HAART Initiation/HIV Treatment for Antiretroviral-Naïve Patients
Ellen Kitchell, M.D.
A “Smorgasbord” of Possibilities

### HIV Medications

#### Nucleoside/Nucleotide Analogues (NRTIs)
- Combivir (zidovudine/lamivudine)
- Emtriva (emtricitabine or FTC)
- Epivir (lamivudine or 3TC)
- Epzicom (abacavir/lamivudine)
- Retrovir (zidovudine/3TC or AZT)
- Trizivir (abacavir/lamivudine/zidovudine)
- Truvada (emtricitabine/tenofovir DF)
- Videx/Videx EC (didanosine or ddC)
- Viread (tenofovir DF or TDF)
- Zerit (stavudine or d4T)
- Ziagen (abacavir or ABC)

#### Multi-Class Drug Combinations
- Atripla (emtricitabine/tenofovir DF)
- Complera (emtricitabine/tenofovir DF)
- Genvoya (tenofovir disoproxil fumarate/tenofovir DF)
- Stribild (dolutegravir/abacavir/lamivudine)

#### Non-Nucleosides (NNRTIs)
- Edurant (raltegravir or RPV)
- Integace (etravirine or ATV)
- Rescriptor (ritonavir or D4T)
- Sustiva (efavirenz or EFV)
- Viramune (nevirapine or NVP)
- Fuzese (enfuvirtide or E733)
- Selzentry (maraviroc or MVC)

#### Protease Inhibitors (PIs)
- Aptivus (tipranavir or TVR)
- Crizantam (indinavir or IDV)
- Evotaz (atazanavir/cobicistat)
- Invirase (saquinavir or SQV)
- Kaletra (lopinavir/ritonavir)
- Lexiva (lopinavir or RTV)
- Norvir (ritonavir or RTV)
- Prez clox (truvada or cobicistat)
- Prevista (darunavir or DRV)
- Reyataz (atazanavir or ATV)
- Viracept (nefelnavir or NTV)
Picking Out A “Delicious Meal” For Your Patient

• There are many fantastic options currently for patients with HIV that have few side effects and with minimal pill burden

• Certain factors influence your decisions in choosing a regimen for an individual patient (no “one size fits all” regimen)

• You are somewhat like a “waiter” to suggest a regimen that your patient will like to take
Goals of Therapy

• To come up with a regimen that a patient can take lifelong
• Durably suppress HIV viral load to <48 copies/mL
• Provide regimen that is compatible with patient’s lifestyle, in order to ensure maximal adherence
• Preserve future therapeutic options
• Restore/preserve immune function
• Minimize toxicity
A very good place to start…

• Department of Health and Human Services Guidelines
  http://www.aidsinfo.nih.gov/guidelines/

• International AIDS Society-USA (IAS-USA)
  https://www.iassusa.org/content/antiretroviral-treatment-adult-hiv-infection-0
STARTING HAART: OPTIMAL TIMING
A Long Story Short…

• All patients regardless of CD4 count should be offered antiretroviral therapy
• Very few exceptions
• 2 rationales:
  – Individual medical benefit
  – Prevention of transmission
The shifting pendulum…

• In the mid-1990s, recommendations were to start everyone on HAART regardless of CD4 count

• …then people started developing disabling side effects and resistance to antiretrovirals, so CD4 cut-offs were developed, which changed over time

• More recent medications considered to have fewer long-term side effects, so recent guidelines have focused on early treatment
Clinical Trials of ARV Initiation

• Earlier trials indicated the benefit, including mortality benefit, of ARV initiation at CD4 <200 cells/uL and 350 cells/uL
START Trial

- Randomized, controlled clinical trial of patients with CD4 count >500 cells/uL
- Randomized to either immediate initiation of therapy versus deferred until CD4 <350 cells/uL or clinician’s judgment
- All antiretrovirals provided free of charge for duration of study (estimated 7 years)
- Evaluation of mortality, non-AIDS events, hospitalizations, bone mineral density, etc.
• 57% reduced risk of serious events or death with immediate ART
• 72% reduced risk of serious AIDS events with immediate ART
• AIDS-related events: any AIDS-defining illness as defined by CDC
• Serious non-AIDS defining events: CV disease, ESRD, death from liver disease, cancer
• Most of these endpoints occurred in pts with CD4+ cell counts > 500 cells/mm³
• Reduced risk of cancers, particularly in rates of Kaposi sarcoma and lymphoma
• No difference in rate of cardiovascular events between the arms, although study had to be stopped early

HPTN 052: Immediate vs Delayed ART for HIV Prevention in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm\(^3\) (N = 1763 couples)

Immediate HAART*
Initiate HAART at CD4+ cell count 350-550 cells/mm\(^3\) (n = 886 couples)

Delayed HAART
Initiate HAART at CD4+ cell count ≤ 250 cells/mm\(^3\)† (n = 877 couples)

*72% of pts received ZDV/3TC + EFV

• Primary efficacy endpoint: HIV transmission
• Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
• Couples received intensive counseling on risk reduction and use of condoms

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

Linked Transmissions: 28

Delayed Arm: 27
Immediate Arm: 1

Single transmission in patient in immediate HAART arm believed to have occurred close to time therapy began and prior to suppression of genital tract HIV

$P < .001$

Update of HPTN 052

- After results returned, ART offered to all pts in study
- No linked HIV transmissions observed when index participant stably suppressed on ART
- Risk reduction attributed to early ART was 93%

### HIV Infections

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Delayed</th>
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<tr>
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<td>19</td>
<td>59</td>
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<tr>
<td>Linked</td>
<td>3</td>
<td>43</td>
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</table>

NEJM 2016; 375(9): 830-9
PARTNER Study

- 1166 sero-discordant couples
- 40% homosexual
- Inclusion criteria of having sexual contact without condoms at least some of the time
- HIV+ partner on ARVs, VL <200 copies/mL
- No documented cases of within-couple HIV transmission

Potential Benefits of Antiretroviral Therapy Initiation at High CD4 Counts

Benefits:

• Prevention of AIDS events, even at high CD4 count
• Possible prevention of cancer, heart disease
• Possible prevention of neurocognitive decline
• Prevention of transmission
Potential Risks of Antiretroviral Therapy Initiation at High CD4 Counts

- Toxicities (including long-term toxicities, which may not be known)
- Development of resistance
- Adherence concerns
- Cost, in resource-limited settings
Antiretroviral therapy (ART) is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection (AI).

ART is also recommended for HIV-infected individuals to prevent HIV transmission (AI).
• “Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence. 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.”
Guidelines for Timing of Antiretroviral Therapy: IAS-USA

- Treatment is recommended for all adults with HIV infection
Guidelines for Antiretroviral Initiation: World Health Organization

• ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count
HAART IN THE TRENCHES: INITIATING IN THE SETTING OF OPPORTUNISTIC INFECTION
Previous Thoughts About ARV Initiation in Patients with Opportunistic Infections

• Concern for immune reconstitution syndrome (IRIS), which can cause clinical worsening when the patient’s immune system starts to “wake up”

• Previously delayed ARVs for weeks to months to avoid this complication
ACTG 5164: “Immediate” versus Deferred Antiretroviral Therapy in the Setting of Opportunistic Infection

- Randomized patients with OIs to starting ART within 14 days versus deferring on average for 45 days
- AIDS progression/death in 14% of “early HAART” versus 24% in deferred arm (not statistically significant)
- However, fewer AIDS progression/deaths and longer time to AIDS progression/death
Caveats to ACTG 5164

• Most patients included in study had *Pneumocystis* pneumonia, which has low risk of IRIS

• Other opportunistic infections more likely to cause life-threatening IRIS
HAART-Immediate Opportunistic Infections

- Symptomatic HIV infection
- Cryptosporidium/Microsporidium
- Kaposi’s Sarcoma
- Lymphoma (especially PCNSL)
- PML
- HIV dementia
What are Opportunistic Infections with High Risk of IRIS to delay therapy?

- Cryptococcal meningitis
  - Increased mortality with early ARV initiation in RCT comparing starting w/in 1-2 weeks versus waiting 5 weeks
  - Recommended to delay 2-10 weeks
  - Worse outcome if initial CSF WBC was <5, increased intracranial pressure
Other Opportunistic Infections

- Tuberculosis
  - Recommendations to start therapy depend on baseline CD4
  - If <50 cells: start therapy w/in 2 weeks
  - If >50, start w/in 8 weeks
  - Caution regarding TB meningitis
• CMV retinitis
  – No specific recommendations, consider delay 1-2 weeks
• Toxoplasmosis
  – No specific recommendations but I typically wait 2-3 weeks
WHAT TO START
# HIV Medications

## Nucleoside/Nucleotide Analog Analogs (NRTIs)

<table>
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<tr>
<th>Combivir</th>
<th>Epivir</th>
<th>Epizol</th>
<th>Retrovir</th>
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<td>(lamivudine or 3TC)</td>
<td>(zidovudine/3TC or AZT)</td>
<td>(abacavir/lamivudine/zidovudine)</td>
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<td>(stavudine or 3T)</td>
<td>(abacavir or FTC)</td>
</tr>
</tbody>
</table>

## Multi-Class Drug Combinations

- **Atripla** (emtricitabine/tenofovir DF)
- **Complera** (emtricitabine/tenofovir DF, tenofovir alafenamide)
- **Genvoya** (emtricitabine/cobicistat/tenofovir alafenamide)
- **Striibl** (emtricitabine/tenofovir DF)
- **Triumeq** (emtricitabine/abacavir/lamivudine)

## Non-Nucleosides (NNRTIs)

- **Edurant** (etravirine or RPV)
- **Intelence** (etravirine or ETV)
- **Rescriptor** (delavirdine or D-LV)
- **Sustiva** (efavirenz or EFV)
- **Viramune** (nevirapine or NVP)

## Entry Inhibitors

- **Fuzion** (enfuvirtide or ENF)
- **Selzentry** (maraviroc or MVC)

## Protease Inhibitors (PIs)

- **Aptivus** (tipranavir or TPV)
- **Crixivan** (indinavir or IDV)
- **Evotaz** (atazanavir/cobicistat)
- **Invirase** (saquinavir or SQV)
- **Kaletra** (lopinavir/ritonavir)
- **Lexiva** (lopinavir/ritonavir or FPV)
- **Norvir** (ritonavir or RTV)
- **Prezobix** (dolutegravir/cobicistat)
- **Prezista** (dolutegravir or DTV)
- **Reyataz** (atazanavir or ATV)
- **Viracept** (nefazodone or NFV)
Considering HAART Options

1. Will the regimen be expected to work against the patient’s virus?
   - Resistance testing results

2. Consider comorbidities, especially hepatitis B and C status
3. Baseline labs, including renal, hepatic function
4. Drug interaction issues
5. Potential side effects of the regimen: how will this affect the patient and adherence to medications
6. Lifestyle issues: ability to adhere to multiple times daily regimen
7. For women, plans for pregnancy
8. Cost/insurance issues
Recommendations from Expert Panels

• DHHS, IAS, WHO
• Have “preferred” regimens selected on efficacy, tolerability
• Sometimes the “preferred” regimen for your patient is not one of these options
“Recommended” Regimens: DHHS Guidelines 2017

- 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) + 3rd active drug
  - Integrase inhibitor (INSTI)
  - Protease inhibitor (PI) boosted with ritonavir
- Have tried 2 drugs and 4+ medications, nothing seems to work as well→ for now, 3 is the magic number!
Preferred Regimens: DHHS

• Integrase inhibitors:
  – **Dolutegravir** (TIVICAY)
    • With abacavir/lamivudine (EPZICOM or TRIUMEQ)
    • With tenofovir DF/emtricitabine (TRUVADA)
    • With tenofovir AF/emtricitabine (DESCOVOY)
Preferred Regimens: DHHS

- Elvitegravir
  - With emtricitabine/tenofovir DF (co-formulated as STRIBILD)
  - With emtricitabine/tenofovir AF (co-formulated as GENVYOYA)
DHHS Guidelines: Preferred

• Raltegravir (ISENTERESS)
  – With emtricitabine/tenofovir DF (TRUVADA)
  – With emtricitabine/TAF (DESCOVY)
DHHS Guidelines: Boosted PI + 2 NRTIs

• Darunavir/ritonavir
  – With tenofovir DF/emtricitabine (TRUVADA)
  – With tenofovir alefenamide/emtricitabine (DESCOVY)
“Alternative” Regimens

- Considered “effective and tolerable,” but with potential disadvantages, limitations for use in certain populations or less supporting data from clinical trials
  - Efavirenz/emtricitabine/tenofovir
  - Efavirenz/emtricitabine/tenofovir alefenamide
  - Rilpivirine/emtricitabine/tenofovir DF or AF*
  - Boosted atazanavir + tenofovir DF or AF
  - Boosted darunavir + abacavir/lamivudine
  - Use of cobicistat as booster
“Other” Regimens

• If HIV RNA <100,000 copies/mL
  – Boosted atazanavir + abacavir/lamivudine
  – Efavirenz + abacavir/lamivudine
  – Raltegravir + abacavir/lamivudine
IAS Recommendations

• 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) + 3rd active drug
• Integrase inhibitor therapy recommended as first choice
WHO Recommendations

- Efavirenz + tenofovir + lamivudine (or emtricitabine)

- Alternative: dolutegravir + 2 NRTIs
## Comparison of Current International Guidelines for Treatment-Naive Pts

<table>
<thead>
<tr>
<th>Regimen</th>
<th>DHHS</th>
<th>IAS-USA</th>
<th>WHO</th>
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<td>RPV/FTC/TDF§</td>
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</table>

- **Recommended**
- **Alternative**
- **Not included**

*Only if HLA-B*5701 negative. †Only if CrCl ≥ 70 mL/min. ‡Only if CrCl ≥ 30 mL/min. §Only if baseline HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm³.

1. DHHS Guidelines. September 2016
Use of Efavirenz in Naïve Patients (SUSTIVA/ATRIPLA)
Efavirenz Is Efficaceous

• Up until recently, efavirenz was non-inferior or superior to other ARVs at suppressing HIV, regardless of baseline viral load or CD4

• Key studies comparing efavirenz to other options:
  – ACTG 5142 efavirenz superior to lopinavir/ritonavir (KALETRA)
  – ACTG 5202: non-inferior to atazanavir/ritonavir
  – ECHO/THRIVE: non-inferior to rilpivirine
  – GS-US-236-0102: non-inferior to elvitegravir
More Recent Efficacy Trials

• In studies of newer integrase-inhibitor regimens, some regimens have demonstrated superiority to efavirenz
• Primarily based on more discontinuations due to adverse effects in efavirenz arm
Adverse Effects of Efavirenz

• Neuropsychiatric side effects are common
• Strange/vivid dreams in ~50%
• Dizziness/feeling “drunk”
• Depression, unstable mania
• Increased suicidality noted among efavirenz patients
• Potential teratogen – not good choice for child-bearing-age females
• Some drug interactions (substrate of CYP3A4 and inducer of 3A4/2D6)
Risks of Failure with Efavirenz

- Low genetic barrier to resistance—single point mutation
  - Easy to develop resistance to this medication with non-adherence and treatment interruptions

- Higher risk of NRTI resistance with NNRTI failure
  - When you fail the regimen, you can fail with a number of mutations to the accompanying drugs

- It’s easier to adhere to this regimen but the implications of non-adherence can be disastrous!
Why choose rilpivirine (EDURANT/COMPLERA)?
ECHO/THRIVE: Rilpivirine vs Efavirenz in Treatment-Naive Patients

- Discontinuations due to side effects more common with EFV vs RPV: 8.5% vs 4.1%
- More virologic failures with RPV vs EFV: 14% vs 7.6%
  - Difference due to more VF between Wks 0-48 at HIV-1 RNA > 100,000
  - NRTI mutations more common with virologic failure on RPV vs EFV
  - Cross-resistance to ETR more common with RPV failure (E138K mutation)

Rilpivirine versus Efavirenz

- Reduced response to rilpivirine vs efavirenz at baseline viral load > 100,000 copies/mL and CD4+ cell counts < 200 cells/mm³

- Virologic failure in rilpivirine-treated subjects led to higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz
Rilpivirine Usage

- Only approved for relatively “well” patients
- CD4 >200 cells/uL
- Viral load <100,000 copies/mL
- PPI lowers absorption – not a good choice for hospitalized patients
Pros and Cons of Rilpivirine

• PROS
  – Fewer neuropsychiatric side effects
  – Very favorable lipid profile
  – Less rash
  – Lower discontinuation rate than efavirenz

• CONS
  – Increased rates of virologic failure (especially in patients with viral load >100,000 copies/mL)
  – Virologic failure leads to resistance to etravirine (2nd generation NNRTI)
  – Needs acid absorptions (no PPIs!) and to be taken with food
  – Some drug interactions (mostly that interfere with rilpivirine levels)
Why use a protease inhibitor-based regimen?
Protease Inhibitors

- Very potent class of medications
- Quicker at restoring CD4 count and viral suppression than NNRTI class
- Very low rates of baseline resistance
- Durable at suppressing virus
- High genetic barrier to resistance
- If patients fail a PI based regimen, rarely develop mutations, and if so, PI mutations are very rare (not true of integrase or NNRTI based regimens)
- Forgiving of non-adherence
Protease Inhibitors

• Recommended by many (including myself) to use in situation where genotype is not available yet
• Hospitalized patients
Adverse Effects of the Protease Inhibitor Class

- Higher pill count
- Gastrointestinal side effects (nausea/vomiting/diarrhea)
- Inhibit cytochrome P450 enzyme system
- Metabolic abnormalities
  - Dyslipidemia
  - Insulin resistance
  - Lipodystrophy, weight gain
  - Older Pis implicated in stroke, MI
Efficacy Trials for Atazanavir (Reyataz)

- ACTG 5202 showed similar efficacy between efavirenz + atazanavir
- GS-236-0103 showed similar efficacy between elvitegravir + atazanavir
- ACTG 5257 showed similar virologic efficacy between atazanavir, darunavir and raltegravir
  - However, more treatment discontinuations in atazanavir group
Unique Adverse Effects to Atazanavir

• Indirect hyperbilirubinemia
  – Functional Gilbert’s syndrome
  – Expected and harmless to patient except for cosmetic appearance
  – Scleral icterus, jaundice
  – Some patients do not like the appearance
  – Is NOT supposed to cause AST/ALT elevation

• Need for acidic gastric pH for absorption

• Nephrolithiasis (rare)
ARTEMIS: Darunavir/ritonavir vs Lopinavir/ritonavir in Antiretroviral-Naive Patients

- Darunavir/ritonavir versus lopinavir/ritonavir
  - Plus tenofovir/emtricitabine
- Darunavir/ritonavir noninferior to lopinavir/ritonavir at week 48; superior at week 96 of patients with undetectable HIV viral load
- CD4+ gain similar between groups

Other Efficacy Trials for Darunavir in Naïve Patients

• ACTG 5257 showed similar virologic efficacy to raltegravir

• FLAMINGO study showed darunavir had lower rate of virologic suppression than dolutegravir
  – Driven by drug discontinuation in darunavir group
Unique Adverse Effects to Darunavir

• Sulfonamide moiety
  – Use in caution with patients with severe sulfa allergy; however most patients with h/o sulfa allergy tolerate darunavir well
<table>
<thead>
<tr>
<th>PI</th>
<th>Daily Pill Burden, Food Requirements</th>
<th>QD?</th>
<th>Other Considerations</th>
</tr>
</thead>
</table>
| ATV/R TV | 1-2, with food                      | Yes | ▪ Absorption impaired with acid-reducing agents  
▪ Associated with rise in unconjugated bilirubin and scleral icterus in 4% to 9% of pts |
| DRV/RTV | 1-2, with food                      | Yes | ▪ Also highly effective against PI-resistant virus in PI-experienced pts  
▪ Rash in ~ 3% of pts; use with caution in pts with sulfa allergy |
Cobicistat

- Can be used as a “booster” for increasing drug levels of protease inhibitors and elvitegravir
- Co-formulated with multiple regimens
- Not recommended as “preferred” in DHHS because not as much clinical trial data
- Likely similar efficacy to ritonavir
Integrase-Inhibitor Based Regimens
• Significantly shorter time to virologic response with RAL vs EFV ($P = .001$)
• Similar CD4+ cell count increases with RAL vs EFV
  – +240 vs +225 cells/mm$^3$; $\Delta$: 15 cells/mm$^3$ (95% CI: -13-42)
Other Efficacy Studies for Raltegravir

• ACTG 5257 compared atazanavir, darunavir and raltegravir in combination with tenofovir/emtricitabine
• Similar virologic efficacy in all arms
• Fewer discontinuations in darunavir and raltegravir arms

ACTG 5257

- Virologic failure with drug resistance occurred infrequently
- More common in patients assigned to raltegravir arm
- Integrase inhibitor mutations found in all patients who developed virologic failure with drug resistance
- Less bone mineral density loss in integrase inhibitor group
Efficacy in Clinical Trials of Raltegravir

• SPRING-2 compared dolutegravir versus raltegravir in naïve patients
• Used background of abacavir/lamivudine or tenofovir/emtricitabine
• No difference in virologic response
Once-Daily Raltegravir: ONCEEMRK

- Use of raltegravir 2 tablets of 600 mg dosage once daily compared with 400 mg twice daily
- In combination with emtricitabine/tenofovir DF
- Similar virologic suppression rates
- Similar side effect profile
- DHHS guidelines not yet updated

Adverse Effects of Raltegravir

• Very well tolerated
• Rarely causes CPK elevations, rhabdomyolysis, myositis
• Rare rashes
• Minimal drug interactions – great for psych patients and herbal medication takers
Raltegravir Versus Other Options

• Benefits of using raltegravir
  – Considered least metabolically toxic, both in terms of lipodystrophy and effect on triglycerides
  – Lack of drug interactions
  – Minimal side effects
  – Quick virologic suppression and immunologic recovery

• Concerns about raltegravir
  – BID dosing previously
  – Lower genetic barrier to resistance than PIs (probably higher than NNRTIs)
  – Cost
Why would you use elvitegravir (STRIBILD or GENVUYA)?
Elvitegravir/Cobicistat Regimen Noninferior to Efavirenz Regimen

- Greater CD4+ count increase with elvitegravir vs efavirenz: 239 vs 206 cells/mm³ ($P = .009$)
- Among pts with confirmed virologic failure or rebound, resistance detected in 8/14 pts in EVG/COBI arm vs 8/17 pts in EFV arm
  - Primary integrase mutations and primary NNRTI mutations observed in 7 and 8 pts in EVG/COBI and EFV arms, respectively
  - All 8 pts in EVG/COBI arm had M184V/I mutation vs 2 pts in EFV arm; 3 and 2 had K65R, respectively

Safety of Elvitegravir/Cobicistat vs Efavirenz

- Elvitegravir very well-tolerated, main side effect was nausea
- Significantly greater incidence of sleep disturbance, dizziness, rash with efavirenz regimen
- 1.4% of patients discontinued elvitegravir regimen due to renal abnormalities vs no patients on efavirenz regimen
  - **Significantly greater increase in median serum creatinine from baseline to Wk 48 in EVG/COBI group: 0.14 vs 0.01 mg/dL ($P < .001$)**
  - **Thought to be related to cobicistat inhibition of creatinine secretion in distal tubule**
- Significantly greater increases in total, LDL, and HDL cholesterol from baseline to Wk 48 in efavirenz vs elvitegravir/cobicistat groups
Elvitegravir versus Atazanavir

- Elvitegravir/cobicistat non-inferior to atazanavir/ritonavir regimen at week 48 and 96
- Similar CD4 cell count increases in both study arms
- In patients with confirmed virologic failure, resistance detected in 5/12 patients in elvitegravir arm; no resistance in atazanavir arm
  - 4/5 had M184V mutation and 4 had primary integrase mutations
Toxicity of Elvitegravir/Cobicistat versus Atazanavir/Ritonavir

• Similar side effects (nausea/diarrhea)
• Significantly greater increase in median creatinine from baseline 0.12 vs 0.08 mg/dL
• Significantly greater increase in triglycerides in atazanavir group
Pros and Cons of Elvitegravir

• **Pros**
  - Low side effect profile  
  - Highly effective at viral suppression  
  - Low pill burden

• **Cons**
  - Drug interactions  
  - Expense  
  - Monitoring renal function
Why use dolutegravir (TIVICAY/TRIUMEQ)?
Dolutegravir + Abacavir/Lamivudine versus Efavirenz/tenofovir/emtricitabine (SINGLE)

A Proportion of Participants with HIV-1 RNA Level <50 Copies/ml

- DTG-ABC-3TC, 88%
- EFV-TDF-FTC, 81%

Difference in response at wk 48, 7 percentage points (95% CI, 2–12)

P = 0.003
Dolutegravir Versus Efavirenz

- Dolutegravir was statistically superior at suppressing viral load at 48 and 96 weeks.
- Virologic failure 4% in both arms.
- No integrase or NRTI mutations detected in patients on dolutegravir.
- Dolutegravir had lower rate of CNS and rash.
- Fewer discontinuations due to AEs in dolutegravir group (10% in Atripla arm).
SPRING-2: Dolutegravir Noninferior to Raltegravir at 96 Wks (81% vs. 76%)

Figure 2: Proportion of patients with less than 50 copies of HIV-1 RNA per mL, by visit. Data are % (95% CI). Snapshot (missing, switch, discontinuation=failure) analysis.
SPRING-2 Virologic Failures

- Virologic failures rare (5% in dolutegravir group, 7% in raltegravir group)
- No patients treated with dolutegravir had emergent integrase or NRTI resistance at failure
- In raltegravir arm, 1 patient developed integrase resistance and 4 developed resistance to NRTIs

FLAMINGO Trial

• Open-label trial comparing dolutegravir to darunavir/ritonavir
• Could use abacavir/lamivudine or tenofovir/emtricitabine
FLAMINGO Results: Dolutegravir Superior to Darunavir in HIV <50 copies/mL (90% vs. 83%)
FLAMINGO Results

• Treatment success driven by higher discontinuation rates for darunavir patients (4% versus 2% in dolutegravir group)
• 2 patients in each group had virologic failure
• No treatment-emergent mutations detected
• Suggests that dolutegravir has high genetic barrier to resistance
Dolutegravir

• Very few adverse events noted
• Insomnia and headache in 2% of patients
• Decreased tubular secretion of creatinine, does not affect renal function
• Very few drug interactions (but still a few!)
  – E.g. metformin, seizure medications, St. John’s wort
• Absorption can be affected when coadministered with polyvalent cations
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>▪ Cost</td>
<td>▪ CNS side effects (not good for bipolar)</td>
</tr>
<tr>
<td></td>
<td>▪ Single-tablet regimen</td>
<td>▪ Teratogenicity</td>
</tr>
<tr>
<td></td>
<td>▪ Long-term data available</td>
<td>▪ Low genetic barrier to resistance</td>
</tr>
<tr>
<td></td>
<td>▪ Teratogenicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Low genetic barrier to resistance</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>▪ Single-tablet regimen</td>
<td>▪ Low genetic barrier to resistance</td>
</tr>
<tr>
<td></td>
<td>▪ Well-tolerated</td>
<td>▪ Higher virologic failures in high viral loads</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Need for acid for absorption</td>
</tr>
<tr>
<td>Protease-inhibitor based</td>
<td>▪ Most forgiving for non-adherent patients</td>
<td>▪ Highest pill burden</td>
</tr>
<tr>
<td></td>
<td>▪ Safe to use in patients without genotype information</td>
<td>▪ Metabolic side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ For atazanavir, jaundice and need for acid for absorption</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>▪ Minimal adverse effects</td>
<td>▪ Twice-daily dosing</td>
</tr>
<tr>
<td></td>
<td>▪ Very few drug-drug interactions</td>
<td>▪ Lower genetic barrier to resistance than protease inhibitors</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>▪ Single tablet regimen</td>
<td>▪ Renal effects</td>
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<tr>
<td></td>
<td>▪ Well-tolerated</td>
<td>▪ Drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Lower genetic barrier to resistance than protease inhibitors</td>
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<tr>
<td>Dolutegravir</td>
<td>▪ Single tablet regimen not yet available</td>
<td>▪ Mild renal effects</td>
</tr>
<tr>
<td></td>
<td>▪ Few side effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Likely a high genetic barrier to resistance</td>
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## 2 NRTIs + NNRTI

<table>
<thead>
<tr>
<th></th>
<th>Alternative</th>
<th>Total Cost</th>
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<tbody>
<tr>
<td>Atripla</td>
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<td>$740-2000</td>
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<tr>
<td>Complera</td>
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<td>$900-2100</td>
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## 2 NRTIs + PI

<table>
<thead>
<tr>
<th></th>
<th>Alternative</th>
<th>Preferred</th>
<th>Total Cost</th>
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<tbody>
<tr>
<td>Truvada</td>
<td>$450-1500</td>
<td>$450-1500</td>
<td>$1050-3000</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>$16-550</td>
<td>$16-550</td>
<td>$1100-3000</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>$600-1400</td>
<td>$650-1300</td>
<td>$1100-3000</td>
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## 2 NRTIs + ISTI

<table>
<thead>
<tr>
<th></th>
<th>Preferred</th>
<th>Preferred</th>
<th>Total Cost</th>
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<tbody>
<tr>
<td>Truvada</td>
<td>$450-1500</td>
<td>$2500-2800</td>
<td>$2500-2800</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>$600-1400</td>
<td>$600-1400</td>
<td>$2500-2800</td>
</tr>
<tr>
<td>Stribild</td>
<td>$1700-2800</td>
<td></td>
<td>$1700-2800</td>
</tr>
<tr>
<td>Genvoya</td>
<td>$2500-3500</td>
<td></td>
<td>$2500-3500</td>
</tr>
<tr>
<td>Triumeq</td>
<td>$2500-2800</td>
<td></td>
<td>$2500-2800</td>
</tr>
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</table>
Choosing Between the NRTIs: Abacavir versus Tenofovir
Abacavir Returned to DHHS!

• Previously had fallen off due to concerns about:
  – Efficacy in comparison with tenofovir
  – Possible Cardiovascular toxicity
  – No activity against hepatitis B infection
ACTG 5202: Abacavir vs Tenofovir + Efavirenz or Atazanavir/ritonavir

Stratified by HIV-1 RNA
< or ≥ 100,000 copies/mL

HIV-infected pts with HIV-1 RNA > 1000 copies/mL
(N = 1858)

- **TDF/FTC*** 300/200 mg QD + **EFV†** 600 mg QD
- **ABC/3TC*** 600/300 mg QD + **EFV†** 600 mg QD
- **TDF/FTC*** 300/200 QD + **ATV/RTV†** 300/100 mg QD
- **ABC/3TC*** 600/300 mg QD + **ATV/RTV†** 300/100 mg QD

ACTG 5202: Abacavir vs Tenofovir

• Study discontinued early
  – More virologic failure observed with abacavir in patients with HIV RNA >100,000 copies/mL versus in tenofovir
HEAT: Abacavir Noninferior to Tenofovir, even at high HIV viral loads

Dolutegravir Trials (SINGLE, FLAMINGO)

• No differences between abacavir or tenofovir in virologic efficacy, even at high viral loads (>100k)
Abacavir in DHHS Guidelines

• Recommended in patients taking dolutegravir (extensively tested)
• Use in efavirenz or atazanavir based regimens only if viral load is <100k
• ***Considered as “alternative”***
  – Probably ok with darunavir based regimens (not tested)
  – Not much data with rilpivirine or raltegravir
Abacavir and Cardiovascular Risk

- D:A:D cohort study has thousands of patients on multiple regimens
- Found that patients recently started (within 6 months) associated with increased risk of MI, particularly in patients with CV risk factors
## Summary of Clinical Trial and Cohort Analyses of ABC Use and CVD Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>CV Events</th>
<th>Effect of ABC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>D:A:D[^1] (N = 33347)</td>
<td>Observational cohort</td>
<td>Prospective, predefined</td>
<td>Yes</td>
</tr>
<tr>
<td>FHDH[^2] (N = 1173)</td>
<td>Case control study</td>
<td>MI retrospectively validated</td>
<td>Yes 1st yr of exposure</td>
</tr>
<tr>
<td>SMART[^3] (N = 2752)</td>
<td>RCT, observational analyses</td>
<td>Prospective, predefined</td>
<td>Yes</td>
</tr>
<tr>
<td>STEAL[^4] (N = 357)</td>
<td>RCT</td>
<td>Prospective</td>
<td>Yes</td>
</tr>
<tr>
<td>GSK analysis[^5]</td>
<td>54 RCTs</td>
<td>Retrospective database search</td>
<td>No</td>
</tr>
<tr>
<td>ALLRT ACTG A5001[^6]</td>
<td>5 RCTs</td>
<td>Retrospective by 2 independent reviewers</td>
<td>No</td>
</tr>
</tbody>
</table>

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All or majority of pts antiretroviral-experienced at ABC initiation

All or majority of pts antiretroviral-naive at ABC initiation

---

Cardiovascular Risk of Abacavir

• Bedimo et. al (CID 2011 53(1): 84-91) used Veterans Association data to calculate risk of MI and stroke in patients on abacavir and other combinations
  – Controlled for chronic kidney disease, smoking, lipids etc.
  – Observed NO association between abacavir use and MI or CVA once CKD accounted for
Cardiovascular Risk and Abacavir

- Meta-analysis of randomized, controlled treatment trials and manufacturer data found no evidence that abacavir-containing regimens carry greater risk of MI
DHHS Guidelines

• “No consensus has been reached on the association between abacavir use and MI risk or the mechanism for such an association.”
Concerns About Tenofovir
ACTG 5224s: Change in Bone Mineral Density

- Substudy of ACTG 5202
  - Tenofovir versus abacavir and efavirenz vs atazanavir/ritonavir
- Primary endpoint
  - Changes in bone mineral density by DXA
- At week 96, significantly greater losses in BMD with
  - Tenofovir vs abacavir in both hip and spine
  - Atazanavir/ritonavir vs efavirenz in spine

Tenofovir: Concerns for Renal Toxicity

- Fanconi’s syndrome known potential toxicity of tenofovir
- Multiple case studies and clinical experience of proximal tubular dysfunction and impaired GFR; several observational cohort studies show rates of renal failure with tenofovir use
- Meta-analysis showed “significantly greater decrease” of -3.92 mL/min and increased risk of acute renal failure (0.7%) in patients receiving tenofovir as compared to other regimens

- Cooper R. CID 2010: 496-505.
Tenofovir alafenamide (TAF)

- TAF (GS-7340), prodrug of tenofovir with lower tenofovir plasma concentrations, increased delivery to hepatocytes, lymphoid cells
Use of Tenofovir Alafenamide vs TDF in Treatment-Naive Pts

• Studies 104/111
• Compared elvitegravir/cobicistat and tenofovir alafenamide versus disoproxil
• Similar virologic suppression
• Smaller eGFR decline with TAF
• Decreased rates of bone loss with TAF
• Higher lipid levels with TAF due to absence of TDF lipid lowering effect

# Tenofovir versus Abacavir

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>▪ Similar efficacy to tenofovir in HEAT and dolutegravir trials&lt;br&gt;▪ Hypersensitivity can be safely avoided with HLA-B*5701 assay</td>
<td>▪ Potential for hypersensitivity reaction&lt;br&gt;▪ Inferior response high viral load in ACTG 5202&lt;br&gt;▪ Association with ↑ risk of myocardial infarction in some studies</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>▪ High level of efficacy in clinical trials&lt;br&gt;▪ Active against hepatitis B</td>
<td>▪ Caution in pts with renal insufficiency&lt;br&gt;▪ Long-term nephrotoxicity and tubular toxicity not fully understood&lt;br&gt;▪ Should not be coadministered with other nephrotoxic drugs&lt;br&gt;▪ Bone toxicity</td>
</tr>
<tr>
<td>Tenofovir AF</td>
<td>▪ Comparable efficacy to tenofovir DF in clinical trials&lt;br&gt;▪ Less effect on bone and renal&lt;br&gt;▪ Active against hepatitis B&lt;br&gt;▪ Can use in patients with CKD to GFR &gt;30 mL/min</td>
<td>▪ Does have some effects on bone and kidney&lt;br&gt;▪ Higher cholesterol levels than TDF</td>
</tr>
</tbody>
</table>
Really Alternative Regimens

- Darunavir/ritonavir plus raltegravir (BID) if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm³ (NEAT)
- Lopinavir/ritonavir + lamivudine (GARDEL)
- If cannot use either abacavir or tenofovir

Antiretrovirals on the Near Horizon

• Bictegravir, a novel integrase inhibitor
  – Fixed dose combination product with emtricitabine/tenofovir alefenamide
  – Comparison trials against dolutegravir/abacavir/lamivudine

• Doravirine, novel NNRTI
  – Comparison trials against efavirenz/emtricitabine/tenofovir and darunavir/ritonavir/tenofovir/emtricitabine
A Little Farther on the Horizon

- Cabotegravir, novel integrase inhibitor
  - Trial of oral medication
  - Injectable formulation
  - In combination with oral or IM rilpivirine
The Art of HAART
Know your patient!

• It is imperative to extensively explore factors that may impact adherence prior to HAART initiation:
  – Drug use (may wish to avoid ritonavir)
  – Concerns about lipoatrophy (avoid zidovudine, stavudine, didanosine, protease inhibitors, possibly efavirenz)
  – Pregnancy/child-bearing age (efavirenz teratogenicity)
  – Works night shifts (efavirenz CNS toxicity)
  – Hepatitis B coinfection (need for tenofovir, emtricitabine, lamivudine)
  – GERD (avoid atazanavir, rilpivirine)
Case 1

- 28 year-old Caucasian male, busy professional, concerned about appearance, has very pale skin. Viral load 350,000; wild-type genotype. CD4 320 cells/uL. Creatinine normal. HLAB5701 positive. Has private insurance. Wants “one pill, once a day” regimen.

- What would be good options for antiretroviral therapy?
Case 1—Better Options

- Elvitegravir-based regimen (Stribild) or Genvoya
  - One pill daily regimen
  - Few side effects
  - Renal toxicity
Case 1: Not as Good Options

- Atazanavir-based
  - Patient has GERD; PPI/H2 blocker will interfere with atazanavir absorption
  - Patient may notice scleral icterus
  - Metabolic complications
  - More than 1 pill

- Darunavir-based
  - More than 1 pill
  - Metabolic complications
Case 1: Not as Good Options

- Raltegravir-based regimen
  - Twice daily but otherwise excellent side effect profile
- Dolutegravir-based regimen
  - Once daily but 2 tablets
- Rilpivirine-based regimen (Complera)
  - Concern about absorption with GERD
  - Concern about efficacy given high viral load
Nucleotide Regimen

- CANNOT use abacavir due to HLAB5701
- Use tenofovir DF or AF/emtricitabine
- Monitor creatinine (and maybe bone mineral density)
Case 2

- 31 year-old African-American female, viral load of 70,000 copies/mL; CD4 60 cells. No past medical history, although screening labs show HBsAg positive. Creatinine normal.
Treatment Options: Case 2

- Elvitegravir-based regimen
  - May be good treatment option for this patient
  - Minimal side effects, low pill burden

- Dolutegravir-based regimen
  - May be good treatment option for this patient
  - Minimal side effects, low pill burden

- Raltegravir-based regimen
  - Twice daily but otherwise excellent side effect profile
Treatment Options: Case 2

• Atazanavir-based therapy:
  – Good option, low pill burden
  – Scleral icterus not as noticeable
  – Protease-inhibitors will help CD4 increase quickly

• Darunavir-based therapy:
  – Higher pill burden but still once daily
  – No scleral icterus or GERD concerns
  – Durable regimen for non-adherent patients
Options for Treatment

• Efavirenz-based therapy:
  – Known teratogen; unless patient willing to use 2+ forms of birth control, don’t use this medication
• Rilpivirine-based regimen (Complera)
  – Excellent side effect profile, low pill burden
  – Pregnancy category B
  – Not recommended for CD4 < 200 cells/uL given higher virologic failure rate
Nucleoside Options

- Tenofovir-based regimen would be preferable in this patient with active hepatitis B; both tenofovir and emtricitabine are active against HBV
Case 3

- 42 year-old African American female, CD4 2, newly-diagnosed PML, viral load 200k

- When would you start medications, and which medications would you start?
Case 3: Timing

• Immediately, do not pass Go, before leaving the hospital! No other treatment options available for PML
Treatment Options: Case 3

• Darunavir-based therapy:
  – Once daily
  – No scleral icterus or GERD concerns
  – Durable regimen for non-adherent patients

• Atazanavir-based therapy:
  – Good option, low pill burden
  – Protease-inhibitors will help CD4 increase quickly
  – If patient hospitalized, will need to worry about PPI initiation
Treatment Options: Case 3

• Elvitegravir-based regimen
  – *May be good treatment option for this patient*
  – *Minimal side effects, low pill burden*

• Dolutegravir-based regimen
  – *May be good treatment option for this patient*
  – *Minimal side effects, low pill burden*

• Raltegravir-based regimen
  – *Twice daily but otherwise excellent side effect profile*
What to Use: Case 3

• Efavirenz-based therapy:
  – Known teratogen; unless patient willing to use 2+ forms of birth control, don’t use this medication
  – Also would expect slower CD4 count rise
  – neurotoxicity
Treatment Options: Case 3

• Rilpivirine-based regimen (Complera)
  – Not recommended in CD4 <200 cells/μL
  – Pregnancy category B
Nucleoside Options

• Efficacy concerns about use of abacavir in non-dolutegravir containing regimens given her high viral load (depending on which study you believe)
Case 4

• 48 year-old African American male, CD4 320, viral load 50,000; CKD with baseline creatinine of 2.4, bipolar with psychotic features during manic episodes. On 5 medications for bipolar, seen through Metrocare.
What to Use: Case 4

• Efavirenz-based therapy:
  – Would be cautious about this therapy given patient’s unstable history of bipolar depression
Treatment Options: Case 4

- Atazanavir-based therapy:
  - Possibility of drug interactions with psych meds
  - Scleral icterus not as noticeable

- Darunavir-based therapy:
  - Possibility of drug interactions with psych meds
  - Once daily
  - No scleral icterus or GERD concerns
  - Durable regimen for non-adherent patients
Treatment Options: Case 4

• Raltegravir-based regimen
  – Twice daily but otherwise excellent side effect profile; may need to worry about adherence in this patient
  – Minimal drug interactions

• Rilpivirine-based regimen (Complera)
  – Not as many psychiatric side effects
  – Excellent adherence essential, higher virologic failure rate
Treatment Options: Case 4

• Elvitegravir-based regimen
  – Stribild not recommended for patients with low creatinine clearance
  – Concern about drug interactions with psychiatry medications
Treatment Options: Case 4

• Dolutegravir-based regimen:
  – Well-tolerated
  – May be forgiving of potential non-adherence
  – Low pill burden
  – Few drug interactions (watch carbamazepine, phenytoin, St. John’s Wort, oxcarbazepine, phenobarbital)
Nucleoside Options

• Caution of using tenofovir DF in patients with chronic kidney disease, needs adjustment if CrCl < 50 mL/min