Financial Relationships With Commercial Entities

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Learning Objectives

After attending this presentation, learners will be able to select antiretroviral therapy in patients who:

- Are starting initial therapy
- Are Elite Controllers
- Are debating between starting TDF or TAF
- Are pregnant
- Have persistent low-level viremia
- Have M184V at baseline
- Have a slow CD4 count response to Rx
Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy immediately at time of diagnosis?

Case 1

• 30 yo male was diagnosed with HIV infection 4 hours ago in the ER
• Asymptomatic
• Initial: No Viral Load, CD4, Resistance Data, or HLA-B57 neg
• Other labs are normal
  WBC 3800 / Lymphocytes 20%
• No prior medical history.
• Ok to start therapy if you think he should

ARS Question 1: When would you choose to start therapy?

1. Right now in the ED
2. Within 1 - 2 days (outpt Clinic)
3. In the next 2 weeks (outpt Clinic)
4. Within 2 – 4 weeks
5. Some other option
Question

What regimen should I use as initial therapy for this patient?

ARS Question 2: At this point which regimen would you choose?

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. ABC/ 3TC / DTG (fdc)
3. TAF / FTC (fdc) + DTG
4. DTG + 3TC
5. TAF / FTC / ELV / cobi (fdc)
6. TAF/ FTC / BIC (fdc)
7. TAF / FTC (fdc) + RAL (once daily)
8. TAF / FTC / RPV (fdc)
9. TAF/ FTC (fdc) + DRV/r (or cobi / fdc)
10. Some other option (e.g., DRV/r + DTG or …)

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
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should

**ARS Question 3:** At this point which regimen would you choose?

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. ABC/ 3TC / DTG (fdc)
3. TAF / FTC (fdc) + DTG
4. TAF / FTC / ELV / cobi (fdc)
5. TAF / FTC / BIC (fdc)
6. 3TC/DTG (fdc)
7. TAF / FTC / RPV (fdc)
8. TAF / FTC (fdc) + DRV/r (or cobi / fdc)
9. Some other option (e.g., DRV/r + DTG or …)

**ARS Question 4:** Would you use TAF or TDF with an InSTI?

1. TAF
2. TDF
3. Either
ADVANCE

DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC

NEJM 381: 803-15, 2019

Renal Toxicity

Hill et al. J Viral Erad 4:73, 2018, updated
Bone Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Event</th>
<th>Total</th>
<th>Weight</th>
<th>M.A. Adjusted (V0, C)</th>
<th>M.A. Adjusted (V1, C)</th>
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<tbody>
<tr>
<td>Unboosted</td>
<td>0</td>
<td>360</td>
<td>2</td>
<td>358</td>
<td>6.00 (0.81, 0.10)</td>
<td>6.00 (0.81, 0.10)</td>
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<tr>
<td>Enhanced</td>
<td>0</td>
<td>916</td>
<td>1</td>
<td>915</td>
<td>5.67 (0.85, 0.10)</td>
<td>5.67 (0.85, 0.10)</td>
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<tr>
<td>ART-526</td>
<td>0</td>
<td>516</td>
<td>0</td>
<td>516</td>
<td>3.66 (0.85, 0.10)</td>
<td>3.66 (0.85, 0.10)</td>
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<tr>
<td>52-09-520</td>
<td>0</td>
<td>535</td>
<td>0</td>
<td>535</td>
<td>3.23 (0.85, 0.10)</td>
<td>3.23 (0.85, 0.10)</td>
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<tr>
<td>Total-10</td>
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<td>1578</td>
<td>1</td>
<td>1577</td>
<td>6.76 (0.85, 0.10)</td>
<td>6.76 (0.85, 0.10)</td>
</tr>
</tbody>
</table>

Test for event: Z = 2.02 (P = 0.04)

Question

Does InSTI therapy cause weight gain?

Case 3

- 47 yo female starts on BIC/FTC/TAF 12 months ago from her original ARV regimen (TDF/FTC/DRV/r)
- Diagnosed 4 years ago
- Initial: HIV RNA 28,000 c/ml (Wildtype virus)
  CD4 count 450 cells/ul
- Current: HIV RNA <20 c/mL / CD4+ count 930 /ul
- Since starting her current regimen her weight has increased from 145 lbs to 171 lbs
ARS Question 5: At this point you would

1. Keep her on her current Rx (TAF/FTC/BIC)
   Or Switch her to:
2. TDF/ FTC (dfc) / DRV/r
3. TAF/ FTC / DRV/c (dfc)
4. TDF / FTC / RPV (dfc)
5. DTG / RLP (dfc)
6. TAF / FTC / ATV/c
7. Some other option

Change in Weight Overtime – NA-ACCORD
Bourgi et al CROI 2019

Change in Weight Overtime – NA-ACCORD
Bourgi et al CROI 2019
What regimen should I use as initial therapy in a pregnant patient?
Case 4

- 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

**ARS Question 6: At this point which regimen would you choose?**

1. TDF / FTC / EFV (fdc)
2. ABC/ 3TC / DTG (fdc)
3. TAF / FTC/ ELV / cobi (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

**Prospective Antiretroviral Pregnancy Registry (APR):**
Integrase Inhibitors (INSTI) and Neural Tube Defects (NTD)

Albano J et al.  CROI 2019 Seattle, WA Abs. 747

- 1,193 live births with INSTI exposure at any time in pregnancy; 604 periconceptional exposure, including 174 DTG, 186 EVG, 244 RAL.
- 2 CNS defect cases were reported with INSTI exposure at any time (both DTG, one 1st trimester, one 2nd/3rd trimester).
- There were no NTD among prospective cases for any INSTI drug.

<table>
<thead>
<tr>
<th>Earliest Trimester of Exposure</th>
<th>Prospective Cases</th>
<th>Periconception</th>
<th>1st Trimester</th>
<th>2nd/3rd Trimester</th>
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</thead>
<tbody>
<tr>
<td>Exposure to any INSTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/604 (2.6%)</td>
<td>6/192 (3.1%)</td>
<td>10/412 (2.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/637 (2.3%)</td>
<td>5/271 (1.9%)</td>
<td>10/366 (2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/112 (4.5%)</td>
<td>3/69 (4.3%)</td>
<td>2/43 (4.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- There were no NTD among prospective cases for any INSTI drug.
More Rapid VL Decline with Dolutegravir than Efavirenz

Primary outcome
- Time on medication before delivery, median 55 days

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Dolutegravir</th>
<th>Efavirenz</th>
<th>aRR DTG vs EFV*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;50</td>
<td>73.8% (90/122)</td>
<td>42.6% (49/115)</td>
<td>1.66 (1.2, 2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VL &lt;1000</td>
<td>82.6% (153/188)</td>
<td>63.8% (120/191)</td>
<td>1.11 (1.0, 1.2)</td>
<td>0.0513</td>
</tr>
</tbody>
</table>

*Adjusted for age, country, VL (<> 100,000), CD4 (<> 200), GA at start ART

Recommendations of Perinatal Guidelines Panel: DTG (November 2019)

- DTG is a preferred INSTI for ART-naïve women irrespective of trimester
  - For pregnant women receiving DTG and present to care in 1st trimester, counsel about risks/benefits of continuing DTG vs switch to alternative regimen. In most cases, continuation of DTG is recommended (AIII)
  - NTDs may have already occurred
  - Additional risk of NTD may be small, depending on current GA
  - Background risk of NTD (0.06% in US)
  - Changes in ART, even in 1st trimester, may increase risk of viral rebound
- DTG + TDF/FTC is recommended with acute HIV in pregnancy
- DTG is an alternative agent for women trying to conceive

Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy for an Elite Controller?
Case 5

- 30 yo male was diagnosed with HIV infection 7 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

ARS Question 7: Would you choose to start therapy at this time?

1. Yes
2. No
3. Maybe

T cell “activation” is lower in treated than untreated adults, but consistently higher than “normal”
Question

What do I do with a patient who has persistently detectable viremia?

Case 6

- 55 yo male referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
- Initial: HIV RNA 936,000 c/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 (did).
  - Now DTG/ DRV/r / 3TC
- No historical resistance tests are available

ARS Question 8: Should you change ARV therapy now?

1. Yes
2. No
3. Not sure
Virologic Responses on Antiretroviral Therapy

**Virologic Suppression**


A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

**Virologic Blip**


After virologic suppression, an isolated detectable HIV RNA level followed by return to virologic suppression.

HIV infected cells can be categorized as:
- Latently infected CD4+ lymphocytes
- HIV virions
- Uninfected activated CD4+ lymphocytes
- Uninfected resting CD4+ lymphocytes
**All-cause mortality**

<table>
<thead>
<tr>
<th>Unadjusted model</th>
<th>Fully adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV 50-100 copies/mL</td>
<td>1.7 (1.2-2.4)</td>
</tr>
<tr>
<td>High-level viremia</td>
<td>2.6 (2.0-3.6)</td>
</tr>
<tr>
<td>HIV 90-1,000 copies/mL</td>
<td>2.3 (1.8-3.3)</td>
</tr>
<tr>
<td>HIV 200-3,000 copies/mL</td>
<td>1.2 (0.8-2.1)</td>
</tr>
<tr>
<td>High-level viremia</td>
<td>2.6 (2.0-3.6)</td>
</tr>
</tbody>
</table>

**Virologic Responses on Antiretroviral Therapy**

**Virologic Failure**

**Question**

How do I manage a heavily experienced patient who is experiencing virologic failure?
Prevalence of Patients with Limited Treatment Options

Virologic Success in Those with or without LTO

Discussion

- Confirm the virologic failure
- Explore all prior regimens and resistance tests
- Identify 2 fully active drugs (if possible)
  - Use Dolutegravir (50 mg) twice daily
  - Some form of Tenofovir (as long as no K65R)
  - Boosted darunavir
  - 3TC or FTC (despite resistance)
    - Ibalizumab
    - Fostemsavir
Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of tamsuvir (TMR)
- Inhibits CD4 binding by binding to gp120
- PK suggests daily dosing without boosting
- Phase 1 dose-escalation over 8 days
  - 5 doses (4 with RTV)
  - up to 1.5 log cps/ml ↓
  - ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms

Nettles JID 2012;206:1002

Fostemsavir (FTR): BRIGHTE (Phase 3)

- Heavily rx-experienced (1-2 remaining ART classes)
- NOT screened for susceptibility
  - Randomized to FTR 600 mg bid or placebo
  - Those with no remaining ART classes non-randomized
  - Day 8 (primary endpoint):
    - mean HIV RNA c. -0.2 log (placebo) vs. -0.8 cps/ml (FTR) (p<0.0001)
  - Then, optimized background ART
  - wk 48: VL <40: 54% (randomized) vs. 38% (non-randomized)
  - Approved July 2020

Aberg/Ackerman Glasgow 2018 #344

Conclusions

- ARV therapy should be initiated with an InSTI-based regimen (unless otherwise indicated), as close to time of Dx as possible
- Do not change Rx in setting of low-level viremia
- Do not change Rx in setting of low CD4 count response
- DTG is drug of choice in (most) pregnant women (GIVE FOLATE)
- Weight gain is associated with initiation of ARV Rx, with more weight gain observed in InSTI- and TAF-containing regimens
- Use two active drugs (if possible) in treating Virologic Failure
Question-and-Answer Session