Antiretroviral therapy: When, How, and What to Start

American Conference for the Treatment of HIV (ACTHIV)
HIV: The Basics
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Learning Objectives

Upon completion of this presentation, learners should be better able to:

- Discuss the optimal timing of the initiation of antiretroviral therapy in antiretroviral naive HIV-infected adults.

- Review recommended treatment regimens for treatment-naive HIV-infected patients

There will be no off-label/investigational uses discussed in this presentation.
Adults and children estimated to be living with HIV | 2011

Total: 34.0 million [31.4 million – 35.9 million]
AIDS Diagnoses among Adult and Adolescent Females, 1985–2010—United States and 6 U.S. Dependent Areas

Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
What percentage of the HIV population in U.S. is not aware of their HIV infection?

1. 5%
2. 10%
3. 15%
4. 20%
5. 25%

How often does the IOM recommend HIV testing in women?

1. At least once between the ages of 13-64
2. Based on her risk factors
3. Once every 5 years unless a new risk factor occurs
4. Annually

**Bold new guideline from IOM committee**

Institute of Medicine (IOM) report  July 19, 2011

- **Recommendation 5.4: Counseling and screening for human immunodeficiency virus infection on an annual basis for sexually active women**

- Gestational DM, HPV, counseling on STDs, contraception, lactation, DV, yearly visits
**Case**

**HPI**: 37 yr old AA female with HIV, never on HAART, Current CD4 290; viral load 70,000. No h/o OIs, no significant past medical history, no medications

Pt single mother of two children; reluctant to start meds historically
Case (cont.)

The patient says she is “maybe” ready to start HIV therapy, but has a number of questions related to her HIV disease – the first one, at what CD4 was she supposed to start meds?
What are the current guidelines on when to start antiretroviral therapy?

1. Only when the patient has the official diagnosis of AIDS
2. As soon as the patient is diagnosed with HIV
3. When CD4 count $\leq 350$ cells/mm$^3$
4. When CD4 count $\leq 500$ cells/mm$^3$
5. When the HIV RNA level (viral load) $>100,000$ copies/mL

When to Begin Treatment for asymptomatic patients - U.S. guidelines – February 2012

HIV Infection

Asymptomatic

CD4+ T cells/mm³

>500

Consider Treatment

50% of panel said treat

50% of panel said optional

<500

Treat

h/o AIDS-defining illness, severe sx, pregnancy, HepB, HIVAN

Treat

Acute OIs

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents; Available at: http://aidsinfo.nih.gov.
When to Begin Treatment for asymptomatic patients - U.S. guidelines – 3/27/12 and even stronger, 2/13/13

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents; Available at: http://aidsinfo.nih.gov March 27, 2012 and February 13, 2013
SMART study

Given toxicities, one idea was to reduce total duration on therapy by going off and on - gave insights on pathogenesis

Strategies for Management of Antiretroviral Therapy (SMART) Study

Eligibility: CD4> 350 (N=5472)

Continuous Treatment

No Treatment until CD4 <250, then treatment until >350, then stop

Baseline CD4: 596-599
CD4 nadir: 250-252
% < 400 copies/mL viral load: 71%
Mean follow-up: 14 months (2% LFU)

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count guided interruption of antiretroviral treatment. NEJM 2006
SMART Study

<table>
<thead>
<tr>
<th>Event</th>
<th># Events</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of Disease/Death</td>
<td>164</td>
<td>2.5</td>
</tr>
<tr>
<td>Death</td>
<td>84</td>
<td>1.9</td>
</tr>
<tr>
<td>Serious HIV events</td>
<td>21</td>
<td>6.1</td>
</tr>
<tr>
<td>Severe non-HIV Complications</td>
<td>114</td>
<td>1.5</td>
</tr>
<tr>
<td>(Cardiac/CVA/renal/hepatic)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increased risk for all clinical outcomes, including death, HIV and non-HIV events with interrupted therapy

Favors off and on  Favors continuous therapy
Balance now tipped on earlier treatment of HIV

WHY WAIT?
- Avoid drug-related toxicity
- Preserve future drug options
- Delay development of drug resistance

WHY NOT WAIT?
- Possibility of irreversible immune system depletion
- Drugs easier to take now
- Increased possibility of progression to AIDS
- Observational cohort data showing survival advantage
- Public health implications
- HIV as chronic inflammatory condition – more CV disease, CA, hepatic, renal
Increased rates of “non-AIDS” defining deaths in HAART era

- D:A:D 1st enrolled 1999 - ~33,000 patients
- 2192 deaths - 13.8 deaths per 1000 person years
- 1/3 AIDS deaths – rest shown (heart disease, cancer)

When to Start: DHHS Guidelines 2/13/2013

Panel's Recommendations

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression.

  The strength and evidence for this recommendation vary by pretreatment CD4 cell count: CD4 count < 350 cells/mm$^3$ (AI); CD4 count 350–500 cells/mm$^3$ (AII); CD4 count > 500 cells/mm$^3$ (BIII).

- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV.

  The strength and evidence for this recommendation vary by transmission risks: perinatal transmission (AI); heterosexual transmission (AI); other transmission risk groups (AIII).

- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence (AII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

*Rating of Recommendations*: A = Strong; B = Moderate; C = Optional

*Rating of Evidence*: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion
What are the current guidelines on when to start antiretroviral therapy in resource limited settings?

1. Only when the patient has the official diagnosis of AIDS
2. As soon as the patient is diagnosed with HIV
3. When CD4 count <= 350 cells/mm$^3$
4. When CD4 count <= 500 cells/mm$^3$
5. When the HIV RNA level (viral load) >100,000 copies/mL

Has there ever been an RCT comparing starting ART upon diagnosis versus a specific CD4 count?

1. Of course, that was called the START trial or something

2. No, but there has been a trial comparing starting at CD4 counts <350 vs <200 cells/mm$^3$

3. No, but there has been a trial comparing starting at CD4 counts <500 vs <350 cells/mm$^3$

4. No, but there has been a trial comparing starting at CD4 counts <500 vs >500 cells/mm$^3$

Randomized controlled trial of earlier versus deferred ART in Haiti: CIPRA HT 001

Start ART at CD4+ < 350, compared to AIDS or CD4+ < 200 cells/mm$^3$

- 816 patients
- First line regimen: AZT, 3TC, EFV
- 23 deaths in deferred group, 6 in early treatment group (p<.001)
- 36 vs. 18 cases of TB in deferred vs early treatment group (p<.013)
- DSMB recommended immediate end of trial

Severe P et al. NEJM 2010
HPTN 052 Study Design

Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm³

Randomization

Immediate ART
CD4 350-550

Delayed ART
CD4 < 250

Primary Transmission Endpoint
Transmission events that were linked to that primary partnership

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death
Probability of Primary Clinical Event
(Death, WHO stage 4 clinical event, pulmonary TB or severe bacterial infection)

HR: 0.6 [0.4, 0.9], P=0.01

Grinsztejn B. IAS 2012
What would you start in this patient as the “anchor” antiretroviral with a dual NRTI backbone?

1. Efavirenz
2. Atazanavir/ritonavir
3. Atazanavir unboosted
4. Raltegravir
5. Darunavir/ritonavir

What to start?

- Review of the HIV lifecycle!!!
HIV meds → HIV viral lifecycle

1) Virus Entry
2) Reverse transcriptase
3) Integration
   - Integrase
4) Transcription
5) Translation
6) Cleavage
7) Packaging
8) Maturation
9) Re-infection

CD4 receptor (CXCR4, CCR5)

Source: speaker
Therapies now available for HIV infection

1) Virus Entry
   - CD4 receptor (CXCR4, CCR5)

2) Reverse transcriptase
   - RNA → DNA

3) Integration
   - RT
   - Nucleoside reverse transcriptase inhibitors (NRTIs)
   - Nonnucleoside reverse transcriptase inhibitors (NNRTIs)

4) Transcription

5) Translation

6) Cleavage
   - Protease inhibitors

7) Packaging

8) Maturation
   - Fusion (entry) inhibitors (T20, envelope protein gp41)
   - CCR5 receptor antagonist

9) Reverse infection

Integrase inhibitor

Nucleoside reverse transcriptase inhibitors (NRTIs)
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
Many options. . . Fewer toxicities

Nucleoside and nucleotide RTIs
- Zidovudine, AZT (Retrovir)
- Abacavir, ABC (Ziagen)
- Lamivudine, 3TC (Epivir)
- Didanosine, ddI (Videx)
- Stavudine, d4T (Zerit)
- Tenofovir, TFV (Viread)
- Emtricitabine, FTC (Emtriva)
  - Combivir (AZT/3TC)
  - Trizivir (AZT/3TC/ABC)
    - Epzicom (3TC/ABC)
    - Truvada (FTC/TFV)

CCR5 receptor blocker
- Maraviroc (Selzentry)

Integrase inhibitor
- Raltegravir (Isentress)
- Elvitegravir (ELV)
- FDA pending- Dolutegravir

NNRTI’s:
- Delavirdine (DLV)
- Nevirapine, NVP (Viramune)
- Efavirenz, EFV (Sustiva)
- Etravirine (Intelence)
- Rilpivirine (Edurant)

Fusion inhibitors:
- Enfuvirtide, ENF or T20 (Fuzeon)

Protease inhibitors:
- Indinavir, IDV (Crixivan)
- Saquinavir, SQV (Invirase, hgc)
- Nelfinavir, NFV (Viracept)
- Amprenavir, APV (Agenerase)
  - Atazanavir, ATZ (Reyataz)
  - Fosamprenavir, FPV (Lexiva)
  - Kaletra (lopinavir/ritonavir)
  - Tipranavir (Aptivus)
  - Darunavir (Prezista)

Combination
- Atripla (EFV/FTC/TFV)
- Complera (RPV/FTC/TFV)
- Stribild (ELV/cobicistat/TDF/FTC)

red – combination agents
Circled – DHHS recommended ARVs for naives
**What to start – DHHS guidelines**

**Preferred regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz + tenofovir + emtricitabine (Atripla)</td>
</tr>
<tr>
<td>Raltegravir + tenofovir + emtricitabine</td>
</tr>
<tr>
<td>Ritonavir-atazanavir + tenofovir + emtricitabine</td>
</tr>
<tr>
<td>Ritonavir-darunavir + tenofovir + emtricitabine</td>
</tr>
</tbody>
</table>

**Alternative regimens:** NNRTIs (RPV or EFV) or other PIs (FPV/r, LPV/r, ATV/r, DRV/r) PLUS ABC/3TC or RPV/TFV/FTC or FPV/r/TFV/FTC or LPV/r/TFV/FTC

ABC/3TC recommended first-line in IAS 2012 guidelines
You start ATV/r/TFV/FTC and the patient returns 6 weeks later for a follow-up visit. She said she feels a little “weird” on the meds and asks you about the side effects of her drugs and the “side effects of all HIV drugs, for that matter”
Adverse Effects: NRTIs

**Abacavir (Ziagen, in Epzicom)** - hypersensitivity reaction 5-8% (less in AA); Screen for HLA-B5701 before starting abacavir now since almost no risk unless HLA-B5701 positive; ?increased risk of CVD

**Tenofovir (Viread, in Truvada, Atripla)** - headache, GI problems, renal impairment (proximal tubular dysfunction)

... 

**ddI (Videx)** - GI intolerance, pancreatitis, peripheral neuropathy (PN); ?increased risk of MI, lactic acidosis and hepatic steatosis highest with d4T and ddI

**d4T (Zerit)** - PN, pancreatitis

**AZT (Retrovir)** - headache, GI problems, pancytopenia, especially anemia

**3TC/FTC** – Not much

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**Tenofovir and Renal Risk**

**TDF nephrotoxicity:**
- **Glomerular:** decreased kidney function
- **Tubular:** Fanconi’s syndrome, phosphate wasting, osteomalacia

**Boosted PIs increase tenofovir levels and may increase nephrotoxicity**, though incidence has been low in trials of first-line therapy.

Tubular toxicity not detected by creatinine alone. Look for glycosuria, proteinuria, phosphate.

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1 Mwafongo. CROI 2013  
Slide courtesy J Eron
Tenofovir and the kidney

- Large study in VA of >10,000 patients on ART 1997-2007
- Each year of TFV associated with 34% increased risk of proteinuria, 11% increased risk of rapid decline & 33% increased risk of CKD
- In those who d/c’d TFV, risk of kidney disease events did not appear to decrease during follow-up

### Table

<table>
<thead>
<tr>
<th>Outcome category of exposure</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir &lt;0.5 years</td>
<td>1.72 (1.50–1.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tenofovir 0.5–1 years</td>
<td>1.59 (1.36–1.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tenofovir 1–3 years</td>
<td>1.68 (1.44–1.95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tenofovir &gt;3 years</td>
<td>2.17 (1.48–3.20)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Rapid decline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir &lt;0.5 years</td>
<td>1.35 (1.16–1.56)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tenofovir 0.5–1 years</td>
<td>1.59 (1.38–1.84)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tenofovir 1–3 years</td>
<td>1.23 (1.07–1.42)</td>
<td>0.0042</td>
</tr>
<tr>
<td>Tenofovir &gt;3 years</td>
<td>1.04 (0.66–1.63)</td>
<td>0.88</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir &lt;0.5 years</td>
<td>1.30 (0.91–1.86)</td>
<td>0.15</td>
</tr>
<tr>
<td>Tenofovir 0.5–1 years</td>
<td>1.85 (1.35–2.53)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tenofovir 1–3 years</td>
<td>1.69 (1.26–2.27)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tenofovir &gt;3 years</td>
<td>1.56 (0.73–3.36)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

CI, confidence interval.

*All estimates based on multivariable adjusted time-dependent Cox models described in Table 2.

*Reference is vs. 0 years.

*Rapid decline in kidney function was defined as an annual decline of 3 ml/min per 1.73 m² or more for two consecutive years.

Scherzer R. AIDS 2012
You had instructed the patient to take her ATV/r-based regimen with food and she is finding that difficult due to a chaotic lifestyle, “crazy at work”

You decide to switch her anchor drug to an NNRTI
Which NNRTI is best taken on an empty stomach?

1. Efavirenz
2. Etravirine
3. Nevirapine
4. Rilpivirine

Adverse effects: NNRTIs

**Nevirapine (Viramune)**
- Rash
- Hepatotoxicity (may be severe and life-threatening)
- Both worse in women, CD4 count cut-offs

**Efavirenz (Sustiva, in Atripla)**
- Teratogen, Pregnancy Class D (controversial), remember to counsel if pt wants to get pregnant (but don’t change if on)
- CNS effects (Dizziness, nightmares, depression, worsening of pre-existing psychiatric disorders)

**Etravirine (Intelence)**
- Rash (F > M) – severe, recent warning; nausea; diarrhea
- Hepatotoxicity (worse in HepB, C)

**Rilpivirine (Edurant)**
- PPIs contraindicated, eat with high-calorie meal, not as effective with starting viral loads >100,000

Source: Package inserts
Toxicities: PIs

All PIs:

• Dyslipidemia
• Insulin resistance syndromes
• Lipodystrophy (body fat changes)
• Hepatic toxicity
• Possible increased bleeding risk in hemophiliacs
• Drug-drug interactions (don’t use simvastatin or lovastatin; atorvastatin with care; fluvastatin, rosuvastatin and pravastatin generally ok); Ritonavir and cobicistat powerful CYP3A4 inhibitors

Source: Package inserts
Adverse Effects: Specific PIs

- **Atazanavir (Reyataz)** – elevated indirect bilirubin; *PPI’s reduce absorption by 75%, food restriction (must take with food)*, nephrolithiasis (rare)
- **Darunavir (Prezista)** – GI intolerance, rash (sulfa moiety), high lipids, *hepatotoxicity* (0.5%), take with food
- **Lopinavir/ritonavir (Kaletra)** - GI intolerance, lipids
- **Fosamprenavir (Lexiva)** - GI intolerance, rash (sulfa moiety)
- **Indinavir (Crixivan)** – nephrolithiasis, GI intolerance, elevated indirect bili
- **Nelfinavir (Viracept)** - diarrhea, lipids, not boosted with ritonavir and less potent, not used much
- **Tipranavir (Aptivus)** – GI intolerance, rash (sulfa moiety), high lipids, hepatotoxicity, Case reports of *intracranial hemorrhage*
**Toxicities: Entry inhibitors and integrase inhibitors**

- **Maraviroc (Selzentry):** Postural hypotension, abdominal pain
- **Raltegravir (Isentress):** Nausea, vomiting, increased CPK, myositis, BID

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\(^1\) Lalezari et al. Enfuviritide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. NEJM 2003;348:2175-85
Case (continued)

- You switch the patient’s regimen to TFV/FTC/EFV and she likes the new food requirement but doesn’t like the “weird dreams”
- You tell her you can switch the EFV to raltegravir (twice a day), but she would like to take it once a day
QDMRK trial – bid vs qd raltegravir

- 770 treatment-naïve patients
- Phase III study - raltegravir 800 mg QD vs. 400 BID, each with TDF/FTC
- Treatment difference of -5.7 % (-10.7 - -0.83 %) meant twice daily raltegravir superior to once daily
- Difference driven by patients with high baseline VL

Case continued

The patient is switched to TFV/FTC and an integrase inhibitor.

She reminds you that she wants a regimen that she does not need to take with food.
Which integrase inhibitor (marketed) does not need food to achieve its maximal effect?

1. Raltegravir
2. Elvitegravir
## Practical tips—Commonly used ARVs and food

<table>
<thead>
<tr>
<th>ARV/combo</th>
<th>Food requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
</tr>
<tr>
<td>NRTIs</td>
<td>None except ddI 2 hrs before food</td>
</tr>
<tr>
<td>NVP/ NVP XR</td>
<td>None</td>
</tr>
<tr>
<td>EFV/ Atripla®</td>
<td>Take on empty stomach (food ↑ levels, may ↑ AEs)</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Take after a meal (fasting ↓ AUCs 50%)</td>
</tr>
<tr>
<td>Rilpivirine (Complera®)</td>
<td>Take with meal (533 kcal; protein shake ↓ AUC 50%)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Take with food</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>Take with food</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>None</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Take with food</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Likely none (food does increase)</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>INIs</strong></td>
<td></td>
</tr>
</tbody>
</table>
Case continued

- You switch her to TFV/FTC + raltegravir BID and you are now her favorite provider!
stop aids. make the promise

Don't turn your back on AIDS.

STOP AIDS. Make the Promise.

Each of us can help stop the spread of HIV and reduce the impact of AIDS. You don't have to be a top scientist working on a cure to make a difference. Protecting yourself and others from HIV infection, welcoming someone living with HIV into your life or even just talking about HIV and AIDS can help. Are you taking action?

Make your promise now at www.worldaidscampaign.org