Cumulative Exposure to DRV/r Increase MI Risk

**Adjusted for** gender, race, HIV exposure group, enrolment cohort, baseline date, prior CVD, nadir CD4 count, current CD4 count**, dyslipidaemia**, BMI**, diabetes**, eGFR**, age (all as fixed variates at baseline), HBV, HCV, smoking, family history of CVD, VL., hypertension, AIDS, cumulative exposure to darunavir/r, atazanavir/r, lopinavir/r & indinavir & recent exposure to abacavir (≤6 months) (all as time-updated variables).

*Factors considered to potentially lie on the causal pathway between PI/r exposure and CVD and values hence fixed at baseline.

Ryom L, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 128LB.
Is this Important?

• Further analyses found significant associations between cumulative darunavir use and myocardial infarction alone (IRR 1.51 per 5 years, 95% CI 1.13 to 2.02) or stroke alone (IRR 1.49 per 5 years, 95% CI 1.08 to 2.07).
CVD outcomes with ATV vs non-ATV ART in Veterans Health Administration

- Historical cohort study of patients initiating first-line ART in VHA with PI, INSTI, or NNRTI and who showed pattern of regular care
- Final cohort of incident-treated pts: N = 10,404
  - ATV ART: n = 1532
  - Non-ATV ART: n = 8827
- MI and stroke events assessed by ICD-9 and ICD-10 codes

**ATV-containing ART** associated with decreased **MI risk** vs non-ATV–containing ART

<table>
<thead>
<tr>
<th>CVD Event</th>
<th>Adjusted HR for CVD Events With ATV vs Non-ATV ART (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>0.65 (0.46-0.91)*</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.01 (0.84-1.22)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.04 (0.86-1.26)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.93 (0.77-1.14)</td>
</tr>
<tr>
<td>MI or stroke</td>
<td>0.93 (0.79-1.09)</td>
</tr>
<tr>
<td>MI, stroke, or death</td>
<td>0.98 (0.86-1.11)</td>
</tr>
</tbody>
</table>

*P = .016.

### Why Not Atazanavir? - VA Cohort Study

**Raised Bilirubin is Associated w/Less AMIs & Heart Failure**

*96373 Participants, 30425 HIV+ 7.4 Years Median Follow Up*

<table>
<thead>
<tr>
<th>Total bilirubin (mg/dL)</th>
<th>N</th>
<th>HF Rate (95% CI)</th>
<th>HF HR (95% CI)</th>
<th>P</th>
<th>AMI Rate (95% CI)</th>
<th>AMI HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4</td>
<td>24229</td>
<td>7.95 (7.50-8.42)</td>
<td>1 (ref)</td>
<td></td>
<td>3.81 (3.51-4.13)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>0.5-0.6</td>
<td>23638</td>
<td>7.39 (6.95-7.85)</td>
<td>0.88 (0.81-0.96)</td>
<td></td>
<td>3.36 (3.08-3.68)</td>
<td>0.85 (0.75-0.96)</td>
<td></td>
</tr>
<tr>
<td>0.7-0.8</td>
<td>17462</td>
<td>6.60 (6.12-7.12)</td>
<td>0.79 (0.72-0.87)</td>
<td>&lt;0.01</td>
<td>3.45 (3.11-3.81)</td>
<td>0.89 (0.78-1.02)</td>
<td>0.02</td>
</tr>
<tr>
<td>≥0.9</td>
<td>18523</td>
<td>6.41 (5.94-6.92)</td>
<td>0.75 (0.68-0.83)</td>
<td></td>
<td>3.07 (2.76-3.41)</td>
<td>0.80 (0.70-0.92)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>12521</td>
<td>4.89 (4.40-5.43)</td>
<td>0.72 (0.61-0.84)</td>
<td></td>
<td>2.01 (1.73-2.34)</td>
<td>0.85 (0.68-1.08)</td>
<td></td>
</tr>
</tbody>
</table>

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*Models adjusted for age, race-ethnicity, systolic blood pressure, smoking, diabetes, total cholesterol, high density lipoprotein cholesterol, HIV, hepatitis C, liver fibrosis measured by FIB-4, alcohol abuse/dependence, cocaine and obesity; HF- heart failure; AMI- acute myocardial infarction; HR- Hazard Ratio; P- p-value test for overall significance of total bilirubin categories.*

The role of NLR on CVD risk in HIV infected patients

NLR is a predictor of CVD risk in HIV-infected patients, independently from the classic risk factors of the disease (Framingham risk score).

Dolutegravir discontinuation and neuropsychiatric AEs in German Pts

- Retrospective study of therapy discontinuation data extracted from 2 German HIV treatment clinics
  - Excluded clinical trial participants

<table>
<thead>
<tr>
<th>Discontinuation Reason</th>
<th>Dolutegravir (n = 985)</th>
<th>Elvitegravir (n = 287)</th>
<th>Raltegravir (n = 678)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, n (%)</td>
<td>67 (6.8)</td>
<td>27 (9.4)</td>
<td>28 (4.1)</td>
</tr>
<tr>
<td>Neuropsychiatric AE,* n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia/sleep disturbances</td>
<td>49 (5.0)</td>
<td>3 (1.0)</td>
<td>14 (2.1)</td>
</tr>
<tr>
<td>Poor concentration/slow thinking</td>
<td>36 (3.7)</td>
<td>2 (0.7)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (0.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache/paresthesia</td>
<td>13 (1.3)</td>
<td>1 (0.3)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>16 (1.6)</td>
<td>1 (0.3)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (0.7)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

*Can include ≥ 1 symptom.

Psychiatric Disorders Observed in HIV+ Patients Using 6 Common 3rd Agents in OPERA

Ricky Hsu1, Jennifer Fusco3, Cassidy Henegar3, Felix Carpio4, Karam Mounzer5, Michael Wohlfeiler6, Yani Vannappagari7, Michael Aboud8, Lloyd Curtis9, Gregory Fusco3

Observational cohort study (OPERA Database)
11,539 HIV+ patients prescribed DTG, EFV, RAL, DRV, RPV or EVG – based cART

KEY FINDING:
DTG use was not associated with an increased risk of psychiatric events or drug discontinuation due to psychiatric events, despite more patients with a history of psychiatric disorders being prescribed DTG treatment

Hsu R et al, Abstract 664, CROI 2017
Comorbidities Increase With Age and With HIV Infection

- Single-center, case-control study


*Comorbidities: bone fractures, CVD, diabetes, hypertension, hypothyroidism.

HIV-Infected Pts (n = 2854)

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

HIV-Uninfected Controls (n = 8562)

Pt's (%)

Age, yrs
2+ Comorbidities, %

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;40y</th>
<th>41-50y</th>
<th>51-60y</th>
<th>&gt;60y</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-Infected</td>
<td>3.9</td>
<td>9.0</td>
<td>20.0</td>
<td>46.9</td>
</tr>
<tr>
<td>HIV-Uninfected</td>
<td>0.5</td>
<td>1.9</td>
<td>6.6</td>
<td>18.7</td>
</tr>
</tbody>
</table>

*Comorbidities: bone fractures, CVD, diabetes, hypertension, hypothyroidism.

ART Considerations in Older Pts

• Comorbidities
• Polypharmacy
  – Drug–drug interaction, dosing, adherence challenges
• Renal or hepatic impairment
  – Alterations in pharmacokinetics, potential for drug toxicity
• Challenges with single-tablet regimens
  – Inability to alter single component dosing
  – Difficulty swallowing large tablets
# Drugs for Common Conditions in the Aging That May Interact With ART

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Comorbidity Drugs</th>
<th>Interacting ARVs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>Antacid PPI</td>
<td>All[1-8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATV/RTV + FTC/TDF or FTC/TAF,[3,4,9] DRV/RTV + FTC/TDF or FTC/TAF[3,4,10] RPV + FTC/TDF or FTC/TAF[11,12]</td>
</tr>
</tbody>
</table>

References in slidenotes
• Low/Middle/High income countries
• “Generic/Branded drugs”
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (CARAC)

February 2017

• High income countries
• Big Pharma
• Medicare/Medicaid

Private Health insurance
• High/middle income countries
• Branded drugs/some generic drugs
• National health systems are different
Linee Guida Italiane sull’utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

17 Dicembre 2016

Dicembre 2016

In collaborazione con:

Ministero della Salute
Sezioni L ed M del Comitato Tecnico Sanitario

SIMIT
Società Italiana di Malattie Infettive e Tropicali

• High income country
• Branded drugs/some generic drugs
• SSN Universalistico