially inactive in vitro and is therefore not recommended in HIV-2

RAL/ELV- phenotypic susceptibility to the 2 available INI is similar to that observed for HIV-1

Parkin NT and Schapiro JM. Antivir Ther 2004. 9:3-12. CROI 2008 Abstract # 886
# Switching to Second-Line Treatment

**WHO Guidelines 2010**

<table>
<thead>
<tr>
<th>Clinical Failure</th>
<th>New or recurrent WHO stage 4 condition</th>
</tr>
</thead>
</table>
| Immunological Failure             | • Fall of CD4 to pre-therapy baseline or below  
|                                   | • 50% fall from the on-treatment peak value  
|                                   | • Persistent CD4 levels below 100        |
| Virological Failure               | Plasma Viral Load above 5000 copies/ml  |
Treatment Failure and Drug Resistance: Virologic, Immunologic, and Clinical Definitions
Resistance Patterns After Initial Failure of Common NRTI Backbones

- ZDV/3TC → M184V → TAMs
- d4T/3TC → M184V
- ABC/3TC → M184V → L74V, K65R
- TDF/3TC → M184V → K65R
Failure of first line regimen

d4T/ZDV + 3TC/FTC + NVP/EFV → TAMs

M184V → K103N → V106M → G190A
Failure of first line regimen

TDF/ABC/d3TC/FTC+NVP/EFV

\[ \text{TDF/ABC/d} \quad \text{dI} + \text{3TC/FTC} + \text{NVP/EFV} \]

K65R

L74V

M184V

K103N

V106M

G190A
<table>
<thead>
<tr>
<th>Nucleoside and Nucleotide Reverse Transcriptase Inhibitors</th>
<th>IAS-USA list</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multi-nRTI Resistance: 151 Complex</strong></td>
<td></td>
</tr>
<tr>
<td>M A D ▼ K</td>
<td>L T K</td>
</tr>
<tr>
<td>Multi-nRTI Resistance: 69 Insertion Complex¹</td>
<td></td>
</tr>
<tr>
<td>M E D K</td>
<td>W Y Q E K L T K</td>
</tr>
<tr>
<td>Multi-nRTI Resistance: NAMs²</td>
<td></td>
</tr>
<tr>
<td>M E D K</td>
<td>W Y Q E K L T K</td>
</tr>
<tr>
<td>Zidovudine³,⁴</td>
<td></td>
</tr>
<tr>
<td>L D N R</td>
<td>W Y Q E K L T K</td>
</tr>
<tr>
<td>Stavudine³,⁵</td>
<td></td>
</tr>
<tr>
<td>L D R N R</td>
<td>W Y Q E K L T K</td>
</tr>
<tr>
<td>Didanosine⁶,⁷</td>
<td></td>
</tr>
<tr>
<td>R V</td>
<td>M</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td></td>
</tr>
<tr>
<td>R D V</td>
<td>V</td>
</tr>
<tr>
<td>Abacavir⁸</td>
<td></td>
</tr>
<tr>
<td>R V</td>
<td>F</td>
</tr>
<tr>
<td>Lamivudine⁹,¹⁰</td>
<td></td>
</tr>
<tr>
<td>E K</td>
<td>V</td>
</tr>
<tr>
<td>Emtricitabine¹⁰</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>V</td>
</tr>
<tr>
<td>Tenofovir¹,¹¹</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>V</td>
</tr>
</tbody>
</table>
Second line regimen: Principles

- Three (at least 2) active drugs (triple therapy)
  - One from a new class (e.g. PI) if initial NNRTI
  - Two NRTIs in the backbone selected on basis of resistance
    - Genotypic resistance testing
    - Anticipate patterns (speculative?)
## Second-line Treatment Regimens

<table>
<thead>
<tr>
<th>d4T or ZDV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 3TC</td>
<td>+</td>
</tr>
<tr>
<td>+ NVP or EFZ</td>
<td>+ ATV/r or DRV/r or LPV/r</td>
</tr>
</tbody>
</table>

3TC or FTC

ATV/r or DRV/r or LPV/r
**ATV/r at YRG CARE Medical Centre, Chennai**

**Number of patients switched to ATV/r = 879**

<table>
<thead>
<tr>
<th>ARV regimen</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF+FTC+ATV/r</td>
<td>398</td>
<td>45</td>
</tr>
<tr>
<td>TDF+3TC+ATV/r</td>
<td>353</td>
<td>40</td>
</tr>
<tr>
<td>AZT+3TC+ATV/r</td>
<td>85</td>
<td>10</td>
</tr>
<tr>
<td>ABC+3TC+ATV/r</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>33</td>
<td>4</td>
</tr>
</tbody>
</table>
Graph Showing the Median CD4 and PVL from Baseline to Month 36
ATV/r at YRG CARE Medical Centre, Chennai

No of pts developed TB at switch or during = 136

INH + Rifabutin 150mgs alt. day + ETM + PZA - 2 months

INH + Rifabutin 150mgs alt. day - 7 months

Rifabutin 150mgs once daily every day (IAS-USA 2012)
Graph showing the median CD4 and PVL among pts on ATV/r and Rifabutin from baseline to Month 12
Treatment Failure and Drug Resistance: Virologic, Immunologic, and Clinical Definitions

- **CD4 Count**
- **Viral Load**
Severe mutations following WHO immunologic failure- Chennai HIV cohort study

Total no. of patients registered for care: 10127

No. pts initiated on 1st line HAART: 3739
(AZT/d4T+3TC+NVP/EFV)
Median CD4 at HAART initiation: 69 IQ (40-125)

No. of pts switched to 2nd line: 336 (9%)
Median CD4 at switch: 144 (90-199)
Median duration on 1st line 3.7yrs (2.2-6.3)

Kumarasamy et al CID 2009; CROI 2008
79% of them had M184V, 71% had NNRTI mutations, (K103N,Y181C,G190A) 60% had TAMS, (M41L,T215Y/F,K70R,L210W,K219E/Q) 11% had Q151M 5% had K65R and 5% had L74V.

26% had 3 or more NNRTI mutations

This data clearly warns that patients with immunological failure with standard WHO criteria have severe mutations and which can jeopardize future 2nd line NRTI options and newer drugs.
DART Study: Evolution of resistance on therapy

DART virology substudy from Uganda and Zimbabwe (n=377) ZDV/3TC + TDF for 48 weeks with limited prospective laboratory monitoring

Plasma HIV RNA <1000 c/mL in 63% of patients at weeks 24 and 48
Baseline resistance in 10% of those analyzed
  NRTI, 6%
  NNRTI, 4%
Persistent viremia resulted in increasing TAMs between Weeks 24 and 48

Pillay D, et al. 14th CROI, Los Angeles 2007, #642
High-level NRTI resistance among Malawians failing 1st line HAART

d4T/AZT+3TC+NVP
CD4 and clinical monitoring
96 failed patients were genotyped
Median CD4: 68; PVL: 4.72log; Duration on ART: 36 months

93%- NNRTI mutations
81%- M184V
23%- K70E or K65R

Mina Hosseinipour, et al. IAC 2008; AIDS 2009
Sequencing Therapy in 2012 and Beyond: How Many Tries Do You Get?

2 NRTIs + 1 NNRTI

2 NRTIs + 1 PI/RTV

1 PI/RTV + Integrase/CCR5 inhibitor ± NRTIs

2nd Gen NNRTI + ENF + other CCR5 inhibitor ± PI/RTV

Maturation inhibitor + other entry inhibitor(s) + ?
Sequencing Therapy in 2012 and Beyond: How Many Tries Do You Get?

2 NRTIs + 1 NNRTI

2 NRTIs/Integrase + 1 PI/RTV

1 PI/RTV + 2\textsuperscript{nd} Gen NNRTI/CCR5 inhibitor ± NRTIs

ENF + other CCR5 inhibitor ± PI/RTV

Maturation inhibitor + other entry inhibitor(s) + ?
2nd line Trials

Secondline International Trial- Univ New South Wales

Multicenter Study of Options for SEcond-Line Effective Combination Therapy (SELECT)- ACTG 5273

EARNEST

Phase IIIb/IV, international, randomised, open label study comparing two regimens. The study will run for 96-weeks

ritonavir boosted lopinavir (LPV/r) + 2N(t)RTIs vs
II. ritonavir boosted lopinavir (LPV/r) + raltegravir
### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients on second-line Therapy (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age in yrs (SD)</td>
<td>35±9</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>Male 79 (74%), Female 28 (26%)</td>
</tr>
<tr>
<td>Mode of HIV transmission</td>
<td>Heterosexual - 97%, BT - 3%</td>
</tr>
<tr>
<td>Median CD4 cells/μL (range)</td>
<td>146 (IQR: 8-472)</td>
</tr>
<tr>
<td>Median PVL copies/mL (range)</td>
<td>76751 (IQR: 1140-1997967)</td>
</tr>
<tr>
<td>Median Period of PI exposure (Months)</td>
<td>13 (2-38)</td>
</tr>
<tr>
<td>Protease Inhibitor</td>
<td></td>
</tr>
<tr>
<td>ATV/r</td>
<td>51%</td>
</tr>
<tr>
<td>IDV/r</td>
<td>46%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>3%</td>
</tr>
</tbody>
</table>

- **TDF/FTC (55%)** was the main NRTI backbone followed by DDI/3TC (24%) and AZT or d4T/3TC (21%).

- Of the 107 patients, **45 (42%)** had detectable PVL (> 1000 copies/mL) and were genotyped.
- Twelve (26.6%) patients had any one of DRV resistance mutation, of which G73S observed in 8 (17.7%), I84V in 2 (4.4%), and each one (2.2%) of L33F, L76V and L89V and none had >3 DRV mutations.

- Darunavir (sensitivity 96%) was the least affected PI by the presence of PR mutations followed by tripanavir (sensitivity 51%) and Lopinavir (44%).

- Of the 17 patients on ATV/r, 8 (47%) developed resistance to LPV.

Saravanan et al., CROI 2010; CID 2012
CONCLUSION

Our data showed a high proportion (53%) of triple-class resistance to NRTI, NNRTI and PI. With less ARV options for subsequent therapy, DRV might be the choice for third line regimens in India but patients who are failing ATV/r could be benefitted with LPV/r if resistance testing is available.
Sequencing Therapy in 2012 and Beyond: How Many Tries Do You Get?

2 NRTIs + 1 NNRTI
2 NRTIs + 1 PI/RTV
1 PI/RTV + Integrase/CCR5 inhibitor ± NRTIs
2nd Gen NNRTI + ENF + other CCR5 inhibitor ± PI/RTV
Maturation inhibitor + other entry inhibitor(s) + ?
POWER 1 and 2: VL < 50 c/mL at Week 48 (ITT-TLOVR)

Effect of Baseline Resistance on Response to DRV

- 11 mutations associated with reduced response

- Baseline fold-change strongest predictor of Week 24 response

Response to HAART

RNA

Ideal Response

RNA

Common Response
Sequencing Therapy in 2012 and Beyond: How Many Tries Do You Get?

2 NRTIs + 1 NNRTI

2 NRTIs + 1 PI/RTV

1 PI/RTV + Integrase/CCR5 inhibitor ± NRTIs

2nd Gen NNRTI + ENF + other CCR5 inhibitor ± PI/RTV

Maturation inhibitor +
other entry inhibitor(s) + ?
HIV Disease/AIDS is

Yet another Chronic Manageable Disease
>18,000 patients registered for care
  - >10,000 patients on HAART

VCT
(OPD, Acute care inpatient facility, adherence/couple/family counseling, Nutritional Counseling, Pharmacy)

AIDS Clinical Trials Group (ACTG)/NIH
HIV Prevention Trial Network (HPTN)/NIH

Brown University-RI, UCSD-California, Johns Hopkins Univ-MD, UCSF-California, Harvard Univ-MA, Emory Univ-Atlanta, Stanford Univ-California, Treat Asia-amFar, Kirby Inst-UNSW, McFarlane Inst, Karolinska Inst-Sweden.
Chennai ART Symposium

ART 2012

Scientific Program

Date:
January 21st & 22nd, 2012

Venue:
Hotel GRT Grand Days,
Southern Crown, T.Nagar
Chennai

In Collaboration with

CFAR
CENTER FOR AIDS RESEARCH
Lifespan/Tufts/Brown

BROWN

NATIONAL INSTITUTES
OF HEALTH

UNIVERSITY OF CALIFORNIA
SAN DIEGO
SCHOOL OF MEDICINE

HIV Medicine Association
of India

Organized by

YRG.CARE

YRG.CARE Medical Centre
YRG Centre for AIDS Research and Education
Voluntary Health Services, Chennai, INDIA

CART 2013
Feb 9th, 10th
Collaborators

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Charles Carpenter
Kartik Venkatesh
Susan Cu Uvin
Bharat Ramratnam
Rami Kantor
Karen Tashima

Harvard University
Kenneth Freedberg
Rochele Walensky
Kenneth Mayer

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Steve Safren
Marcy, Rodney

Stanford University
David Katzenstein

UCSF
Joel Palefsky
Maria Ekstrand
Kirby Inst-UNSW
David Cooper
Mathew Law

UCSD
Constance Benson
Robert Schooley
Davey Smith
Scot Letendre
Ajay Bharati

Tufts University
Christine Wanke

Rush University
Alan Landay

Emory Univ
Amara Rao
Carlos Del Rio
Univ of W. Australia
Martyn French

McFarlane,Melbourne
Suzzane Crowe

Johns Hopkins Univ
David Celentano
Shruti Mehta

Karolinska,Sweden
Vinod Diwan

NIH, ACTG, HPTN, EU, amfAR/TA, GFATM, USAID, Gates Foundation, ICMR