CROI 2012 – New Frontiers

TM Rossouw
Outline

- When to start?
- What to start with?
- Any new drugs?
- Long-term complications
- Prevention
- Basic science
When to Start?

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

Delayed ART
NA-ACCORD: Early vs Deferred ART

Risk of Death With Deferral of ART*

<table>
<thead>
<tr>
<th>CD4+ Cell Count</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>351-500</td>
<td>1.69 (1.26-2.26)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>&gt;500</td>
<td>1.94 (1.37-2.79)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

- Study controlled for sex, age, and BL CD4+ cell counts
- HIV-1 RNA response similar in early vs deferred arms
- Results similar when IDUs excluded
- Limitations: observational study with potential for unmeasured confounding

*Without inclusion of HIV-1 RNA data.

HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

- HIV-infected, sexually active serodiscordant couples; infected partner CD4+ cell count of 350-550
  (N = 1763 couples)

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

Delayed ART
Initiate ART at CD4+ cell count ≤ 250*
(n = 877 couples)

- Primary efficacy endpoint: virologically linked HIV transmission
  Based on 2 consecutive values of ≤ 250 cells/mm³.

- 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.

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

Unlinked or TBD Transmissions: 11

Immediate Arm: 1

Delayed Arm: 27

Single transmission in patient in immediate ART - close to initiation & prior to suppression of HIV-1 RNA

$P < .001$

DSMB recommended release of results as soon as possible following 4/28/11 review; follow-up continues but all HIV-positive partners offered ART after release of results.

Benefit To The Individual?

- No direct evidence
  - Waiting for data from START trial (initiate ART at CD4 350 vs. >500)

- Indirect evidence mounting
  - SMART and ESPRIT control groups
    - SMART CD4>350
    - ESPRIT CD4>300
  - Main results: Mortality rate among virologically suppressed ART-treated subjects with CD4 > 350
### SMART & ESPRIT

<table>
<thead>
<tr>
<th>Overall</th>
<th>Most recent eligible CD4 count (cells/uL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>350-499</td>
</tr>
<tr>
<td><strong>Person-years of follow-up</strong></td>
<td>12357 (100%)</td>
</tr>
<tr>
<td><strong>Observed deaths</strong></td>
<td>62</td>
</tr>
<tr>
<td><strong>Expected deaths</strong></td>
<td>49.82</td>
</tr>
<tr>
<td><strong>SMR</strong></td>
<td>1.24 (0.95-1.59)</td>
</tr>
</tbody>
</table>

Mortality rate standardised by age, sex and country

Rodger et al. Paper 638 CROI 2012:
## Association Between Current CD4+ Cell Count and Non-AIDS Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-AIDS Cancer/Death</th>
<th>Renal Disease/Death</th>
<th>CVD Events/Death</th>
<th>Liver Disease/Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td>Yes</td>
<td>Yes</td>
<td>Trend</td>
<td>No</td>
</tr>
<tr>
<td>D:A:D</td>
<td>Yes</td>
<td>Yes</td>
<td>Trend</td>
<td>Yes</td>
</tr>
<tr>
<td>CASCADE</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SMART</td>
<td>Trend</td>
<td>Trend</td>
<td>Trend</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Association of CD4+ Cell Count Nadir With Clinical Outcomes

- Low CD4+ count nadir associated with
  - Increased rates of HIV-associated neurocognitive disorders[1]
  - Arterial stiffness contributing to CV risk[2]
  - Coronary heart disease [3]
  - Increased risk of fracture[4]

Inflammatory Markers in Treatment Interruption Studies

- INSIGHT/SMART study group: nested case-control study of pts who died from any cause classified as early deaths (≤ 2 yrs after randomization,  n = 95) or late deaths (> 2 yrs, n = 71)

![Graph showing OR of Death (95% CI) for hsCRP, IL-6, and D-dimer in early and late deaths.](image-url)
When to Start Therapy: Balance Now Favours Earlier ART

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

- ↑ potency, durability, simplicity, safety of current regimens
- ↓ emergence of resistance
- ↓ toxicity with earlier therapy
- ↑ subsequent treatment options
- Risk of uncontrolled viremia at all CD4+ cell count levels
- ↓ transmission

Delayed ART

Early ART
When Do We Start?

- Starting CD4s have improved dramatically since 2002
- USA only country where average starting CD4 is > 300
- San Francisco policy of recommending ART for all with HIV as a public health measure has substantially raised the CD4 at treatment initiation in that city – model to follow for SA?
  - But pts initiating ART at CD4+ counts > 350 cells/mm³ significantly more likely to be white, older, MSM, nonpoor, and diagnosed by private provider[2]
- Even so, only 44% of patients diagnosed with HIV in the USA are receiving care

Patients Starting ART at Higher CD4+ Cell Counts Overall, but Disparities Remain

- CD4+ cell count at start of ART (cells/mm³), 2009[1]

What To Start With?

EFV

ATV/RTV

TDF/FTC +

_DRV/RTV

RAL

STARTMRK: RAL vs EFV in ART-Naive Patients, 192-Wk Data

- Randomized phase III trial; double-blind through follow-up

Δ (RAL-EFV) = +9.0 (95% CI: 1.6-16.4; noninferiority $P < .001$)

ECHO, THRIVE: Rilpivirine vs EFV in ART-Naive Patients

- Randomized, double-blind phase III trials

Stratified by BL HIV-1 RNA < 100,000 vs ≥ 100,000, NRTI use*

**Wk 48 primary analysis**
- RPV 25 mg QD + TDF/FTC (n = 346)
- EFV + TDF/FTC (n = 344)

**Wk 96 final analysis**
- RPV 25 mg QD + 2 NRTIs† (n = 340)
- EFV + 2 NRTIs† (n = 338)

*THRIVE only. †Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.

ECHO/THRIVE: HIV-1 RNA < 50 c/mL at Wk 96

HIV-1 RNA < 50 c/mL, %

- **RPV 25 mg QD (n = 686)**
  - Week 0: 80%
  - Week 96: 84%

- **EFV 600 mg QD (n = 682)**
  - Week 0: 82%
  - Week 96: 78%

ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients: Results by VL

HIV-1 RNA < 50 copies/mL at Wk 48 by BL VL

ECHO and THRIVE: Causes of Failure at Wk 96

- More virologic failures with RPV vs EFV
- Difference due to more VF between Wks 0-48 at VL > 100,000; VF similar Wks 48-96
- NRTI mutations more common with VF on RPV vs EFV
- Cross-resistance to ETR more common with RPV failures (E138K mutation)
- D/C due to AE more common with EFV vs RPV

New Drugs?

- Three drugs investigated
  - Quad
    - Co-formulated TDF/FTC/elvitegravir/cobicistat
    - Submitted for FDA review
  - Dolutegravir
    - 96-week coverage of phase II data
    - Phase III data later this year
  - GS-7340
    - New formulation of Tenofovir
Quad

- One tablet, once daily
- Cobicistat inhibits tubular secretion without changing GFR
- Creatinine increases in first 2 weeks & stabilizes by week 8
- Randomized, double-blind, placebo-controlled
  - Pts: ARV-naive, 90% men, ~62% white, HCV 4%
  - Mean CD4 ~385, VL 4.7 log10, 33% VL>100K
Elvitegravir/Cobicistat/TDF/FTC vs EFV/TDF/FTC in Treatment-Naive Patients

- Multicenter, randomized, double-blinded, active-controlled phase III study

Stratified by baseline HIV-1 RNA > or ≤ 100,000 copies/mL

HIV-infected treatment-naive patients with HIV-1 RNA ≥ 5000 copies/mL, any CD4+ cell count, CLCR ≥ 70 mL/min

(N = 700)

Wk 48 primary analysis

Elvitegravir/Cobicistat/TDF/FTC QD + EFV/TDF/FTC placebo QD (n = 348)

Planned follow-up to Wk 192

EFV/TDF/FTC QD + Elvitegravir/Cobicistat/TDF/FTC placebo QD (n = 352)

Elvitegravir/Cobicistat Regimen Noninferior to EFV Regimen at Wk 48

- Greater CD4+ count increase with EVG/COBI vs EFV: 239 vs 206 cells/mm³ ($P = .009$)
- Virologic failure or rebound: resistance 8/14 in EVG/COBI arm vs 8/17 in EFV arm
  - Primary integrase mutations and primary NNRTI mutations observed in 7 and 8 patients in EVG/COBI and EFV arms
  - All 8 pts in EVG/COBI arm had M184V/I mutation vs 2 pts in EFV arm; 3 and 2 had K65R

Safety of Elvitegravir/Cobicistat Regimen vs EFV Regimen

- Significantly greater incidence of nausea with EVG/COBI regimen
- Significantly greater incidence of sleep disturbance, dizziness, rash with EFV regimen
- 1.4% of patients discontinued EVG/COBI regimen due to renal abnormalities vs no patients on EFV regimen
  - Significantly greater increase in median serum creatinine from baseline to Wk 48 in EVG/COBI group: 0.14 vs 0.01 mg/dL ($P < .001$)
  - Majority of increase in serum creatinine clearance occurred within 2 wks of starting treatment and progressed minimally over time
- Significantly greater increases in total, LDL, and HDL cholesterol from baseline to Wk 48 in EFV vs EVG/COBI groups (all $P \leq .001$)
Elvitegravir/Cobicistat/TDF/FTC vs ATV/RTV + TDF/FTC in Tx-Naive Patients

- Multicenter, randomized, double-blinded, active-controlled phase III study

Stratified by baseline HIV-1 RNA > or ≤ 100,000 copies/mL

HIV-infected treatment-naive patients, HIV-1 RNA ≥ 5000 copies/mL, any CD4+ cell count, CLCR ≥ 70 mL/min

(N = 708)

Wk 48 primary analysis

Elvitegravir/Cobicistat/TDF/FTC QD + ATV/RTV + FTC/TDF placebo QD (n = 353)

Planned follow-up to Wk 192

ATV/RTV + TDF/FTC QD + Elvitegravir/Cobicistat/TDF/FTC placebo QD (n = 355)

Elvitegravir/Cobicistat Regimen Noninferior to ATV/RTV Regimen at Wk 48

- Similar CD4+ cell count increases in both study arms at Wk 48
- Virologic failure or rebound: resistance 5/12 in EVG/COBI vs 0/8 in ATV/RTV
  - 4/5 pts in EVG/COBI arm had M184V/I mutation; 4 had primary integrase mutations

Safety of Elvitegravir/Cobicistat Regimen vs ATV/RTV Regimen

- Similar rates of grade 3/4 adverse events between arms: 13% in EVG/COBI and 14% in ATV/RTV arm
  - Most common adverse events: diarrhea, nausea

- Grade 3/4 hyperbilirubinemia more common in ATV/RTV group: 58% vs 1%

- Significantly greater increase in median serum creatinine from baseline to Wk 48 in EVG/COBI group: 0.12 vs 0.08 mg/dL ($P < .001$
  - Majority of increase in serum creatinine clearance occurred within 2 wks of starting treatment and progressed minimally over time

- Significantly greater increase in median triglycerides from baseline to Wk 48 in ATV/RTV group: 23 vs 8 mg/dL ($P = .006$); otherwise no difference in lipid values

Dolutegravir

- Once daily integrase inhibitor
- No need for boosting, low PK variability
- DTV metabolized UGT1A1
- No effect on GFR
- Randomized, partially blind, dose-finding study
  - Pts: ARV-naive, 86% men, 80% white
  - mean CD4 324, VL 4.5 log10, 21% VL>100K
SPRING-1: Phase IIb Trial of Dolutegravir vs Efavirenz in Tx-Naive Patients

- Comparable efficacy among arms
- No cases of virologic failure in 50-mg arm
- Minimal variations in serum creatinine observed across treatment arms
  - Alterations did not progress over time
  - Previous study showed DTG had no effect on glomerular filtration rate by iohexol clearance\textsuperscript{[2]}

GS-7340

- Novel phenyl monophosphoramidate prodrug of TDF
- Engineered to readily enter PBMCs
- 10 day randomized, placebo-controlled dose finding study in ARV-naïve or pts. off ARVs without GT resistance to TDF
- 38 pts, 90% male, med.CD4 444, VL 4.6 log10
GS-7340

- Lower TDF plasma concentrations, higher intracellular concentrations obtained with GS-7340 vs TDF
  - Hypothesized that this may result in greater efficacy, reduced toxicity
- Previous study evaluated higher doses of GS-7340: 50 mg and 150 mg\textsuperscript{[1]}

HIV-infected treatment-naive or -experienced patients with no genotypic resistance to TDF, HIV-1 RNA ≥ 2000 copies/mL, CD4+ count ≥ 200 cells/mm\textsuperscript{3}[2]

(N = 38)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Dose</th>
<th>Group Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF 300 mg QD</td>
<td>(n = 6)</td>
<td></td>
</tr>
<tr>
<td>GS-7340 8 mg QD</td>
<td>(n = 9)</td>
<td></td>
</tr>
<tr>
<td>GS-7340 25 mg QD</td>
<td>(n = 8)</td>
<td></td>
</tr>
<tr>
<td>GS-7340 40 mg QD</td>
<td>(n = 8)</td>
<td></td>
</tr>
<tr>
<td>GS-7340 Placebo QD</td>
<td>(n = 7)</td>
<td></td>
</tr>
</tbody>
</table>

10 days

Greater Antiviral Activity of GS-7340 25 mg and 40 mg vs TDF

- Higher intracellular tenofovir diphosphate levels and lower circulating plasma tenofovir levels with GS-7340 vs TDF
GS-7340

- No premature drug discontinuation
- Most AEs mild-moderate
- Unanswered question: does higher intracellular levels cause more renal toxicity?
- GS-7340: better antiviral activity with 1/10th TDF’s mass (potential for single tablet regimens)
Integrins

- Potential new class – attachment receptor
- Family of large cell-surface proteins - leukocyte surface molecules
- HIV binding to integrin alpha-4 beta-7 initiates a signaling cascade inside the target cell, activating another integrin, alpha-L beta-2, which then binds to another protein on the surface of an infected cell. This establishes a virological synapse, allowing much more effective cell-to-cell transmission of the virus
- No cross resistance to RAL and complementary action
- No single mutation
Seattle – New Frontiers

- **Industry**
  - From a lumbering town to a technological hub – dot-com boom, Amazon, eBay
Long-term Complications

- Cardiovascular risk
- HAND
- Bone loss
Inflammation

- Late ART era patients still have about a 10 year reduction in life expectancy
- Age-associated morbidity and mortality caused by a combination of lifestyle factors, ART toxicity, persistent inflammation
- Unresolved questions:
  - How much does HIV itself contribute to persistent inflammatory state?
  - To what degree does inflammation drive specific end-organ disease?
  - Are some ART regimens better than others?
  - Which bio markers are the best predictors of clinical effect?
Limited Association of CVD Events With Immune Suppression in D:A:D Study

- D:A:D includes > 49,000 patients with HIV-1 infection from 11 cohorts in Europe, US, and Australia[1]
- Aim to investigate association of ARVs and risk of CVD and other major disease events
- Previous study showed arterial stiffness, and thus CV risk, associated with CD4+ cell count nadir[2]
- However, current study showed CD4+ cell count nadir not associated with any CVD event[1]

<table>
<thead>
<tr>
<th>Latest CD4+ Relative Rates of Event (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
</tr>
<tr>
<td>100-199</td>
</tr>
<tr>
<td>200-299 Reference</td>
</tr>
<tr>
<td>300-399</td>
</tr>
<tr>
<td>400-499</td>
</tr>
<tr>
<td>≥ 500</td>
</tr>
</tbody>
</table>

*CHD: MI, sudden cardiac death or invasive coronary procedure; CVD: first CHD or stroke.
D:A:D: No Association Between ATV and Increased Risk of MI or Stroke

- > 49,000 HIV-infected patients from 11 cohorts in Europe, US, and Australia

Similar lack of association observed with ATV use and stroke

Hypertension/Pre-hypertension Associated With Higher AMI Risk in HIV+ Veterans

- 27,365 HIV-infected and 55,125 HIV-uninfected persons from Veterans Aging Cohort Study included in analysis
- 443 AMI events during median 4.6 yrs of follow-up

<table>
<thead>
<tr>
<th>SBP Categories/mm Hg</th>
<th>HIV+ Hazard Ratio (95% CI)</th>
<th>HIV- Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 140, with/without BP meds</td>
<td>2.4*</td>
<td>1.6*</td>
</tr>
<tr>
<td>&lt; 140, with BP meds</td>
<td>2.2*</td>
<td>1.5</td>
</tr>
<tr>
<td>120-139, without BP meds</td>
<td>1.7*</td>
<td>1.1</td>
</tr>
<tr>
<td>&lt; 120, without BP meds</td>
<td>1.2</td>
<td>1.0 (HIV- ref)</td>
</tr>
</tbody>
</table>

Model adjusted for age, sex, race/ethnicity, diabetes, LDL, HDL, triglycerides, statins, smoking, hepatitis C, BMI, renal disease, cocaine, alcohol use, hemoglobin.

Biomarkers

- **CRP**
  - Treatment with ABC (or EFV) initially increases CRP
  - Other randomized studies (STEAL & HEAT) found nothing
  - But ACTG 5095 (in which all patients received ABC or EFV or both) showed raised CRP
  - Uncertain clinical significance – linked to ABC cardiovascular risk?

- **Markers of inflammation/immune activation/coagulation**
  - Switching PI to RAL improves the biomarkers. Uncertain clinical significance

- **Levels of arterial inflammation**
  - PET scans in patients with virologic suppression and no CVD
  - HIV+ patients similar inflammation to patients with established atherosclerotic disease. Significantly greater than HIV- controls matched by Framingham risk
Statins

- Effect of statins on reducing risk of serious non-AIDS defining events and non-accidental death (ACTG/ALLERT)

- N = 3601 patients not on a statin initially
  - 481 started a statin
  - Did not include outcomes that occurred in the first 8 weeks on a statin
# ALLERT Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>N=3601</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>39</td>
</tr>
<tr>
<td>Gender: M/F</td>
<td>83%/17%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>• Black</td>
<td>30%</td>
</tr>
<tr>
<td>• White</td>
<td>47%</td>
</tr>
<tr>
<td>• Hispanic</td>
<td>21%</td>
</tr>
<tr>
<td>Median BMI</td>
<td>25</td>
</tr>
<tr>
<td>Current smoker</td>
<td>38%</td>
</tr>
<tr>
<td>Median systolic BP</td>
<td>120 mmHg</td>
</tr>
<tr>
<td>Median LDL</td>
<td>2.7 mmol/l</td>
</tr>
<tr>
<td>CD4 nadir</td>
<td>180 cells/mL</td>
</tr>
<tr>
<td>CD4 current</td>
<td>346 cells/mL</td>
</tr>
</tbody>
</table>
## ALLERT Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>No events</th>
<th>Event rate: statin users (per 100py)</th>
<th>Event rate: non-statin users (per 100py)</th>
<th>Crude HR</th>
<th>Baseline adjusted HR</th>
<th>Adjusted and weighted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV event</td>
<td>62</td>
<td>0.5</td>
<td>0.4</td>
<td>1.44</td>
<td>0.82</td>
<td>0.89</td>
</tr>
<tr>
<td>Non-CV event</td>
<td>580</td>
<td>4.2</td>
<td>3.8</td>
<td>1.18</td>
<td>0.82</td>
<td>0.85</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>144</td>
<td>0.7</td>
<td>0.9</td>
<td>0.96</td>
<td>0.96</td>
<td>1.25</td>
</tr>
<tr>
<td>Incident DM</td>
<td>158</td>
<td>1.3</td>
<td>1.0</td>
<td>1.52</td>
<td>1.02</td>
<td>0.87</td>
</tr>
<tr>
<td>Renal events</td>
<td>135</td>
<td>1.4</td>
<td>0.7</td>
<td>1.58</td>
<td>1.00</td>
<td>0.85</td>
</tr>
<tr>
<td>Cancer</td>
<td>89</td>
<td>0.5</td>
<td>0.5</td>
<td>1.03</td>
<td>0.71</td>
<td><strong>0.43</strong></td>
</tr>
<tr>
<td>Death</td>
<td>143</td>
<td>0.5</td>
<td>0.9</td>
<td>0.47</td>
<td>0.41</td>
<td>0.82</td>
</tr>
</tbody>
</table>
Statins Conclusions

- Non-significant (but maybe clinically meaningful) reduction in non-AIDS events and deaths
  - Consistent with a Hopkins study of 1538 patients: 3 fold reduction in death rate with statin use (More, Plos One 2011)

- Significant reduction in malignancies
  - Consistent with a Kaiser study of 1554 patients: 45% reduction in NHL cases with statin use (Chao, AIDS 2011)

- Benefits of statin use increased with increasing age and higher nadir CD4 count
HAND

- HAND - HIV Associated Neurocognitive Disorder
- HAND present in 30-50% of patients
HAND Tests

- Self Reporting (SR) Tests
  - Partial Assessment of Own Functioning Inventory (PAOFI)
  - Activities of Daily Living (ADL)

- Performance Based (PB) Tests
  - Medication Management Test-Revised (MMT-R)
  - Valpar System 3000 Work Samples and Computerized Assessment
Baseline Predictors of Decline in Cognitive Function

Yes: Older age, less education, female sex, substance abuse, co-morbid conditions, AIDS dx, CD4 nadir and HCV infection

No: Ethnicity, ARV treatment, current CD4, estimated duration of HIV infection
HAND Conclusion

- Asymptomatic mild HAND increases the risk for future symptomatic decline: CHARTER Study
- Patients with ANI have a 3-5 RR of developing symptomatic HAND compared to normal pts even after adjusting for baseline predictors
- Earlier cognitive decline is more common in women, those with substance abuse and other comorbid conditions and those with a lower CD4 nadir, an AIDS Dx, HCV infection and lower follow up CD4 counts
Bone Loss

- **Background**
  - ART initiation associated with a 2-6% decline in BMD and greater reductions are seen in TDF
  - BMD reductions correlate with increases in biomarkers of bone turnover such as CTX-1 (resorption) and osteocalcin & P1NP (formation)
Bone Loss

- Impact of Switching from AZT/3TC to TDF/FTC on BMD and bone metabolism in virologically suppressed patients
- PREPARE sub-study # 125LBA multi-center, randomized, controlled study
  - N = 54 patients, all on AZT/3TC for > 2 years with suppressed viral load
  - Median age 45-47, mostly white males, median CD4 ~ 490
# Bone Loss

<table>
<thead>
<tr>
<th></th>
<th>Continue AZT/3TC</th>
<th>Switch to TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median change</td>
<td>Within group p-value</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>-0.18</td>
<td>0.91</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.14</td>
<td>0.74</td>
</tr>
</tbody>
</table>
Bone Loss Conclusion

- In virologically suppressed patients on AZT/3TC; switching to TDF/FTC leads to marked increases in bone turnover
- Changes in bone turnover correlate with loss of BMD in the lumbar spine
Seattle – New Frontiers

Music

- From jazz - Ray Charles, Quincy Jones, Ernestine Anderson
- To rock - Jimi Hendrix
- To "grunge" - Melvins, Nirvana, Soundgarden, Alice in Chains, Pearl Jam
- To indie rock and indie dance music
Prevention

- Why did the FEM-PrEP study fail to show protection of TDF/FTC?

- Poor adherence
  - Detectable drug levels in fewer than 50% of infected women assigned to active arm
FEMPrEP: Low Adherence Rates in Oral TDF/FTC Pre-Exposure Prophylaxis Trial

- Phase III study of oral TDF/FTC vs placebo for 52 wks in African women
  - TDF/FTC: 1062 women; placebo: 1058 women

- TDF/FTC associated with 6% estimated reduction in risk of HIV acquisition in primary analysis (HR: 0.94; 95% CI: 0.59-1.52; \(P = .81\))
  - Trial stopped for futility in April 2011

- Pregnancy common in both arms; TDF/FTC vs placebo: 11.2% vs 7.5%

- Self-reported adherence overestimated
  - Pts reported 95% adherence; pill counts indicated ~ 86% to 89% adherence
  - However, < 40% of treated women (both infected cases and uninfected controls) had plasma drug levels ≥ 10 ng/mL, indicating pills taken in prior 48 hrs

Partners PrEP: TDF and TDF/FTC Significantly Reduce HIV Acquisition

- 4747 HIV-negative partners in HIV-serodiscordant heterosexual couples randomized to receive oral TDF, oral TDF/FTC, or placebo

- Both PrEP strategies associated with significant reduction in HIV transmission vs placebo in both men and women[1]
  - TDF efficacy: 71% in women, 63% in men
  - TDF/FTC efficacy: 66% in women, 84% in men

- In contrast to FEMPrEP, adherence levels high
  - Estimated that 97% of pills were taken based on monthly pill counts[1]
  - TDF detected in plasma at higher rates in uninfected pts vs those who seroconverted, according to case cohort study[2]
    - Infected pts with detectable TDF in TDF and TDF/FTC arms: 31% and 25%
    - Uninfected pts with detectable TDF in TDF and TDF/FTC arms: 83% and 81%

ACTG A5247: Herpes Zoster Live Vaccine in HIV-Infected Patients on Stable ART

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

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

Secondary endpoints
- VZV antibody titer 6 wks after vaccine dose
- VZV-specific cell-mediated immune response in 40 pts in each CD4+ cell count subgroup

ACTG A5247: Herpes Zoster Live Vaccine Safe in HIV-Infected Pts on Stable ART

Clinical VZV or VZV-like rash reported in 3 pts in vaccine arm and 2 pts in placebo arm

- Wild-type VZV detected in 1 pt in each arm, herpes simplex virus in 1 pt in vaccine arm, whereas rashes in remaining 2 pts negative for VZV
- No vaccine-strain virus in any of the rashes

<table>
<thead>
<tr>
<th>Safety Outcomes, % (95% CI)</th>
<th>Herpes Zoster Live Vaccine  (n = 295)</th>
<th>Placebo  (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met primary safety endpoint</td>
<td>5.1 (2.9-8.2)</td>
<td>2.1 (0.3-7.3)</td>
</tr>
<tr>
<td>Injection-site reaction*</td>
<td>42 (36.3-47.9)</td>
<td>12.4 (6.6-20.6)</td>
</tr>
<tr>
<td>Rash</td>
<td>5.1 (2.9-8.2)</td>
<td>4.1 (1.1-10.2)</td>
</tr>
<tr>
<td>Fever</td>
<td>4.1 (2.1-7.0)</td>
<td>6.2 (2.3-13.0)</td>
</tr>
</tbody>
</table>

*P < .001 for difference between arms.
ACTG A5247: Immunogenicity of Herpes Zoster Live Vaccine in HIV-Infected Pts

VZV Antibody Levels by gpELISA

Low CD4+ Stratum (< 350 cells/mm³)

High CD4+ Stratum (≥ 350 cells/mm³)

No apparent benefit to second vaccine dose

Zoster Vaccine Conclusion

- Safe and immunogenic
- Remaining question
  - Who do we give it to?
    - All with HIV?
    - Just those over 60? Over 50?
    - Those with virologic suppression?
    - Over a certain CD4 threshold?
Seattle – New Frontiers
Basic Science

- Latency
- Superinfection
Latency

The latent reservoir for HIV-1

Frequency: around 1 per million
Size: $10^5$ to $10^6$ cells
Half-life: 44 months
Time to eradicate: around 70 years
Experimental design

First visit

Generate in vitro latent infection

Reactivation with SAHA

1-3% latent infection

CD4⁺ T cells from patient on HAART (VL ≤ 50)

Second visit

Autologous CD8⁺ T cells

Co-Culture (1:1)

Measure GFP percentage with FACS

From day 0 to day 8
Conclusions:

Hypothesis:
- Viral reactivation with small molecules that reverse latency without global T cell activation ➔ CTL response ➔ Viral cytopathic effect

Our findings:
- Viral reactivation with small molecules that reverse latency without global T cell activation ➔ CTL response (defective) ➔ Viral cytopathic effect (insufficient)

Our solution:
- Viral reactivation with small molecules that reverse latency without global T cell activation ➔ Stimulation of HIV-1-specific CTLs ➔ Resting CD4+ T cells ➔ Latently infected resting CD4+ T cells ➔ CD8+ T cells
Administration of Vorinostat Disrupts HIV-1 Latency in Patients on ART

- Resting CD4+ T cells primary reservoir of persistent infection
  - Histone deacetylases maintain latency
  - HDAC inhibitor suberoylanilide

- Hydroxamic acid (SAHA – Vorinostat) induces expression of latent HIV from resting CD4+ T cells ex vivo

- Stimulation of HIV-1-specific cytolytic T cells facilitates elimination of latent viral reservoir after virus reactivation

David Margolis et al
Latency

- First direct measurement of disruption of latent HIV in vivo
- Optimal dosing schedule?
- Can vorinostat deplete latent infection?
- What about mutagenic potential?
Superinfection

• Rakai cohort. SI seems to be similar to the incidence of HIV in the area. 1.3 infections per 100 person-years. 3.6/100py in Mombassa.

• Questions
  • Does this mean that the immune response to HIV does not protect against new infection?
  • Or does it mean that because HIV depletes the immune capacity, it predisposes to super-infection?

• These cases are early cases of superinfection. There are data showing that the immune system takes a few years to give protection
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