Highlights of AIDS 2012
CCO Official Conference Coverage
of the XIX International AIDS Conference

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Guidelines

• Context
  – Ever evolving, often with significant changes in practice
  – Raises the question of how best GL should be reviewed and revised; published, disseminated and adopted
When to start

- Still no RCT supporting when to start in the higher CD4 count strata
- Previous concerns regarding early treatment initiation were largely driven by drug related issues [(cost), toxicity, resistance, limiting future options]
- Drugs no longer the limiting factor
  - now more tolerable, convenient, potent
  - broader range;
  - monitoring strategies to support multiple lines of ART available
- Early ART initiation associated with better outcomes – mortality, morbidity, tolerability of treatment, less resistance, public health benefit
- Higher CD4 counts on ART with suppressed viral load associated with better outcomes
DHHS Guidelines, March 2012: When to Start

- Antiretroviral therapy recommended for all HIV-infected patients; *strength* of recommendation varies according to CD4+ cell count or condition

<table>
<thead>
<tr>
<th>CD4+ Cell Count or Clinical Condition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 + count &lt; 350 cells/mm³ (AI)</td>
<td></td>
</tr>
<tr>
<td>CD4 + count 350-500 cells/mm³ (AII)</td>
<td></td>
</tr>
<tr>
<td>CD4 + count &gt; 500 cells/mm³ (BIII)</td>
<td></td>
</tr>
<tr>
<td>History of AIDS-defining illness (AI)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy (AI)</td>
<td></td>
</tr>
<tr>
<td>HIV-associated nephropathy (AII)</td>
<td></td>
</tr>
<tr>
<td>HBV co-infection (AII)</td>
<td></td>
</tr>
<tr>
<td>TB co-infection</td>
<td></td>
</tr>
<tr>
<td>At risk of transmitting HIV to sexual partners (AI, heterosexuals; AIII, others)</td>
<td></td>
</tr>
</tbody>
</table>
Median baseline CD4 and 5-year survival (AIDSRelief Global)

<table>
<thead>
<tr>
<th>Country</th>
<th>Median Baseline CD4+ Cell Count, cells/mm³</th>
<th>5-Yr Survival Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>134</td>
<td>0.56*</td>
</tr>
<tr>
<td>Tanzania</td>
<td>135</td>
<td>0.56</td>
</tr>
<tr>
<td>Guyana</td>
<td>191</td>
<td>0.71</td>
</tr>
<tr>
<td>Kenya</td>
<td><strong>195</strong></td>
<td><strong>0.71</strong></td>
</tr>
<tr>
<td>Uganda</td>
<td>204</td>
<td>0.57</td>
</tr>
<tr>
<td>Nigeria</td>
<td>212</td>
<td>0.57</td>
</tr>
<tr>
<td>Rwanda</td>
<td>259</td>
<td>0.85†</td>
</tr>
</tbody>
</table>

*At 48 months. †At approximately 52 months.

# IAS-USA Guidelines, July 2012: What to Start

## Recommended Regimens

<table>
<thead>
<tr>
<th>Type</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI based</td>
<td>EFV/TDF/FTC or EFV + ABC/3TC*†</td>
</tr>
<tr>
<td>Boosted PI based</td>
<td>ATV/RTV + TDF/FTC or ATV/RTV + ABC/3TC*†</td>
</tr>
<tr>
<td></td>
<td>DRV/RTV + TDF/FTC</td>
</tr>
<tr>
<td>INSTI based</td>
<td>RAL + TDF/FTC</td>
</tr>
</tbody>
</table>

## Alternative Regimens‡

<table>
<thead>
<tr>
<th>Type</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI based</td>
<td>NVP + TDF/FTC or NVP + ABC/3TC*†</td>
</tr>
<tr>
<td></td>
<td>RPV/TDF/FTC or RPV + ABC/3TC*†</td>
</tr>
<tr>
<td>Boosted PI based</td>
<td>DRV/RTV + ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>LPV/RTV† + TDF/FTC or LPV/RTV† + ABC/3TC*†</td>
</tr>
<tr>
<td>INSTI based</td>
<td>RAL + ABC/3TC†</td>
</tr>
<tr>
<td></td>
<td>EVG/COBI/TDF/FTC</td>
</tr>
</tbody>
</table>

*HLA-B*5701 screening is recommended before ABC administration to reduce the risk of hypersensitivity reaction.

†Avoiding the use of ABC or LPV/RTV might be considered for pts with or at high risk of cardiovascular disease.

‡ZDV/3TC is an alternative NRTI component of NNRTI-, PI/RTV-, and RAL-based regimens, but toxicity profile of ZDV reduces its utility.

Epidemiology
CDC: Differences in Continuum of Care in HIV-Infected Patients

- CDC study shows that only ~ 25% of US patients with HIV have suppressed HIV-1 RNA
- Study further evaluated continuum of care in US by sex, age, race, and transmission category
- Individuals 25-34 yrs of age less engaged in each stage of care compared with all older age groups

![Bar chart showing percentages of patients in different stages of care: 82% diagnosed, 66% linked to care, 37% retained in care, 33% prescribed ART, 25% viral suppression.](image)
Laboratory monitoring
Context

• Which tests and at what frequency?
  – Patient outcomes in relation to laboratory monitoring
    • DART trial suggests routine lab monitoring associated with a higher mortality after 2 years
    • Modeling studies do not show value of added viral load to routine patient care
  
• What to do with viral load results that are detectable but not >200/1000
Frequent CD4+ count monitoring not necessary for patients with CD4+ > 300

- Retrospective review of VA laboratory database of > 25,000 paired VL and CD4+ counts from 1821 unique pts (1998-2011)
- Eligible pts had “sequences”: consecutive VL/CD4+ pairs with
  - VL < 200 copies/mL
  - CD4+ count > 200 cells/mm³
  - %CD4+ > 14
  - < 390 days between CD4+ counts
- Analysis of pts with sequences (n = 846) who experienced CD4+ “dips” < 200 during periods of virologic suppression (n = 61)
  - 24 with clinical causes of lymphopenia
- Virologically suppressed pts with CD4+ > 300 extremely unlikely to have CD4+ count dip < 200
- CD4+ testing may be undertaken less frequently in these pts

Low-level viremia not associated with short-term risk of virologic failure

• Retrospective study of 656 pts at 1 institution
  – Stable ART for ≥ 6 mo
  – ≥ 3 VL tests in 1 yr (“inclusion period”), all < 50 copies/mL
  – ≥ 3 VL tests in following 12 mo

• Comparison of virologic outcomes among 2 groups of pts:
  – LLV- : No low-level viremia during follow-up; VL consistently < 20 copies/mL
  – LLV+: VL 20-50 copies/mL on ≥ 2 occasions

• During follow-up, no difference in frequency of VF between LLV- and LLV+ groups
  – 4% vs 8%, respectively (P = 0.32)

• ART regimens did not differ between LLV- and LLV+ groups

<table>
<thead>
<tr>
<th></th>
<th>LLV- (n = 413)</th>
<th>LLV+ (n = 25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All VL &lt; 20,%</td>
<td>65</td>
<td>44</td>
<td>.053</td>
</tr>
<tr>
<td>VL 20-50 on ≥ 2 occasions, %</td>
<td>2</td>
<td>16</td>
<td>.002</td>
</tr>
<tr>
<td>2 consecutive VL &gt; 50, %</td>
<td>4</td>
<td>8</td>
<td>.320</td>
</tr>
</tbody>
</table>

Antiretroviral Drugs
Context

• Need for new drugs
  – Convenience
  – Tolerability/toxicity
    • Metabolic/cardiovascular
  – Resistance and options
    • Acquired drug resistance
  – Co-morbid conditions (TB)
  – Pregnancy

• Need for new strategies
  – Tolerability
  – Simplification
  – Resistance (pre-existing)
Cobicistat-boosted vs Ritonavir-boosted Atazanavir in ART-naïve patients

- Randomized, multicenter, placebo-controlled phase III trial
  - Primary endpoint: VL < 50 c/mL at Wk 48 (FDA snapshot analysis)

Stratification by HIV-1 RNA ≤ vs > 100,000 copies/mL

Wk 48
Primary endpoint

Atazanavir/Cobicistat* + Tenofovir/Emtricitabine (n = 344)

Atazanavir/Ritonavir† + Tenofovir/Emtricitabine (n = 348)

ATV/COBI vs ATV/RTV: non-inferior virologic suppression at 48 weeks

- CD4+ count gain: +213 with ATV/COBI vs +219 with ATV/RTV
- Among 24 pts with suboptimal virologic response and genotype: no primary PI or TDF resistance; M184V/I in 2 pts in COBI arm, 0 in RTV arm

Elvitegravir/Cobicistat/TDF/FTC vs EFV/TDF/FTC: subgroup responses

- Randomized, double-blind phase III trial (N = 700)\(^1,2\)
  - Primary endpoint results: EVG/COBI/TDF/FTC noninferior to EFV/TDF/FTC at Wk 48\(^2\)

\[\Delta-3.6\% \quad P = .15 \quad P = .47 \quad P = .68 \quad P = .40 \quad P = .68 \quad P = .039\]

Elvitegravir/Cobicistat/TDF/FTC vs ATV/RTV + TDF/FTC: subgroup responses

- Randomized, double-blind phase III trial (N = 708)\cite{1,2}
  - Primary endpoint results: EVG/COBI/TDF/FTC noninferior to ATV/RTV + TDF/FTC at Wk 48\cite{2}


Graphic reproduced with permission.
SPRING-2: Dolutegravir QD vs Raltegravir BD in ART-naive patients at 48 weeks

- Randomized, double-blind, placebo-controlled phase III trial
  - Primary endpoint: VL < 50 c/mL at Wk 48 (FDA snapshot analysis)

**Stratified by screening HIV-1 RNA**
- ≤ vs > 100,000 copies/mL
- and NRTI backbone

**Wk 48**
- Primary endpoint

**Wk 96**

Antiretroviral-naive pts,
- VL ≥ 1000 c/mL
- (N = 822)

**Dolutegravir 50 mg QD + 2 NRTIs* (n = 411)**

**Raltegravir 400 mg BID + 2 NRTIs* (n = 411)**

*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

SPRING-2: Dolutegravir non-inferior to Raltegravir at 48 weeks

Per protocol response: 90% (DTG) vs 88% (RAL) by snapshot analysis; Δ 1.6% (95% CI: -2.7% to 5.9%)

- No significant differences between arms in virologic response by baseline VL or NRTI backbone
- CD4+ gain of +230 cells/mm³ from BL in both arms

STARTMRK: final 5-yr phase III results of Efavirenz vs Raltegravir in ART-naive patients

- At week 240 analysis, RAL superior to EFV by VL < 50 c/mL (ITT, NC = F)
- CD4+ gain: +374 (RAL) vs +312 (EFV)
- Generally consistent virologic and immunologic effects in various demographic and prognostic subgroups (eg, baseline CD4+/VL, age, sex, race, etc)
- Low levels of genotypic resistance among patients with VF and VL > 400 c/mL in both arms
  - RAL, n = 7; EFV, n = 12
- Fewer pts with drug-related adverse events in RAL arm
- Significantly smaller increases in TC, HDL-C, LDL-C, and TG levels with RAL vs EFV

SPIRIT: switch to RPV/TDF/FTC from boosted-PI regimens in suppressed Pts

- Multicenter, randomized, open-label switch study
  - Primary endpoint: maintenance of VL < 50 c/mL at Wk 24 (FDA snapshot analysis)

Rilpivirine/Tenofovir/Emtricitabine (n = 317)

Ritonavir-Boosted PI* + 2 NRTIs
(n = 159)

Rilpivirine/ Tenofovir/Emtricitabine
(n = 159)

Pts with VL < 50 c/mL on stable ritonavir-boosted PI + 2 NRTIs for ≥ 6 mos, no previous NNRTI use (N = 476)

PIs: ATV/RTV, 37%; LPV/RTV, 33%; DRV/RTV, 20%; FPV/RTV, 8%; SQV/RTV, 2%.

SPIRIT: switch to RPV/TDF/FTC non-inferior to continued boosted PI

- Switch to RPV/TDF/FTC non-inferior to maintaining boosted-PI regimen at week 24
  - 93.7% vs 89.9% with VL < 50 c/mL
  - Non-inferiority observed regardless of pre-ART VL

- All 17 pts with baseline K103N who switched to RPV/TDF/FTC maintained virologic suppression

- Improved lipid profile and in 10-yr Framingham score ($P = .001$) at week 24 among RPV/TDF/FTC switch patients

*Excludes 23 RPV and 14 boosted PI pts lacking baseline VL while ARV naive.

Treatment as prevention/PREP
HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

### Immediate ART
- Initiate ART at CD4+ cell count 350-550 cells/mm³ (n = 886 couples)

### Delayed ART
- Initiate ART at CD4+ cell count ≤ 250 cells/mm³* (n = 877 couples)
  - *Based on 2 consecutive values ≤ 250 cells/mm³.

**Participants:**
- HIV-infected, sexually active serodiscordant couples;
- CD4+ cell count of the infected partner: 350-550 cells/mm³ (N = 1763 couples)

**Endpoints:**
- **Primary efficacy endpoint:** virologically linked HIV transmission
- **Primary clinical endpoints:** WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- **Couples received intensive counseling on risk reduction and use of condoms**

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**References:**
HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

Total HIV-1 Transmission Events: 39 (4 in immediate arm and 35 in delayed arm; $P < .0001$)

Linked Transmissions: 28

Delayed Arm: 27

Immediate Arm: 1

Unlinked or TBD Transmissions: 11

Single transmission in patient in immediate ART arm believed to have occurred close to time therapy began and prior to HIV-1 RNA suppression

$P < .001$

HPTN 052: decrease in AIDS-related events in immediate vs delayed ART arms

Subjects Experiencing ≥ 1 AIDS-Related Event

<table>
<thead>
<tr>
<th>Event</th>
<th>Delayed</th>
<th>Immediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis, n (%)</td>
<td>34 (4)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Serious bacterial infection, n (%)</td>
<td>13 (1)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>WHO stage 4 event, n (%)</td>
<td>19 (2)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Esophageal candidiasis, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cervical carcinoma, n</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cryptococcosis, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HIV-related encephalopathy, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Herpes simplex (chronic), n</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma, n</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CNS lymphoma, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Pneumocystis</em> pneumonia, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HIV wasting, n</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bacterial pneumonia, n</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Non-AIDS events infrequent, with similar numbers of events in each arm

HPTN-052: Decrease in self-reported risk behavior over study duration

- As part of HPTN-052, all participants received extensive risk counseling, condoms, and STD testing and treatment\(^1\)
  - Recounseled at every 3-mo visit
- Substudy assessed time trends of risk behaviors and compared the change between the 2 treatment arms, adjusting for baseline characteristics including sex, region, substance use, and HIV-1 RNA level\(^2\)
- Heterosexual pts with detectable VL and having unprotected sex at 24 mos
  - Immediate arm: 1%; delayed 3%

HPTN-052: Cost-effectiveness of early vs delayed ART in South Africa and India

- Cost-effectiveness* model using HPTN-052 data on transmission and clinical and resource utilization data from South Africa and India†
- In South Africa, early ART projected to increase survival, decrease transmission events, and be cost saving at 5 yrs and very cost-effective on lifetime horizon
- In India, early ART also projected to increase survival, dramatically decrease HIV transmissions, and be cost-effective at 5 yrs and very cost-effective on lifetime horizon

*WHO thresholds: very cost-effective: < 1 x per capita GDP; cost-effective: < 3 x per capita GDP.
†Assumptions: mean CD4+ cell count 449 cells/mm³; HIV-1 RNA suppression at Wk 48: 92%; lost to follow-up: 3.4 per 100 pt-yrs; average partners: 1.011/mo; transmission rate: 0.103-1.483/100 pt-yrs; GDP South Africa: US$8100; India: US$1400.

Vaccines
HPV Vaccine in HIV infected patients

• Context
  – Risk of cervical dysplasia and cervical cancer high in HIV infected women, regardless of ART or immunologic status
  – Cervical cancer number one cancer in HIV+ women
  – HPV vaccine increasingly available in RLS
  – There has been no evidence to support the use of HPV vaccine in this population
  – Herspes zoster still a significant cause of morbidity in PLHA
Immunogenicity of HPV Vaccine in HIV-Infected Women

- Open-label, 48-wk phase II trial in HIV+ women, age 16-23 yrs (n = 99)
  - Group A: ART naive or no ART for ≥ 6 mos
  - Group B: on ART for ≥ 6 mos, with 2 VL < 400 c/mL
  - Historical controls: HIV- women aged 16-23 yrs (n = 267)
- All pts received quadrivalent HPV vaccine at vaccine at Day 1, wk 8, and wk 24, then followed for 24 wks
- No AEs > grade 3 evaluated as related to vaccine

Seroconversion at Wk 48 (%)

ACTG 5240: HPV Vaccine in HIV-Infected Women

- Open-label phase II trial in HIV+ women age 13-45 yrs (n = 319) from US, Brazil, and South Africa
  - Stratum A: CD4+ > 350 (n = 130)
  - Stratum B: CD4+ 200-350 (n = 95)
  - Stratum C: CD4+ ≤ 200 (n = 94)
- All pts received quadrivalent HPV vaccine at Day 1, Wk 8, and Wk 24
  - Titers assessed 4 wks after last dose
- High rates of seroconversion at Wk 28 in Strata A and B who were seronegative at BL*

<table>
<thead>
<tr>
<th>Seroconversion, %</th>
<th>Stratum A</th>
<th>Stratum B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-6</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(n = 50)</td>
<td>(n = 48)</td>
</tr>
<tr>
<td>HPV-11</td>
<td>97.6</td>
<td>98.3</td>
</tr>
<tr>
<td></td>
<td>(n = 82)</td>
<td>(n = 58)</td>
</tr>
<tr>
<td>HPV-16</td>
<td>98.4</td>
<td>98.2</td>
</tr>
<tr>
<td></td>
<td>(n = 64)</td>
<td>(n = 55)</td>
</tr>
<tr>
<td>HPV-18</td>
<td>90.7</td>
<td>84.3</td>
</tr>
<tr>
<td></td>
<td>(n = 75)</td>
<td>(n = 70)</td>
</tr>
</tbody>
</table>

*Stratum C not reported.

- 3 subjects with grade 3 or higher AEs possibly related to vaccine
  - 1 each with chest pain, back pain, rash

ACTG A5247: Herpes zoster live vaccine in HIV-infected patients on stable ART

Stratified by CD4+ cell count (< vs ≥ 350 cells/mm³)

HIV-infected pts on stable ART with HIV-1 RNA < 75 copies/mL, CD4+ cell count ≥ 200 cells/mm³, VZV seropositive or previous VZV/herpes zoster (N = 392)

Day 0 dose 1*

Wk 6 dose 2*

Wk 24

Follow-up

Herpes Zoster Live Vaccine (n = 295)

Placebo Vaccination (n = 97)

*Vaccination delayed in persons with CD4+ cell count < 160 cells/mm³, HIV-1 RNA > 5000 copies/mL, or contraindication

• Primary endpoint: ICH-defined SAE or NIAID Division of AIDS grade 3/4 signs, symptoms, or AEs within 6 wks of vaccine dose

Secondary endpoints

– VZV antibody titer 6 wks after vaccine dose

– VZV-specific cell-mediated immune response in first 40 patients in each CD4+ cell count subgroup

ACTG A5247: immunogenicity of herpes zoster live vaccine in HIV-infected patients


VZV Antibody Levels by gpELISA

Low CD4+ Stratum (< 350 cells/mm³)

High CD4+ Stratum (≥ 350 cells/mm³)

Tuberculosis
Context

• Little or no reduction in incident TB in many countries including Kenya
• Limited use of IPT
  – IPT effective, but impact limited to the duration of IPT
• In implementing IPT who should get it and for how long?
• Co-management of HIV and TB: which ARV drugs?
• Lack of new drugs in a long time
• M/XDR TB
Isoniazid Preventive Therapy in HIV-infected patients with latent TB

- Randomized, double-blind, placebo-controlled trial in Khayelitsha, Cape Town, South Africa
  - Primary endpoint: incident TB (definite, probable, or possible)

HIV-1-infected patients on established ART or initiating ART (N = 1329)*

- Isoniazid 5 mg/kg/day† (n = 662)
- Placebo (n = 667)

Yr 1

Pts followed for 1-3 additional yrs

*40 additional pts randomized but excluded from analysis due to presence of culture-positive TB (n = 39) or failure to receive study drug (n = 1).
†Maximum of 300 mg; co-administered with pyridoxine.

Isoniazid Preventive Therapy reduces incidence of TB in patients on ART

• 95 TB cases observed, resulting in overall TB rate of 2.9/100 patient-years
• 37% lower rate of incident TB in INH arm vs placebo
  – 2.3 vs 3.6/100 pt-yrs \( (P = .03) \)
• No significant difference in mortality
  • 0.9 vs 1.2 /100 pt-yrs \( (P = .32) \)
• More patients receiving INH stopped study therapy due to grade \( \geq 3 \) increase in ALT
  – 2.9% vs 1.3% \( (P = .05) \)

ANRS REFLATE: EFV- vs RAL-based ART in HIV/TB co-infected patients

- Multicenter, randomized, open-label phase II trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

**Wk 24**

Primary endpoint

- **Raltegravir 400 mg BID + Tenofovir + Lamivudine** (n = 51)
- **Raltegravir 800 mg BID + Tenofovir + Lamivudine** (n = 51)
- **Efavirenz + Tenofovir + Lamivudine** (n = 52)

**Wk 48**

- **Raltegravir 400 mg BID + Tenofovir + Lamivudine**

**ART-naive co-infected patients initiating rifampin-containing TB treatment** (N = 154)

*Rifampin-containing therapy initiated before ART and consisted of rifampin, isoniazid, pyrazinamide, and ethambutol for 2 mos, followed by rifampin and isoniazid for 4 mos.*
Virologic Failure at Wk 24
RAL 400 (n = 51)  
RAL 800 (n = 51)  
EFV (n = 51)

VL > 50 c/mL, n (%) 12 (24) 4 (8) 15 (29)

REFLATE: virologic suppression at week 24 by ART regimen
REFLATE: adverse events through week 24

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>RAL 400 mg (n = 51)</th>
<th>RAL 800 mg (n = 51)</th>
<th>EFV (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE ≥ grade 2, n (%)</td>
<td>37 (73)</td>
<td>37 (73)</td>
<td>39 (76)</td>
</tr>
<tr>
<td>Grade 3 or 4 clinical AE, n (%)</td>
<td>11 (22)</td>
<td>12 (22)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>AE leading to drug discontinuation, n</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hepatotoxicity*</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cutaneous rash</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade 3 or 4 IRIS, n</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>AIDS-defining events, n (%)</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Death,† n (%)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

*Both related to TB drugs: fulminant hepatitis with liver transplant in 1 patient
†Causes of death: EFV arm: 1 TB meningitis Wk4, 1 sepsis related to TB Wk6; RAL 800 arm: 1 unknown Wk2, 1 TB meningitis Wk12
HIV/TB co-management

- In summary, these results provide confidence to move forward to a larger phase III study to define the best ARV regimen to combine with TB treatment.
- This study does not provide guidance on which ARV regimen to use in combination with TB therapy.
Early bactericidal activity of Sutezolid (PNU-100480) in HIV+/- patients with TB

- South African (2 centers), open-label phase IIa trial
  - Sutezolid, an oxazolidinone antimicrobial

**Day 14**

- Sutezolid 600 mg BID (n = 25)
- Sutezolid 1200 mg QD (n = 25)
- Isoniazid/Rifampin/Ethambutol/Pyrazinamide (HREZ) (n = 9)

Early bactericidal activity of Sutezolid

- Significant log CFU reductions with both sutezolid regimens during the 14-day treatment period
  - 600 mg BID: -0.09 log/day (90% CI: -0.06 to -0.11)
  - 1200 mg QD: -0.07 log/day (90% CI: -0.04 to -0.09)
  - Trend toward superior response with BID dosing
- Both dosing schedules generally safe and relatively well tolerated
  - 7/50 sutezolid-treated pts experienced ALT increases to 2-3 ULN

Early bactericidal activity of novel combinations of TB drugs

- Phase IIa trial in TB-infected pts

HIV- or HIV+ pts* with newly diagnosed pulmonary smear and culture positive drug sensitive TB (N = 85)

Diagonals:
- Bedaquiline (TMC 207) (n = 15)
- Bedaquiline + Pyrazinamide (n = 15)
- Bedaquiline + PA-824 (n = 15)
- PA-824 + Pyrazinamide (n = 15)
- PA-824 + Pyrazinamide + Moxifloxacin (n = 15)
- Isoniazid/Rifampicin/Ethambutol/Pyrazinamide (HREZ) (n = 10)

6 HIV+ subjects

Early bactericidal activity of novel TB regimes

TB: new drugs

• The 2-drug regimens demonstrated comparable activity to the current standard 4-drug regimen used to treat TB
• The 3-drug regimen of PA-824/pyrazinamide/moxifloxacin yielded the best bactericidal activity of all the regimens assessed.
• These exciting data support the move into planned phase IIb studies for the PA-824/pyrazinamide/moxifloxacin regimen.
• The findings also support the move toward combination therapy for drug-resistant tuberculosis.