Overview of Current Issues in HIV and Aging

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Disclosures

Calvin Cohen, MD

• Consulting Fees: Gilead, ViiV, BMS, Janssen, Merck
• Contracted Research: Gilead, BMS; Janssen
• Other: Gilead (expert testimony)
Patient AE

• Mr. E comes in to review treatment

• He is a 29 year old male - first tested positive 2 years ago
  • His VL consistently 5-10,000 c/mL
  • CD4 counts have remained >500/mm3
  • Most recent CD4 count was 761/mm3
  • His partner is also HIV+

• Unsure about starting treatment
  • States he would “probably be good” at adherence
  • Has never taken daily meds
  • Is a pharmacist – knows the pros and cons about medications
Question 1

- Would you recommend starting HIV medication now for his health?
  - 1. Yes – HIV meds are right for anyone
  - 2. Unsure – I’d leave it up to him to decide
  - 3. No – CD4 is high enough, and viral load low enough – it is fine to wait if he is unsure
  - 4. Something else
Question 2

• Would your answer be different if he was 59 years old?
• 1. Yes – HIV meds are more important in older patients
• 2. Unsure – I’d still leave it up to him to decide
• 3. No – CD4 is high enough, and viral load low enough – it is fine to wait if he is unsure
• 4. Something else
<table>
<thead>
<tr>
<th>Organization</th>
<th>CD4 Count (cells/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States DHHS (2013)</td>
<td>Yes</td>
</tr>
<tr>
<td>IAS-USA (2014)</td>
<td>Yes</td>
</tr>
<tr>
<td>European AIDS Society (2013)</td>
<td>Yes</td>
</tr>
<tr>
<td>British HIV Association (2013)</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO (2013)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AIDS, HIV-Related Symptoms, or CD4 < 350

Aging in 2014 DHHS Guidelines

• Antiretroviral therapy (ART) is recommended in patients >50 years of age, regardless of CD4 cell count (BIII)
  • Risk of non-AIDS related complications may increase
  • Immunologic response to ART may be reduced in older HIV-infected patients

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 2014.
Aging in 2014 DHHS Guidelines

• ART-associated adverse events may occur more frequently in older HIV-infected adults

• Close Monitoring of
  • Bone
  • Kidney
  • Metabolic
  • Cardiovascular
  • Liver

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 2014.
Earlier Medical Morbidities Associated with HIV Infection

Percent of Co-morbidities among HIV+ Patients in Metabolic Clinic in Modena vs. HIV- Population in CINECA ARNO Database

- No age-related diseases
- 1 comorbidity
- 2 comorbidities
- 3 comorbidities
- 4 comorbidities

Aging in 2014 DHHS Guidelines

• The increased risk of *drug-drug interactions* between antiretroviral (ARV) drugs and other medications commonly used in older HIV-infected patients should be assessed regularly
• Both when starting or switching ART and/or concomitant medications

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision May 2014.
Rising Need for Polypharmacy

Projected Use of Co-medications 2010-2030

- 3 or More Co-medications
- 2 Co-medications
- 1 Co-medication
- No Co-medication

Smit M, et al. 20th IAC; Melbourne, Australia; July 20-25, 2014; Abst. MOPE107.
Which Regimen to Select?
Study 102/103: Efficacy by Age <50 and ≥50

**Virologic Success**

- **EVG/COBI/FTC/TDF**
  - <50 years: 88%
  - ≥50 years: 84%
  - Difference (95% CI): 3.6% (-2% to 9%)

- **EFV/FTC/TDF**
  - <50 years: 86%
  - ≥50 years: 82%
  - Difference (95% CI): 3.7% (-11% to 18%)

- **ATV + RTV + FTC/TDF**
  - <50 years: 89%
  - ≥50 years: 94%
  - Difference (95% CI): 2% (-3% to 8%)

~14% per arm were > 50 yrs old

Richmond G et al. ICAAC 2012; H-879
## Comparing Regimens: Copays and Numbers of Pills

- Ordered by increased approx monthly copay
- 2NRTIs standardized as TDF/FTC except for co-formulated DTG/ABC/3TC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Schedule</th>
<th># Copays</th>
<th>Pills Per Day</th>
<th>App $ per month AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC/EFV</td>
<td>QD</td>
<td>1</td>
<td>1</td>
<td>2402</td>
</tr>
<tr>
<td>TDF/FTC/RPV</td>
<td>QD</td>
<td>1</td>
<td>1</td>
<td>2463</td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td>QD</td>
<td>1</td>
<td>1</td>
<td>2600</td>
</tr>
<tr>
<td>2 NRTI + RAL</td>
<td>BID</td>
<td>2</td>
<td>3</td>
<td>2800</td>
</tr>
<tr>
<td>TDF/FTC/EVG/c</td>
<td>QD</td>
<td>1</td>
<td>1</td>
<td>2950</td>
</tr>
<tr>
<td>2 NRTI + ATV/r</td>
<td>QD</td>
<td>3</td>
<td>3</td>
<td>3200</td>
</tr>
<tr>
<td>2 NRTI + DRV/r</td>
<td>QD</td>
<td>3</td>
<td>3</td>
<td>3200</td>
</tr>
</tbody>
</table>

2011-2012 DHHS Guidelines: What to Start: Four Preferred Regimens

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) The preferred regimens for nonpregnant patients are arranged by chronological order of FDA approval of components other than nucleosides and, thus, by duration of clinical experience.

**NNRTI – Based Regimen**
EFV/TDF/FTC (AI)

**Comments:**

**EFV** should not be used during the first trimester of pregnancy or in women of childbearing potential trying to conceive or not using effective and consistent contraception.

**TDF** should be used with caution in patients with renal insufficiency.

**ATV/r** should not be used in patients who require >20mg omeprazole equivalent per day.

**PI – Based Regimens (in alphabetical order)**
- ATV/r + TDF/FTC (AI)
- DRV/r (once daily) + TDF/FTC (AI)

**INSTI – Based Regimen**
RAL + TDF/FTC (AI)
### STaR: Adverse Events Leading to Discontinuation of EFV/FTC/FTC - Wk 48 & 96

<table>
<thead>
<tr>
<th></th>
<th>Baseline-Week 48</th>
<th>Week 48-Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Discontinuations</em> Due to AE, n (%)</em>*</td>
<td>34 (9%)</td>
<td>+9 (2.3%)</td>
</tr>
<tr>
<td><strong>AE leading to discontinuation in &gt;1 subject in either arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (1.3%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>18 (5%)</td>
<td>+6 (1.5%)</td>
</tr>
<tr>
<td>Abnormal Dreams/Nightmares</td>
<td>6 (1.5%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (0.8%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (1.8%)</td>
<td>+4 (1%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (0.5%)</td>
<td>+0</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>2 (0.5%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td>GI, General, Skin Disorders</td>
<td>15 (4%)</td>
<td>+0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (0.5%)</td>
<td>+0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (0.5%)</td>
<td>+0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (0.5%)</td>
<td>+0</td>
</tr>
<tr>
<td>Toxic Skin Eruption</td>
<td>2 (0.5%)</td>
<td>+0</td>
</tr>
</tbody>
</table>

Cohen C, et al. EACS Brussels 2013, LBPE7/17
Efavirenz and Time to Suicidality
Primary Analysis


*Person Years, sum of at-risk follow-up

As-treated HR 2.16 (1.16-4.00)

Hazard ratio (95% CI)
2.28 (1.27 to 4.10), p=0.006

EFV: 47 events/5817 PY*
(8.08/1000 PY)

No EFV: 15 events/4099 PY*
(3.66/1000 PY)
**ACTG 5257: Study Design**

- **Primary Endpoints**
  - Time to HIV-1 RNA >1000 c/mL wk 16 to before wk 24, or >200 c/mL at or after wk 24 (VF)
  - Time to discontinuation of randomized component for toxicity (TF)

- **Pre-planned Composite Endpoint**
  - The earlier occurrence of either VF or TF in a given participant

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**HIV-infected patients, ≥18 yr, with no previous ART, VL ≥ 1,000 c/mL at U.S. Sites (N=1,809)**

**Randomized 1:1:1 to Open Label Therapy**
- Stratified by screening HIV-1 RNA level (≥ vs. <100,000 c/mL), A5260s metabolic substudy participation, cardiovascular risk

**RAL 400 mg BID + FTC/TDF QD (N=603)**

**DRV 800 mg QD + RTV 100 mg QD + FTC/TDF QD (N=601)**

**ATV 300 mg QD + RTV 100 mg QD + FTC/TDF QD (N=605)**

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Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.
## ACTG 5257: Toxicity Associated Discontinuation

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>RAL (N=603)</th>
<th>DRV/r (N=601)</th>
<th>ATV/r (N=605)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Toxicity Discontinuation</td>
<td>8 (1%)</td>
<td>32 (5%)</td>
<td>95 (16%)</td>
</tr>
<tr>
<td>Gastrointestinal Toxicity</td>
<td>2</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Jaundice/Hyperbilirubinemia</td>
<td>0</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>Other Hepatic Toxicity</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Skin Toxicity</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Metabolic Toxicity</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Renal Toxicity (All Nephrolithiasis)</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal Chem/Heme (Excl. LFTs)</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other Toxicity</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.
# DHHS Guidelines May 2014: Ten Recommended Regimens

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Efavirenz/emtricitabine/tenofovir DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Atazanavir + ritonavir + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Darunavir + ritonavir (QD) + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>INSTI</td>
<td>Raltegravir + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir/cobicistat/emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir + abacavir/lamivudine</td>
</tr>
<tr>
<td></td>
<td>Dolutegravir + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>Additional options if the VL &lt;5 log:</td>
<td>Efavirenz + abacavir/lamivudine</td>
</tr>
<tr>
<td></td>
<td>Atazanavir + ritonavir + abacavir/lamivudine</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine/tenofovir DF/emtricitabine (if CD4 count &gt;200/mm³)</td>
</tr>
</tbody>
</table>

DHHS. Available at: [http://aidsinfo.nih.gov/contentfiles/AdultARV_INSTIRecommendations.pdf](http://aidsinfo.nih.gov/contentfiles/AdultARV_INSTIRecommendations.pdf), Update May 2014
Cardiovascular Risk
# HIV Infection: An Independent CVD Risk Factor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimated effect (mm)</th>
<th>Internal carotid</th>
<th>Common carotid</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td></td>
<td>0.15 †</td>
<td>0.033 *</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.13 ‡</td>
<td>0.054 ‡</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>0.17 ‡</td>
<td>0.020 †</td>
</tr>
<tr>
<td>Past smoker</td>
<td></td>
<td>0.09 ‡</td>
<td>0.020 ‡</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>0.12 ‡</td>
<td>0.026 ‡</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td></td>
<td>0.16 ‡</td>
<td>0.073 ‡</td>
</tr>
<tr>
<td>Systolic BP (per 10 mmHg)</td>
<td></td>
<td>0.05 ‡</td>
<td>0.025 ‡</td>
</tr>
<tr>
<td>Diastolic BP (per 10 mmHg)</td>
<td></td>
<td>-0.07 ‡</td>
<td>-0.026 ‡</td>
</tr>
<tr>
<td>Total cholesterol (per 10 mg/dL)</td>
<td></td>
<td>0.009 ‡</td>
<td>0.004 ‡</td>
</tr>
<tr>
<td>HDL (per 10 mg/dL)</td>
<td></td>
<td>-0.020 ‡</td>
<td>-0.011 ‡</td>
</tr>
</tbody>
</table>

* p<0.01, † p<0.001, ‡ p<0.0001

Grünfeld C et al. AIDS 2009
DAD: Predictive Factors for the Risk of CV Events

Endpoint of CVD: n=663 includes MI (n=366), Stroke (N=138), invasive CV procedures (n=134) and other CV related deaths (n=25)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir (per additional year)</td>
<td>1.04</td>
<td>1.00-1.08</td>
</tr>
<tr>
<td>Lopinavir/r (per additional year)</td>
<td>1.08</td>
<td>1.02-1.14</td>
</tr>
<tr>
<td>Abacavir (current exposure)</td>
<td>1.63</td>
<td>1.38-1.92</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.70</td>
<td>1.32-2.18</td>
</tr>
<tr>
<td>Age (per 5 years older)</td>
<td>1.42</td>
<td>1.37-1.47</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>1.43</td>
<td>1.16-1.77</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>2.35</td>
<td>1.92-2.87</td>
</tr>
<tr>
<td>Ex-smoking</td>
<td>1.27</td>
<td>1.00-1.61</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.92</td>
<td>1.55-2.38</td>
</tr>
<tr>
<td>Total cholesterol (per mmol/L higher)</td>
<td>1.21</td>
<td>1.16-1.27</td>
</tr>
<tr>
<td>HDL cholesterol (per mmol/L higher)</td>
<td>0.67</td>
<td>0.55-0.82</td>
</tr>
<tr>
<td>Systolic blood-pressure (per 10mmHg higher)</td>
<td>1.05</td>
<td>1.03-1.08</td>
</tr>
</tbody>
</table>

Relative Risks similar when predicting risk of MI only.
**ACTG5202: Lipid Changes**

**ABC/3TC vs TDF/FTC & ATV/r vs. EFV**

- **Cholesterol**
  - ATV/r vs. EFV: \( P < 0.001 \)
  - ATV/r vs. EFV: \( P < 0.001 \)

- **LDL**
  - ATV/r vs. EFV: \( P < 0.001 \)
  - ATV/r vs. EFV: \( P = 0.002 \)

- **HDL**
  - ATV/r vs. EFV: \( P < 0.001 \)
  - ATV/r vs. EFV: \( P < 0.001 \)

- **Triglycerides**
  - ATV/r vs. EFV: \( P = 0.07 \)
  - ATV/r vs. EFV: \( P = 0.26 \)

**P-values:**

- ATV/r vs. EFV

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Daar E, et al. 17th CROI; San Francisco, CA; February 16-19, 2010. Abst. 59LB.
ACTG5202: Lipid Changes
ABC/3TC vs TDF/FTC & ATV/r vs. EFV

Cholesterol
\( P < 0.001 \)  \( P < 0.001 \)

LDL
\( P < 0.001 \)  \( P = 0.002 \)

HDL
\( P < 0.001 \)  \( P < 0.001 \)

Triglycerides
\( P = 0.07 \)  \( P = 0.26 \)

\( P \)-values:
ATV/r vs. EFV

Daar E, et al. 17th CROI; San Francisco, CA; February 16-19, 2010. Abst. 59LB.
ACEG 5206: Double Blind Pilot Study
Adding TDF in Patients with Virologic Suppression: Median Change Lipid Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>TDF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>non HDL</td>
<td>-4</td>
<td>-32</td>
<td>0.01</td>
</tr>
<tr>
<td>TC</td>
<td>-6</td>
<td>-39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL</td>
<td>-3</td>
<td>-12</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL</td>
<td>-2</td>
<td>2</td>
<td>0.91</td>
</tr>
<tr>
<td>TG</td>
<td>-14</td>
<td>-36</td>
<td>0.83</td>
</tr>
</tbody>
</table>

• **Primary Endpoint:**
  • Non-inferiority (12% margin) to PI + RTV + 2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 c/mL at 24 weeks
SPIRIT Categorical Analysis of Total Cholesterol: HDL Ratio

At Week 24, P<0.001 for comparison between groups (Cochran-Mantel-Haenszel Row Mean Score test using modified ridit scores)

Tebas P et al. ID Week 2013 SF, CA #672
ACTG 5257: Changes in Non-HDL Cholesterol and Carotid Intima-Media Thickness

Non-HDL-C: Mean Change (95% CI)

Stein J et al, J Am Coll Cardiol. 2014;63(12_S): Abstract A1112
D:A:D Study:
Update on MI Risk and Abacavir Use

- Prospective cohort (2000-2013)
  - N= >49,000
  - 11 cohorts – US, Europe, Australia
- Results - No difference pre vs. post-2008 in impact of ABC
  - Stable after controlling for Framingham risk group, renal function, dyslipidemia, HTN
- Results suggest effect less likely due to channeling bias

<table>
<thead>
<tr>
<th></th>
<th>Not on abacavir</th>
<th>On abacavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/PYs</td>
<td>600/295,642</td>
<td>341/71,917</td>
</tr>
<tr>
<td>Rate/PYs (95% CI)</td>
<td>0.20 (0.19, 0.22)</td>
<td>0.47 (0.42, 0.52)</td>
</tr>
<tr>
<td>Overall Pre 3/2008</td>
<td>1.98</td>
<td>1.97</td>
</tr>
<tr>
<td>Overall</td>
<td>1.97</td>
<td>1.97</td>
</tr>
</tbody>
</table>

PY: person-years.
ACTG 5224s: High Sensitivity CRP

**hsCRP, NRTI Components**

- **TDF/FTC**
- **ABC/3TC**

**Fold Change**

- **Study Week**
  - 0
  - 24
  - 96

**P-values**
- **P=0.008**
- **P=0.021**

ABC Association with MI:
FDA Meta-analysis

• FDA completed trial-level meta-analysis of 26 completed RCTs of ABC in adults, with N>50 subjects

<table>
<thead>
<tr>
<th>Studies</th>
<th>Events/Subjects</th>
<th>ABC</th>
<th>Non-ABC</th>
<th>Risk Difference (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>6/2341</td>
<td>9/2367</td>
<td>-0.11% (-0.43%, 0.21%)</td>
<td>0.70 (0.25, 2.00)</td>
<td></td>
</tr>
<tr>
<td>NIH</td>
<td>12/1985</td>
<td>9/1610</td>
<td>0.03% (-0.45%, 0.51%)</td>
<td>1.08 (0.43, 2.61)</td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>6/702</td>
<td>4/863</td>
<td>0.31% (-0.53%, 1.16%)</td>
<td>1.60 (0.46, 5.62)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>24/5028</td>
<td>22/4840</td>
<td>0.008% (-0.26%, 0.27%)</td>
<td>1.02 (0.56, 1.84)</td>
<td></td>
</tr>
</tbody>
</table>

ABC and Myocardial Infarction

• 5.5 Myocardial Infarction

• In a published prospective, observational, epidemiological study designed to investigate the rate of myocardial infarction in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of myocardial infarction (MI). In a sponsor-conducted pooled analysis of clinical trials, no excess risk of myocardial infarction was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are inconclusive.

• As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, and smoking).
Renal Risk
ACTG 5202: Median Change in Creatinine Clearance

Wk 48, P=0.17
Wk 96, P=0.33

Wk 48, P=0.001
Wk 96, P<0.001

P-values: ATV/r vs. EFV

Daar E, et al. CROI 2010, 59LB.
GS 903/934: EFV/TDF + 3TC or FTC
Pts ≥50 yrs at BL - Median Estimated GFR

Gallant JE, et al., WAIDS 2008; Poster #THPE0186
Glomerular Filtration

#3 blocked by:
- Cimetidine
- Cobicistat
- Dolutegravir
- Raltegravir
- Ritonavir
- Rilpivirine
- Trimethoprim

http://en.wikipedia.org/wiki/Renal_function
Study 102 and 103 (Pooled Renal Analysis Through 144 Weeks)

Creatinine by Baseline Renal Function

Change from BL in Serum Cr (mg/dL)
(Median [IQR])

STB ≥90mL/min
STB <90mL/min

Cohen C, et al. IAC 2014. Melbourne, Australia. #WEPE063
### Renal Safety Parameters by Baseline Renal Function - eGFR and Tubular Abnormalities

<table>
<thead>
<tr>
<th>BL eGFR (mL/min)</th>
<th>STB (n=701)</th>
<th>ATR (n=352)</th>
<th>ATV+RTV+TVD (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70 to &lt;90 (n=95)</td>
<td>≥ 90 (n=606)</td>
<td>70 to &lt;90 (n=52)</td>
</tr>
<tr>
<td>Changes in eGFR, Median [IQR]</td>
<td>-7.7 [-14.9 to 0.6]</td>
<td>-15.2 [-25.4 to -4.1]</td>
<td>-0.5 [-7.7 to 4.7]</td>
</tr>
<tr>
<td>Hypophosphatemia*</td>
<td>1.1%</td>
<td>1.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Normoglycemic glycosuria*</td>
<td>2.1%</td>
<td>0.5%</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria*</td>
<td>14.9%</td>
<td>15.6%</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

*Confirmed ≥ 1-grade increase

Cohen C, et al. IAC 2014. Melbourne, Australia. #WEPE063
Study 102 and 103 (Pooled Renal Analysis Through 144 Weeks)

Rates of Proteinuria at Each Study Visit

Prevalence of new or worsening
graded proteinuria (%)

Week

STB
ATV/r+TVD
ATR

Cohen C, et al. IAC 2014. Melbourne, Australia. #WEPE063
Bone Issues
A5224s: Mean Percent Change in Lumbar Spine Bone Mineral Density

- Hip BMD: Significantly greater percent decline with TDF/FTC than ABC/3TC; not significant for NNRTI/PI
- No significant difference in fracture rate between arms

McComsey, G, et al. CROI 2010, 106LB.
Tenofovir Alafenamide (TAF) Study GS-0102

Phase 2 study (48 weeks)
- Treatment-naïve
- Double-blind
- HIV RNA > 5,000 copies/mL
- eGFR > 70 mL/min
- Stratified by HIV RNA ≤100K and > 100K copies/mL
- Any CD4 count

Randomization 2:1
- Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/c/FTC/TAF) (n=112)
- Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF (EVG/c/FTC/TDF) (n=58)

Primary Endpoint
- Week 24
- HIV RNA < 50 Copies/mL (FDA Snapshot)

Study GS-0102: TAF vs TDF
Percent Change in Spine and Hip BMD

Multiple Issues – What if the Pt has reduced Kidney function, and a high CV risk?
GARDEL Study: Study Design

Stratified by Screening
HIV RNA
(\leq or > 100,000 copies/mL)

ARV-naive patients
\geq 18 years
HIV RNA >1,000 copies/mL
No IAS-USA defined NRTI or
PI resistance at screening
HB(s)Ag negative
(N=426)

Week 48
Primary Endpoint

Dual Therapy (DT):
LPV/r 400/100 mg BID
+ 3TC 150 mg BID
(n=217)

Triple Therapy (TT):
LPV/r 400/100 mg BID + 3TC or FTC
and a third investigator-selected NRTI in
fixed-dose combination (n=209) –
ZDV, TDF or ABC

GARDEL Study: Primary Efficacy Outcome

**VL <50 copies/mL (ITTe)**

- **DT**: 88.3%
- **TT**: 83.7%

**Percent Patients**

*Week 48 <50 copies/mL (ITTe)*

<table>
<thead>
<tr>
<th>Week</th>
<th>DT (95.5%)</th>
<th>TT (96.6%)</th>
<th>Difference</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W12</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>W24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P*=0.171, difference +4.6%

[CI 95%: -2.2% to +11.8%]

HIV Prevention Issues

WHEN IT COMES TO SEX...
AGE IS NOT A CONDOM

Talk to your doctor about your sex life.
Learn more. Be safe. Get tested.
NYS 800-541-AIDS  800-541-2437
NYC 800-TALK-HIV  800-825-5448
ageisnotacondom.org
HIV Screening Recommendations

- CDC
  - 2006: Test all patients aged 13 to 64 years
- ACP
  - 2007: Test all persons aged 15 to 75 years
- USPSTF
  - 2013: Test all patients aged 15 to 65 years
Number of HIV diagnoses of HIV among over 50's in the UK

CDC Advocates PrEP
iPrex Open Label Extension: HIV Incidence and Drug Concentrations

Follow-up %  
26%  12%  21%  12%

Risk Reduction  
44%  84%  100%  100%

95% CI  
-31 to 77%  21 to 99%  86 to 100% (combined)

## iPrex: Correlates of TDF Drug Concentration

<table>
<thead>
<tr>
<th>Predictor of Drug Concentration</th>
<th>Adjusted OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-condom Receptive Anal Intercourse at Entry</td>
<td>1.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;=5 Sexual Partners in the Past 3 Months</td>
<td>1.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Known HIV Positive Partner</td>
<td>1.40</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>1.08</td>
<td>0.19</td>
</tr>
<tr>
<td>30-39</td>
<td>2.02</td>
<td>0.0002</td>
</tr>
<tr>
<td>40+</td>
<td>3.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than Secondary</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>1.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post-secondary</td>
<td>2.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Transgender</strong></td>
<td>0.72</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Future Possibilities to Improve Care

• Data on any important PK differences in ARVs (hepatic, renal) for older patients

• Longer term safety data specifically in older pts with current standard treatments

• Understanding the interpretation and relevance of CNS penetration of ARVs

• Understanding and treating inflammation

• Newer ARVs that improve on safety concerns with current treatments
Pt Mr. RR

- Mr. R comes in to start ARVs
- He is a 67 year old male; just tested HIV+
- CD4 is 290, viral load 55,600c/mL
  - No resistance on genotype

- On no other medications
- Ready to start meds for HIV today
- Normal renal, liver function
Which Regimen do you feel is the safest one for him to start on – the NRTIs

• 1. TDF/FTC
• 2. ABC/3TC
• 3. Just 3TC or FTC
• 4. Not Sure
• 5. Another choice
And with which “third agent”? 

- 1. Efavirenz 
- 2. Rilpivirine 
- 3. Raltegravir 
- 4. Elvitegravir/c 
- 5. Dolutegravir 
- 6. Atazanavir/r 
- 7. Darunavir/r 
- 8. Another choice (e.g., lopinavir/r, etravirine, nevirapine) 
- 9. I’ve no idea
Summary and Conclusions

• Given the success of HIV treatment, the issues associated with aging will only increase in importance

• Several factors to consider:
  • Diagnosis of HIV in older populations
  • Data on if/how HIV treatment choices should be altered
  • More PK data to guide dosing

• Ensuring we have a sufficient range and adequate numbers of trained clinicians to manage this growing issue