Financial Relationships With Commercial Entities

- Dr Saag has received research grants and support awarded to his institution from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Merck, and ViV Healthcare. He has also served as a consultant for Bristol-Myers Squibb, Gilead Sciences, Inc, Merck, Teva Pharmaceutical Industries, Ltd, and ViV Healthcare. (Updated 05/10/17)
Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy for an **Elite Controller**?

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Case 1

- 30 yo Male was diagnosed with HIV infection 4 years ago
- Asymptomatic
- **Initial**: HIV RNA < 50 c/ml (HIV DNA positive)
  - CD4 count 870 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype determined from DNA is wild-type
- No prior medical history.
- Ok to start therapy if you think he should

---

Would you choose to start therapy at this time?

1. Yes
2. No
3. Maybe
Elite controllers have higher levels of CD8 "activation" than other aviremic groups, including those on HAART and HIV negatives.

![Graph showing activation levels in different groups](slide6.png)

- Activation higher in elites than other "aviremic" groups even after adjustment of CD4, age and other factors.

Elite controllers also have higher levels of atherosclerosis than HIV negatives, after controlling for all known risk factors.

![Graph showing atherosclerosis levels in different groups](slide9.png)

- Mean intima-medial thickening (mm)

Hsue et al, AIDS 09

Hunt JID 2008

(see also Lopez Abstract 2008)
Question

What regimen should I use as initial therapy?

Case 2

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial**: HIV RNA 28,000 c/ml
  - CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should

At this point which regimen would you choose?

1. TDF / FTC / EFV (fdc)
2. ABC / 3TC / DTG (fdc)
3. TAF / FTC / ELV / c (fdc)
4. TAF / FTC / RPV (fdc)
5. TAF / 3TC (fdc) / DTG (fdc)
6. TAF / FTC / DRV/r (or cobi / fdc)
7. TAF / FTC / ATV/r (or cobi / fdc)
8. TAF / FTC / RAL (once daily)
9. DTG / 3TC
10. Some other option
Case 3
- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- Initial: HIV RNA 760,000 c/ml
  CD4 count 21 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should

At this point which regimen would you choose?
1. TDF / FTC / EFV (fdc)
2. ABC / 3TC / DTG (fdc)
3. TAF / FTC / ELV / c (fdc)
4. TAF / FTC / RPV (fdc)
5. TAF / 3TC (fdc) / DTG (fdc)
6. TAF / FTC / DRV/ r (or cobi / fdc)
7. TAF / FTC / ATV/r (or cobi / fdc)
8. TAF / FTC / RAL (once daily)
9. Some other option
Recommended regimens

**INSTI-based**
- RAL + FTC/TAF (or TDF)
- EVG/COBI/FTC/TAF (or TDF)
- DRV + FTC/TAF (or TDF)
- DTG/FTC/ABC
- EVG/COBI/FTC/TAF (or TDF)

**Alternative regimens**

**NNRTI-based**
- EFV/FTC/TDF
- RPV/FTC/TAF or TDF (VL <100,000; CD4 >200)

**PI-based**
- ATV/c + FTC/TDF (CrCl >70)
- ATV/r + FTC/TDF
- DRV/r + FTC/TDF
- (DRV/c or DRV/r) + 3TC/ABC
- DRV/c + FTC/TDF (CrCl >70)

The 6 initial regimens we'll probably be using most

**INSTI-based**
- EVG/COBI/FTC/TAF
- DRV + FTC/TAF
- DTG + FTC/TAF
- RAL + FTC/TAF (once daily)

**NNRTI-based**
- RPV/FTC/TAF
Minimum Costs of ARV treatments

<table>
<thead>
<tr>
<th>Combination</th>
<th>Estimated price / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/3TC/ATV/r</td>
<td>$279</td>
</tr>
<tr>
<td>TDF/FTC/ELV/c</td>
<td>$184</td>
</tr>
<tr>
<td>ABC/3TC/DTG</td>
<td>$179</td>
</tr>
<tr>
<td>TDF/FTC/EFV600</td>
<td>$144</td>
</tr>
<tr>
<td>TDF/3TC/EFV600</td>
<td>$130</td>
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<tr>
<td>TDF/3TC/EFV400</td>
<td>$100</td>
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<tr>
<td>TAF/3TC/DTG</td>
<td>$60</td>
</tr>
<tr>
<td>DTG/3TC</td>
<td>$46</td>
</tr>
</tbody>
</table>

GREEN – FULLY GENERIC WORLDWIDE IN 2017

RED – STILL PATENTED TO 2025+: VOLUNTARY LICENSES

Question

What regimen should be used as initial therapy when an M184V mutation is present?

Case 4

- 30 yo Female presents with newly diagnosed HIV infection
- Asymptomatic
- Initial: HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype shows M184V mutation
- No prior medical history. No children. Does not plan to become pregnant.
- Ok to start therapy if you think she should
At this point which regimen would you choose?

1. TDF / FTC / EFV (fdc)
2. ABC / 3TC / DTG (fdc)
3. TAF / FTC / ELV / c (fdc)
4. TAF / FTC / RPV (fdc)
5. TAF / 3TC(fdc) / DTG (fdc)
6. TAF / FTC (fdc) / DRV/r (or cobi / fdc)
7. TAF / FTC / ATV/r (or cobi / fdc)
8. TAF / FTC / RAL (once daily)
9. DTG / 3TC
10. Some other option

---

Question

Should I switch from EFV / FTC / TDF (fdc) in a patient who has been on it for the last 10 years?
Case 5

- 45 yo Female referred to you for evaluation
- Diagnosed 10 years ago with HIV infection
- Initial: HIV RNA 36,000c/ml
  - CD4 count 150 cells/ul
- Current: HIV RNA <20 c/ml
  - CD4 count 525 cells/ul
- Generally feels well

At this point you would:

1. Continue her current Antiretroviral Rx
2. Change her ARV Rx to 2 nucs and RPV
3. Change her ARV Rx to 2 nucs and a boosted PI
4. Change her ARV Rx to 2 nucs and an InSTI (integrase inhibitor)
5. Something else
Question

Should I give PrEP to a sero-negative partner of a successfully treated HIV patient?

Case 6

• 45 yo Male makes an appointment to request PrEP
• His partner is HIV positive and has been on successful ARV Rx for 17 years (consistently <50 c/ml)
• Generally feels well
• No significant PMHx
• No medications
• Denies any partners outside of his relationship with his partner

At this point you would:

1. Prescribe PrEP
2. Not prescribe PrEP
3. Not sure what to do
At this point you would:

Prescribe PrEP
Not prescribe PrEP
Not sure what to do.

Case 7

- 46 yo male newly diagnosed 4 years ago
  - HIV RNA 128,000 c/ml (HLA-B5701 negative)
  - CD4 count 280 cells/ul
- On DRV-r / TDF / FTC; HIV RNA < 20 c/ml (CD4 550/ul)
- Initial HIV resistance assay: Wild-type virus
- Smoker / H/o DM / Neg Fam Hx for CAD
- Slow increase in S-creatinine:
  - Now 2.3 mg/dl (eCrCl = 35 cc/min)
- HBsAb+  HBcAb-  HBsAg-

Question

Can I use TAF in patients with impaired renal function?
Which regimen would you start?

1. TDF every other day, FTC, DRV/rit
2. TAF / FTC / DRV/rit
3. ABC / 3TC / DRV/rit
4. TAF / FTC / ELV / cobi
5. ABC / 3TC / DTG
6. TAF / FTC / DTG
7. DRV/ rit / DTG
8. Some other option

TAF vs. TDF: Mechanism of Action

**Question**

Should I stop abacavir in a patient with CAD?
Case 8

- 59 yo male started on ARV Rx years ago (resistance history: wild type virus) returns to you for care after 4 years (Rx’d elsewhere)
- Has been through several regimens; now on ABC/ 3TC / DTG
- Now: HIV RNA < 20 c/ml (persistently)
  - CD4 560 cells/ul
  - Cholesterol 220 mg/dl (HDL 32 / LDL 172)
  - Creat 1.3 / eCrCl = 80 cc/min
- Smoker / Diabetic
- Had a heart attack 4 months ago; medical Rx (ASA, statin, beta blocker)

Besides asking him to quit smoking, what would you do?

1. Continue his current ARV Rx
2. Change his ABC/3TC to TAF / FTC
3. Change his ABC/3TC to DRV/rit
4. Some other option
Universal Definition of MI

Plaque rupture with thrombus

Vasospasm

Supply demand mismatch

Type 1 / Primary

Type 2 / Secondary

MI Classification Protocol

Secondary MIs common in HIV-infected individuals before age 50

<table>
<thead>
<tr>
<th>Condition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis/bacteremia</td>
<td>35</td>
</tr>
<tr>
<td>Cocaine induced/illicit drug</td>
<td>14</td>
</tr>
<tr>
<td>Hypertensive urgency/emergency</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>9</td>
</tr>
<tr>
<td>Non-coronary cardiac</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5</td>
</tr>
<tr>
<td>Procedure related</td>
<td>4</td>
</tr>
<tr>
<td>GI bleed</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic</td>
<td>2</td>
</tr>
<tr>
<td>Overdose</td>
<td>2</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>8</td>
</tr>
</tbody>
</table>

*Crane et al. Am J Epidemiol Apr 15 2014

Question

Should I change a regimen when low level detectable virus is present?
Case 9

- 55 yo male referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
- **Initial:** HIV RNA 936,000c/ml
  CD4 count 70 cells/ul
- **Current:** HIV RNA 85 c/ml (prior value 62 c/ml)
  CD4 count 525 cells/ul
- Started on NEL/D4T/3TC; subsequently treated with
  LOP/r / TDF/FTC
  EFV/ FTC/ TDF (lic).
  Now DTG / DRV/c / 3TC
- No historical resistance tests are available

Should you change ARV therapy now?

1. Yes
2. No
3. Not sure
Question

What regimen should I use as initial therapy in a pregnant patient?

Case 10

- 30 yo Female presents with newly diagnosed HIV infection
- Asymptomatic, 2.5 months pregnant
- **Initial:** HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype is Wild-type virus
- No prior medical history. First pregnancy
- Ok to start therapy if you think she should

At this point which regimen would you choose?

1. TDF / FTC / EFV (fdc)
2. ABC/ 3TC / DTG (fdc)
3. TAF / FTC/ ELV / c (fdc)
4. TDF / FTC / RPV (fdc)
5. TAF/ 3TC(fdc) / DTG (fdc)
6. TDF/ FTC (fdc) / DRV/r (or cobi / fdc)
7. TAF/ FTC / ATV/r  (or cobi / fdc)
8. TDF / FTC / ATV/r  (or cobi / fdc)
9. Some other option
Intracellular concentration of Tenofovir-DP is 4-5 times higher for TAF compared to TDF.

Does this expose the fetus to a higher risk of birth abnormalities?

Does this lower the risk of vertical transmission?

Andrew Hill, 2016 WHO meeting

Dolutegravir in pregnancy: Background

- No fetal toxicity or teratogenicity in animal studies described in manufacturer’s submission for regulatory approval
- High placental transfer of DTG relative to other ARVs in an ex vivo study
- "Unexpected placental transfer of DTG with fetal accumulation and then slow neonatal clearance"
Conclusion

- Debate about whether to treat Elite Controllers
- Presence of M184V does not effect initial Rx much (except for use of ABC at higher viral load)
- Primary and Secondary MIs are distributed equally in HIV patients
- Hold off on using TAF or DTG in pregnant women, pending more data
- Do not need to change ARV therapy if persistent low level viremia

Antiretroviral Therapy: Interactive Cases From the Clinic(ians): Case-Based Panel Discussion

Michael S. Saag, MD
Professor of Medicine
Associate Dean for Global Health
University of Alabama at Birmingham
Birmingham, Alabama

Question

How can I simplify a complex regimen in a highly treatment-experienced patient?
Case 4

- 57 year old man diagnosed with HIV in 1991; multiple opportunistic infections and complains of ‘Pill Fatigue’
- Has taken most existing antiretroviral drugs available; no exposure to maraviroc, DTG, or ELV
- Currently on TDF / FTC / ETV / DRV-t / RAL (1st InSTI)
  - CD4+ count 330 / uL (nadir CD4 = 6)
  - HIV RNA <40 c/mL (max VL 667,000)

Case 12

- 57 year old man diagnosed with HIV in 1991; multiple opportunistic infections and complains of ‘Pill Fatigue’
- Has taken most existing antiretroviral drugs available; no exposure to maraviroc, DTG, or ELV
- Currently on TDF / FTC / ETV / DRV-t / RAL (1st InSTI)
  - CD4+ count 330 / uL (nadir CD4 = 6)
  - HIV RNA <40 c/mL (max VL 667,000)

At this point which regimen would you choose?

1. Continue current therapy  (9 pills)
2. TAF / FTC / ELV / c (fdc) / DRV/c (2 pills)
3. ABC/ 3TC / DTG (fdc) / DRV/c  (2 pills)
4. TAF / FTC / RAL / DRV/c  (4 pills)
5. TAF / FTC / DTG / DRV/c  (3 pills)
6. Some other regimen