# *Treatment of HIV: Basic Principles*

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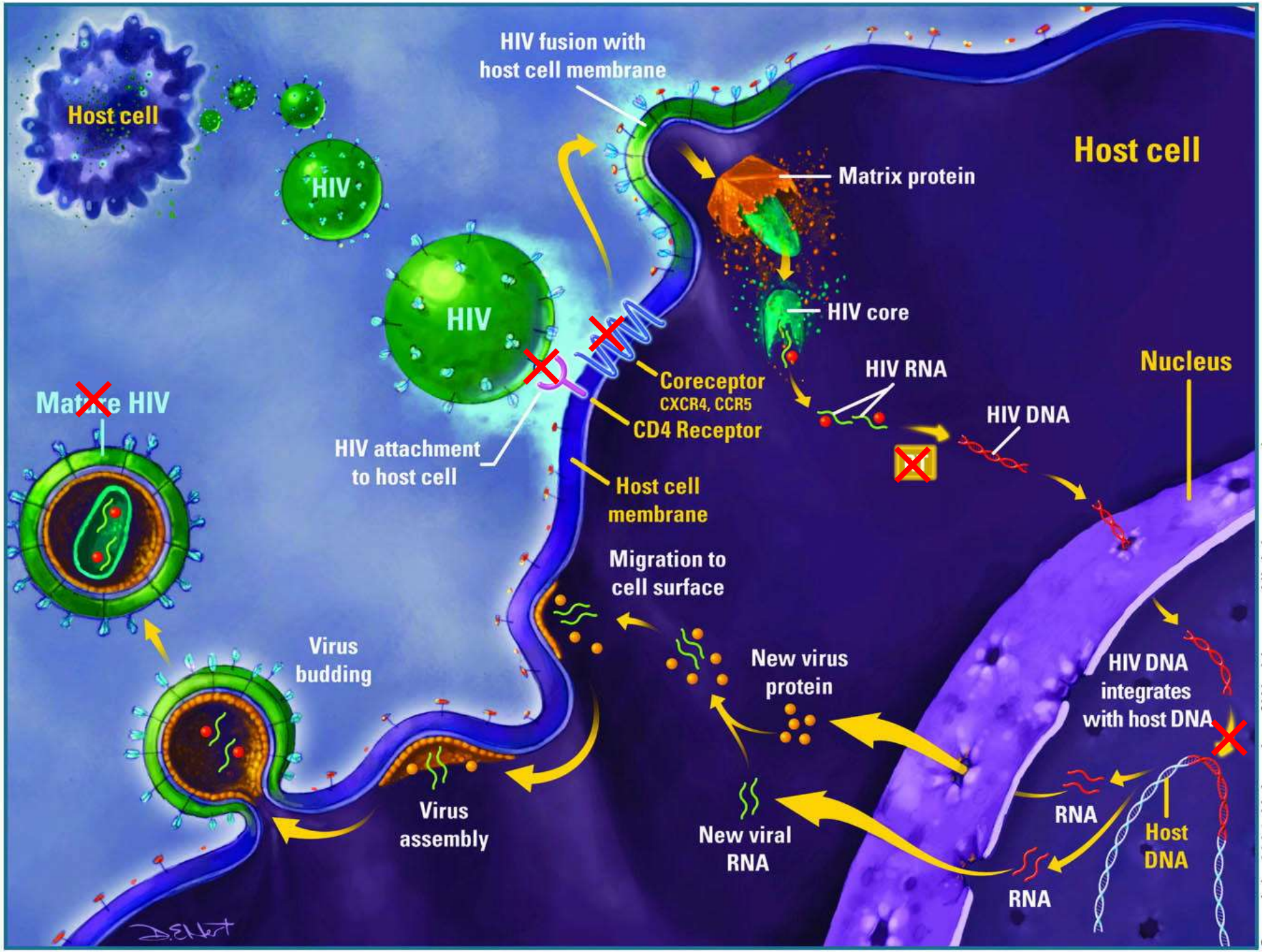
*It is much more important to know what sort of patient has a disease than what sort of disease a patient has.*

*William Osler*



# Current ARV Medications

## NRTI

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

## NNRTI

- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)

## PI

- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

## Integrase Inhibitor (II)

- Raltegravir (RAL)

## Fusion Inhibitor

- Enfuvirtide (ENF, T-20)

## CCR5 Antagonist

- Maraviroc (MVC)

# Program Overview

- **When to start treatment**
- Treatment goals
- What to start with
- Assessing treatment failure, when to change and what to change

# When to Start Treatment

| Clinical Category | CD4 Cell Count (cells/mm$^3$) | Viral Load (copies/mL) | 2009 DHHS Guidelines | 2008 IAS-USA Guidelines |
|---|---|---|---|---|
| AIDS-defining illness or severe symptoms* | Any value | Any value | Treat | |
| Asymptomatic | <350 | Any value | Treat | |
| | 350 to 500 | Any value | Treat* | Consider treatment |
| | >350 | ≥100,000 | Treat* | Consider treatment |
| | >350 | <100,000 | Treat* | Consider treatment (some patients) |
| | >500 | Any value | Treat/Optional* | Defer |
| Pregnant women | Any value | Any value | Treat | |
| HIV-associated nephropathy | Any value | Any value | Treat | |
| HIV/HBV coinfection when HBV treatment is indicated | Any value | Any value | Treat | |

*New recommendation.

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision December 1, 2009; Hammer SM, et al. *JAMA.* 2008;300:555-570.

# Potential Benefits and Risks of Early Therapy

## Benefits

- Maintain higher CD4 count and prevent potentially irreversible damage to the immune system
- Decreased risk for HIV-associated complications
  - Tuberculosis, non-Hodgkin's lymphoma, Kaposi's sarcoma, peripheral neuropathy, HPV-associated malignancies, and HIV-associated cognitive impairment
- Decreased risk of nonopportunistic conditions
  - Cardiovascular disease, renal disease, liver disease, and non–AIDS-associated malignancies and infections
- Decreased risk of HIV transmission

## Risks

- Treatment-related side effects and toxicities
- Development of drug resistance due to incomplete viral suppression
  - Loss of future treatment options
- Less time for patient adjustment to disease and treatment requirements
- Increased total time on medication
- Premature use of therapy before potentially better/safer future options are available
- Transmission of drug-resistant virus in patients who do not maintain full virologic suppression

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009.

# Conditions Favoring More Rapid Initiation of HAART

- Older age
- Pregnancy
- AIDS-defining conditions
- Acute opportunistic infections
- Lower CD4 counts (eg, <200 cells/$mm^3$)
- Rapidly declining CD4 counts (eg, >100 cells/ $mm^3$ decrease per year)
- Higher viral loads (eg, >100,000 copies/mL)
- HIV-associated nephropathy
- HBV coinfection when treatment for HBV is indicated

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision December 1, 2009.

# When To Start HAART: DHHS Guidelines

- All patients with a history of an AIDS-defining illness or with CD4 count <350 cells/$mm^3$
  - CIPRA HT-001
  - SMART
- All patients with CD4 counts between 350 and 500 cells/$mm^3$
  - NA-ACCORD study
  - ART Cohort Collaboration
- Patients with CD4 counts >500 cells/$mm^3$ (50% of Panel recommend therapy, 50% view therapy as optional)
  - NA-ACCORD study
  - ART Cohort Collaboration

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision December 1, 2009.

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# Treatment Goals

- **Primary goals**
  - **Maximally and durably suppress plasma HIV viral load**
  - **Reduce HIV-associated morbidity and prolong survival**
  - **Improve quality of life**
  - **Restore and preserve immunologic function**
  - **Prevent vertical HIV transmission**

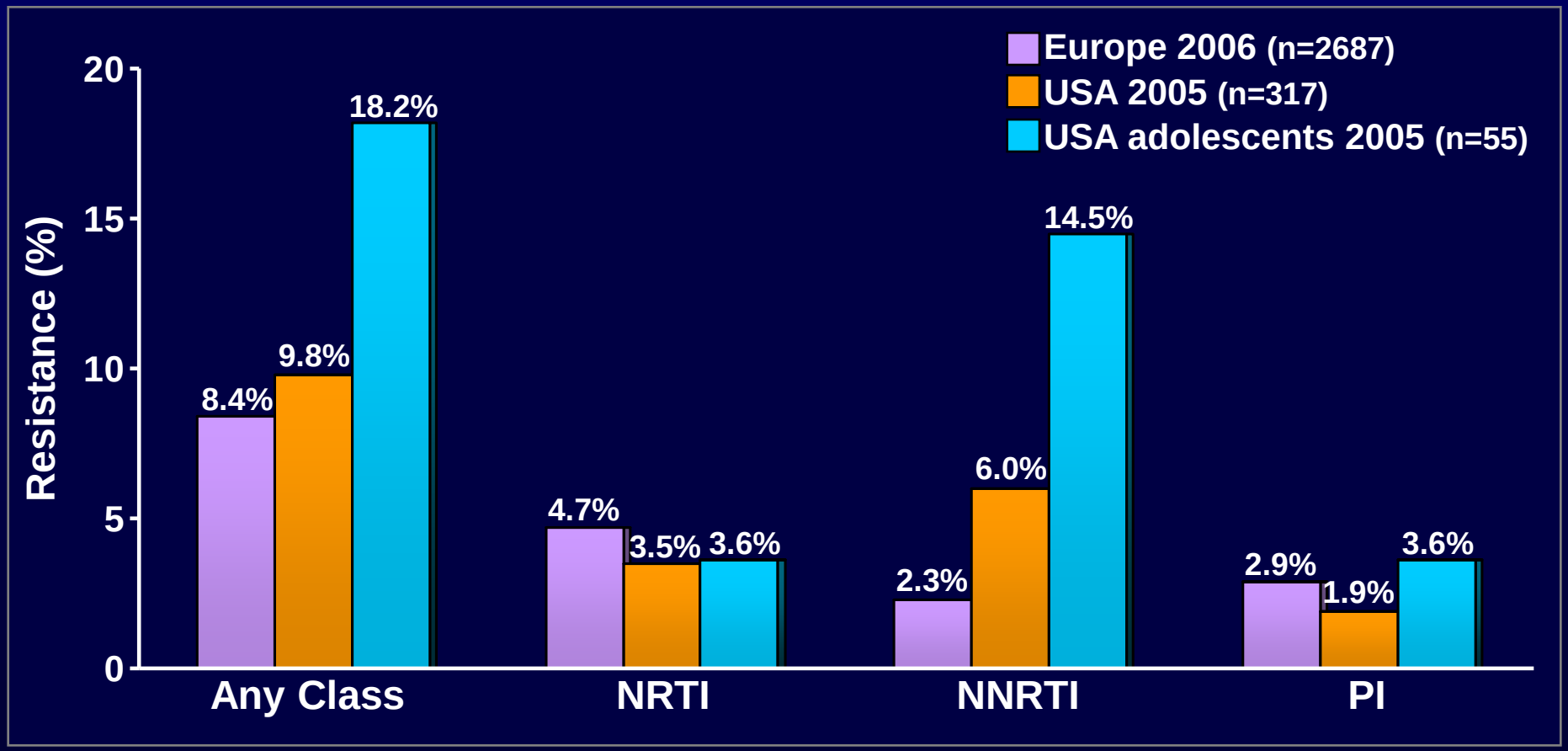
Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009

# Maximal Viral Suppression in Initial Therapy

- Use two, preferably three, active drugs from multiple drug classes
- HIV RNA <50 copies/mL usually occurs within the first 12 to 24 weeks of therapy
- Predictors of virologic success
  - High potency of antiretroviral regimen
  - Excellent adherence to treatment regimen
  - Low baseline HIV RNA level
  - Higher baseline CD4 cell count
  - Rapid reduction in HIV RNA level in response to treatment
    - ≥1 $\log_{10}$ copies/mL in 1 to 4 months

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision December 1, 2009.

# Prevalence of Transmitted Drug Resistance





Vercauteren J, et al. *J Infect Dis*. 2009;200:1503-1508.
Ross L, et al. *HIV Clin Trials*. 2007;8:1-8.
Viani R, et al. *J Infect Dis*. 2006;194:1505-1509.

# HLA-B*5701 Screening

- **Recommended before starting abacavir-containing regimen**
  - **Reduce the risk of hypersensitivity reaction**
- **HLA-B*5701 positive**
  - **Avoid abacavir**
  - **Record as abacavir allergy in patient's medical record**
- **If HLA-B*5701 screening is not readily available**
  - **Reasonable to initiate abacavir with appropriate clinical counseling and monitoring for any signs of hypersensitivity reaction**

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009.
Hammer SM, et al. *JAMA.* 2008;300:555-570.

# Program Overview

- When to start treatment
- Treatment goals
- **What to start with**
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# DHHS Guidelines: Regimen Classification for Treatment-Naïve Patients

- Preferred regimens
- Alternative regimens
- Acceptable regimens
- Regimens that may be acceptable but more definitive data are needed
- Regimens to be used with caution

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009.

# DHHS Guidelines: Preferred Regimens

| | |
|---|---|
| **NNRTI** | **Efavirenz[1]/emtricitabine[2]/tenofovir DF** |
| **PI** | **Atazanavir[3] + ritonavir + emtricitabine[2]/tenofovir DF**<br>**Darunavir + ritonavir (qd) + emtricitabine[2]/tenofovir DF** |
| **INSTI** | **Raltegravir + emtricitabine[2]/tenofovir DF** |
| **Pregnant women** | **Lopinavir/r bid + zidovudine/lamivudine[2]** |

INSTI: Integrase strand transfer inhibitors.
[1]Efavirenz should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
[2]Lamivudine may substitute for emtricitabine or visa versa.
[3]Atazanavir + RTV should not be used in patients who require >20 mg omeprazole equivalent/day.

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009.

# DHHS Guidelines: Alternative Regimens

| | |
|---|---|
| **NNRTI** | **Efavirenz + (abacavir[1] or zidovudine)/lamivudine[2]**<br>**Nevirapine[3] + zidovudine/lamivudine[2]** |
| **PI** | **Atazanavir + ritonavir + (abacavir[1] or zidovudine)/lamivudine[2]**<br>**Fosamprenavir + ritonavir (qd or bid) + either ([abacavir[1] or zidovudine]/lamivudine[2]) or emtricitabine[2]/tenofovir DF**<br>**Lopinavir/r[4] (qd or bid) + either ([abacavir[1] or zidovudine]/lamivudine[2]) or emtricitabine[2]/tenofovir DF**<br>**Saquinavir + ritonavir + emtricitabine[2]/tenofovir DF** |

[1]Abacavir should not be used in patients who test positive for HLA-B*5701. Use abacavir with caution in patients with high risk of cardiovascular disease or pretreatment HIV RNA >100,000 copies/mL.
[2]Lamivudine may substitute for emtricitabine or visa versa.
[3]Nevirapine should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C); or in women and men with pre-antiretroviral therapy CD4 >250 and >400 cells/mm$^3$, respectively.
[4]Once-daily lopinavir/r is not recommended in pregnant women.

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009.

# IAS-USA Guidelines Recommendations for Treatment-Naïve Patients

| | Select 1 NNRTI or 1 PI Plus a Dual NRTI | | |
|---|---|---|---|
| | **NNRTI** | **PI** | **Dual NRTI** |
| **Preferred** | **Efavirenz** | **Lopinavir + ritonavir** | **Emtricitabine/tenofovir DF[1]** |
| | | **Atazanavir + ritonavir** | **Abacavir/lamivudine[2]** (if test negative for HLA-B*5701) |
| | | **Fosamprenavir + ritonavir** | |
| | | **Darunavir + ritonavir** | |
| | | **Saquinavir + ritonavir** | |
| **Alternative** | **Nevirapine** | | **Zidovudine/lamivudine** |
| | | | **Didanosine + emtricitabine** |
| | | | **Didanosine + lamivudine** |

[1]A baseline urinalysis and estimation of creatinine clearance or glomerular filtration rate for assessment of renal function are recommended. All patients receiving tenofovir should be observed for development of renal dysfunction. Lamivudine can be substituted for emtricitabine.

[2]Emtricitabine can be substituted for lamivudine.

Hammer SM, et al. *JAMA.* 2008;300:555-570.

# Factors to Consider When Selecting an Initial Regimen

- Comorbidity or conditions
- Potential adverse effects
- Potential drug interactions
- Pregnancy potential
- Results of genotypic drug testing
- Gender and pretreatment CD4 cell count if considering nevirapine
- HLA-B*5701 testing if considering abacavir
- Coreceptor tropism assay if considering maraviroc
- Patient adherence potential
- Dosing convenience and frequency, food and fluid considerations

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision December 1, 2009.

# Study 934: Emtricitabine + Tenofovir DF Versus Fixed-Dose Zidovudine/Lamivudine

- Treatment-naïve patients (n=509)
  - Open-label, non-inferiority trial
  - Baseline
    - HIV RNA: 5.0 $\log_{10}$ copies/mL
    - CD4: 237 cells/$mm^3$
- Efavirenz-based regimens
  - Emtricitabine + tenofovir DF qd
  - Zidovudine/lamivudine bid
- At week 144, FTC + TDF arm
  - Significantly greater proportion of responders
    - Similar proportion <50 copies/mL and CD4 cell gains
  - Fewer discontinuations due to adverse events

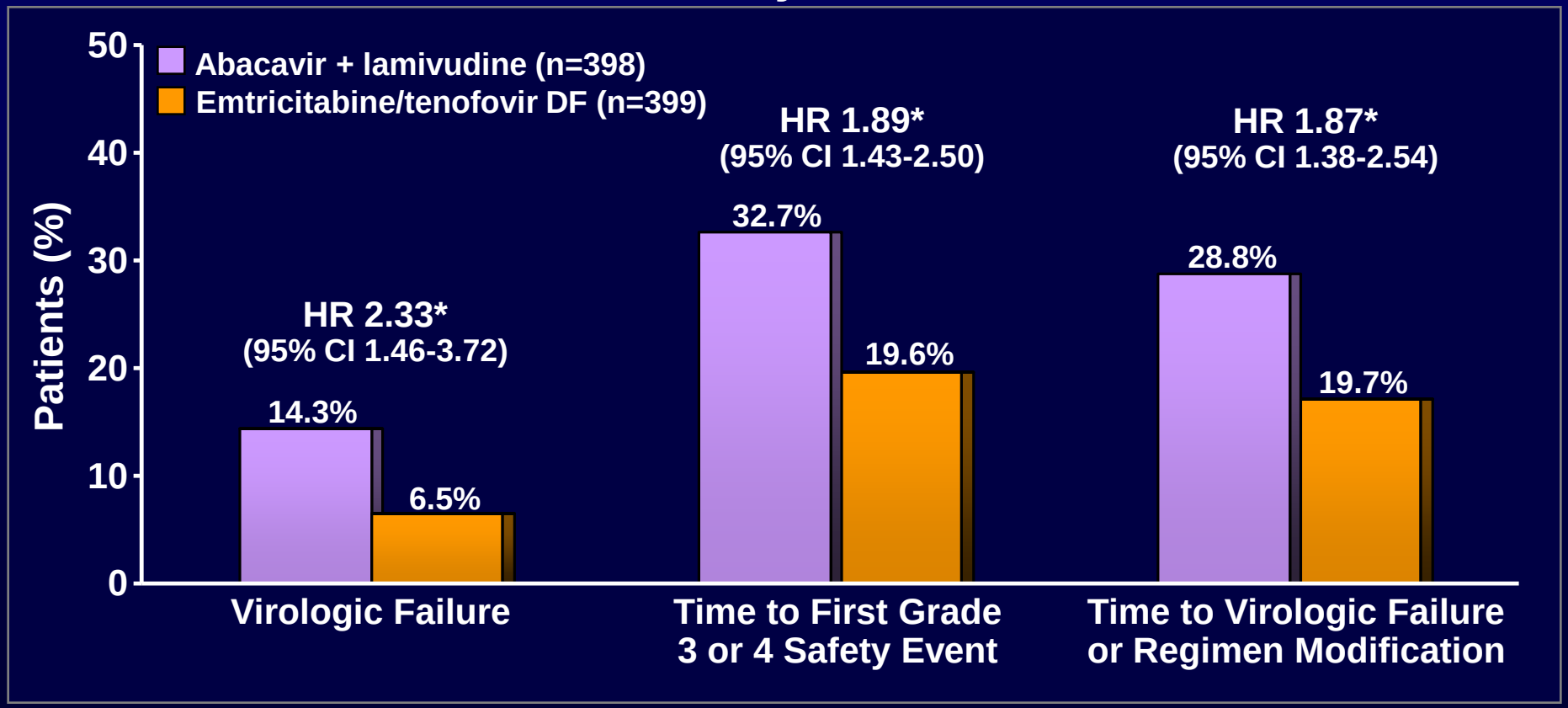
| Outcomes at Week 144 | FTC + TDF (n=227) | ZDV/3TC (n=229) |
|---|---|---|
| Responders (%) | 71* | 58 |
| Virologic failures (%) | 2 | 5 |
| HIV RNA <50 copies/mL (%) | 64 | 56 |
| CD4 cell gain (cells/$mm^3$) | 312 (n=152) | 271 (n=122) |
| Discontinuation due to adverse events (%) | 5 | 12 |

Responders: HIV RNA <400 copies/mL (TLOVR).
*$P$=0.004 versus ZDV/3TC.

Arribas JR, et al. *JAIDS*. 2008;47:74-78.

# ACTG 5202: Analysis of the Baseline HIV RNA ≥100K Copies/mL Stratum

## Week 108 Major Outcomes




*$P$<0.001 for between groups.

Sax PE, et al. *N Engl J Med.* 2009;361:2230-2240.

# Abacavir and CVD Risk: Summary of Key Studies/Analyses

| | Study Design | Event Assessment | Effect of Abacavir Found on CVD Risk |
|---|---|---|---|
| D:A:D (n=33,347) | Prospective, observational cohort | Prospective, predefined | Yes[1] |
| FHDB (n=289 cases; 884 controls) | Case control in observational cohort | Prospective (validated retrospectively) | Yes[1] (1st year of exposure) |
| SMART (n=2752) | Randomized control trial, observational analysis | Prospective, predefined | Yes[1] |
| STEAL (n=357) | Randomized control trial | Prospective | Yes[1] |
| QPHID (n=142 cases; 1420 controls) | Case control in observational cohort | ICD 9 code, acute MI not validated | Yes[1] |
| GSK analysis (n=14,174) | Randomized control trials (n=54) | Retrospective, database search | No[2] |
| ALLRT ACTG (n=3205) | Randomized control trials (n=5) | Retrospective | No[2] |
| VACCR (n=19,424) | Retrospective observational cohort | ICD 9 code, acute MI not validated | No[1] |

FHDB: French Hospital Databaseon HIV; QPHD: Quebec's public health insurance database; VACCR: Veterans Administration's Clinical Case Registry.

[1]All or majority of patients were treatment-experienced at abacavir initiation.

[2]All or majority of patients were treatment-naïve at abacavir inclusion.

Behrens GM, et al. *Curr Opin Infect Dis.* 2010;23. [Epub ahead of print].

# *Raltegravir and CCR5 Blockers*

# RAL: Pros and Cons

- **PROs**
  - New class
  - No baseline resistance in ARV-naïve pts
  - Well Tolerated
  - Relatively few significant drug interactions
  - Great efficacy in experienced pts
  - No apparent teratogenicity
  - No lipoatrophy based on early (48 week) data
- **CONs**
  - BID
  - No long-term data
  - No randomized data with NRTIs other than TDF/FTC
  - PK/PD relationship unclear
  - Resistance data still emerging
  - No second generation agent available

# STARTMRK: Raltegravir Versus Efavirenz in Treatment-Naïve Patients

- Treatment-naïve patients (n=563)
  - Double-blind, 96-week study
- Treatment arms
  - Raltegravir 400 mg bid
  - Efavirenz 600 mg qd
  - All patients: emtricitabine/ tenofovir DF
- Primary efficacy endpoints
  - HIV RNA <50 copies/mL
  - CD4 cell change from baseline
  - Safety and tolerability

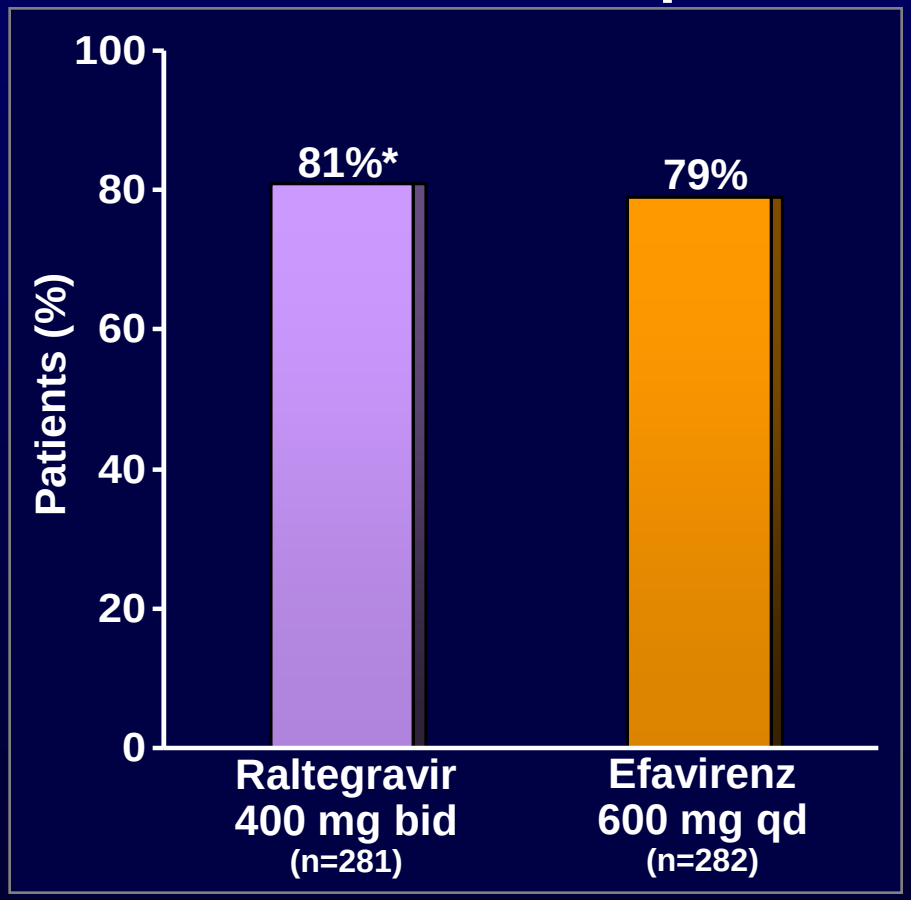
**Baseline Characteristics**

| | RAL (n=281) | EFV (n=282) |
|---|---|---|
| Male (%) | 81 | 82 |
| Race (%) | | |
| White | 41 | 44 |
| Non-white | 59 | 56 |
| HIV RNA ($log_{10}$ copies/mL) | 5.0 | 5.0 |
| Mean CD4 (cells/$mm^3$) | 219 | 217 |
| CD4 <200 cells/$mm^3$ (%) | 47 | 49 |

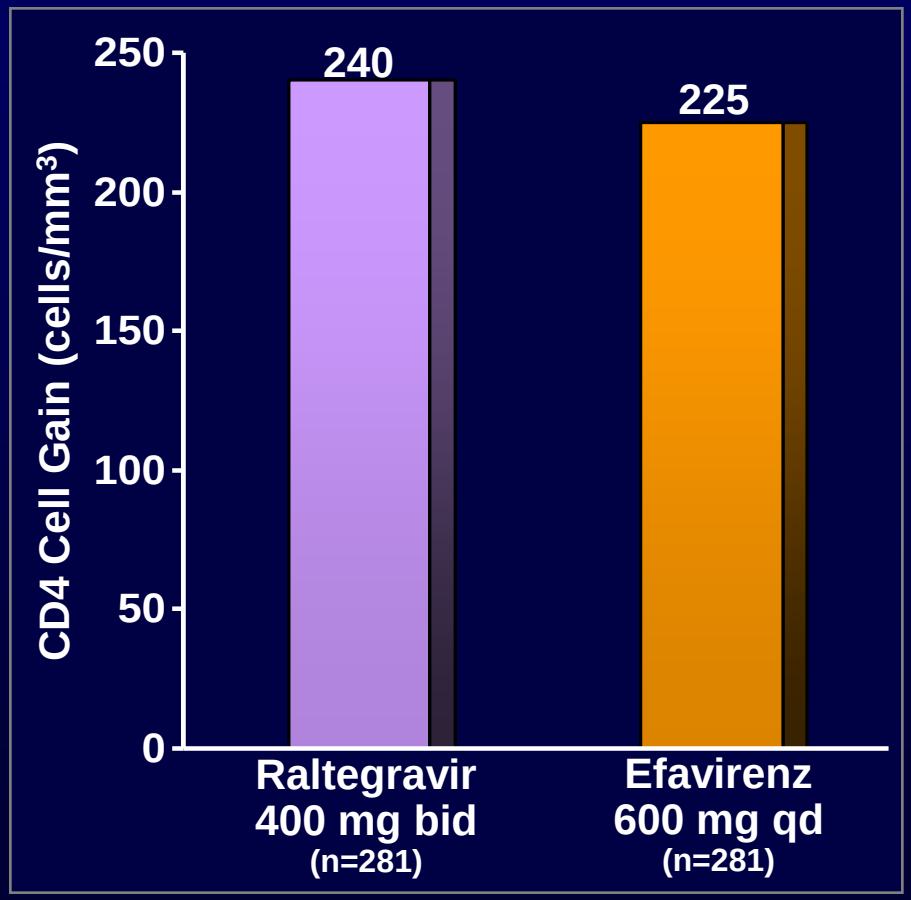
Lennox J, et al. *Lancet.* 2009;374:796-806.
Lennox J, et al. 49th ICAAC. San Francisco, 2009. Abstract H-924b.

# STARTMRK: 96-Week Outcomes

## HIV RNA <50 Copies/mL




## CD4 Cell Gain




*Raltegravir met criteria for non-inferiority (*P*<0.001).
All patients received emtricitabine/tenofovir DF.
Lennox J, et al. 49th ICAAC. San Francisco, 2009. Abstract H-924b.

# Prevalence of HIV Co-receptor Usage

| | Co-receptor Usage (%) | | |
|---|---|---|---|
| | R5 | R5/X4 | X4 |
| **Treatment-naïve patients** | | | |
| Coakley 2006 (n=1428)[1] | 85 | 14.7 | 0.3 |
| Homer cohort (n=979)[2] | 82 | 18 | <1 |
| Chelsea & Westminster cohort (n=402)[3] | 81 | 19 | <1 |
| Demarest (n=325)[4] | 88 | 12 | 0 |
| **Treatment-experienced patients** | | | |
| Chelsea & Westminster cohort (n=141)[3] | 78 | 22 | <1 |
| Demarest (n=117)[4] | 67 | 28 | 5 |
| MOTIVATE 1 and 2 (n=3244)[5] | 61 | 37.2 | 1.8 |
| TORO 1 and 2 (n=724)[6] | 50 | 48 | 2 |
| ACTG 5211 (n=391)[7] | 50 | 46 | 4 |

[1]Coakley E, et al. 2nd IWTHIVE. Boston, 2006. Abstract 8.

[2]Brumme ZL, et al. *J Infect Dis.* 2005;192:466-474.

[3]Moyle GJ, et al. *J Infect Dis.* 2005;191:866-872.

[4]Demarest J, et al. 44th ICAAC. Washington, DC, 2004. Abstract H-1136.

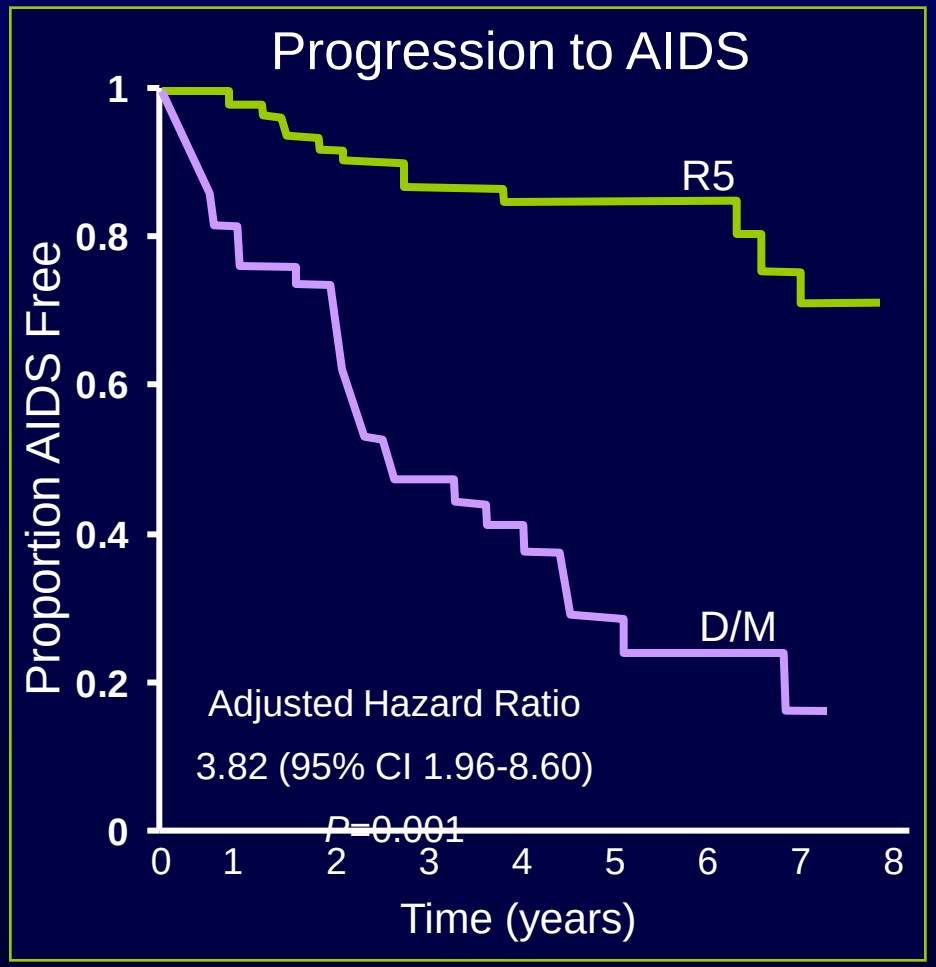
[5]Gulick RM, et al. *N Engl J Med.* 2008;359:1429-1441.

[6]Melby T, et al. *J Infect Dis*. 2006;194:238-246.

[7]Wilkin T, et al. *Clin Infect Dis*. 2007;44:591-595.

# Baseline Tropism Predicts Disease Progression

- **Hemophilia Growth and Development cohort (1989-1997)**
  - **Recombinant phenotypic assay**
  - **126 children and adolescents**
- **Baseline characteristics at time of tropism assay**
  - **Age: 13.8 years**
  - **HIV duration: 7 years**
  - **HIV RNA: 3.7 $\log_{10}$ copies/mL**
  - **CD4 (cells/$mm^3$)**
    - **R5 (n=75): 449**
    - **D/M (n=51): 200**




Daar ES, et al. *Clin Infect Dis.* 2007;45:643-649.

# Enhanced Phenotype Tropism Assay: In Vitro Validation

- **Original assay validated in clinical trials**
  - **Did not detect minor CXCR4 species comprising <10% of population**
  - **Sensitivity in detecting CXCR4 HIV**
    - **100% when 10% of population is CXCR4**
    - **85% when 5% of population is CXCR4**
- **Enhanced phenotype tropism assay validated using in vitro HIV *env* clones**
  - **Sensitivity in detecting CXCR4 HIV**
    - **100% when 0.3% of population is CXCR4**
    - **81% when 0.1% of population is CXCR4**

Trinh L, et al. 48th ICAAC. Washington, DC, 2008. Abstract H-1219.

# Tropism Testing and CCR5 Antagonist Therapy

- **Co-receptor tropism assay should be performed whenever the use of a CCR5 antagonist is being considered**
- **Both tropism result and treatment history should guide use of maraviroc**
- **Role of Maraviroc in HIV treatment is unclear**

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Revision November 3, 2008.

Hammer SM, et al. *JAMA.* 2008;300:555-570.

# *Protease Inhibitors*

# ARTEMIS: Darunavir/r Versus Lopinavir/r

- Treatment-naïve patients (n=689)
  - Open-label, non-randomized, non-inferiority trial
- Regimens
  - Darunavir/r (800/100 mg qd)
  - Lopinavir/r
    - 400/100 mg bid or
    - 800/200 mg qd
  - All patients received emtricitabine/tenofovir DF
- Primary endpoint
  - HIV RNA <50 copies/mL

| Baseline Characteristics | LPV/r (n=346) | DRV/r (n=343) |
|---|---|---|
| Male (%) | 70 | 70 |
| Caucasian (%) | 44 | 40 |
| HIV RNA (copies/mL) | 62,100 | 70,800 |
| ≥100K copies/mL (%) | 35 | 34 |
| Median CD4 (cells/mm$^3$) | 218 | 228 |

Mills A, et al. *AIDS*. 2009;23:1679-1688.

# ARTEMIS: Virologic Failure and Tolerability at Week 96

| | Lopinavir/r (n=346) | Darunavir/r (n=343) |
|---|---|---|
| Virologic failure (%) | 17 | 12* |
| Discontinuations due to adverse events (%) | 9 | 4 |
| Grade 2-4 adverse event (%) | | |
| Diarrhea | 11 | 4† |
| Nausea | 3 | 2 |
| Change in lipids (%) | | |
| Total cholesterol | 23 | 15† |
| LDL-C | 18 | 14 |
| HDL-C | 19 | 15‡ |
| Triglycerides | 50 | 12† |

**P*=0.0437, TLOVR, non-censored.
†*P*<0.001 and ‡*P*=0.0103 versus lopinavir/r

Mills A, et al. *AIDS*. 2009;23:1679-1688.

# CASTLE Study: Atazanavir/r Versus Lopinavir/r + FTC/TDF

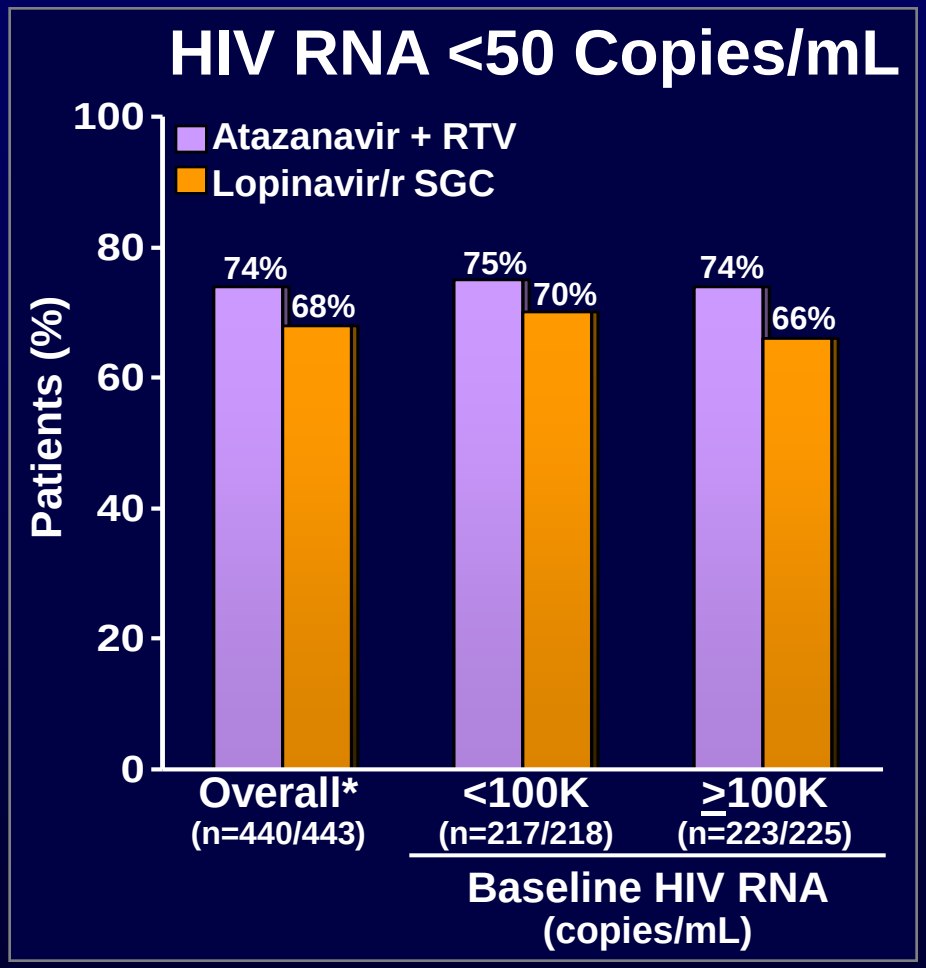
- Treatment-naïve patients (n=883)
  - Open-label, 96-week study
- Once-daily regimens
  - Atazanavir + RTV 300/100 mg qd
  - Lopinavir/r 400/100 mg bid (soft-gel capsules)
  - All patients received emtricitabine/tenofovir DF
- Non-inferiority
  - Lower confidence interval ≤10%
- Primary efficacy endpoint
  - Proportion of patients with HIV RNA <50 copies/mL at week 48

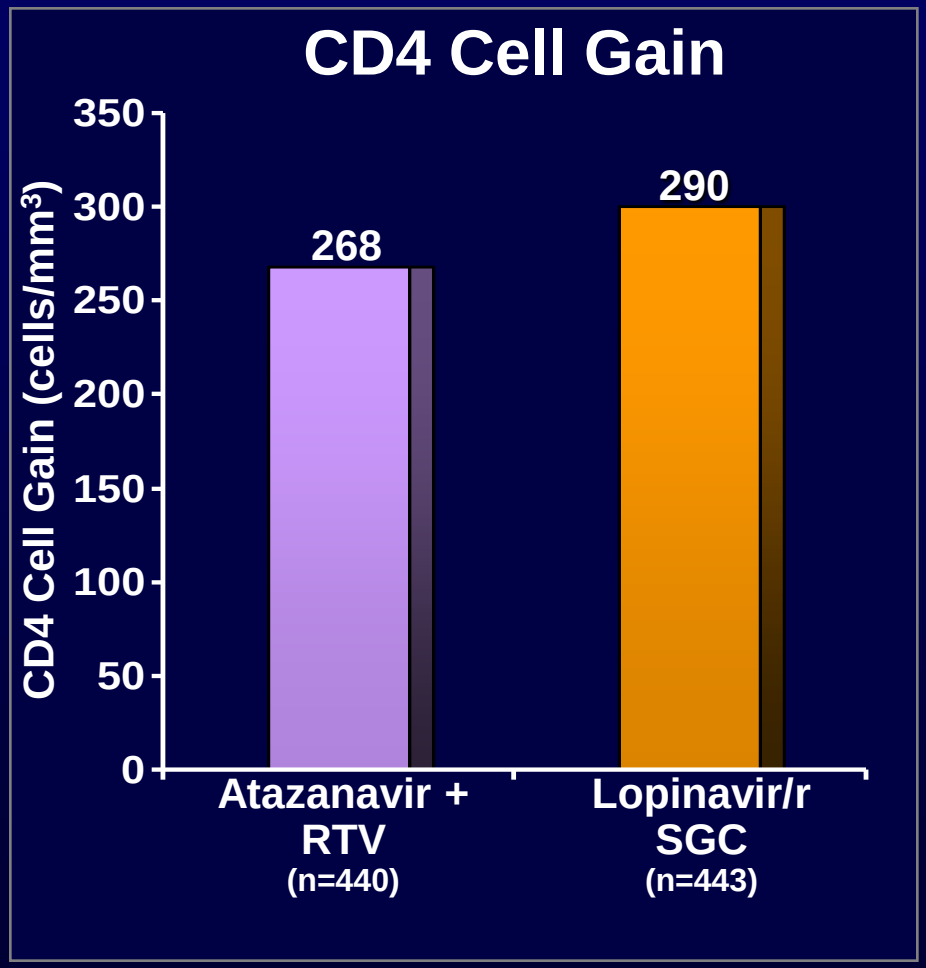
| Baseline Characteristics | ATV + RTV (n=440 | LPV/r SGC (n=443) |
|---|---|---|
| Male (%) | 69 | 69 |
| HIV RNA ($log_{10}$ copies/mL) | 5.01 | 4.96 |
| ≥100K copies/mL (%) | 51 | 51 |
| Median CD4 (cells/$mm^3$) | 205 | 204 |
| CD4 <50 cells/$mm^3$ (%) | 13 | 11 |
| Prior AIDS-defining event (%) | 4 | 5 |

**SGC=soft-gel capsules.**

Molina JM, et al. *JAIDS*. 2009;Dec 23. [Epub ahead of print].

# CASTLE Study: 96-Week Outcomes




****P*<0.05, atazanavir + RTV was non-inferior lopinavir/r (95% CI treatment difference 0.3, 12.0).**
**All patients received emtricitabine/tenofovir DF. SGC=soft-gel capsules.**

Molina JM, et al. *JAIDS*. 2009;Dec 23. [Epub ahead of print].

# *NNRTIS*

# DUET Studies: Etravirine in Treatment-Experienced Patients

- **Two phase 3, 96-week studies**
  - **Treatment-experienced patients with evidence of resistance to current NNRTIs**
  - **Stratified by baseline enfuvirtide use, previous darunavir use, and HIV RNA (<30K, ≥30K copies/mL)**
- **Treatment arms**
  - **Etravirine 200 mg bid or placebo**
  - **All patients received optimized background therapy**
    - **Darunavir + RTV plus optimized NRTIs and optional enfuvirtide**

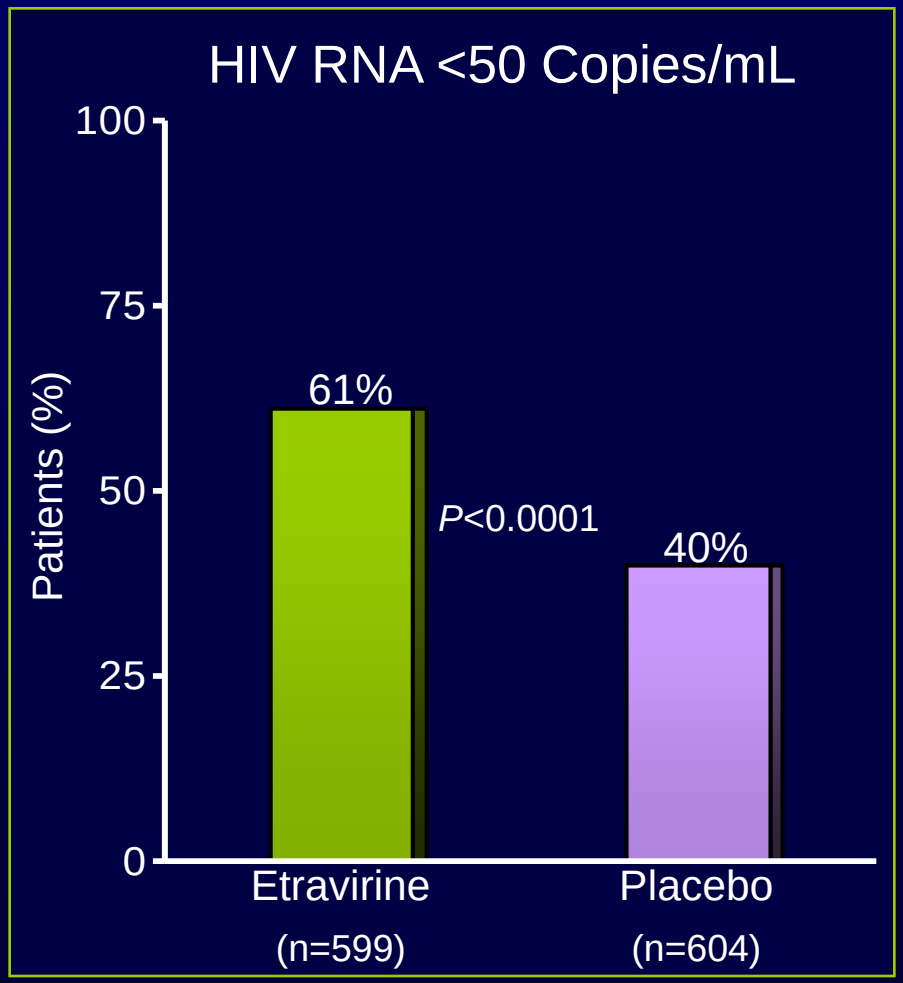
Baseline Values

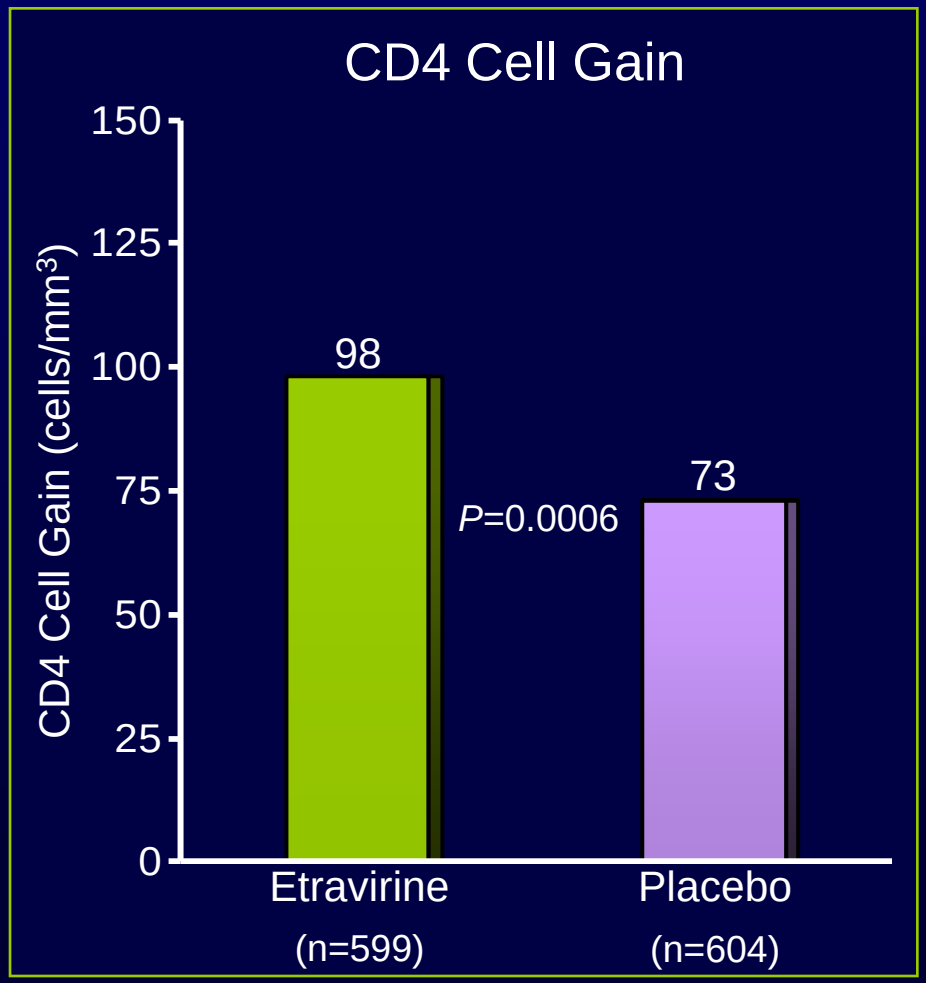
| | Placebo (n=604) | Etravirine (n=599) |
|---|---|---|
| Median CD4 (cells/mm$^3$) | 109 | 99 |
| Mean HIV RNA ($log_{10}$ copies/mL) | 4.8 | 4.8 |
| OBT (%) | | |
| Enfuvirtide | 47 | 46 |
| 0 active drugs | 16 | 17 |
| 1 active drug | 39 | 37 |

Haubrich R, et al. 15th CROI. Boston, 2008. Abstract 790.

Johnson M, et al. 15th CROI. Boston, 2008. Abstract 791.

# DUET Studies: Combined 48-Week Analysis



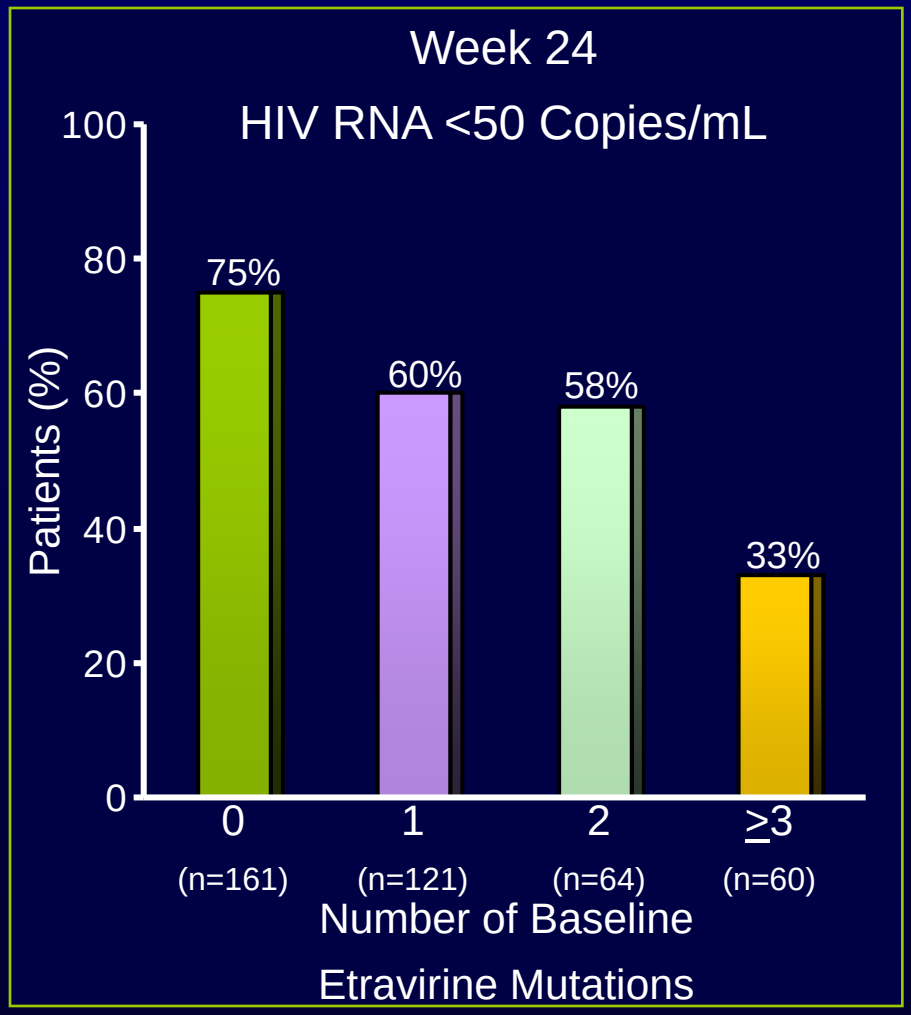




Haubrich R, et al. 15th CROI. Boston, 2008. Abstract 790.

Johnson M, et al. 15th CROI. Boston, 2008. Abstract 791.

# DUET Studies: Baseline Etravirine Mutations and Virologic Response

- **13 mutations associated with etravirine resistance**
  - **V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S**
- **Presence of ≥3 etravirine resistance mutations was associated with response similar to placebo + OBR**
  - **Etravirine resistance mutations at baseline**
    - **0 or 1: 70% of patients**
    - **≥3: 15%**




Picchio G, et al. 15th CROI. Boston, 2008. Abstract 866.

# Selecting a regimen in Naïve patients

- Based on the ARTEMIS study DRV/r appears to be a better tolerated than LPV/r
- Based on CASTLE study ATZ/r appears to be better tolerated than LPV/r
- Based on ACTG 5202 tenofovir/emtricitabine is better than abacavir/lamivudine

# Program Overview

- When to start treatment
- Treatment goals
- What to start with
- **Assessing treatment failure, when to change and what to change**

# Antiretroviral Treatment Failure

- **Often associated with virologic failure, immunologic failure, and/or clinical progression**
- **Factors associated with an increased risk of treatment failure**
  - **Baseline patient factors**
  - **Incomplete medication adherence and missed clinic appointments**
  - **Drug adverse events and toxicity**
  - **Suboptimal pharmacokinetics**
  - **Suboptimal potency**

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009.

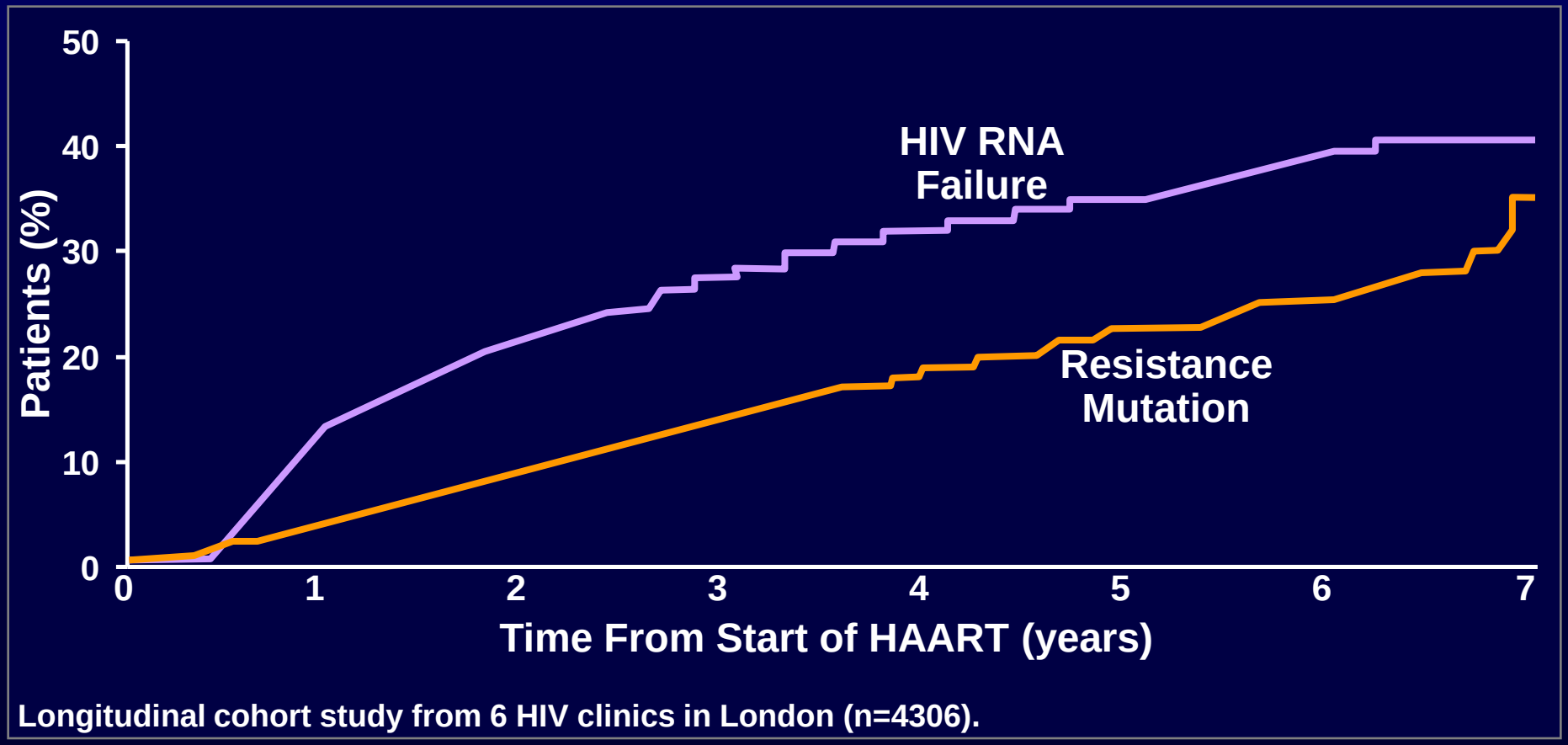
# Assessing Causes of Treatment Failure

- **Review medical history**
  - **HIV RNA and CD4 cell count change over time**
  - **Occurrence of HIV-related clinical events**
  - **Treatment history**
  - **Results of prior resistance testing**
  - **Adherence issues**
  - **Tolerability of medications**
  - **Concomitant medications and comorbidities**
- **Assess for signs of clinical progression**

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision December 1, 2009.
Hammer SM, et al. *JAMA.* 2008;300:555-570.

# UK CHIC Study: Consequences of Treatment Failure

## Long-Term Probability of Developing Resistance




**Longitudinal cohort study from 6 HIV clinics in London (n=4306).**

Phillips AN, et al. *AIDS*. 2005;19:487-494.

# General Approaches to the Management of Virologic Failure

- Goal is to re-establish maximal virologic suppression to a HIV RNA level of <50 copies/mL
- Identify fully active agents
  - Add at least two, and preferably three, fully active agents on the basis of drug history, resistance testing, or new mechanistic class
  - Drug potency and viral susceptibility are more important than the number of drugs prescribed
  - Adding a single, fully active antiretroviral drug is not recommended
    - Risk rapid development of resistance
- Discontinuing or briefly interrupting therapy is not recommended
  - Increases risk of clinical progression

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Revision December 1, 2009.
Hammer SM, et al. *JAMA.* 2008;300:555-570.

# General Approaches to the Management of Virologic Failure

- When ever a patients fails the first HIV regimen a HIV genotype must be done.
- If resources are available when the second regimen fails a phenotype must be done
- If the patient fails a NNRTI as the first regimen you can either use etravirin with a Pi or use a sensitive NNRTI based on the genotype and a boosted PI.
- You can use Raltegravir if available with a boosted PI