ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals
Initial Therapy for Antiretroviral Naïve HIV Infected Patients

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Disclosures

Scientific Advisory Board
Gilead Sciences

There will be no off-label/investigational uses discussed in this presentation.
Learning Objectives

1. Describe the IAS-USA and DHHS guidelines for initial treatment of HIV infected patient

2. Discuss recommendations for treatment in special populations and co-morbidities

3. Review recommendations for lab monitoring post initiation of antiretroviral treatment
Initial Evaluation of the Patient with HIV

4 Steps

**Step 1:** History, Examination and Lab Tests

**Step 2:** Opportunistic infection prophylaxis (if indicated)

**Step 3:** Antiretroviral therapy: when and what to start; how to monitor

**Step 4:** Preventive care
Patient care recommendations are drawn from the US Department of Health and Human Services (DHHS) guidelines unless otherwise noted.

Panel on anti-retroviral guidelines for adults and adolescents. Guidelines for the use of anti-retroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Available at HTTP://aidsinfo.nih.gov/contentfiles/1vguidelines/adultandadolescentGL.pdf
Lab Evaluation: HIV-specific Tests

- HIV confirmation test
  
do if HIV not clearly documented
- CD4 cell count and percent
- HIV RNA viral load or VL
- HIV drug resistance test (genotype)
- HLA-B5701: if considering abacavir containing regimen
- Tropism test (phenotypic or genotypic): if considering CCR5 inhibitor

E Phillips, CID, 2006; Aberg, J et al CID 2014
Resistance Testing

- Genotypic testing for reverse transcriptase and protease resistance mutations is recommended prior to treatment initiation.

- Routine screening for integrase resistance is currently NOT recommended prior to treatment initiation unless the source virus is suspected to have been from someone in whom treatment containing an integrase strand transfer inhibitor failed.
Life Expectancy of HIV-Infected Patients

• Comparison of life expectancy of Athena cohort patients to general population (n=4174)

• Expected life years remaining at age 25 was 53.1 (44.9-59.5) for general population and 52.7 for asymptomatic HIV+ patients

• The modeled life expectancy of patient presenting at an older age and women were slightly lower that general population

van Sighem A, AIDS, 2010
General Principles

The goal is start and maintain treatment to prevent disease, maintain quality of life, and prevent transmission of HIV to others.

“The sooner, the better.” – reduces size of the reservoir, decreased inflammation, can consider starting before all test results are available.

Ideally we want to start a regimen that patients can comply with for a long period of time.

- Fewest number of pills
- Fewest times needed to be taken in a day
- Fewest complaints - best side effect profile
Role of the Multidisciplinary Care Team

- Interventions to improve linkage, retention, and adherence to care are essential.
- Barriers to adherence to ART and appointments should be assessed prior to initiating therapy and thereafter, as needed.
- Multidisciplinary approaches to address adherence issues are often necessary.
  - Collaboration with social work and case management to help mitigate competing priorities (e.g. housing, food insecurity, transportation, employment status, out-of-pocket costs) is recommended
  - Linking patients to counseling to overcome stigma, substance use, or depression improves outcomes.
  - A care team approach to continued education and linkage to resources to overcome barriers is encouraged.

**Multidisciplinary Team Members**

- Social Work
- Case Management
- Mental Health
- Harm Reduction
- Nursing
- Entitlement Specialist
- Peer Educators
- Pharmacist
- Clinical Providers
Initial Treatment: When and Who to Start

- Antiretroviral therapy (ART) is recommended for all patients with established HIV infection, a detectable viral load, and regardless of CD4 cell count.

- Initiation of ART is recommended as soon as possible in the setting of acute HIV infection.

- Initiation of ART is recommended for individuals who have persistent undetectable viral load (elite controllers) without ART but have declining CD4 cell counts.

Clinical Scenario

33 yo AA F presents to clinic after recent hospital admission for pneumonia. During the hospitalization, she accepted HIV testing and her test was confirmed positive yesterday.

Pt denies any prior illness. Her labs were only significant for a mildly elevated WBC. Has h/o unprotected sex with 5 male partners in her lifetime and is now in a committed relationship. Denies any recreational drug use or excessive alcohol use. Smokes 1ppd x 19 years.

A CD4 and VL were obtained yesterday. CD4 267 17%, viral load and genotype are pending.

Pt feels weak, but was symptomatically improved at time of discharge. You order additional blood work in your office.

She has no barriers to care, has been educated about HIV, and is eager to start treatment.
Question 1

1. Make an return appointment in 4 weeks when genotype result will have returned.

2. Make an return appointment in 2 weeks to re-assess her readiness to start, review labs.

3. Start treatment with DTG/ABC/3TC

4. Start treatment with EVG/c/TDF/FTC

5. Start treatment with RPV/TAF/FTC
Rapid Initiation of ARV

- Accelerated ART initiation, including starting ART on the same day as HIV diagnosis, can lead to improved clinical outcomes
  - Important for people with very low CD4+ cell counts, for whom the risk of death is high

- ART initiation on the same day as HIV is diagnosed should be offered to those patients who are ready to start

- Genotype and safety labs should be obtained, but do not have to wait for results prior to start
  - ABC containing regimens are not recommended for same day start given need for HLA testing results
  - TAF/FTC containing regimens can be used with CrCl > 30 mL/min
## Available Antiretroviral Agents

### Nucleoside RTIs
- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Tenofovir (TDF)
- Tenofovir Alafenamide (TAF)

### Nonnucleos(t)ide RTIs
- Nevirapine (NVP)
- Delavirdine (DLV)
- Etravirine (ETR)
- Rilpivirine (RPV)
- Efavirenz (EFV)

### Protease Inhibitors
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Lopinavir/r (LPV/r)
- Darunavir (DRV)
- Atazanavir (ATV)

### Integrase Inhibitors
- Raltegravir (RAL)
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Bictegravir (BIC)

### CCR5 Antagonist
- Maraviroc (MVC)

### Boosters
- Ritonavir (RTV)
- Cobicistat (cobi)

### Fusion Inhibitor
- Enfuvirtide (T-20)
Initial Treatment

An integrase inhibitor based regimen containing TAF/FTC or ABC/3TC is recommended for initial in treatment naïve individuals

- Bictegravir/TAF/emtricitabine
- Dolutegravir/abacavir/lamivudine
- Elvitegravir/cobicistat/TAF/emtricitabine
- Dolutegravir plus TAF/emtricitabine
- Raltegravir plus TAF/emtricitabine

* Bictegravir/TAF/emtricitabine was added to the DHHS HIV guidelines as a first line recommended regimen on March 27, 2018. It has not yet been added to the IAS-USA guidelines.
New Integrase Inhibitor Single Tablet Regimen
Bictegravir/FTC/TAF

- Comparable virologic outcomes to DTG based regimens
- High genetic barrier to resistance
- No need for pretreatment HLA testing
- Does not include a pharmacologic booster, decreasing its potential for drug-drug interactions
- Can be used in patients with a CrCl as low as 30 mL/min
- Co-administration with rifampin is contraindicated due to the effect of rifampin on the BIC component

Virologic Outcomes of BIC/F/TAF Treatment
Naïve Trials 1489 and 1490 at Week 48

<table>
<thead>
<tr>
<th></th>
<th>Trial 1489</th>
<th>Trial 1490</th>
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<tbody>
<tr>
<td>HIV-1 RNA &gt; 50</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>CD4 increase</td>
<td>233</td>
<td>229</td>
</tr>
<tr>
<td>Discontinued due to AE or Death</td>
<td>0</td>
<td>1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>17%</td>
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<tr>
<td>Headache</td>
<td>5%</td>
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Pros and Cons

**BICTEGRAVIR**
- high barrier to resistance
- safe in renally impaired, co-formulated with TAF/FTC
- few drug interactions
- contraindicated with rifamycins
- decreased clinical experience

**DOLUTEGRAVIR**
- high barrier to resistance
- superior to EFV and boosted DRV based regimens in clinical trials
- higher rates of insomnia, CNS AE in some studies
- inhibition of tubular secretion of Cr
- largest STR

**ELVITEGRAVIR**
- co-formulated with TAF/FTC
- more drug interactions due to boosting cobicistat
- inhibition of tubular secretion of Cr

**RALTEGRAVIR**
- twice daily dosing, no co-formulation

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Tenofovir Alafenamide (TAF)

- 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV
- less effect on renal tubular and overall proteinuria and eGFR than TDF
- little to no effect on bone density

Abacavir

- Requires HLA-B5701 testing prior to start
  - Approximately half of patients positive for the allele experience ABC hypersensitivity reaction
  - 8% of US whites, ~2% of US African-Americans and Hispanics

- The association between abacavir and HIV associated cardiovascular disease remains controversial
  - ABC is lipid neutral, no change in insulin or limb fat loss
  - leukocyte and platelet–endothelial cell interactions via ATP-2 receptors → increased vascular inflammation response
  - augment adhesion of WBC to the endothelium
  - Increased platelet activation

References:

Recommendations for Initial Regimen in Certain Clinical Situations

Boosted PI + 2 NRTIs: *In general, boosted DRV is preferred over boosted ATV*

(DRV/c or DRV/r) + tenofovir /FTC

(ATV/c or ATV/r) + tenofovir /FTC

(DRV/c or DRV/r) + ABC/3TC — if HLA-B*5701–negative

(ATV/c or ATV/r) + ABC/3TC — if HLA-B*5701–negative and HIV RNA 200 cells/mm³

INSTI + 2 NRTIs:

RAL + ABC/3TC - if HLA-B*5701–negative and HIV RNA < 100,000 copies/mL

Regimens to Consider when ABC, TAF, and TDF **Cannot** be Used

DRV/r + RAL (BID) - if HIV RNA > 200 cells/mm³

LPV/r + 3TC (BID)

*NNRTI regimens are *not recommended* as alternative regimens in the DHHS guidelines*
IAS-USA Guideline Recommendations for When Integrase Inhibitors are not an Option

Darunavir (boosted) plus TAF/emtricitabine or abacavir/lamivudine

Rilpivirine/TAF/emtricitabine

Efavirenz/TDF/emtricitabine
Pros and Cons

DARUNAVIR
- low rate of resistance even with poor adherence
- drug interactions with required boosting
- inferior to integrase inhibitor based regimens

RILPIVIRINE
- small size
- not recommended for VL > 100,000 or CD4, 200
- must be taken with meal
- staggered dosing with PPI

EFAVIRENZ
- longest track record
- low genetic barrier to resistance
- CNS side effects
Special Considerations
Clinical Scenario

33 yo AA F presents to clinic after recent hospital admission for pneumonia. During the hospitalization, she accepted HIV testing and her test was confirmed positive.

You write her prescription to start EVG/c/TAF/FTC today.

While she is getting her labs done, your nurse lets you know that her POC urine pregnancy test is reactive.
Question 2

1. You start the same ART, EVG/c/TAF/FTC today as planned.

2. You explain that ART will be started after the 1st trimester to minimize effects to the baby.

3. You decide to start DRV/cobi + TDF/FTC today

4. You decide to start RAL + TDF/FTC

5. You decide to start RPV/TDF/FTC
Pregnancy

• Addressing the fertility desires, preferred method of birth control, and pregnancy testing should be done in women of childbearing potential prior to the initiation of ART

• Goal start treatment as soon as possible is to promote the health of the pregnant woman throughout and to prevent vertical transmission (i.e. maternal VL < 1000 copies)

• ART should be uninterrupted for women who conceive while on treatment or as soon as possible for newly diagnosed unless regimen is contraindicated (ddI, d4t, and elvitegravir/cobi)

• NNRTI are no longer considered first line therapy for pregnant women

# Pregnancy

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<thead>
<tr>
<th></th>
<th>RECOMMENDED</th>
<th>ALTERNATIVE</th>
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<tbody>
<tr>
<td>NRTI backbone</td>
<td>TDF/TFC, ABC/3TC, TDF + 3TC</td>
<td>AZT/3TC</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td>EFV, RPV</td>
</tr>
<tr>
<td>PI</td>
<td>ATZ/r, DRV/r *</td>
<td>LPV/r</td>
</tr>
<tr>
<td>Integrase</td>
<td>RAL</td>
<td>DTG</td>
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*DRV/r: must be used twice daily in pregnancy
TAF: Insufficient data on TAF PK and safety in pregnancy
EVG/c: Reports of inadequate drug levels in 2nd and 3rd trimesters with viral breakthroughs
Hepatitis Co-Infection

Hepatitis B

- regimen should contain two NRTIs with anti-Hep B activity: TDF or TAF, FTC, 3TC
- addition of entectavir recommended if few than two active Hep B NRTIs are not used
- risk of Hep B flare if regimen is changed to an option that doesn’t have anti-Hep B activity

Hepatitis C

- goal is to have a regimen that has the fewest drug-drug interactions
- BIC/TAF/FC, DTG/ABC/3TC, and DTG or RAL + TAF/FTC have the best DDI profile in combination with HCV treatments
Renal Disease

- Urinalysis should be obtained at initiation and at least annually
- TDF (especially with a boosted PI) increased the risk of chronic kidney disease.
- TDF is not recommended for patients with an eGFR below 50 mL/min.
- TAF/FTC can be used for CrCl 30 mL/min or above
- ABC does not require dose adjustment in renal insufficiency

Patients may lose 2% to 6% of their bone mineral density at the hip and spine, within the first 18 – 24 months after the initiation of ARV therapy.

Rates of osteoporosis and fractures are increased in HIV-infected compared to age / risk factor matched controls.

TAF-containing regimens have a more favorable decline in BMD compared to TDF regimens.

Avoid TDF in patients with pre-existing osteopenia / osteoporosis.

Clinical Scenario

33 yo AA F presents to clinic after recent hospital admission for pneumonia. During the hospitalization, she accepted HIV testing and her test was confirmed positive.

She insists that she is not pregnant.

Your nurse returns to clarify that there was a lab error and that her repeat pregnancy test is in fact negative.

As you are about to write a prescription for her ART, you get a call from the DOH that her BAL specimen is positive for TB, with no evidence of drug resistant TB.
1. You hold on starting ART, refer her to pulmonary, and have her return after 2 months of TB treatment.

2. You start the same ART, EVG/c/TAF/FTC, today as planned.

3. You explain that ART will be started 2 weeks after TB treatment.

4. You decide to start DRV/cobi + TDF/FTC today

5. You decide to start DTG + TDF/FTC
Initiating Therapy with an ActiveOI

• ART should be started within the first 2 weeks after diagnosis for most acute opportunistic infections
  – Drug interactions and tolerability should be considered when choosing a ART regimen

• ART should be started within the first 2 weeks of initiation of tuberculosis treatment for those with CD4 cell counts of 50/μL or less and within the first 2 to 8 weeks for those with CD4 cell counts above 50/μL

• TAF, BIC, and elvitegravir/cobi are not recommended with rifamycin drugs

• A boosted protease inhibitor–based regimen should be used only if an integrase strand transfer inhibitor is not an option
SAPiT Trial: Mortality in Sequential Arm Occurred Late

Kaplan-Meier Survival Curve

Sequential Arm 97d

Integrated Arm 21d

Post –TB Treatment

Delayed ARV Start with Meningitis

Delayed start is recommended in the setting of cryptococcal and TB meningitis

- ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy
  - In resource limited settings, mortality was lower when ART was delayed until 5 weeks after diagnosis
  - In settings where optimized regimens, frequent monitoring, and testing of ICP are available, an earlier start of ARV is recommended
- Early initiation of ART in the setting of TB meningitis may be associated with severe IRIS

Cost Considerations

• Here in the US, approximately 75% of the cost of treating HIV is related to the cost of medications.

• It is cost effective to treat HIV even if ARVs are full price.

• As more ART components become generic, cost considerations continue to factor into the debate on resource constraints and best practice on a larger scale.

• Guidelines often persuade payors as to which regimens are covered by individual prescription drug plans.

• Individual state ADAP formularies and insurance plans may lag or exclude recommended options.
Monitoring after Starting ART

HIV RNA
- 4 - 6 weeks after starting ART; then every 4-8 weeks until undetectable
- First 1 year of ART: every 3-4 mo.
- After 1 year of virologic suppression, can extend to every 6 months

CD4 count:
- 3 mo. after initiating ART, until Cd4 > 350
- First 2 years of ART: every 6 months
- After 2 years of virologic suppression, CD4 300-500: every 12 mo.; CD4 >500, optional

Aberg J et al, CID, 2014
Monitoring after Starting ART

Chemistries, BUN/Cr, LFTs: wk 2-8 after starting ART, then every 3-6 mo

CBC/diff: every 3-6 mo

Fasting glucose or HbA1c: every 3-6 mo. If previously abnormal; every 12 mo. If normal

Lipids: if abnormal, every 6 mo; normal: every 12 mo.

U/A annually; every 6 mo. if receiving TDF

Summary

The overriding principles for initial ART regimen are patient safety, efficacy, tolerability, and options that lead to improved compliance.

Integrase inhibitor based regimens are recommended by guidelines as first line therapy based on data from comparative clinical trials.

Attention should be given to choice and timing of initial ART regimen in special populations at increased risk of adverse events and drug-drug interactions.

Adherence, safety, cost, and access are among the factors to consider when choosing initial therapy. The interplay of cost effectiveness and the availability of lower priced generics is evolving.

“Guidelines are just that . . . Guidelines”
- Judith Aberg
Thank You