BHIVA ‘Best of CROI’ Feedback Meetings

London  |  Birmingham
Haydock  |  Newcastle
Cardiff  |  Wakefield
Edinburgh
Opportunistic infections and complications

Dr Frank Post
King’s College London
MI and vascular disease
Early antiretroviral therapy does not improve vascular function: a START sub study

- START sub-study (n=332)
- Mean age 35 years, 70% male, 66% non-white, 30% smokers, low CVD risk
- Two groups were matched.
- FU through 36 months.
- Immediate ART did not improve arterial elasticity compared with deferred ART
Aspirin fails to impact immune activation or endothelial function in treated HIV

- ACTG A5331 - double-blind RCT
- Randomized to daily aspirin (100 or 300mg) or placebo for 12 weeks
- No major impact on immune activation (sCD14), endothelial function (FMD) or coagulation (d-dimer) when added to fully suppressive ART
- This study does not support the use of aspirin as anti-inflammatory in HIV patients

O’Brien ML, et al, CROI 2016, #44LB
Comparing Cardiovascular Disease Risk Scores in HIV

Population: 10,832 HIV+ pts with 229 incident MIs, FU: 4.3 yrs
Outcomes: Discrimination and calibration

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Type 1 MI</th>
<th>Type 2 MI</th>
<th>All MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham</td>
<td>0.73*</td>
<td>0.63*</td>
<td>0.68*</td>
</tr>
<tr>
<td>ATP3</td>
<td>0.74*</td>
<td>0.63*</td>
<td>0.69*</td>
</tr>
<tr>
<td>ACC/AHA ASCVD</td>
<td>0.73*</td>
<td>0.62*</td>
<td>0.63*</td>
</tr>
<tr>
<td>D:A:D</td>
<td>0.72</td>
<td>0.72</td>
<td>0.74</td>
</tr>
</tbody>
</table>

All Myocardial Infarctions Expected vs observed event rates for 4 risk scores: Framingham, ATP-3, ACC/AHA ASCVD, D:A:D

Crane H, et al. CROI 2016; Boston #O42; Clement ME, et al. CROI 2016. Poster 642
The DAD score underestimates the observed risk of CVD.

The addition of HIV-specific variables as in the DAD score did not improve discrimination compared with ASCVD.

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Crane H, et al. CROI 2016; Boston #O42; Clement ME, et al. CROI 2016. Poster 642
ABC Use and Recurrent Myocardial Infarction

Retrospective analysis (1999-2014) on 816 pts of D:A:D cohort with a MI (baseline)

- A total of 102 recurrent MI occurred over 3863 PY (rate 2.64/1000 PY; 95%CI:2.13, 3.15)
- Rate of recurrent MI was 3.47 (95%CI:2.37, 4.57)/1000 PY for pts currently receiving ABC post-MI vs. 2.31 (95%CI:1.75, 2.88)/1000 PY for those who were not in ABC

<table>
<thead>
<tr>
<th>Associations between use of ABC at initial MI, current post-MI use and cumulative exposure to ABC post-MI and risk of recurrent MI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
</tr>
<tr>
<td>Receipt of ABC at initial MI</td>
</tr>
<tr>
<td>Current post-MI use of ABC</td>
</tr>
<tr>
<td>Cumulative exposure to ABC (/5 years)</td>
</tr>
</tbody>
</table>

The association between post-MI exposure to ABC and recurrent MI appeared to be largely explained by ABC use in earlier years

O’Brien ML, et al, CROI 2016, #44LB
Incidence of Stroke in HIV-Infected Patients in Spain (1997-2011) Stratified by HCV Status

CVD: Take-home messages

- No benefit from early ART or aspirin in low risk patients with preserved CD4 cell count
- Superiority of DAD CVD risk score not confirmed
- The incidence of stroke has declined in HIV+ patients who do not have HCV
Bone disease and fractures
Single dose zoledronic acid prevents antiretroviral-induced bone loss (O-47)

Study design: Phase II, double-blind, randomized, placebo-controlled

- **Intervention:** Day 0
  - ZOL x 1 dose (5 mg IV)
  - Placebo x 1 dose (220 mg mannitol + 24 mg sodium citrate IV)

- **Timeline (Weeks):** 0, 2, 12, 24, 36, 48, 72, 96, 120, 144
  - **Early Period**
  - **Late Period**

- **Randomization:** stratified by screening HIV-1 RNA (<100,000 or ≥100,000 copies/mL), age (≥30 and <40 or ≥40 and <50), and sex

N=63
Zolendronate prevents BMD loss by inhibiting bone resorption.

- Significant trends were also observed at the hip and femoral neck.
- Similar rates of virologic suppression and mean CD4 T cell increase over 48 weeks
- No major side effects.

LS BMD at 48 weeks: +1.8% vs. -4.4%
74% reduction in CTx at 12 weeks
BMD recovery after stopping TDF/FTC PrEP

- Patients with TFV-DP concentrations $\geq 16$ fmol/10$^6$ cells experienced 1-2% reductions in BMD
- BMD changes were reversible after TDF/FTC discontinuation

Grant et al. 48LB
Risk factors for fractures and osteonecrosis in EuroSIDA

- 11820 HIV+ patients: 86118 PYFU

- Baseline characteristics
  - Median age 41y, 75% male, 86% white, median CD4 440/mm$^3$ and 70.4% virologically suppressed

- 618 fractures: incidence 7.2 (6.6-7.7) per 1000 PYFU

- 89 cases of osteonecrosis: incidence 1.0 (0.8-1.3) per 1000 PYFU
After adjustment, fractures were associated with:

- **Older age, white race, lower BMI, IV drug use, lower baseline CD4, HCV-coinfection, prior osteonecrosis, prior fracture, recent non-AIDS cancer and recent cardiovascular disease (last 12 months), TDF exposure**

Osteonecrosis was associated with

- **White race, lower nadir CD4, prior osteonecrosis, prior fracture and prior AIDS**
Vitamin D and calcium supplementation

- ACTG A5280 is an RCT of the effects of Ca+/Vit D supplementation on BMD in patients starting Atripla.

- Daily supplementation with vitamin D3/calcium attenuated the loss in bone mineral density (BMD) by approximately 50% over 48 weeks.

- Effect of ART initiation and ART plus vitamin D/calcium supplementation on bioavailable 25OHD in blacks and non-blacks in ACTG A5280.

Yin et al, poster 700
Vitamin D and calcium supplementation

**Table 2. Baseline and Absolute Change from 0 to 48wks by race [Median (Q1, Q3)]**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline &amp; Change 0-48 week</th>
<th>Placebo</th>
<th>Vitamin D/calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 25OHD (ng/mL)</td>
<td>N=65</td>
<td>N=64</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.2 (16.0, 27.3)</td>
<td>23.0 (14.6, 25.1)</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>-2.5 (-6.3, 4.3)</td>
<td>32.2 (14.3, 42.6)*</td>
<td>22.5 (14.2, 34.1)*</td>
</tr>
<tr>
<td>YDBP (ug/mL)</td>
<td>N=63</td>
<td>N=60</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>179 (92, 299)</td>
<td>93 (77, 255)</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>25.9 (-4.8, 40.6)*</td>
<td>9.4 (-0.2, 28.3)</td>
<td>27.0 (0.0, 60.0)*</td>
</tr>
<tr>
<td>Bioavailable 25OHD (ng/mL)</td>
<td>N=61</td>
<td>N=59</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.6 (1.4, 4.3)</td>
<td>4.4 (1.8, 5.3)</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>-0.1 (-1.4, 0.1)</td>
<td>3.9 (1.4, 7.3)*</td>
<td>1.1 (0.4, 2.2)*</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>N=69</td>
<td>N=65</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.9 (25.9, 34.0)</td>
<td>27.5 (22.5, 35.5)</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>5.9 (-0.4, 12.2)*</td>
<td>-0.9 (-8.2, 4.2)</td>
<td>1.7 (-1.9, 7.2)</td>
</tr>
</tbody>
</table>

* *p<0.05 within race group change from baseline.
* *p<0.05 difference between race groups (black vs. non-black) in change from baseline.

- Bioavailability of 25(OH)D similar in black vs. other participants
- PTH responses to TDF were similarly abrogated in these patients

Yin et al, poster 700
BMD and Fractures: Take-home messages

- Bone loss with initial ART can be prevented with bisphosphonates
- Effect of TDF-PrEP on BMD is reversible upon discontinuation
- Fracture risk in increased with immunodeficiency and TDF exposure
Liver disease and cancer
Statins Reduce Liver Fat in NAFLD Over 12 Months

In HIV/HCV patients, statin use was associated with a reduced incidence of:

- Liver cirrhosis (aHR 0.73, CI 0.58-0.92) [2]
- Hepatocellular carcinoma (aHR 0.51, 95% CI 0.36, 0.72) [3]

Risk factors for liver fibrosis progression (FIB-4 ≥3.25) in subjects without significant liver disease (FIB-4 <1.45) at BL

Table. Factors Associated with Progression to Advanced Liver Fibrosis Among Patients with Baseline FIB<1.45

<table>
<thead>
<tr>
<th>Factor</th>
<th>Overall (n=14,198)</th>
<th>HIV-monoinfected (n=12,532)</th>
<th>HCV-coinfected (n=1,666)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aHR</td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.02</td>
<td>0.88-1.17</td>
<td>0.82</td>
</tr>
<tr>
<td>Race (reference: White)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.93</td>
<td>0.63-1.05</td>
<td>0.26</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.95</td>
<td>0.80-1.14</td>
<td>0.59</td>
</tr>
<tr>
<td>Other</td>
<td>0.76</td>
<td>0.56-1.04</td>
<td>0.09</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>1.85</td>
<td>1.63-2.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>1.45</td>
<td>1.17-1.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol use disorder</td>
<td>1.35</td>
<td>1.17-1.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>1.87</td>
<td>1.56-2.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 count*, cells/mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500 (referent)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>350-500</td>
<td>1.29</td>
<td>1.10-1.53</td>
<td>0.002</td>
</tr>
<tr>
<td>200-349</td>
<td>1.90</td>
<td>1.62-2.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100-199</td>
<td>2.88</td>
<td>2.39-3.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;100</td>
<td>6.93</td>
<td>5.80-8.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV viral level*, copies/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;500 (referent)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>500-9999</td>
<td>1.27</td>
<td>1.07-1.52</td>
<td>0.007</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>1.43</td>
<td>1.22-1.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥100,000</td>
<td>2.60</td>
<td>2.19-3.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline FIB-4 per unit</td>
<td>3.89</td>
<td>3.23-4.69</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Time-varying
Does HPV vaccination prevent persistent anal infection with vaccine types in HIV+ MSM and women without infection at baseline?

- N=575, Age 47, 18% female, 46% white
- CD4 602, VL 90%<200 cpm
- B/L Infection: Anal 60%, Oral 11% ≥ 1 4vHPV type

- DSMB stopped early (2.6 yrs FU)
- No safety issues

Study did not support routine vaccination of older HIV+ adults for prevention of anal HPV infection or improving anal HSIL outcomes
Renal disease
Comparison of renal outcomes with ECF-TAF vs. ECF-TDF in ART-naïve patients (GS-0104/0111)

1733 patients
Comparison of renal outcomes with ECF-TAF vs. ECF-TDF in ART-naïve patients (GS-0104/0111)

<table>
<thead>
<tr>
<th></th>
<th>ECF-TAF</th>
<th>ECF-TDF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>3</td>
<td>11</td>
<td>0.06</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>(albuminuria or eGFR &lt;60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal discontinuations</td>
<td>0</td>
<td>6</td>
<td>0.03</td>
</tr>
</tbody>
</table>

1733 patients
Comparison of renal biomarkers with ECF-TAF vs. ECF-TDF in patients stratified by D:A:D CKD risk score (GS-0104/0111)
Safety of ECF-TAF in patients with renal impairment (GS-0112)

242 patients
Safety of ECF-TAF in patients with renal impairment (GS-0112)
Risk Factors for severe Tenofovir (TDF)-Associated Renal Tubulopathy (Fanconi syndrome)

Objective:
- To define the risk factors for treatment-limiting renal tubulopathy in patients receiving tenofovir (TDF)

Methods:
- Retrospective case ascertainment
  - Proximal tubulopathy
    - ≥2 of: normoglycaemic glycosuria, hypophosphataemia <0.64 mmol/L, protein-creatinine ratio >300 mg/mmol
    - Acute tubular injury on kidney biopsy
  - Poisson regression (using data from the UK CHIC cohort)
Risk Factors for severe Tenofovir (TDF) Associated Renal Tubulopathy

- 15,983 subjects received TDF for >4 weeks between Oct 2002-July 2013
  - 69 (0.4%) developed tubulopathy (PT: n=52; ATI: n=17) after a median (IQR) of 43 (26, 67) months of TDF exposure
  - At presentation, 83% were taking ritonavir-boosted PI
    - 44% lopinavir, 35% atazanavir, 16% darunavir, 5% other

Table 1: Factors associated with developing TDF associated renal tubulopathy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Multivariate$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>P-value</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>1.30 (1.16, 1.46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ethnicity (black vs. white/other)</td>
<td>0.28 (0.12, 0.64)</td>
<td>0.003</td>
</tr>
<tr>
<td>Calendar year at TDF start</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000-2003</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2004-2007</td>
<td>0.46 (0.26, 0.81)</td>
<td>0.007</td>
</tr>
<tr>
<td>2008-2010</td>
<td>0.31 (0.15, 0.63)</td>
<td>0.001</td>
</tr>
<tr>
<td>2011-2014</td>
<td>0.39 (0.15, 0.97)</td>
<td>0.043</td>
</tr>
<tr>
<td>Time on TDF (per year increase)*</td>
<td>1.11 (1.01, 1.21)</td>
<td>0.025</td>
</tr>
<tr>
<td>Years on ARVs at TDF start</td>
<td>1.06 (1.01, 1.11)</td>
<td>0.030</td>
</tr>
<tr>
<td>ARV regime (PI based vs NNRTI based)*</td>
<td>4.05 (2.44, 6.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD4 cell count (per 50 cell increase)*</td>
<td>0.93 (0.88, 0.98)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Predicting Drug Discontinuation in TDF-Tolerant Patients: A Prospective PK/PG Study

Methods:
- Adult HIV-positive patients on TDF-containing HAARTs (>6 months), with CrCl >60 ml/min and no significant comorbidity were included
- Tenofovir (TFV) plasma and urinary concentration were measured (LC/MS)
- Single nucleotide polymorphisms in: \textit{ABCB1, ABCC2, ABCC4, ABCC10, SLC22A6, SLC28A2}.
- Patients were followed prospectively for drug discontinuations due to renal toxicity (eCrCl <60 ml/min, nephrolithiasis, persisting 24h urine abnormalities)

Results:
- 310 patients (73% male, 85% Caucasian, median age 46 years, BMI 23.5 kg/m$^2$, median CrCl 91 (80-107) ml/min) - median follow up of 20.6 months
- 24 patients interrupted TDF for renal toxicity
- Factors associated with TDF discontinuation (multivariate):
  - Age (p=0.005), male gender (p=0.047), PI use (p=0.002) and \textit{ABCB1} (encoding P-glycoprotein) TT genotype (p=0.0042)
Higher Cumulative TFV/FTC Levels Associated With Decline in Renal Function (iPrEX trial)

Results:

- Hair data and creatinine measures were available for 1144 person-visits in 202 participants followed for a median of 16.8 months.
- Median age 29 years (19-70); 91% MSM.
- Baseline CrCl of 112 mL/min (99-128).
- Greater reductions in eGFR were observed with increasing quartiles of hair level for TFV (p 0.008) and FTC (p 0.006).

- Mean % eGFR change from baseline:
  - -2.6 (SE 0.8) ml/min at visits with TFV Q1 levels.
  - -5.6 (SE 0.7) ml/min at visits with TFV Q4 levels.

- The odds of CrCl <70 ml/min (6.1% of sample) increased with increasing quartile of TFV/FTC concentration (OR 4.4 [1.1-17.4] for Q4 vs. Q1 TFV).
Renal: Take-home messages

- TAF associated with fewer clinically significant renal events

- TAF appears safe in patients with renal impairment up to 96 weeks

- Older age, white ethnicity and PI use are risk factors for TDF-induced Fanconi syndrome

- Greater renal function decline during PrEP with greater TFV exposure

- Dr Jasmini Alagaratnam
- Prof Brian Angus
- Dr David Asboe
- Dr Sanjay Bhagani
- Dr Daniel Bradshaw
- Dr Kate Childs
- Dr Duncan Churchill
- Dr Amanda Clarke
- Dr Paul Collini
- Mr Simon Collins
- Prof Satyajit Das
- Dr Annemiek de Ruiter
- Prof David Dockrell
- Prof Lucy Dorrell
- Dr Ellen Dwyer
- Dr Sarah Fidler

- Dr Julie Fox
- Dr Andrew Freedman
- Dr David Hawkins
- Prof Saye Khoo
- Prof Clifford Leen
- Prof Derek Macallan
- Dr Achutya Nori
- Dr Ed Ong
- Dr Chloe Orkin
- Dr Adrian Palfreeman
- Dr Brendan Payne
- Dr Frank Post
- Dr Iain Reeves
- Dr Jonathan Underwood
- Dr Ed Wilkins
- Dr Jaime Vera