Initial Treatment of HIV

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Thank you to Delaney Taylor for assistance with these slides
Learning Objectives

• Individualize initial antiretroviral therapy for a person with HIV infection

• Evaluate new options for treating HIV

Faculty and Planning Committee Disclosures

• Please consult your program book or the conference App

• Any off-label or investigational uses will be indicated in the presentation
Outline

• When to Start

• What to Start
  – In most people with HIV
  – In persons in whom integrase inhibitors are not optimal
  – In a woman of child-bearing potential considering pregnancy
  – Two drug therapy
  – Future ART

ARS Question: When to Start

• 40 yo MSM with fever and sore throat for 1 week. Recent new sexual partner.
• No other medical conditions. Exam normal.
• HIV Ab/Ag positive; HIV differentiation Ab negative; HIV RNA 10 million.
• CD4 cell count pending; creatinine pending; genotype pending; HLA-B5701 pending.
• He says he’s willing to start treatment
• When would you start ART?
  1) Same day
  2) Within 2-3 days
  3) When all his labs return (7-10 days later)
  4) Next available clinic slot (4 weeks later)
HIV Therapy Recommended Regardless of CD4: START

- HIV-infected adults with CD4 >500
- Randomized to immediate or deferred ART
- TB, KS, lymphoma — most common AIDS-related events — all less frequent in immediate-ART group
- Cancer rates (combining AIDS/non-AIDS) lower in immediate-ART group

When to Start ART in Patients with Acute OI: ACTG 5164

- 282 HIV pts with acute OI
- ~2/3 PCP. TB excluded
- Randomized to:
  - Early ART: ~2 wks after OI therapy
  - Deferred ART: ~6 wks after OI therapy
- Rate of AIDS progression/death lower in “early” ART group
When to Start ART in Patient with OI

<table>
<thead>
<tr>
<th>OI</th>
<th>When to start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidiosis, microsporidiosis, PML</td>
<td>As part of initial therapy of OI</td>
</tr>
<tr>
<td>PCP, MAC, Toxoplasma, most other OIs</td>
<td>Within 2 weeks</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>If CD4 &lt;50: within 2 wk</td>
</tr>
<tr>
<td></td>
<td>If CD4 &gt;50: within 8-12 wks</td>
</tr>
<tr>
<td></td>
<td>(TB meningitis: close monitoring/consultation)</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>4-5 wks after anti-fungal Rx</td>
</tr>
</tbody>
</table>

When patient presents with OI or low CD4 count, ART should be started in hospital or soon after discharge


Should ART be started on day of diagnosis?

- **International studies**
  - **South Africa** (Rosen S et al PLoS Med 2016)
  - **Haiti** (Koenig S et al, PLoS Med 2017)
  - **Lesotho** (Labhardt ND et al. JAMA 2018)
- **US**
  - **San Francisco** (Pitcher CD et al, JAIDS 2016; Coffey S et al, AIDS, 2019)
  - **Atlanta** (Colasanti J et al, OFID, 2018)
- **My take:**
  - Each care setting should develop sustainable programs to deliver ART as quickly as possible: same-day or soon thereafter

**Diagram:**

- **Time to VL suppression**
  - **RAPID**
  - **Standard of care universal ART**
  - **CD4-guided ART (started when <500)**

Median time from referral to viral suppression, 1.8 mo in RAPID vs. 4.3 mo. in Standard p<0.001
ARS Question: What to Start

- 40 yo MSM with fever and sore throat for 1 week. Recent new sexual partner.
- HIV Ab/Ag positive; HIV differentiation Ab negative; HIV RNA 10 million.
- CD4 cell count pending; creatinine pending; genotype pending; HLA-B5701 pending.
- He says he’s willing to start treatment. What do you start?
  1) Dolutegravir + FTC/tenofovir AF
  2) Bictegravir/emtricitabine/tenofovir AF
  3) Dolutegravir/abacavir/lamivudine
  4) Dolutegravir + lamivudine
  5) Doravirine/lamivudine/tenofovir DF
  6) Darunavir/cobi/FTC/tenofovir AF
  7) Something else

Choosing An Initial Regimen
ART 2019: > 30 options

### Nucleoside/nucleotide RTIs (NRTI)
- Zidovudine, AZT (Retrovir)
- Abacavir, ABC (Ziagen)
- Lamivudine, 3TC (Epivir)
- Didanosine, ddl (Videx)
- Stavudine, d4T (Zerit)
- Tenofovir DF, TDF (Viread)
- Emtricitabine, FTC (Emtriva)
- AZT/3TC (Combivir)
- AZT/3TC/ABC (Trizivir)
- ABC/3TC (Epzicom)
- TDF/3TC (Cimduo)

### Protease inhibitors (PI):
- Indinavir, IDV (Crixivan)
- Saquinavir, SQV (Invirase)
- Nelfinavir, NFV (Viracept)
- Amprenavir, APV (Agenerase)
- Atazanavir, ATV (Reyotaz)
- Osaprenavir, PPV (Lexiva)
- Lopinavir/ritonavir (Kaletra)
- Tipranavir (Aptivus)
- Darunavir (Prezista)
- Darunavir/cobicistat (Prexobiax)
- Atazanavir/cobicistat (Evotaz)

### Non-nucleoside RTIs (NNRTI)
- Delavirdine (DLV)
- Nevirapine, NVP (Viramune)
- Efavirenz, EFV (Sustiva)
- Etravirine, ETR (Intelicence)
- Rilpivirine, RPV (Edurant)
- Doravirine, DOR (Pifeltro)

### CCR5 receptor blocker
- Maraviroc (Selzentry)

### Fusion inhibitors
- Enfuvirtide, ENF, T20 (Fuzeon)
- CD4 Post-attachment inhibitor
- Ibalizumab (Trogarzo)

### Single pill combinations (n=10)
- EFV/FTC/TDF (Atripla)
- EFV/3TC/TDF (Symfji)
- EFV400/3TC/TDF (Symfji-lo)
- RPV/FTC/TDF (Complera)
- RPV/FTC/TAF (Odefsey)
- EVG/cobi/FTC/TDF (Strihibl)
- EVG/cobi/FTC/TAF (Genvoya)
- DTG/ABC/3TC (Triumeq)
- BIC/TAF/TAF (Bikarvy)
- DOR/TDF/3TC (Delstrigo)

### Integrase strand transfer inhibitors (INSTIs)
- Raltegravir, RAL (Isentress)
- Elvitegravir, EVG
- Dolutegravir, DTG (Tivicay)
- Bictegravir, BIC

### What to Start in Most People with HIV:
Integrase Inhibitor + 2 NRTI

<table>
<thead>
<tr>
<th>DHHS (10/2018) Recommended for Most People with HIV</th>
<th>IAS-USA (7/2018) Recommended Initial Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir/TAF/FTC</td>
<td>Bictegravir/TAF/FTC</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/3TC</td>
<td>Dolutegravir/abacavir/3TC</td>
</tr>
<tr>
<td>Dolutegravir + TAF/FTC or TDF/FTC</td>
<td>Dolutegravir + TAF/FTC</td>
</tr>
</tbody>
</table>

- Fewer long-term safety and efficacy data with BIC than with DTG
- If substantial cost difference, TDF (with FTC or 3TC) is effective and generally well-tolerated, esp. if pt not at high risk for bone, renal disease
- Differences between TAF and TDF accentuated when TDF is used with ritonavir or cobicistat

References:
<table>
<thead>
<tr>
<th>Regimen</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/3TC/DTG</td>
<td>• Not nephrotoxic</td>
<td>• Must confirm HLA-B5701 negative</td>
</tr>
<tr>
<td></td>
<td>• Single pill combination</td>
<td>• Some studies, but not all, show association with cardiac events</td>
</tr>
<tr>
<td>TDF/FTC + DTG</td>
<td>• TDF lowers lipids</td>
<td>• Greater nephrotoxicity than ABC and TAF (avoid if CrCl &lt;60)</td>
</tr>
<tr>
<td></td>
<td>• Good option for HIV/HBV</td>
<td>• Larger decline in bone mineral density than with ABC or TAF (avoid in people with osteoporosis)</td>
</tr>
<tr>
<td>TAF/FTC + DTG</td>
<td>• TAF has more favorable effects on renal and bone markers than TDF</td>
<td>• Two pills per day</td>
</tr>
<tr>
<td></td>
<td>• Good option for HIV/HBV</td>
<td>• Do not use TAF if CrCL &lt;30</td>
</tr>
<tr>
<td>TAF/FTC/BIC</td>
<td>• Single pill combination</td>
<td>• Less long-term data</td>
</tr>
<tr>
<td></td>
<td>• Good option for HIV/HBV</td>
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Expert opinion

Customizing ART: Drug Interactions

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Therapy Anticipated</td>
<td>Often use raltegravir, dolutegravir, bictegravir: fewer drug interactions</td>
</tr>
<tr>
<td>Acid-lowering therapy</td>
<td>Avoid or caution: rilpivirine, atazanavir</td>
</tr>
<tr>
<td>CYP3A4 metabolized medications, including many inhaled and injected steroids(^1)</td>
<td>Avoid or caution with PIs, cobi (Among inhaled steroids, beclomethasone OK to use with PIs, cobi(^2))</td>
</tr>
</tbody>
</table>

Useful site: [http://www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)

\(^1\)Hyle E et al, JAIDS, 2013; \(^2\)Boyd S et al, JAIDS, 2013
Are integrase inhibitors perfect for everyone with HIV?

### Integrase Inhibitor Drug Interactions

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvalent Cations</td>
<td>Stagger dosing of integrase inhibitors</td>
</tr>
<tr>
<td>Metformin</td>
<td>DTG doubles metformin exposure; don’t exceed &gt;1000 mg daily</td>
</tr>
</tbody>
</table>

[http://www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
Weight Gain and Integrase Inhibitors

• NA-ACCORD: observational study of 24,001 participants initiating ART
  – INSTIs, PIs associated with greater weight increase than NNRTI
  – DTG and RAL associated with greater weight gain than EVG

![Graph showing weight gain over time for different ART groups](image)

Bourgi K et al, CROI 2019, #670

Weight Gain and Integrase Inhibitors

• Switch studies showing association between INSTIs and weight gain:
  – ACTG (n=972): increased weight after switching to INSTI; DTG associated with greatest gain
  – HOPS: BMI trajectory slopes: DTG > RAL or EVG
  – WIHS: observational switch study in women

• Studies showing mixed result or no association:
  – TRIO study: associated in bivariate analysis, not multivariable model
  – HPTN 077: Cabotegravir in people without HIV

Lake J et al, CROI 2019, #669; Kerchberger A et al, CROI 2019, #672; Pallela F et al, CROI 2019, #674; McComsey G et al, CROI 2019, #671; Landovitz R et al, CROI 2019, #34
My Take: Are INSTI-Based Regimens associated with weight gain?

• Accumulating data that INSTI-based regimens may be associated with greater weight gain than some other regimens; randomized data from initial therapy trials needed

• Whether there are differences between INSTIs and the role of the NRTI in the regimen are uncertain

• Mechanism of weight gain and distribution of fat after initiation of modern regimens, including INSTI-based therapies, should be evaluated

• In patients with significant weight gain, the impact of changing to a non-INSTI based regimen needs to be studied

Other Treatment Options When You Don’t Think an Integrase Inhibitor is Optimal

• Generic EFV/TDF/3TC

• Rilpivirine/FTC/TDF or Rilpivirine/FTC/TAF
  – Food requirement (about 400 calorie meal)
  – Do not use with proton-pump inhibitor; stagger dosing if on H2 blocker

• Doravirine/3TC/TDF or Doravirine + FTC/TAF

• Darunavir/cobi/FTC/TAF
  – Drug interactions with CYP3A4 metabolized medications
Doravirine: A New NNRTI

• Active in vitro against HIV resistant to first-generation NNRTI (K103N, Y181C, G190A, E101K, E138K)\(^1\)
• Once daily. Low potential for drug interactions
• In phase 3 randomized trials (DRIVE-FORWARD\(^2\), DRIVE-AHEAD\(^3,4\)), non-inferior to darunavir/ritonavir and efavirenz in virologic suppression
  – DOR: better lipid effects than DRV/r; fewer neuropsychiatric effects than EFV
• In switch study (DRIVE-SHIFT)\(^5\), changing to DOR/3TC/TDF non-inferior to continuing baseline ART
• DOR available alone and coformulated with TDF/3TC

\(^1\)Lai AAC 2014;58:1652-1663. \(^2\)Molina JM, 22nd IAC, Abstract LBPEB017. \(^3\)Orkin. IDWeek 2018. Abstr LB1.
**Doravirine (DOR) Resistance**

- 7/747 (0.9%) in phase 3 DOR trials developed resistance
  - V106I and F227C
  - F227C: hypersusceptible to some NRTI, including the investigational agent, MK-8591 (NRTTI) (in phase 2 with DOR and 3TC)
- Most isolates with DOR mutations remain susceptible to ETR
- Most EFV-resistant viruses remain susceptible to DOR

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**Darunavir/cobi/FTC/TAF**

- High virologic suppression rate
- High barrier to resistance: no participant in phase 3 AMBER study developed tenofovir or DRV resistance
- Promising results in single arm DIAMOND study of rapid initiation (n=109): ~90% virologic suppression rate
ARS Question

32 yo F with HIV. She and her boyfriend (who is not infected with HIV) are hoping to have children soon. Which regimen do you start?

1. Dolutegravir + FTC/tenofovir DF
2. Bictegravir/FTC/tenofovir AF
3. Elvitegravir/cobi/FTC/tenofovir AF
4. Raltegravir + FTC/tenofovir DF
5. Raltegravir + FTC/tenofovir AF
6. Atazanavir/r + 3TC/tenofovir DF
7. Something else

Pregnancy and ART

• Approximately 5000 women with HIV give birth each year in the US

• Comprehensive care, including ART during pregnancy, improves maternal outcomes and prevents HIV transmission to the infant

• Regardless of CD4 cell count, ART should be started as early as possible during pregnancy or, even better, before conception

### Birth Outcomes When EFV or DTG Started During Pregnancy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EFV/TDF/FTC (N=4,593)</th>
<th>DTG/TDF/FTC (N=1,729)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse outcome</td>
<td>35.0%</td>
<td>33.2%</td>
</tr>
<tr>
<td>Any severe adverse outcome</td>
<td>11.3%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Preterm &lt;37 wk GA</td>
<td>18.5%</td>
<td>18.0%</td>
</tr>
<tr>
<td>Very preterm &lt;32 wk GA</td>
<td>3.8%</td>
<td>3.5%</td>
</tr>
<tr>
<td>SGA 10%ile wt for GA</td>
<td>18.5%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Very SGA 3%ile wt for GA</td>
<td>6.1%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>1.3%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Zash R et al., *Lancet Global Health* 2018;6:e804-10

### Tsepmamo: Birth Outcomes Surveillance Study in Botswana

- Dolutegravir at conception and neural tube defects (NTD)
  - May 1, 2018: 4 infants with NTD born among 426 women
  - July 15, 2018: 1 additional infant with NTD exposed to DTG during pregnancy [8 wks gestational age]
  - Updated prevalence: 4/596 (0.67%, 95% CI 0.26%, 1.7%)
  - Next formal analysis: after 3/19

What to Start in Pregnancy: DHHS Guidelines Dec 7, 2018

**Two NRTIs**
- Abacavir/3TC
- or
- TDF/FTC or TDF/3TC

**Integrase inhibitor:**
- Raltegravir (twice daily) or
- Dolutegravir (after 1st trimester)
  - or
- Protease inhibitor:
  - Darunavir/ritonavir (twice daily) or
  - Atazanavir/ritonavir

**DO NOT USE:**
- TAF (insufficient data)
- Bictegravir (insufficient data)
- Elvitegravir/cobi (PK concerns)
- DRV/cobi (PK concerns)
- ATV/cobi (PK concerns)
- DOR (insufficient data)

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**What is the role of two-drug therapy for HIV?**
ARS Question

- 50 yo HIV+ M with diabetes, hypertension, chronic renal insufficiency (creatinine clearance of 25)
- HIV RNA 30,000, CD4 cell count 450
- HLA-B5701 positive
- You want to choose a regimen that avoids TAF, TDF, ABC

1. Darunavir/cobicistat + FTC
2. Darunavir/ritonavir + raltegravir
3. Darunavir/ritonavir + dolutegravir
4. Darunavir/ritonavir + 3TC
5. Dolutegravir + 3TC
6. Dolutegravir + rilpivirine
7. Atazanavir + elvitegravir/cobicistat

NRTI-limiting Regimens for Initial Therapy

- **DRV/r + RAL (NEAT001)\(^1,2\)**
  - Non-inferior to DRV/r + TDF/FTC
  - CD4 <200: DRV/r + RAL inferior to DRV/r + 2 NRTI
  - VL >100 K: more failures with DRV/r + RAL

- **DRV/r + 3TC\(^3\) (ANDES)**
  - Non-inferior to DRV/r + FTC/TDF (n=145)

GEMINI-1 and -2 Studies: 
Dolutegravir + Lamivudine in Treatment-Naïve Patients

Identical phase 3 studies
Treatment-naïve
Double-blind (week 0-48)
Open-label (week 48-144)
Non-inferiority
HIV RNA >1K-500K copies/mL
No major IAS-USA resistance mutations
No HBV or need for HCV therapy

Who was in GEMINI?
Male: 85%.
Age: 32-33 years.
Black: 12%.
HIV RNA level:
Mean: 4.4 log₁₀ copies/mL
>100K copies/mL: 20%.
CD4 count:
Mean: 462 cells/µL.
≤200 cells/µL: 8%.

Drop in VL comparable between 2DR and 3DR


Eron J et al, HIV DART and Emerging Viruses, 2018, Miami, FL.
GEMINI-1 and -2 Studies: Pooled Virologic Outcomes With Dolutegravir + Lamivudine in Treatment-Naive Patients

No treatment-emergent INSTI or NRTI mutations in either arm

My take: Are 2-Drug Regimens Optimal for Most Persons With HIV?

- For initial therapy, DTG + 3TC looks promising
  - Single-tablet formulation of DTG/3TC approved by FDA on April 8, 2019 for initial treatment of adults with no known or suspected resistance to its components
    - One pill once daily with or without food
    - Should not be used in people with HIV/HBV (test for HBV)
  - Longer term data awaited before guidelines recommend DTG/3TC for most persons with HIV
  - In a patient for whom ABC, TAF and TDF are not optimal, DTG/3TC is a recommended regimen

Future ART?

• Injectable Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI – both are investigational
• Long-acting formulations; half-lives of months
• Phase 3 studies
  • FLAIR: Treatment naïve people with HIV; suppress with oral ART; then switch to monthly IM LA CAB/RPV or continue oral ART
  • ATLAS: Suppressed people with HIV; switch to monthly IM LA CAB/RPV or continue oral ART
  • ATLAS-2M (ongoing): Suppressed people with HIV; every 4 week vs. every 8 week IM LA CAB/RPV

FLAIR: Monthly Injectable CAB/RPV
Non-inferior to Oral ART

<table>
<thead>
<tr>
<th>Virologic Outcomes</th>
<th>Adjusted Treatment Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic response (&lt;50 c/mL)</td>
<td>CAB LA + RPV LA vs DTG/ABC/3TC</td>
</tr>
<tr>
<td>Proportion of Participants (%)</td>
<td>93.6 vs 93.3</td>
</tr>
</tbody>
</table>

Similar results in ATLAS: in people who are virologically suppressed, CAB/RPV comparable to continuing oral ART

Summary

• When to Start? Initiate ART in people with HIV as soon as possible
• Integrase inhibitor based regimens are preferred for most people with HIV
• Options when integrase inhibitors are not optimal include NNRTI- and PI-based regimens
• In women considering pregnancy, pay special attention to safety of different regimens
• Accumulating data supporting 2-drug therapy; longer-term follow-up needed
• Injectable long-acting regimens advancing