TAF versus TDF – what is the difference in safety?
First-line treatment with either:

TDF/FTC/DTG or TDF/3TC/DTG

PrEP with either: TDF/FTC or TDF/3TC (US PEPFAR guidelines as well)

TAF/FTC is not recommended for routine treatment of HIV by WHO:
- No clear safety data for pregnant women
- Concerns over weight gain

TAF/FTC should only be used for people with impaired renal function or osteoporosis
“Boosted” versus “Unboosted” TDF

“Boosted” TDF
TDF/FTC/DRV/c
TDF/FTC/ELV/c
TDF/FTC/ATV/r

“Unboosted” TDF
TDF/FTC/EFV
TDF/FTC/DTG
TDF/3TC/DOR
The Safety and Efficacy of Tenofovir DF (TDF) in Combination with Lamivudine (3TC) and Efavirenz (EFV) in Antiretroviral-naïve Patients Through Seven Years

JVR Madruga¹, I Cassetti², A Etzel², J Suleiman³, Y Zhou³, AK Cheng³, and J Enejosa⁶ for the 903E Study Team

¹Centro de Referencia e Treinamento DST/AIDS, Sao Paulo, Brazil; ²Fundacion Centro Estudios Infectologicos, Buenos Aires, Argentina; ³Hospital Guilherme Álvaro, Santos, Brazil; ⁴Brasilmed Assistência Médica e Pesquisas, São Paulo, Brazil; ⁵Gilead Sciences, Inc., Foster City, CA, USA

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Glasgow, UK

TDF/3TC/EFV - unboosted
Figure 6. Mean % Change from Baseline in Spine and Hip BMD Through 7 Years

TDF/3TC/EFV
Figure 5. Median Glomerular Filtration Rate (IQR) by Cockcroft-Gault (mL/min) and MDRD (mL/min/1.73m^2) through 7 Years

TDF/3TC/EFV
Through 7 years of therapy in antiretroviral naïve patients, TDF+3TC+EFV demonstrated the following:

- Sustained, durable antiretroviral efficacy
- Continued CD4 cell count increases
- No discontinuations due to renal adverse events
- No evidence of clinically relevant bone effects
- Significant increases in limb fat from Years 2 through 7
Safety of unboosted TDF/FTC vs TAF/FTC
Meta-analysis of 5 treatment trials, n=3181

Hill et al, J Virus Erad 2018, 4:72-78
PrEP: Safety of TDF/FTC vs placebo
Meta-analysis of 13 PrEP trials, 22,730 person-years of follow up

- **Grade 3/4 Adverse Events**
  - TDF/FTC: 17.4%
  - Placebo: 16.8%
  - p = n.s.

- **Serious Adverse Events**
  - TDF/FTC: 9.4%
  - Placebo: 10.1%
  - p = n.s.

- **Fractures**
  - TDF/FTC: 3.7%
  - Placebo: 3.3%
  - p = n.s.

- **Creatinine Elevations (Grade 3+)**
  - TDF/FTC: 0.1%
  - Placebo: 0.1%
  - p = n.s.

- **Creatinine Elevations (Grades 1-4)**
  - TDF/FTC: 4.3%
  - Placebo: 2.3%
  - p = 0.04
There have been reports of increased body weight and clinical obesity across a range of randomised HIV clinical trials and cohort studies.

Rises in weight tend to be larger for people taking integrase inhibitors, especially with TAF (or without TDF).

There are also reports of larger rises in lipids, fasting glucose and diabetes for people taking TAF versus TDF.

What is the risk-benefit of taking TAF versus TDF?
## Grade 3 / 4 glucose and LDL elevations: HBV Phase 3 trials

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>TAF</th>
<th>TDF</th>
<th>Ref: Lancet 2016, September (Buti et al, Chan et al)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbeAg positive trial:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Glucose</td>
<td>26/516 (5%)</td>
<td>3/286 (1%)</td>
<td>p=0.003</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>23/560 (4%)</td>
<td>0/282 (0%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>HbeAg negative trial:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Glucose</td>
<td>15/277 (5%)</td>
<td>2/127 (1%)</td>
<td>p=0.10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>14/277 (5%)</td>
<td>1/135 (1%)</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>
# Lipids and diabetes in EMERALD trial (HIV)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>TAF/FTC/DRVc</th>
<th>TDF/FTC/DRV/c</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4 elevations:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>48/737 (6%)</td>
<td>6/364 (2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>27/737 (4%)</td>
<td>5/364 (1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes cases</td>
<td>9/763 (1.2%)</td>
<td>0/378 (0.0%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Ref: Eron et al, Antiviral Research 2019; clinicaltrials.gov [EMERALD trial]
Drivers of weight gain/loss on ART

A Hill et al. Journal of Virus Eradication 2019
Use of TDF versus TAF, ABC or nothing – effects on body weight (Week 48 results)

DISCOVER (PrEP): +0kg on TDF/FTC, +1kg on TAF/FTC

STEAL (treatment): +0kg on TDF/FTC, +1kg on ABC/3TC

AMBER (treatment): +0.8kg on TDF/FTC/DRV/c +1.8kg on TAF/FTC/DRV/c

GEMINI (treatment): +2.1kg on TDF/FTC/DTG +3.1kg on DTG/3TC
TDF as PrEP: weight loss >5%

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners (Daily TDF/FTC)</td>
<td>4</td>
<td>1579</td>
<td>6</td>
<td>1584</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>140</td>
<td>1204</td>
<td>135</td>
<td>1209</td>
</tr>
<tr>
<td>VOICE (Daily TDF/FTC)</td>
<td>28</td>
<td>1003</td>
<td>17</td>
<td>1009</td>
</tr>
<tr>
<td>TDF 2 (TDF/FTC)</td>
<td>113</td>
<td>611</td>
<td>72</td>
<td>608</td>
</tr>
<tr>
<td>iPRES (Daily TDF/FTC)</td>
<td>34</td>
<td>1251</td>
<td>19</td>
<td>1248</td>
</tr>
<tr>
<td>FEM–PrEP (Daily TDF/FTC)</td>
<td>1</td>
<td>1025</td>
<td>0</td>
<td>1033</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>6673</td>
<td></td>
<td>6691</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>320</td>
<td></td>
<td>249</td>
<td></td>
</tr>
</tbody>
</table>

Odds Ratio = 1.32 (1.11 to 1.58)

P = 0.002
ADVANCE study: Trial design

Inclusion criteria:
- Treatment-naïve, HIV-1 RNA level >500 copies/mL in the last 60 days

1053 Participants

- DTG + TAF + FTC
  - n = 351
- DTG + TDF + FTC
  - n = 351
- EFV + TDF + FTC
  - n = 351

Open-label, 96-week study in Johannesburg, South Africa
Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84 and 96
ADVANCE: Mean change in weight (kg) to Week 96: women

- TAF/FTC+DTG
- TDF/FTC+DTG
- TDF/FTC/EFV

Wilcoxon rank-sum comparison at Week 96:
* p<0.05, ** p<0.01, *** p<0.001

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ADVANCE: BMI category over time: women (obese at baseline excluded)
Clinical implications of obesity (BMI >30)

Type II diabetes

Cardiovascular disease: myocardial infarction / death

Alzheimer’s disease

Obstetrics / birth outcomes: Gestational diabetes, Pre-eclampsia, venous thromboembolism, Maternal death, birth defects

4-year reduction in life-expectancy
Predicting clinical consequences: risk equations

Validated, well established risk equations to predict 10-year risks:

Myocardial infarction / death: Framingham, QRISK

Diabetes: QDIABETES

Individual risks can be calculated for each patient in a trial, at baseline and at annual visits.

Other risk equations are available
FRAX Equation


Estimates the 10-year risk of developing bone fractures or hip fracture

Variables included in equation:
- Age
- Sex
- Ethnicity
- Hip Bone Mineral Density (BMD)
- Body Mass Index
- Smoking status
- Alcohol
- History of fractures
- Arthritis
- Use of glucocorticoids
Why do we need a new trial of TDF/FTC vs TAF/FTC in cis-gender women?

TDF/FTC is already very well tolerated as PrEP in women – no clear differences from placebo in meta-analysis. Will there be any significant benefits for TAF/FTC?

No established safety database of TAF/FTC for pregnant women

Concerns over safety of TAF in women – higher chances of weight gain

Branded TAF/FTC is over 30 times more expensive ($1900/month) than generic TDF/FTC ($50 per month in UK, US prices falling) – are these higher prices justified?
Conclusions

It is not clear whether TAF has a better or worse safety profile than TDF.

When TDF is used unboosted, there is no clear evidence for an increase in either bone fractures or Grade 3 / 4 renal adverse events.

Cardiovascular risk equations can be used to predict the 10-year risks of myocardial infarction or diabetes from changes in weight, lipids, glucose and blood pressure for TAF versus TDF.

For African-American women, TDF could be better tolerated—lower risk of clinical obesity.