Antiretroviral Therapy
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Albany Medical College
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Disclosures

• Co-Investigator for studies at Albany Medical Center sponsored by Gilead and GSK Pharmaceuticals
Objectives

• Review the latest recommendations on when to initiate antiretroviral therapy (ARV)

• Identify the preferred ARV regimens

• Review ARV side effects, drug interactions and monitoring

When to Start
Case #1

- African American female, age 23, accepts HIV testing
- Rapid test is positive, and confirmed
- CD4 600, VL 9650 copies/ml
- Asymptomatic and other labs normal

DHHS: Changing Criteria for Initiating ART

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<tbody>
<tr>
<td>&gt; 500</td>
<td>Offer if VL &gt; 20,000</td>
<td>Offer if VL &gt; 55,000</td>
<td>Consider if VL ≥ 100,000</td>
<td>Consider in certain groups</td>
<td>Consider</td>
<td>Treat</td>
</tr>
<tr>
<td>350-500</td>
<td>Offer if VL &gt; 20,000</td>
<td>Consider if VL &gt; 55,000</td>
<td>Consider if VL ≥ 100,000</td>
<td>Consider in certain groups</td>
<td>Treat</td>
<td>Treat</td>
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<tr>
<td>200-350</td>
<td>Offer if VL &gt; 20,000</td>
<td>Offer, but controversy exists</td>
<td>Offer after discussion with patient</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
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<tr>
<td>&lt; 200 or symptomatic disease</td>
<td>Treat</td>
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</table>
Possible Exceptions

- Long term non-progressors
  - HIV antibody positive >7 yrs
  - CD4 count > 450
  - No OIs
  - Naïve to ARV
  - Low levels of detectable viral load
- Elite or HIV controllers
  - Maintain undetectable Viral load

Potential Benefits of Early Therapy: Supporting Data (2)

- CD4 count >500 cells/µL
  - Cohort study data are not consistent; some show survival benefit if ART initiated early
  - Other considerations (eg, potential benefit of ART on non-AIDS complications, HIV transmission risk) support recommendation for ART
  - Data not entirely conclusive, especially for patients with very high CD4 counts...
Why treat at CD4 >500 cells/mm3?

- Untreated HIV infection and ongoing viremia associated with development of non-AIDS defining diseases such as
  - Cardiovascular Disease
  - Renal disease
  - Liver disease
  - Neurologic complications
  - Malignancy

NA-ACCORD: Survival Benefit of Earlier HAART by Baseline Factor

<table>
<thead>
<tr>
<th>Parameter Associated With Risk of Death*</th>
<th>Relative Hazard† (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferral of HAART until &lt; 500 cells/mm³ (vs starting at ≥ 500 cells)</td>
<td>1.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.2</td>
<td>.117</td>
</tr>
<tr>
<td>Older age (per 10 yrs)</td>
<td>1.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Baseline CD4+ cell count (per 100 cells/mm³ increase)</td>
<td>1.0</td>
<td>.696</td>
</tr>
</tbody>
</table>

*All causes of death unspecified. †Stratified by cohort and calendar year.

CD4 counts and AIDS-Defining Illness

Mocroft, et. al CID 2013

Treatment and Care

Linkage to effective treatment for HIV-positive individuals:
• Prolongs life
• Delays progression to AIDS
• Provides opportunity to counsel regarding risk behaviors
• Reduces:
  − Hospitalizations
  − Opportunistic infections
  − Drug resistance
• Greatly reduces the transmission of HIV
**Risks and Benefits of Earlier Initiation of ART**

**Benefits**
- Prevention of progressive immune dysfunction (reduced immune activation)
- Delayed progression to AIDS and prolonged survival
- Decreased risk of non-AIDS/HIV-related morbidity (HIVAN, malignancies, neurocognitive dysfunction, cardiovascular disease, etc)
- Decreased drug resistance
- Decreased risk for some ARV toxicities
- Decreased HIV transmission

**Risks**
- Reduced quality of life
- Development of drug resistance if adherence is suboptimal
- Limitation in future choices of ART if drug resistance occurs
- Uncertain long-term toxicities and duration of effectiveness for some drugs/regimens
- Possible transmitted drug resistance

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**HPTN 052: Treatment as Prevention in HIV+ Persons**

1,763 discordant couples (97% heterosexual) in Africa, Asia, Americas. Those HIV+ had CD4 rage of 350-550

HIV+ partner randomized to start HIV treatment immediately or deferred until CD4 <250

DSMB Interim analysis:
- 90% on ART had HIV RNA <400
- 40 incident cases of HIV
- 29 linked genetically to partner

**96% reduction in transmission!**

Cohen IAS 2011 #MOAX0102 and NEJM 2011;365:493
Community Viral Load Mirrors Reduced Rate of New HIV Cases in San Francisco

- Retrospective analysis of relationship between community viral load (CVL; mean of summed individual HIV-1 RNA results per yr) and new HIV diagnoses

*Data insufficient to prove significant association with reduced HIV incidence.

HIV CDC Classification

CLINICAL
- Category A – Seroconversion & asymptomatic phase
- Category B – Symptomatic, without AIDS
  - E.g. oral thrush, herpes zoster
- Category C – AIDS-defining illnesses
  - E.g. *Pneumocystis jirovecii* pneumonia or Kaposi’s sarcoma

LABORATORY
- Classification 1 – CD4 >500
- Classification 2 – CD4 200 -499
- Classification 3 – CD4 < 200

Rating Scale for Recommendations

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Strong recommendation for the statement</td>
<td>I. One or more randomized trials with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B. Moderate recommendation for the statement</td>
<td>II. One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C. Optional recommendation for the statement</td>
<td>III. Expert opinion</td>
</tr>
</tbody>
</table>

Recommendations for Initiating ART: CD4 Count or Clinical Category

- **Recommended for all CD4 cell counts**
  - CD4 cell counts <350 cells/μL (AI)
  - CD4 cell counts 350-500 cells/μL (AII)
  - **CD4 cell counts > 500 cells/μL (BIII)**

- **Recommended regardless of CD4 cell count**
  - Pregnancy (AI)
  - History of AIDS-defining illness (AI)
  - HIV-associated nephropathy - HIVAN (AII)
  - Chronic hepatitis B coinfection (AII)
  - Chronic hepatitis C coinfection (BII)
Patient Readiness

- 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 (AIII). 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.

When to Start ART: IAS–USA Recommendations 2012

- Patient readiness should be considered when deciding to initiate antiretroviral therapy (ART)
- ART should be offered regardless of CD4 cell count (increasing strength of the recommendation as CD4 decreases)
  - CD4 < 500 cells/µL (AIIa)
  - CD4 > 500 cells/µL (BIII)
  - Pregnancy (AIIa)
  - Chronic HBV (AIIa)
  - HCV (may delay until after HCV treatment if CD4 > 500) (CIII)
  - Age older than 60 (BIIa)
  - HIV-associated nephropathy (AIIa)
  - Acute phase of primary HIV infection, regardless of symptoms (BIII)

Thompson et al, JAMA, 2012

Downloaded from https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection on 10/12/13.
Treatment as Prevention

• 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 (A1); heterosexual transmission (A1); other transmission risk groups (AIII).

START (Strategic Timing of ART)

• INSIGHT Network: Multinational trial conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
• Study population: Adults with CD4 >500 cells/cmm
• Study treatment randomization is 1:1
  • Immediate ART
  • Deferred until CD4 <350 cells/cmm or AIDS event or other symptoms
• Study endpoints:
  • Serious AIDS-defining illness, non-AIDS illness, death
• Sample size:
  • N=900 (pilot for feasibility; enrollment completed)
  • N=3100 (definitive)
• Duration: Participants followed up to 5 years

http://www.clinicaltrials.gov
What to Start

Case # 2

Caucasian Male, 50 years old, with Type 2 Diabetes, Chronic Hepatitis B and Hypertension

No symptoms

CD4 count 200, VL 289,000 copies/ml
### Approved Antiretroviral Agents 1987-2013

![Diagram of Approved Antiretroviral Agents 1987-2013](image)

#### Current ARV Medications

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>PI</th>
<th>Integrase Inhibitors</th>
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<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Atazanavir (ATV)</td>
<td>Dolutegravir</td>
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<tr>
<td>Didanosine (ddI)</td>
<td>Darunavir (DRV)</td>
<td>Elvitegravir (EVG)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Fosamprenavir (FPV)</td>
<td>Raltegravir (RAL)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Indinavir (IDV)</td>
<td><strong>Fusion Inhibitor</strong></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Lopinavir (LPV)</td>
<td>Enfuuvirtide (ENF, T-20)</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>Nelfinavir (NFV)</td>
<td><strong>CCR5 Antagonist</strong></td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>Ritonavir (RTV)</td>
<td>Maraviroc (MVC)</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td>Saquinavir (SQV)</td>
<td><strong>Single Tablet Regimens</strong></td>
</tr>
<tr>
<td>Delavirdine (DLV)</td>
<td>Tipranavir (TPV)</td>
<td>Atripla</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td></td>
<td>Complera</td>
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<tr>
<td>Etravirine (ETR)</td>
<td></td>
<td>Stribild</td>
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<tr>
<td>Nevirapine (NVP)</td>
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<tr>
<td>Rilpivirine (RPV)</td>
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2011 – rilpivirine (RPV) and TDF/FTC/RPV fixed dose tablet
2012 – elvitegravir (ETG) and TDF/FTC/ETC/Cobi STR

[www.aidsetc.org](http://www.aidsetc.org)
Targets of HIV Therapy

HIV

Nucleus

RNA

Protease

DNA

Reverse transcriptase

Entry Inhibitors:
Fusion, CD4, CCR5

CXCR4

Reverse transcriptase inhibitors:
NRTI (nucleosides, nucleotides)

NNRTI

Integrase Inhibitors

Protease inhibitors

Basics of Highly Active Antiretroviral Therapy (HAART)

• Combination therapy
  • At least 3 active agents

• Utilization of multiple classes of agents
  • Typically 3 agents representative of 2 classes of agents
Five Classes of Antiretroviral Medications

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
   • Nucleotide RTI (tenofovir)

2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI’s)

3. Protease Inhibitors (PIs)

4. Entry Inhibitors: enfuvirtide, CCR5 antagonists

5. Integrase Inhibitors

Building an Initial HAART Regimen

- Combination Therapy ("Cocktail")

- Utilize at least 3 active agents together
  1. NNRTI + 2 NRTIs
  2. PI (± ritonavir boosting) + 2 NRTIs
  3. Integrase Inhibitor + 2 NRTIs

Initial Treatment: Choosing Regimens

- Fusion inhibitor, CCR5 antagonist not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice

Initial ART Regimens: DHHS Categories

- Preferred
  - Randomized controlled trials show optimal efficacy and durability
  - Favorable tolerability and toxicity profiles
- Alternative
  - Effective but have potential disadvantages
  - May be the preferred regimen for individual patients
- Other
  - May be selected for some patients but are less satisfactory than preferred or alternative regimens
Initial Regimens: Preferred

<table>
<thead>
<tr>
<th>NNRTI based</th>
<th><em>Efavirenz/tenofovir/emtricitabine</em>¹,²</th>
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<tbody>
<tr>
<td>PI based</td>
<td><em>Atazanavir/ritonavir+ tenofovir/emtricitabine</em>²</td>
</tr>
<tr>
<td></td>
<td><em>Darunavir/ritonavir+ tenofovir/emtricitabine</em>²</td>
</tr>
<tr>
<td>II based</td>
<td><em>Raltegravir + tenofovir/emtricitabine</em>²</td>
</tr>
<tr>
<td>Pregnant women</td>
<td><em>Lopinavir/r (BID) or atazanavir/r + zidovudine/lamivudine</em>²</td>
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</table>

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa. TDF should be used with caution in patients with renal insufficiency.

Alternative regimens

- **NNRTI-Based Regimens (in alphabetical order)**
  - EFV + ABC/3TC (BI)
  - RPV/TDF/FTC (BI)
  - RPV + ABC/3TC (BII)
- **PI-Based Regimens (in alphabetical order)**
  - ATV/r + ABC/3TC (BI)
  - DRV/r + ABC/3TC (BII)
  - FPV/r (once or twice daily) + ABC/3TC or TDF/FTC (BI)
  - LPV/r (once or twice daily) + ABC/3TC or TDF/FTC (BI)
- **INSTI-Based Regimen**
  - EVG/Cobi/TDF/FTC (BI)
  - RAL + ABC/3TC (BIII)
- **CCR5 Antagonist based regimens**
  - MVC + ZDV/3TC
  - MVC + TDF/FTC or ABC/3TC

http://Aidsinfo.nih.gov/guidelines
HIV-infected pregnant women

- Perinatal Guidelines
  - http://aidsinfo.nih.gov/guidelines

Goals of HIV Therapy

- Reduce Viral Load
- Restore and preserve the immune system
  - Increase CD4 count
- Lower the risk of HIV-related illness
- Lower the risk of transmission
- Improve quality of life
How do you decide?

- Considerations in choosing a regimen
  - Side effects (matched with patient comorbidities)
  - Adherence potential (pill burden/frequency)
    - 3 single tablet regimens now available
  - Drug interaction potential
  - Resistance pattern
  - Efficacy

**Atazanavir/Ritonavir/FTC/TDF (Truvada)**

- Efficacy
- At 1/day

**Darunavir/Ritonavir/FTC/TDF**

- Efficacy
- At 3/day

**EFV/FTC/TDF (ATRIPLA)**

- Efficacy
- At 1/day

**Raltegravir (BID)/FTC/TDF**

- Efficacy
- At 3/day
**Tenofovir Disoproxil fumarate (TDF/Viread/Truvada)**

- Favored nucleotide background
- Combined with Emtricitabine (FTC)
- Small risk for renal tubular acidosis
  - Renal insufficiency
  - Glycosuria in absence of diabetes
  - Hypophosphatemia
- Predisposes to bone mineral loss, that stabilizes after initial therapy
- New formulation under study, tenofovir alafenamide (TAF), thought to minimize the risk for renal and bone toxicity

**EFV/FTC/TDF Key Points (ATRIPLA)**

- 3 drugs in one tablet
- Efavirenz/tenofovir/emtricitabine
- Dosed at bedtime usually
- Pregnancy Category D
- CNS side effects common in first few weeks
  - Caution: screen for depression and suicidal ideation
- Renal side effects possible with tenofovir
Atazanavir/Ritonavir/FTC/TDF

Key Points

- 3 pills daily
- “Boosted” PI regimen
- Dosed once a day with food
- GI side effects, minimal effect on lipids
- Hyperbilirubinemia, nephrolithiasis, cholelithiasis
- Proton Pump Inhibitor interaction
- Renal side effects possible with tenofovir

Darunavir/ Ritonavir/FTC/TDF

Key Points

- 3 tablets daily (800mg tablet)
- “Boosted” PI regimen
- Dosed once a day with food, twice daily (600mg with 100mg Ritonavir BID) in experienced
- GI side effects, minimal effect on lipids
- Sulfa moeity
- Renal side effects possible with tenofovir
- **400mg off market now!**
Raltegravir/FTC/TDF Key Points

- 3 tablets
- Isentress dosed twice a day
  - Once daily dosing possible, but not yet recommended
- Well tolerated, no effect on lipids
- Renal side effects possible with tenofovir
- No cytochrome P450 interactions

Maraviroc (MVC)

- CCR5 antagonist class
- Targets host protein (viral coreceptor)
- Need to perform tropism assay before use
- 150mg, 300mg or 600mg BID depending on concomitant medications
- Dose adjusted CrCl
- Substrate of CYP3A and P-glycoprotein
- Category B pregnancy
- Limited clinical experience in treatment naïve patients

aidsinfo.nih.gov/guidelines
Dolutegravir (Tivicay)

- FDA-approved August 12, 2013
- New integrase inhibitor dosed as a 50 mg tablet
  - Once daily for treatment-naïve patients and experienced integrase inhibitor naive
  - Twice daily for integrase treatment-experienced patients
- Can be taken with or without food
- Pregnancy category B
- Adverse events > 2% were insomnia and headache
- Contra-indicated to be given with dofetilide, an anti-arrhythmic
- Plans for a STR of Epzicom/dolutegravir for 2013

ARV Medications: Should **NOT** Be Offered at **ANY** Time

- ARV regimens not recommended:
  - Monotherapy with NRTI*
  - Monotherapy with boosted PI
  - Dual-NRTI therapy
  - 3-NRTI regimen (except ABC + 3TC + ZDV or possibly TDF + 3TC + ZDV)

ZDV monotherapy is not recommended for prevention of perinatal HIV transmission but might be considered in certain circumstances; see *Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.*
ARV Medications: Should **NOT** Be Offered at **ANY** Time

- ARV components not recommended:
  - Didanosine + stavudine
  - Didanosine + tenofovir
  - Emtricitabine + lamivudine
  - Stavudine + zidovudine
  - Darunavir, saquinavir, or tipranavir as single, unboosted PIs
  - Atazanavir + Indinavir

www.aidsetc.org

ARV Medications: Should **NOT** Be Offered at **ANY** Time

- ARV components not recommended:
  - Efavirenz during first trimester of pregnancy and in women with significant potential for pregnancy
  - Nevirapine initiation in women with CD4 counts of >250 cells/µL or in men with CD4 counts of >400 cells/µL
  - Etravirine + unboosted PI
  - Etravirine + boosted Atazanavir, fosamprenavir or tipranavir
  - Any combination of 2 NNRTIs

www.aidsetc.org
Preferred **Initial** Regimen Summary

- Atripla, single tablet regimen “gold standard”
  - CNS ADRs initially, minimal effect on lipids
- Preferred Norvir Boosted Protease Inhibitors
  - Minimal rates of resistance, including in NRTI class
  - Smallest effect on lipids (worse than efavirenz)
  - Kaletra, only preferred in pregnancy
  - GI ADRS common, especially diarrhea, nausea
  - Drug interactions complex, but manageable
- Integrase Inhibitor
  - Raltegravir BID dosing
  - Minimal side effects, lipid neutral
- Beyond 1st regimen, depends on tolerability and resistance

Current Single tablet regimen “STR” Approved by FDA

- Atripla
  - Efavirenz/tenofovir/emtricitabine
  - NNRTI + 2 NRTIs
  - DHHS Preferred Regimen
- Complera
  - Rilpivirine/tenofovir/emtricitabine
  - NNRTI + 2 NRTIs
  - DHHS Alternative Regimen
- Stribild
  - Elvitegravir/cobicistat/tenofovir/emtricitidine
  - II + booster (cobicistat) + 2 NRTIs
  - DHHS Alternative Regimen
Complera
Rilpivirine/tenofovir/emtricitabine

- STR once daily
- Food required
- Take antacids at least 2 hours before or at least 4 hours after
- Take H-2 blockers at least 12 hours before or at least 4 hours after
- PPIs are contraindicated

Stribild – FDA Approved
August 2012

- 4 drugs in one tablet
  - Elvitegravir – a new integrase inhibitor
  - Cobicistat – a new booster (does the same thing as RTV)
  - Tenofovir – preferred NRTI
  - Emtricitabine – preferred NRTI
- Head to head data with Atripla and Reyataz/Norvir/Truvada showed similar results (noninferior at 48 weeks)
- Should not be used in those with GFR<70
- Avoid in regimens that contain PIs (3 way interaction)

Cobicistat – Additional Information

• Booster for the elvitegravir
• Similar to Norvir for drug interactions
• Increased creatinine levels due to inhibition of tubular secretion of creatinine back into bloodstream in the kidney
  • Similar to cimetidine

**Diagram:**

- **Tubular Reabsorption:** Substances reabsorbed back into blood from the renal tubule
- **Tubular Secretion:** Substances secreted from the blood back into renal tubule for elimination
- **Blocking Tubular Secretion:** Cobicistat BLOCKS tubular secretion of creatinine, causing an increase in blood levels of creatinine
Inhibition of Creatinine Secretion

- Cobicistat in Stribild
- Dolutegravir
- Results in a pseudo-elevation in serum creatinine
  - Up to 0.4 mg/dL of creatinine increase

- True clearance of creatinine not impacted, as demonstrated by iohexol clearance studies.

Future developments

STRs
- ELV/COBI/Emtricitabine/Tenofovir alafenamide(TAF)
- Dolutegravir/abacavir/lamivudine
- Darunavir/cobicistat/TAF/emtricitabine
- Other combinations in the works as well

Other
- Long acting injections using nanosuspension
Monitoring, drug interactions and side effects

Monitoring for Failure or Success

- Genotype resistance testing

- **Viral Load:**
  - Baseline
  - 2 to 8 weeks after start of new regimen
  - Every 3-4 months thereafter

- **CD4 cells counts:**
  - Baseline
  - 4, 8 to 12, 16, and 24 weeks after start
  - Every 3 months thereafter
  - Every 6-12 months when clinically stable and viral load is undetectable
Therapy goals

- **Undetectable viral load (VL<50 copies/mL)**
  - Within first 24-48 weeks of therapy
  - If patients do not reach this goal, therapy should be evaluated and possibly changed

- **CD4 response**
  - Should see rise in CD4 count with successful antiretroviral therapy
  - CD4 response lags behind VL response

Resistance Testing

- **Recommended when patients enter into care, regardless of whether therapy will be initiated immediately or deferred**
  - If therapy is deferred, repeat testing at the time of ART initiation should be considered

- **Testing should be performed when managing sub-optimal viral load reduction and in the setting of virologic failure**
  - Testing should be performed while patients still on meds or at least within 4 weeks of therapy discontinuation

Top 5 Drug Interaction List

- Proton pump inhibitors
- Statins
- Inhaled corticosteroids
- colchicine
- BPH and ED medications

Proton Pump Inhibitors and Atazanavir

- Do not use if unboosted – ie on Atazanavir 400mg daily without ritonavir
- If ARV experienced, proton pump inhibitors not recommended to be taken with Atazanavir
- If naïve, can use up to the equivalent of omeprazole 20mg daily, IF boosting with ritonavir
- If on Atazanavir/Ritonavir with omeprazole & tenofovir (Viread) increase to 400mg with 100mg RTV daily
**H2 Blockers and Atazanavir**

- **Boosted Atazanavir**
  - H2 blockers simultaneously with or 10 hours after the H2RA
  - If also on tenofovir – use 400mg atazanavir + 100mg ritonavir if treatment experienced
  - Max H2RA dose equivalent to famotidine 20mg BID for tx experienced, 40mg BID for naives
- **Unboosted atazanavir – treatment naïve**
  - Atzanavir given 2 hours before and at least 10 hours after the H2RA
  - Max H2RA dose equivalent to famotidine 20mg BID

**Complera**

Rilpivirine/tenofovir/emtricitabine

- STR once daily
- Food required
- Take antacids at least 2 hours before or at least 4 hours after
- Take H-2 blockers at least 12 hours before or at least 4 hours after
- PPIs are contraindicated
CYP450 & Drug Metabolism

- Key points
  - Majority of drugs metabolized by CYP3A4 & CYP2D6
  - CYP3A4 & CYP2D6 extensively involved with PI/NNRTI metabolism
  - Enzymes can be induced or inhibited

Adapted from Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed.

Lipid-Lowering Agents and PIs: Drug-Drug Interactions

- Use cautiously
  - Statin + fibrate
  - Atorvastatin
  - Rosuvastatin
  - Niacin

- Contraindicated
  - Lovastatin
  - Simvastatin

- Low interaction potential
  - Fibrates
  - Fluvastatin
  - Pravastatin*
  - Ezetimibe
  - Fish oil

* AUC↑↑↑ with DRV.

Inhaled Fluticasone and Protease Inhibitors

Prednisone and methylprednisolone are substrates for CYP3A4 and likely to be increased
Nasal fluticasone likely to be increased
Switch to beclomethasone

Inhaled fluticasone likely to be increased
Switch to beclomethasone

Inhaled budesonide likely to be increased
Switch to beclomethasone

PIs can also increase salmeterol levels

Colchicine (Colcrys®)

- Fatalities reported with concurrent use of colchicine and clarithromycin, a strong CYP3A4 inhibitor
- Increases in colchicine expected with ritonavir-boosted protease inhibitors, ketoconazole, itraconazole, also new Hepatitis C Virus (HCV) PIs
- Dosing if on a protease inhibitor + ritonavir
  - Acute attack – Max of 0.6mg, followed by 0.3mg (1/2 tab) one hour later. Do not repeat for 3 DAYS!
  - Prevention – cut dose in half – IE: if on 0.6mg daily, max per day is 0.3mg
BPH Meds & CYP3A4 Inhibitors

• Avodart (dutasteride)
  • Metabolized by CYP3A4,
  • CONTRAINDIATED in Ritonavir Label, would avoid with HCV PIs as well
• Uroxatral (alfuzosin)
  • Metabolized by CYP3A4
  • CONTRAINDIATED with potent CYP3A4 inhibitors, including HCV PIs
• Cardura (doxazosin)
  • Metabolized by 3A4, drug levels can be increased by HCV PIs
• Flomax (tamsulosin)
  • Metabolized by CYP3A4 and CYP2D6, drug levels can be increased by HCV PIs
• Detrol LA (tolteridine)
  • Not metabolized by 3A4, safest option from a drug interaction standpoint


Conclusions

• HIV therapy is clearly indicated for those with CD4 cell counts < 500 cells/cmm.
• HIV therapy is appropriate for those with CD4 cell counts > 500 cells/cmm, per expert opinion of DHHS and IAS-USA guidelines committees.
• Early diagnosis and treatment allow for better health, with greater likelihood of a normal lifespan, and added benefit of decreasing risk for transmission of HIV.
Conclusions

• Combination of 2NRTIs + NNRTI, PI or Integrase inhibitor is preferred for most patients

• Check Cytochrome P450 drug interactions when starting PIs and NNRTIs

Measuring Regimen Efficacy

• Remember our goals of therapy!
  • Suppressed viral load
  • Improve immune function

• Monitor with laboratory testing accordingly (VL’s / CD4 counts)
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Web Resources of Interest

- DHHS Guideline Tables – BEST RESOURCE
  - http://www.aidsinfo.nih.gov/guidelines/

- NY/NJ AIDS Education and Training Center
  - http://www.nynjaetc.org/

- Clinical Options Drug Interaction Tool
  - http://www.clinicaloptions.com/
• Questions?