

Florida Caribbean
AETC
ADVANCED EDUCATION TRAINING CENTER

Keeping with the Pace: 2010 Clinical Update

Jennifer Janelle, MD
Clinical Assistant Professor
University of Florida, Gainesville
Faculty, Florida/Caribbean AETC

Disclosure of Financial Relationships

This speaker has no significant financial relationships with commercial entities to disclose.

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

Florida Caribbean
AETC
ADVANCED EDUCATION TRAINING CENTER

Objectives

- Discuss the DHHS guidelines for initiation of antiretroviral therapy in adults and adolescents published December 2009
- Discuss management of resistance to antiretroviral treatment.

Florida Caribbean
AETC
ADVANCED EDUCATION TRAINING CENTER

Life Expectancy After HIV Infection

- Prior to widespread availability of HAART, progression from HIV infection to AIDS took about 10 years
- Once AIDS developed, death typically occurred within 2 years
- However, there was wide variability between individual patients

Florida Caribbean
AETC
ADVANCED EDUCATION TRAINING CENTER

Typical Course of an HIV Infected Individual

Munier ML and Kelleher AD.
Immunol Cell Biol. 2007 Jan;85(1):6-15. Epub 2006 Dec 5

Florida Caribbean
AETC
ADVANCED EDUCATION TRAINING CENTER

Factors That Modify Life Expectancy in Those with HIV

- **Increase life expectancy**
 - Access to antiretroviral medications
 - Compliance with antiretroviral medications
- **Decrease life expectancy**
 - Aggressiveness of the virus causing infection
 - Other medical conditions such as liver and renal disease
 - Lifestyle issues – IV drug abuse, smoking, alcohol intake
- **Increase or decrease**
 - Host factors that modify infection

Florida Caribbean
AETC
ADVANCED EDUCATION TRAINING CENTER

Life Expectancy After HIV Diagnosis Based on National HIV Surveillance Data From 25 States, United States
 Kathleen McDavid Harrison, PhD, MPH, Ruiqiang Song, PhD, and Xijian Zhang, PhD

124 | www.jaids.com | J Acquir Immune Defic Syndr • Volume 53, Number 1, January 1, 2010

- Average life expectancy after HIV diagnosis increased from 10.5 to 22.5 years from 1996 to 2005



Initiation of ART: Case

A 59 yo man recently presented to the medical clinic for HIV care. He was diagnosed with HIV 3 months ago after being named in a contact investigation.

- Labs one month after diagnosis were significant for CD4 380 cells/mm³ and HIV viral load 90,000 copies/mL.
- Repeat CD4 count 1 month ago was 370 cells/mm³
- He has no history of opportunistic infections and has never been treated with antiretroviral medications.

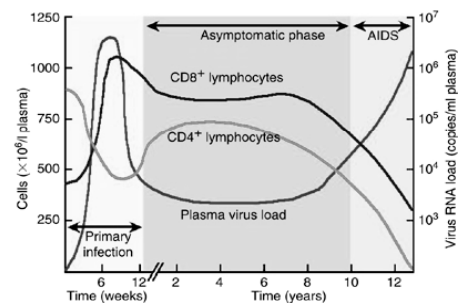


Should You Initiate Treatment at This Time?

1. Yes
2. No
3. Maybe

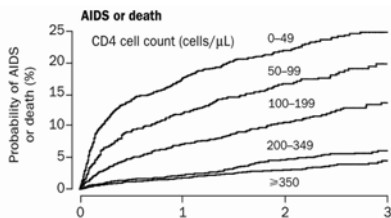


Typical Course of an HIV Infected Individual



Munier ML and Kelleher AD. Immunol Cell Biol. 2007 Jan;85(1):6-15. Epub 2006 Dec 5

Effect of Baseline CD4 Count on Response to Initial ART



Egger et al. Lancet 2002; 360:119-30.



CD4 Cell Count

- Major clinical indicator of immunodeficiency
- Most important factor in deciding whether to initiate ART and prophylaxis for opportunistic infection
- Strongest predictor of subsequent disease progression and survival



HIV Viral Load

- Not as closely linked to short term risk of AIDS/death
- High viral load predicts more rapid progression to AIDS overall and is sometimes taken into consideration when deciding whether to initiate antiretroviral therapy



Current DHHS Guidelines Definitely Start Treatment if:

- History of AIDS-defining illness
- CD4 count <350 cells/mm³
- Pregnant woman
- HIV-associated nephropathy (HIVAN)
 - Not clearly related to CD4 decline; ART may preserve renal function

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1st, 2009. Available online at www.aidsinfo.nih.gov



Current DHHS Guidelines Definitely Start Treatment if:

- Hepatitis B co-infection, if HBV treatment is needed
 - Tenofovir + (lamivudine or emtricitabine) is recommended
 - If ART is not started, HBV therapy should not include agents that may select for resistance to ARVs



What about asymptomatic patients with CD4 counts over 350?

- The exact CD4 count at which to initiate therapy in someone without symptoms related to HIV is not known.
- Recent evidence points to starting antiretroviral treatment at higher CD4 counts than we have in the recent past.



NA-ACCORD Trial

- North American AIDS Cohort Collaboration on Research and Design Study
 - Two parallel analyses involving a total of 17,517 asymptomatic patients with HIV infection who were ART naive in the US and Canada who received medical care between 1996 and 2005.
 - Patients were stratified according to the CD4 count at the initiation of antiretroviral therapy.
 - Outcome: All cause mortality

Kitahata MM, et al. N Engl J Med 2009;360:1815-26.



Stratification of Patients According to CD4+ Count at Baseline

Table 1. Stratification of Patients According to CD4+ Count at Baseline.*

Variable	351-to-500 CD4+ Count	More-Than-500 CD4+ Count
Patients with a CD4+ count within prespecified range and no history of previous antiretroviral therapy or AIDS-defining disease — no.	8362	9155
Patients who initiated antiretroviral therapy within 6 mo — no.	2084	2220
Patients who deferred antiretroviral therapy — no.	6278	6935
Patients who deferred therapy and who either transitioned to a lower CD4+ count status or not		
Transition — no. (no. of cells)	3449 (<350 cells/mm ³)	3881 (<500 cells/mm ³)
No transition — no.	2829	3054
Timing of initiation of therapy among patients who deferred therapy and who transitioned to a lower CD4+ count		
Within 6 mo — no.	803	539
Not within 6 mo — no.	2646	3342

* The CD4+ count was measured in cells per cubic millimeter.

Kitahata MM et al. N Engl J Med 2009;360:1815-1826



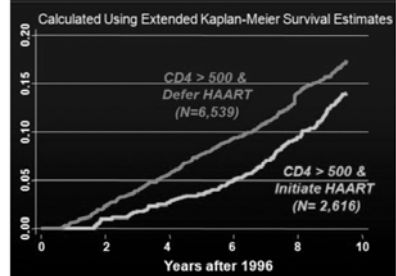
NA-ACCORD Trial

- **First analysis**
 - 69% increased risk of death in those who deferred therapy until CD4 less than 351 cells/mm³
- **Second analysis**
 - 95% increased risk of death in those who deferred therapy until CD4 less than 500 cells/mm³
- **Findings support starting HAART with a CD4 greater than 350 cells/mm³**

Kitahata MM. N Engl J Med 2009;360:1815-26.



Cumulative Mortality Estimates



Kitahata M, et al. 16th Conference on Retroviruses and Opportunistic Infections, February 2009, Abstract 71.



Current DHHS Recommendations

- The current DHHS guidelines for initiation of antiretroviral therapy in those naïve to therapy recommend starting antiretrovirals at a CD4 count less than 500.



You decide that you should initiate treatment. He has not had a resistance test. Should you perform a genotype prior to initiation of treatment?

1. Yes
2. No
3. Maybe



Prevalence of ART Resistance Among Patients Newly HIV Infected

- 377 patients with newly acquired HIV infection in 10 cities in North America
- Prevalence of antiretroviral resistance increased from 3.4% in 1995-1998 to 12.4% in 1999-2000
- Frequency of multi-drug resistance at presentation increased from 1.1% to 6.2%

Little SJ et al. N Engl J Med 347;6:385-394.394



Preexisting Resistance Predicts Failure of Drug Regimen

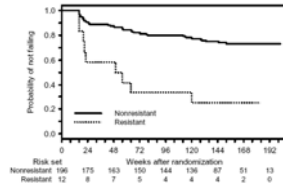
- **ACTG A5095**
 - Randomized, controlled trial comparing efficacy of efavirenz plus a fixed-dose combination of zidovudine/lamivudine or zidovudine/lamivudine/abacavir in previously untreated HIV-1 infected subjects
 - Case cohort study done to determine prevalence of NNRTI resistance and its impact on treatment outcome

Kuritzkes KR et al. JID 2008;197:867-70.



Preexisting NNRTI Resistance Predicts Failure of an Efavirenz-Based Regimen in ART Naïve Patients

- Prevalence of baseline NNRTI resistance was 5%
- Risk of virologic failure for subjects with baseline NNRTI resistance was higher than that for subjects without such resistance



Kuritzkes KR et al. JID 2008;197:867-70.



Current DHHS Guideline Recommendation

- HIV drug resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether therapy will be initiated immediately.
- A genotypic assay is preferred for antiretroviral naïve persons



Case

- Your patient returns after his genotype is obtained. He has no resistance mutations.
- His CD4 count is 320 and his HIV viral load is 90,000. He has no history of opportunistic infections and has never been treated with antiretroviral medications.
- He appears to understand the importance of good adherence and states he would like to start therapy.



Case

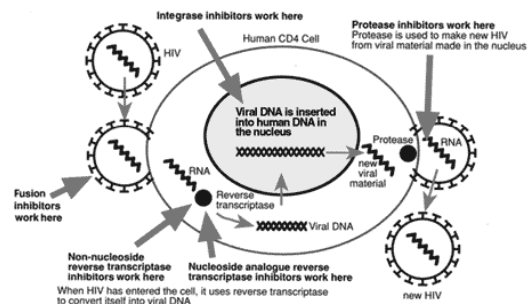
- He has a history of hypertension, diabetes, and chronic renal insufficiency (Estimated GFR 40 mL/min/1.72m²)
- What regimen would you recommend?



Selecting the Initial ART Regimen



Site of Action of Antiretrovirals



The Pharmaceutical Journal Vol 264 No 7079 p96-97

Current Antiretroviral Medications

NRTI

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTI

- Delavirdine
- Efavirenz
- Etravirine
- Nevirapine

PI

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Fusion Inhibitor

- Enfuvirtide

CCR5 Antagonist

- Maraviroc

Integrase Inhibitor

- Raltegravir



ARV Therapy in Adults & Adolescents

May 2010

Editors: Jeffrey Beal, MD, AAHIVS
Joanne J. Orrick, PharmD, AAHIVE

Managing Editor: Kim Molnar, MAcc

Layout: Maximo Lora, BA



Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009. Accessed May 4, 2010. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>



ART Therapy for Treatment Naïve Patients: DHHS Guidelines

- 1 NNRTI + 2 NRTI or
- PI (preferably boosted with ritonavir) + 2 NRTI or
 - Boosting with ritonavir
 - PIs are metabolized in the liver by cytochrome P450
 - Ritonavir inhibits this enzyme thereby increasing the serum levels of most PIs
 - Low doses of ritonavir can be used to increase the potency and simplify dosing of PI-based regimens
- Integrase inhibitor + 2 NRTIs

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1st, 2009. Available online at www.aidsinfo.nih.gov



“Preferred” Regimens for Treatment-Naïve Patients

- Efavirenz/tenofovir/emtricitabine or
- Atazanavir/r + tenofovir/emtricitabine or
- Darunavir/r (once daily) + tenofovir/emtricitabine or
- Raltegravir + tenofovir/emtricitabine

Note: /r = low-dose ritonavir for boosting on this and subsequent slides.

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1st, 2009. Available online at www.aidsinfo.nih.gov



Preferred Regimen Options: Notes

- Efavirenz
 - Do not use during 1st trimester of pregnancy or in women with pregnancy potential
 - Use with caution in patients with unstable psychiatric disease
- Atazanavir/r
 - Do not use in patients who require high-dose (> 20 mg of omeprazole or equivalent per day) proton pump inhibitor (PPI); use with caution in patients requiring any acid-reducing agent
- Tenofovir
 - Caution in patients with underlying renal insufficiency

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1st, 2009. Available online at www.aidsinfo.nih.gov



“Alternative” NNRTI –based Regimens

- Efavirenz + (abacavir¹ or zidovudine)/ lamivudine or
 - Nevirapine² + zidovudine/lamivudine
1. Abacavir: Do not use in patients who test positive for HLA-B*5701, use with caution in patients with high CV disease risk or pre-treatment viral load > 100,000 copies/mL
 2. Nevirapine: Do not use in patients with moderate-severe hepatic impairment; do not use in women and men with pre-ARV CD4 counts > 250 and > 400 cells/mm³, respectively

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1st, 2009. Available online at www.aidsinfo.nih.gov



“Alternative” PI-based Regimens

- Atazanavir/r + (abacavir or zidovudine)/ lamivudine or
- Fosamprenavir/r (once or twice daily) + either [(abacavir or zidovudine)/lamivudine] or tenofovir/emtricitabine or
- Lopinavir/r (once¹ or twice daily) + either [(abacavir or zidovudine)/lamivudine] or tenofovir/emtricitabine or
- Saquinavir/r + tenofovir/emtricitabine

¹ Once daily lopinavir/r not recommended in pregnant women

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1st, 2009. Available online at www.aidsinfo.nih.gov



“Acceptable” Regimens

- Efavirenz + didanosine + (lamivudine or emtricitabine) or
- Atazanavir + (abacavir or zidovudine)/lamivudine

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1st, 2009. Available online at www.aidsinfo.nih.gov



Case

- Your patient’s genotype shows no preexisting resistance mutations. The patient appears to understand the importance of good adherence and states he would like to start therapy.
- He has a history of hypertension, diabetes, and chronic renal insufficiency (Estimated GFR 40 mL/min/1.72m²)



Which of the following would be most concerning to you regarding initiating ARV therapy in your patient?

1. Abacavir due to renal insufficiency
2. Protease inhibitor due to diabetes
3. Emtricitabine due to renal insufficiency
4. Tenofovir due to renal insufficiency



Case

- You start him on lamivudine + abacavir (HLA-B*5701 negative) + atazanavir + ritonavir
- He has an undetectable viral load and his CD4 count increases to 375 in 4 weeks
- He maintains an undetectable viral load for the next 3 years and his CD4 count increases to 625



Case

- After three years of doing well with an undetectable viral load and CD4 count above 500, his mother dies and he becomes depressed. He starts to drink alcohol and misses many appointments and medication doses.
- After enrolling in counseling services and initiation of antidepressants, he returns to clinic. He is found to have a CD4 count of 350 and viral load of 15,000 despite being back on his prior medications for 4 weeks.



Antiretroviral Treatment Failure

- **Virologic failure:**
 - HIV RNA >400 copies/mL after 24 wks, >50 after 48 wks, or >400 copies/mL after viral suppression
- **Immunologic failure:**
 - Failure to achieve and maintain adequate CD4 increase despite virologic suppression
- **Clinical progression:**
 - Occurrence of HIV-related events (after ≥ 3 months on therapy; excludes immune reconstitution syndromes)



Antiretroviral Therapy Failure

- **General Principles**
 - Assess drug resistance:
 - Drug resistance test
 - Prior treatment history
 - Drug resistance usually is cumulative – consider all previous treatment history and test results
 - DHHS guidelines recommend use of genotype in patients failing first or 2nd regimen
 - Addition of phenotype to genotype should be considered when more complex resistance expected



Changing an ART Regimen Due to Failure

General Principles

- Add at least 2 (preferably 3) fully active agents to an optimized background ARV regimen
- Consider potent ritonavir-boosted PIs and drugs with new mechanisms of action plus an optimized ARV background



Changing and ART Regimen Due to Failure

- **General principles**
 - 1 active drug should not be added to a failing regimen (drug resistance is likely to develop quickly)
 - Consult with experts (you are not alone!)
 - www.FCAETC.org/RTC



Resources

- DHHS guidelines available at www.aidsinfo.nih.gov/Guidelines
- FCAETC general consultation link www.fcaetc.org/consultation
- Pocket cards available through FCAETC at www.fcaetc.org/resources
- FCAETC provides assistance with management of resistance at www.FCAETC.org/RTC

