HIV 101: Evaluation and Treatment of People Newly Diagnosed with HIV

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Pretest Question #2
A woman in her 30s, who is in her 2nd trimester of pregnancy, is diagnosed with HIV. Which of the following antiretroviral medications should not be prescribed?
1. Dolutegravir
2. Raltegravir
3. Atazanavir/ritonavir
4. Darunavir/ritonavir
5. Atazanavir/ritonavir
Case

- 45 yo MSM is tested for HIV
- HIV 4th generation antigen/antibody and confirmatory tests are positive
- No previous HIV testing
- He asks you the following questions:
  - When should I start therapy for HIV?
  - What should I be treated with?
  - What are the options if I don’t want to take a medicine every day?

Approach to a Person with HIV: 3 Steps

Step 1: History, examination, and lab tests
Step 2: Opportunistic infection prophylaxis (if indicated)
Step 3: Antiretroviral therapy: when and what to start

Step 1: History and Exam

- Risk behaviors; approx. date of infection
- Exposures: tuberculosis, endemic fungi, sexually transmitted infection (STIs)
- Medications, including alternative meds
- Disclosure
- Exam:
  - Skin
  - Fundoscopic exam → ophthalmologist if CD4 <50 (risk of cytomegalovirus retinitis)
  - Oropharynx
  - Lymph nodes → biopsy if dominant node, rapid enlargement
  - Cervical pap; rectal exam for anal masses, cytology
Dermatologic & Oropharyngeal Findings

Protopus nodularis
Kaposi Sarcoma
Aphthous ulcers
Oral candidiasis

Lab Evaluation: Routine Tests

- Chemistries, BUN/Cr, liver enzymes
- CBC/diff
- Lipids and glucose (repeat fasting if abnormal)
- G6PD: blacks; males from Mediterranean, India, Southeast Asia
- Urinalysis (U/A)

Labs: Screening for Infection

- Serologic testing for infections that can reactivate:
  - If CD4 count <100/µl: toxoplasma IgG, consider serum cryptococcal antigen
  - Varicella IgG if no history of chickenpox or shingles
  - Tuberculin skin test (TST) or IGRA (IGRA preferred if history of BCG vaccination)
    - TST >5 mm is positive in PWH
    - If negative and CD4 count <200/µl, repeat TST or IGRA after immune reconstitution
- STI screening (syphilis, GC, chlamydia): annually; every 3-6 months if exposures; in MSM: urethral, rectal, oral
- Hepatitis serologies (A, B, C)
  - HCV antibody annually for at-risk MSM, people who inject drugs

Images courtesy of www.idimages.org.
Images courtesy of U.S. Army photo.
Images courtesy of MSF, Michael Shawn, and MaxPixel.
Lab Evaluation: HIV-specific Tests

- CD4 cell count:
  - Best predictor of risk of opportunistic infection or cancer
  - Used to decide when to start opportunistic infection prophylaxis
- HIV RNA ("viral load")
  - Most important predictor of response to therapy; should decline to undetectable within few months of starting treatment

HIV Resistance Testing

<table>
<thead>
<tr>
<th>Patient</th>
<th>Resistance Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly Diagnosed or Treatment Naive</td>
<td>Genotype – mutations in viral genes</td>
</tr>
<tr>
<td></td>
<td>(Reverse transcriptase and protease)</td>
</tr>
<tr>
<td>Virologic Failure to 1st or 2nd Lines of Therapy</td>
<td>Genotype (Integrate genotype if integrase inhibitor is failing)</td>
</tr>
<tr>
<td>Suspected Complex Resistance Resistance</td>
<td>Phenotype and Genotype</td>
</tr>
</tbody>
</table>

Interpretation:
- www.islaa.org/content/hiv-drug-resistance-mutations
- Stanford HIV Drug Resistance: http://hivdb.stanford.edu/

Approach to the Person with HIV: 3 Steps

- **Step 1**: History, Examination and Lab Tests
- **Step 2**: Opportunistic infection (OI) prophylaxis (if indicated)
- **Step 3**: Antiretroviral therapy
Case - Continued

- 45 yo MSM with newly diagnosed HIV
- PMH: gastroesophageal reflux disease (GERD), allergic rhinitis, hypertension, smoking, elevated lipids
- Medications: omeprazole, fluticasone
- Cr 1.5 (estimated GFR = 48)
- CD4 count 550, HIV RNA 650,000 copies/mL
- HIV genotype: no resistance mutations
- HbsAg negative

Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

- Pneumocystis pneumonia (PCP) prophylaxis (trim/sulfap DS daily) if:
  - CD4 count <200 (CD4 percentage <14)
  - History of thrush
- Mycobacterium avium complex prophylaxis no longer routinely recommended

Approach to the Person with HIV: 3 Steps

- Step 1: History, Examination and Lab Tests
- Step 2: Opportunistic infection prophylaxis (if indicated)
- Step 3: Antiretroviral therapy: when and what to start
When should I start treatment?
HIV Therapy Recommended Regardless of CD4: START

- Adults with HIV and CD4 >500
- Randomized to immediate or deferred ART (CD4 <350)
- 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

Number of Serious Events

<table>
<thead>
<tr>
<th></th>
<th>Defined ART (n=2350)</th>
<th>Immediate ART (n=2250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>CD4 Enlarged</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>AIDS Related</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>Non-AIDS Related</td>
<td>34%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Components: Clinical Events

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>(72 h 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.
**Case – What to Start?**

Which regimen would you start?
1. Dolutegravir/abacavir/3TC
2. Dolutegravir + TAF/FTC
3. Bictegravir/TAF/FTC
4. Doravirine/TDF/3TC
5. Darunavir/ritonavir/TAF/FTC
6. Dolutegravir/3TC

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**Sites of Action of Major Classes of Current Antiretroviral Medications**

Entry inhibitors:
1. Fusion inhibitor
2. CCR5 Antagonist
3. CCR5 post-attachment inhibitor, Raltegravir
4. gp120 attachment inhibitor, Indinavir

Reverse Transcriptase inhibiters (RTIs)
5. Nucleoside RTI (NRTI), including tenofovir (TFV) and abacavir (ABC)
6. Non-nucleoside RTI (NNRTI)

7. Integrase strand transfer inhibitors (INSTI), including dolutegravir, Raltegravir

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**ART 2021: >30 options**

<table>
<thead>
<tr>
<th>Nucleoside/nucleotide RTIs</th>
<th>Integrase inhibitors</th>
<th>Protease inhibitors</th>
<th>CCR5-receptor blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir, ABC</td>
<td>Tenofovir, TFV</td>
<td>Raltegravir, DRV</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Didanosine, ddI</td>
<td>TDF</td>
<td>Efavirenz, EFV</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Zidovudine, AZT</td>
<td>TDF, FTC</td>
<td>Amprenavir, APV</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Lamivudine, 3TC</td>
<td>TDF, FTC</td>
<td>Tipranavir, Tmc</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Tenofovir, TFV</td>
<td>TDF, FTC</td>
<td>Kivexa, Krvx</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Atazanavir, 3TC</td>
<td>TDF, FTC</td>
<td>Enfuvirtide, EM 101</td>
<td>Maraviroc</td>
</tr>
</tbody>
</table>

**Red - combination agents**

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The virtual 2021 Ryan White HIV/AIDS Program (RWHAP) CLINICAL CONFERENCE, October 3-6, 2021
Preconference Virtual Session
Choosing An Initial Regimen

- DTG
- BIC
- RAL
- EFV
- ATV
- DRV
- ATV

Initial Therapy for PWH: What do the Guidelines Say?

**Dept. Health & Human Services (DHHS)**
- Bictegravir/FTC/TAF
- Dolutegravir/3TC/abacavir (TAF or TDF)
- Dolutegravir + FTC (or FTC + 3TC) or TAF or TDF
- Dolutegravir/3TC

**IAS-USA**
- Bictegravir/FTC/TAF
- Dolutegravir + FTC/TAF or TDF
- Dolutegravir + 3TC/TDF
- Dolutegravir/3TC

*Except for individuals with baseline HIV RNA >500,000 copies/mL, with HCV or for whom results of HIV genotypic resistance testing or HIV testing are not yet available. Limited data in people with CD4 cell count <200.

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GEMINI-1 and -2: DTG + 3TC vs DTG + TDF/FTC in Treatment Naive People with HIV

- International, double-blind phase 3 studies
- ART-naive adults
- Viability: 1000-5000,000
- No major RT or PI resistance
- No HCV Infection
- viRNA level: Median: 6.4, log10 copies/mL >1000, 20% CD4 count: Mean: 462, ±200%

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The virtual 2021 Ryan White HIV/AIDS Program (RWHAP) CLINICAL CONFERENCE, October 3-6, 2021
Preconference Virtual Session
My take on 2-drug therapy with DTG/3TC

- DTG/3TC is a reasonable option, particularly for people who match GEMINI population (HIV RNA <500,000, CD4 cell count >200)
  - Avoid: HBV coinfection; pregnancy/women trying to conceive
- When initiating ART immediately after diagnosis, often starting with 3-drug therapy with plans to “step-down” to DTG/3TC in the future (supported by results of TANGO and SALSA studies)
- No longer using ABC in people on first-line therapy

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC + DTG</td>
<td>TDF associated with lower lipids</td>
<td>Greater nephrotoxicity than ABC and TAF (avoid if CKD &gt;40)</td>
</tr>
<tr>
<td></td>
<td>(non-nucleoside lipids), less weight gain than TDF</td>
<td>Larger decline in bone mineral density than with ABC or TAF (avoid if osteopenia/osteoporosis)</td>
</tr>
<tr>
<td></td>
<td>May be used with raltegravir</td>
<td>DTG increases metformin levels</td>
</tr>
<tr>
<td></td>
<td>(give DTG twice daily)</td>
<td></td>
</tr>
<tr>
<td>TAF/FTC + DTG</td>
<td>TAF: more favorable effects on renal</td>
<td>Two pills per day</td>
</tr>
<tr>
<td></td>
<td>and bone markers than TDF</td>
<td>TAF: greater weight gain than TDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TAF: higher lipids than TDF (non-nucleoside lipids)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTG increases metformin levels</td>
</tr>
<tr>
<td>TAF/FTC/3TC</td>
<td>Single pill combination</td>
<td>TAF: greater weight gain than TDF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TAF: higher lipids than TDF (non-nucleoside lipids)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bictegravir not recommended during pregnancy</td>
</tr>
<tr>
<td>DTG/3TC</td>
<td>Similar virologic efficacy as 3-drug therapy</td>
<td>Bictegravir should not be given with rifampin</td>
</tr>
<tr>
<td></td>
<td>Fewer medications</td>
<td></td>
</tr>
</tbody>
</table>

What to Start in Pregnancy: DHHS Guidelines Feb 10, 2021

**Two NRTIs**
- Abacavir/3TC
- TDF/FTC or TDF/3TC
- TAF/FTC – alternative NRTI

**Integrase Inhibitor:**
- Raltegravir (twice daily)
- Dolutegravir (Preferred ARV throughout pregnancy and for those who are trying to conceive)

**PI:**
- Darunavir/ritonavir (twice daily)
- Atazanavir/ritonavir

Bictegravir (insufficient data)
**Tsepamo: Decreasing Rate of Neural Tube Defects (NTDs) in Women with HIV who Conceive While on DTG**

- 2018: unplanned analysis found increase in NTD prevalence among infants born to Botswana women who conceived on DTG (DTG vs non-DTG: 0.94% vs. 0.12%)
- As more data have accrued, NTD prevalence with DTG has decreased; not significantly different from non-DTG ART at conception

<table>
<thead>
<tr>
<th>Conception</th>
<th>DTG</th>
<th>Non-DTG</th>
<th>EFV</th>
<th>HIV Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total NTD% per pregnancy, n/N</td>
<td>0/580</td>
<td>7/222.7</td>
<td>8/192.7</td>
<td>97/1444.967</td>
</tr>
<tr>
<td>NTD prevalence, % (95% CI)</td>
<td>0.13</td>
<td>0.10</td>
<td>0.10</td>
<td>0.07</td>
</tr>
<tr>
<td>(0.00-0.32)</td>
<td>(0.00-0.51)</td>
<td>(0.00-0.52)</td>
<td>(0.00-0.36)</td>
<td></td>
</tr>
<tr>
<td>Prevalence dif. for NTD at conception, % (95% CI)</td>
<td>Rel</td>
<td>0.06</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>(-0.03 to 0.26)</td>
<td>(-0.03 to 0.26)</td>
<td>(-0.03 to 0.26)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IMPAACT 2010: DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF for First-line ART During Pregnancy**

- Randomized trial in women (mostly in Africa) initiating ART during pregnancy (14-28 wk of gestation)
- Results through delivery:
  - Viral load efficacy of DTG-based ART superior to that of EFV/FTC/TDF (98% vs 91%; P = .0002)
  - Adverse pregnancy outcomes significantly less frequent with DTG + FTC/TAF (24%) vs DTG + FTC/TDF (33%) or EFV/FTC/TDF (33%)
  - Neonatal death significantly less frequent with DTG + FTC/TAF vs EFV/FTC/TDF (1% vs 5%; P = .019) and with DTG + FTC/TDF vs EFV/FTC/TDF (2% vs 5%; P = .05)

**Are integrase inhibitors perfect for everyone with HIV?**

- Drug interactions:
  - Polyvalent cations
  - Dolugravid increases metformin levels
- Side effects – weight gain
Weight Gain after Initiation of ART

- Industry-sponsored randomized trials of people initiating ART (n=5680)
- 96-wk median wt gain: 2 kg
- Risk factors for wt gain >10%
  (32.8% of participants)
  - Low CD4, high HIV RNA
  - Female sex, black race
  - BIC = DTG > EVG/c
  - TAF > ABC, TDF > AZT

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

- 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
- Darunavir/cobic/FTC/TAF
  - Drug interactions with CYP3A4 metabolized medications, like inhaled fludicasone, certain statins
Monitoring after Starting ART

- HIV RNA monthly until undetectable; then every 3-6 months
- Expect HIV RNA to be undetectable within few months of starting ART; best indicator that treatment is working
- Chemistry: BUN/Cr, liver enzymes: week 2 to 8; then every 3-6 mo.
- CBC/HIV: every 3-6 mo.
- Glucose and lipids: before starting ART; if normal, every 12 mo. (repeat fasting if abnormal)
- U/A annually (on TDF: every 6 months)
- Consider urine protein/Cr; urine albumin/Cr
- CD4 cell count every 3 to 6 months during first 1 to 2 years of ART; when HIV RNA suppressed and CD4 cell count >250-300, can space out to every 12 months; optional when CD4 cell count >500

What are the options if I don’t want to take a medicine every day?

Long-Acting ART

- Injectable Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI
- Long-acting formulations; half-lives of months
- Phase 3 studies
  - FLAIR: Treatment naive 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

Monthly LA Cabotegravir/Rilpivirine in PWH with Suppressed HIV RNA: ATLAS/FLAIR Week 48 Pooled Results

- No virologic failure (VF) at Week 48
- Primary Endpoint: LA monotherapy to Cell f/u at Week 48 (VF = 0) at Week 48
- Adjusted treatment difference 95% CI

Note: LA CAB + RPV not active against HIV
Approach to a Person with HIV

**Step 1: History, Examination, Labs**
- 45 yo M with HIV
- GERD, allergic rhinitis, hypertension, smoker
- Meds: omeprazole, fluticasone (interact with several commonly used regimens)
- CD4 cell count 550, HIV RNA 650,000
- HIV Genotype: no resistance mutations

**Step 2: OI Prophylaxis**
- CD4 count 550: OI prophylaxis not indicated

**Step 3: ART – individualizing therapy**
- On fluticasone: don’t use PI or cobi-containing Rx
- Estimated GFR 48: avoid TDF; TAF OK
- HIV RNA >500,000: avoid DTG/3TC

**Case – Bringing it all back home**
- Initiated Bictegravir/FTC/TAF
- Monitor HIV RNA monthly until undetectable then every 3 – 6 months (space out once patient has durable suppression)
- Monitor safety labs (kidney function, liver enzymes; CBC) – space out once patient is stable
- Counseled him about U = U (undetectable = untransmissible)
Posttest Question #2

A woman in her 30s, who is in her 2nd trimester of pregnancy, is diagnosed with HIV. Which of the following antiretroviral medications should not be prescribed?
1. Dolutegravir
2. Raltegravir
3. Atazanavir/cobicistat
4. Darunavir/ritonavir
5. Atazanavir/ritonavir