



NORTHWEST AIDS EDUCATION AND TRAINING CENTER

# 2012 Antiretroviral Guideline Update

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Last Updated: August 6, 2012

# US Department of Health and Human Services (DHHS) March 27, 2012 Antiretroviral Therapy Guidelines



## Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Visit the *AIDSinfo* website to access the most up-to-date guideline.

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# DHHS Antiretroviral Therapy Guidelines: March 2012

## Rating Scheme

### Rating Scheme for Recommendations

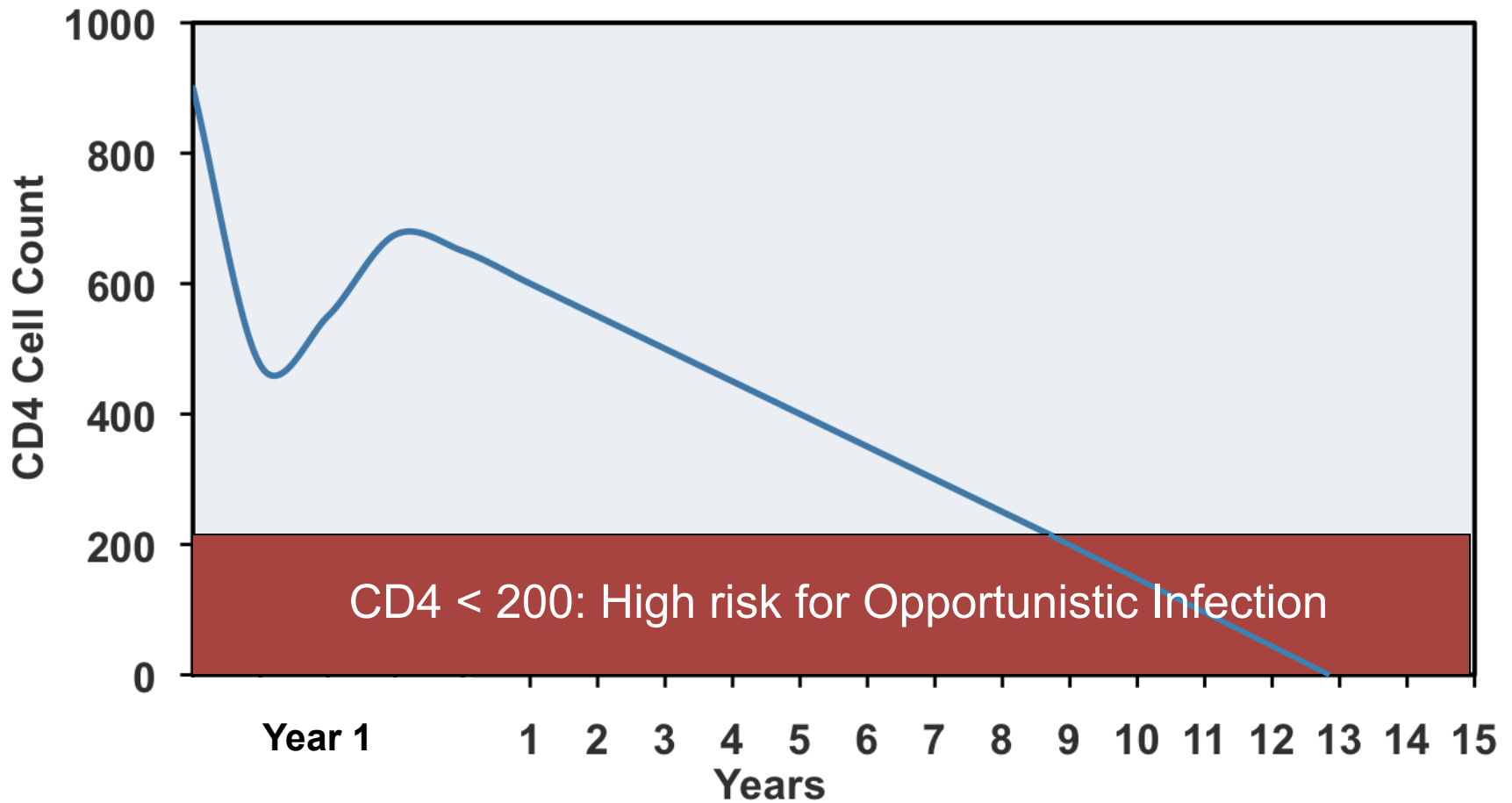
*Updated March 27, 2012*

Rating of Recommendation	Rating of Evidence
A: Strong Recommendation	I = Data from randomized controlled trials
B: Moderate Recommendation	II = Data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional Recommendation	III = Expert opinion

# WHEN TO START

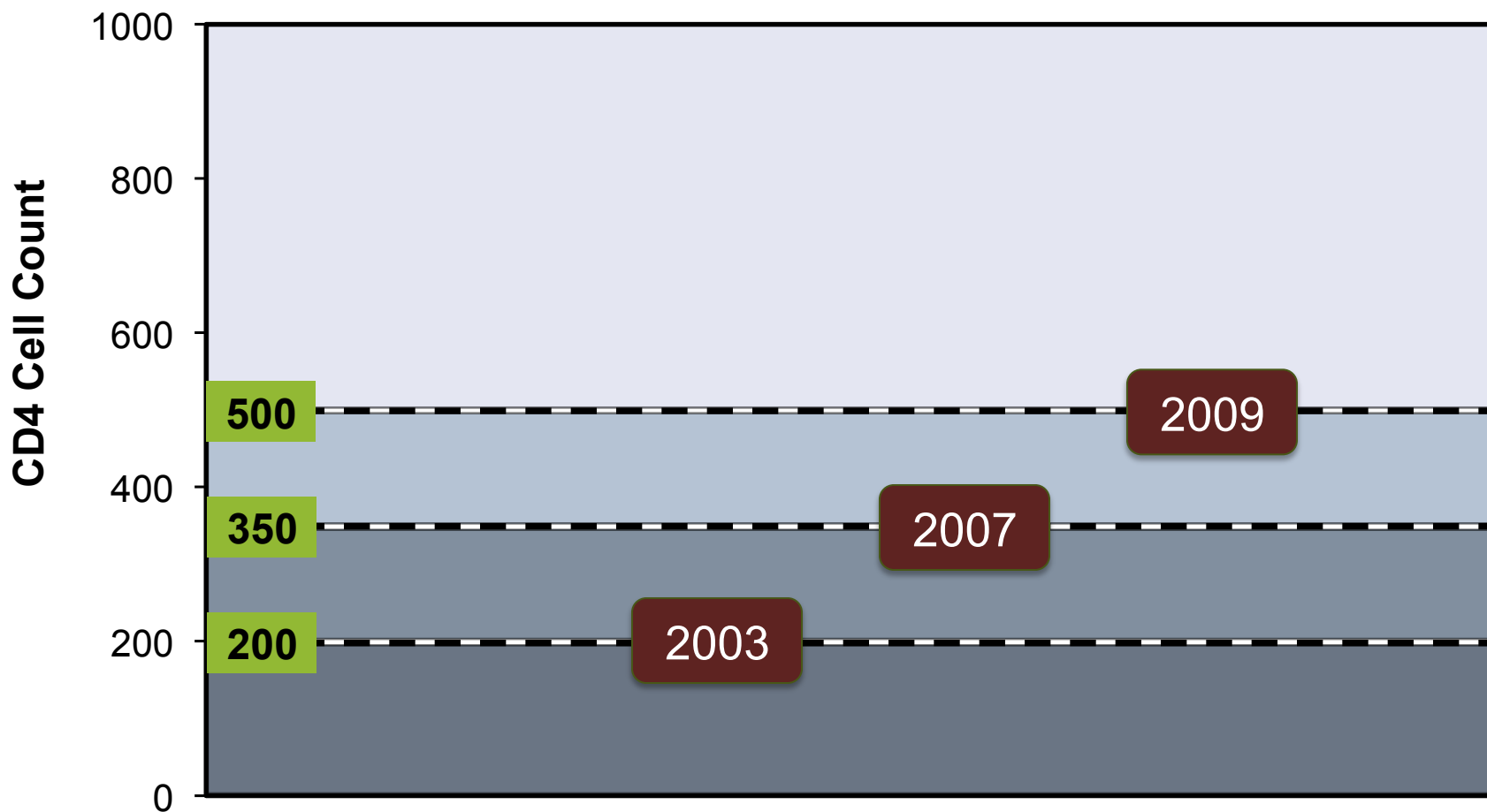
- March 2012 DHHS Guidelines
  - Supporting Evidence Base

# Natural History of Untreated HIV Infection



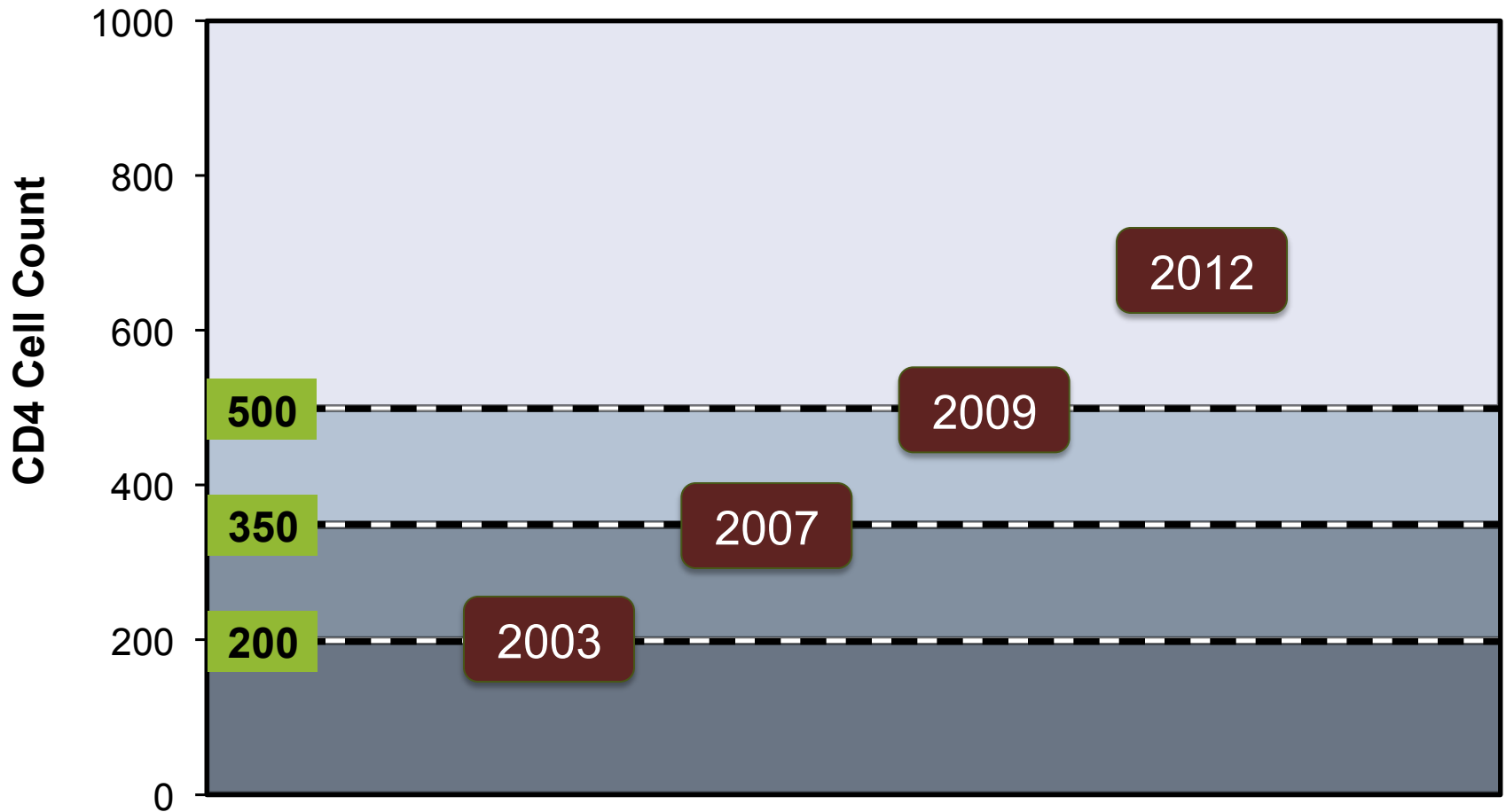
# Initiating Antiretroviral Therapy in Treatment-Naïve Patients

## Change in CD4 Threshold in DHHS Guidelines

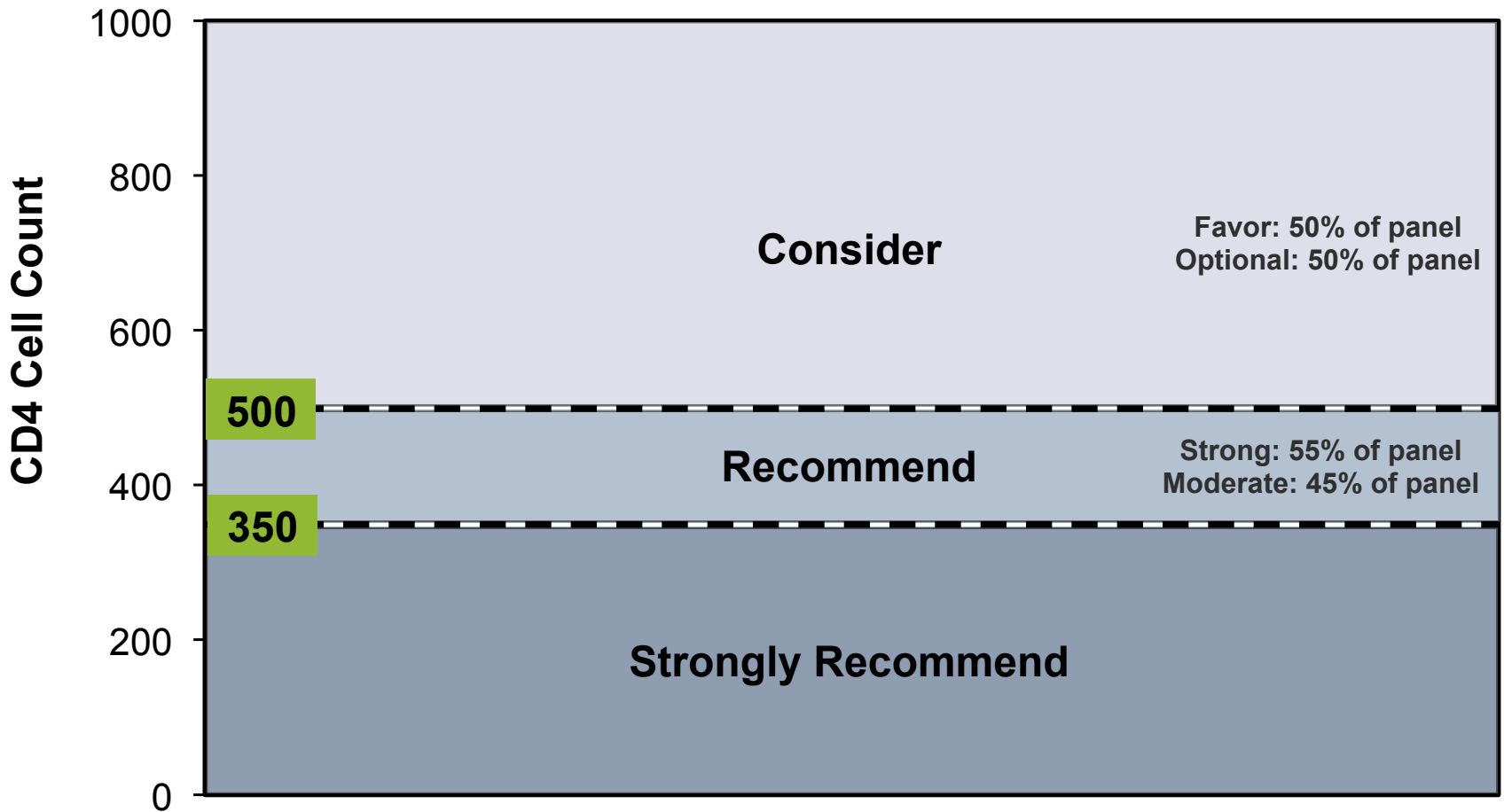


# Initiating Antiretroviral Therapy in Treatment-Naïve Patients

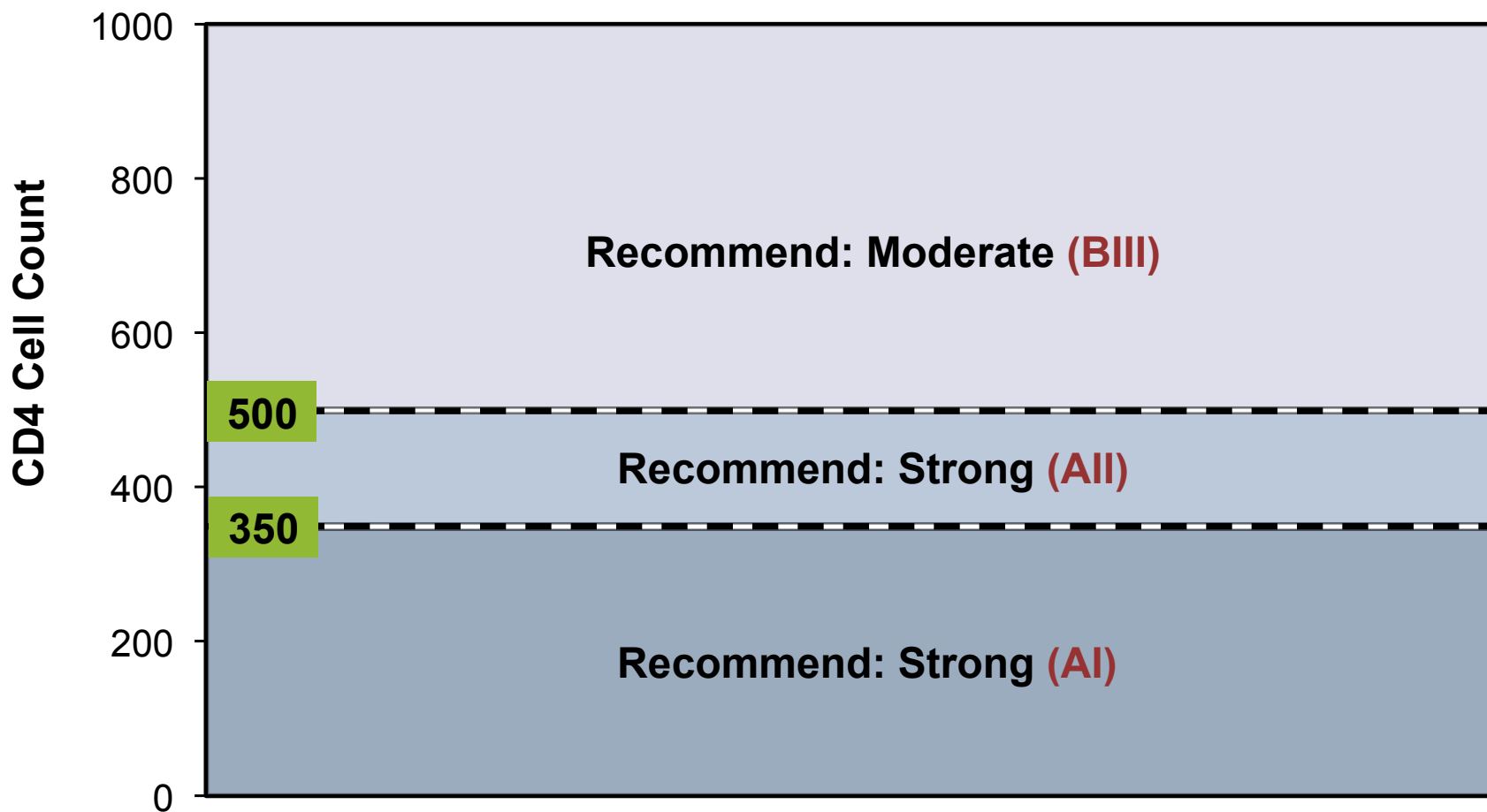
## Change in CD4 Threshold in DHHS Guidelines



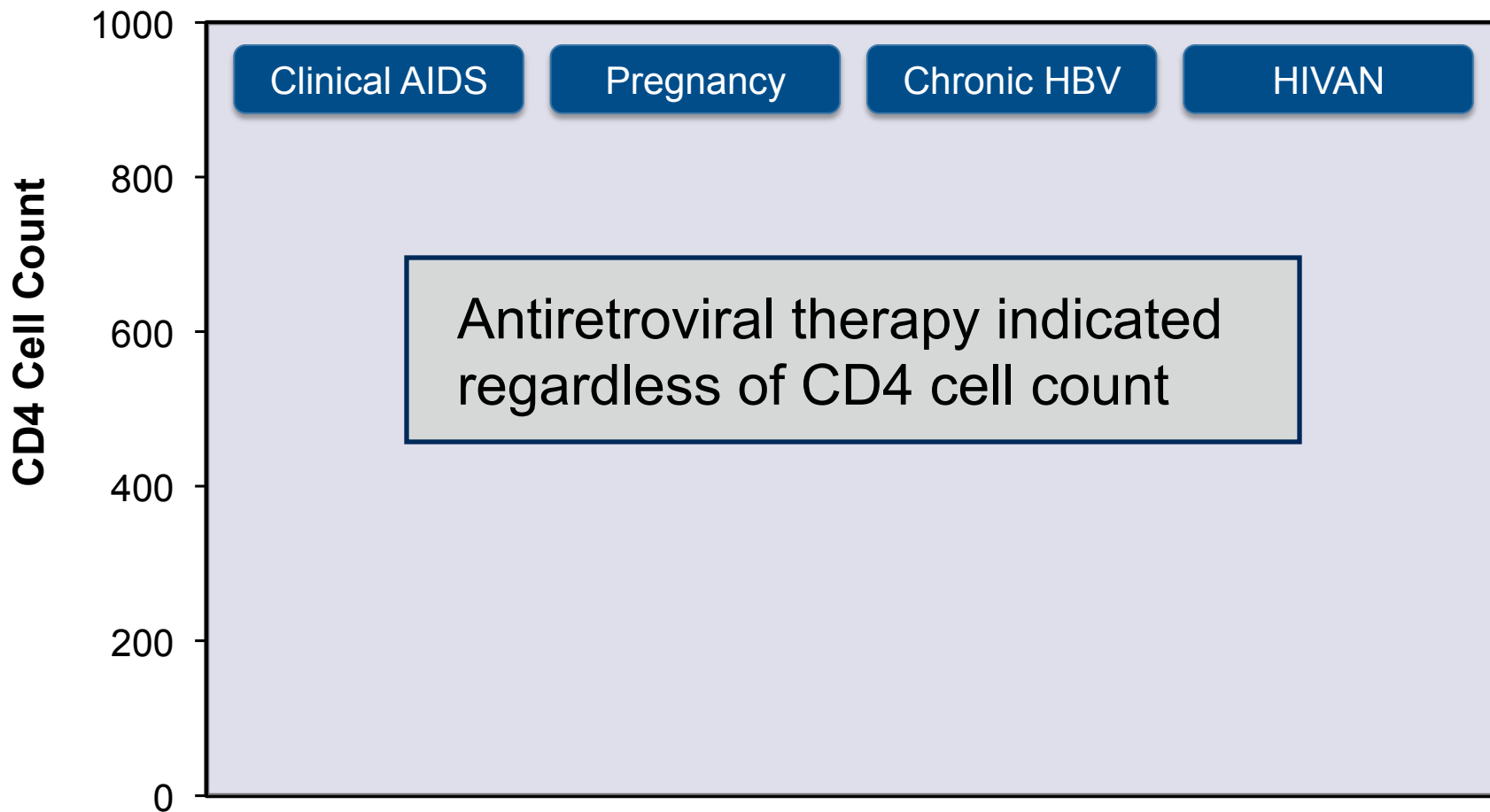
# DHHS Antiretroviral Therapy Guidelines: October 2011 Initiating Therapy in Treatment-Naïve Patients



# DHHS Antiretroviral Therapy Guidelines: March 2012 Initiating Therapy in Treatment-Naïve Patients



# DHHS Antiretroviral Therapy Guidelines: October 2011 Initiating Therapy in Treatment-Naïve Patients



# DHHS Antiretroviral Therapy Guidelines: March 2012 Initiating Therapy in Treatment-Naïve Patients

## Initiating Antiretroviral Therapy Regardless of CD4 Count\*

### Strong Recommendation

Clinical AIDS

**AI**

Pregnancy

**AI**

Chronic HBV

**AII**

HIVAN

**AII**

### Moderate Recommendation

Age > 50

**BIII**

### Consider

Chronic HCV

**BII**

\*ART should be offered to patients who are at risk of transmitting HIV to sexual partners

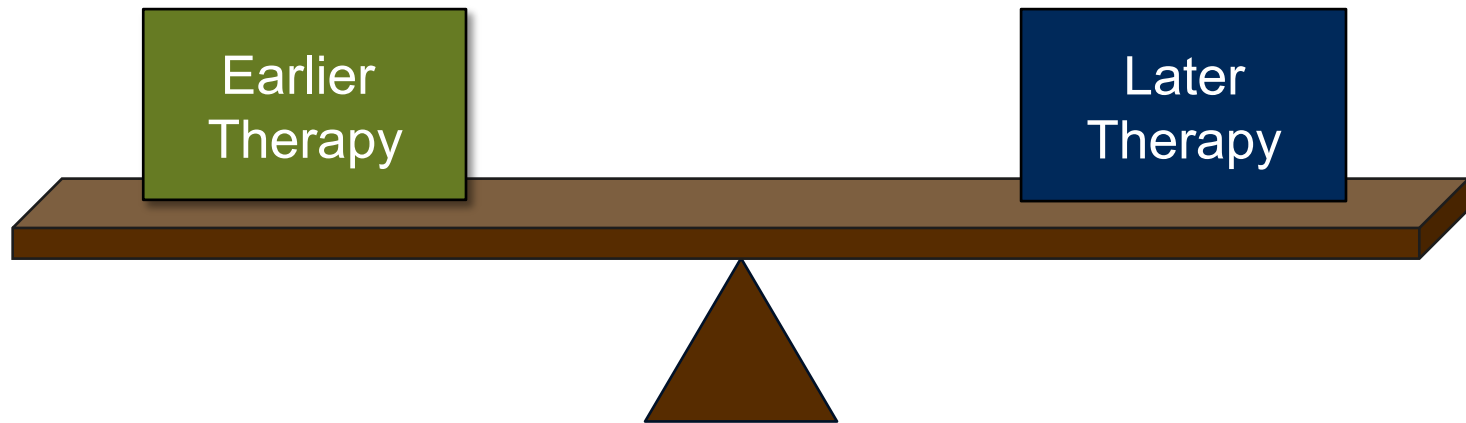
**AI** Heterosexuals

**AIII** other groups

# Mounting Evidence supporting Earlier HAART

Study	Type	Setting	Main Findings
<b>CIPRA</b> HT 001	RCT	Haiti	Deferring ART until CD4<200 associated with higher mortality than starting when CD4 between 200 and 350
<b>SMART</b> substudy	RCT	Europe, Australia	Deferring ART until CD4<250 associated with higher mortality than starting when CD4 between 350 and 250
<b>ART-CC</b>	Obs	Europe, North America	Significant increase in risk of AIDS and death when therapy was delayed until patients CD4+ counts fell below 350 cells/mm <sup>3</sup> compared to earlier treatment.
<b>NA-ACCORD</b>	Obs	North America	69% lower mortality in those who initiated in 350-500 range than those who deferred; 94% lower mortality in those who initiated at CD4 > 500 than in those who deferred
<b>Partners</b>	Obs	Africa	92% drop in transmission of HIV when index pt on ART
<b>HPTN 052</b>	RCT	Africa, Asia, S. America US, Asia, S. America	96% decrease in transmission of HIV in serodiscordant couples when one partner on ART; 41% decrease in AIDS-related events (extra-pulmonary TB) for those on ART (treatment threshold 350 cells/mm <sup>3</sup> )

# DHHS Antiretroviral Therapy Guidelines: March 2012 Initiating Therapy in Treatment-Naïve Patients

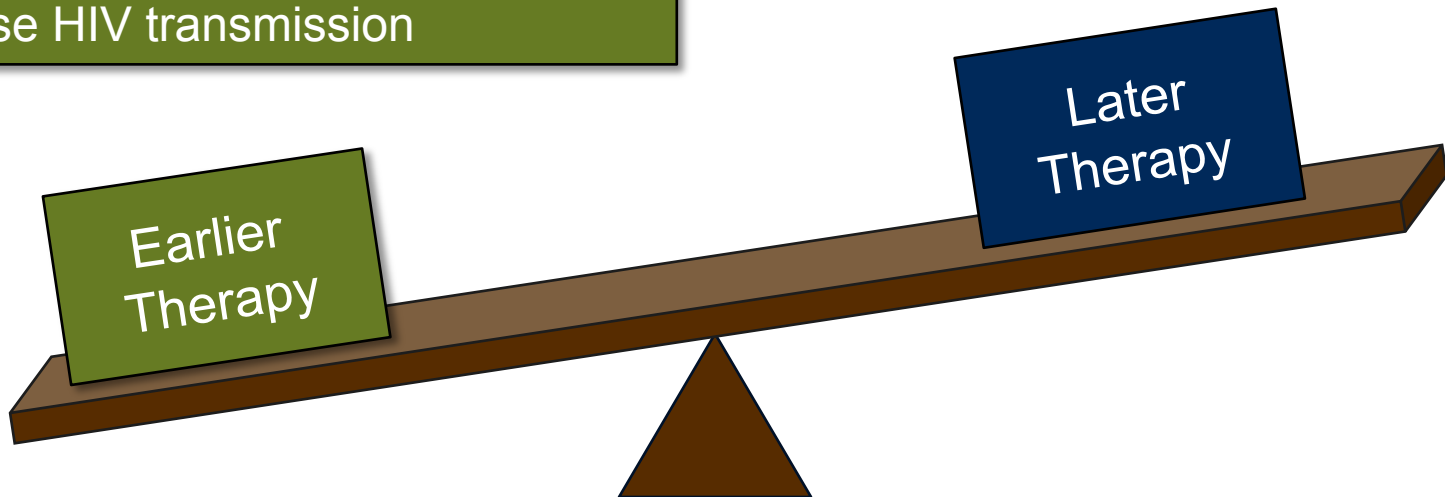


# DHHS Antiretroviral Therapy Guidelines: March 2012

## Factors Affecting Decision on When to Initiate Therapy

- More effective regimens
- More convenient regimens
- Better tolerated therapy
- Less long-term toxicity
- Better immune recovery
- Lower rates of resistance
- More treatment options
- Concerns for uncontrolled viremia
- Decrease HIV transmission

- Lack of RCT data supporting early Rx
- Potential drug toxicity
- Drug and monitoring cost
- Potential negative impact on QOL



# START (Strategic Timing of ART)

## Insight Network: international recruiting

### Study Design

#### Protocol

- N = 4000
- Randomized 1:1
- 237 study sites in 36 countries
- Antiretroviral naïve
- Age  $\geq$  18 years
- CD4  $\geq$  500 cells/mm<sup>3</sup> x 2 within 60 d
- No prior AIDS condition
- No Malignancy, hemodialysis, CV event

### Early ART

Initiate immediately on Randomization

(n = 2,000)

### Deferred ART

Defer until CD4 < 350 cells/mm<sup>3</sup> or AIDS

(n = 2,000)

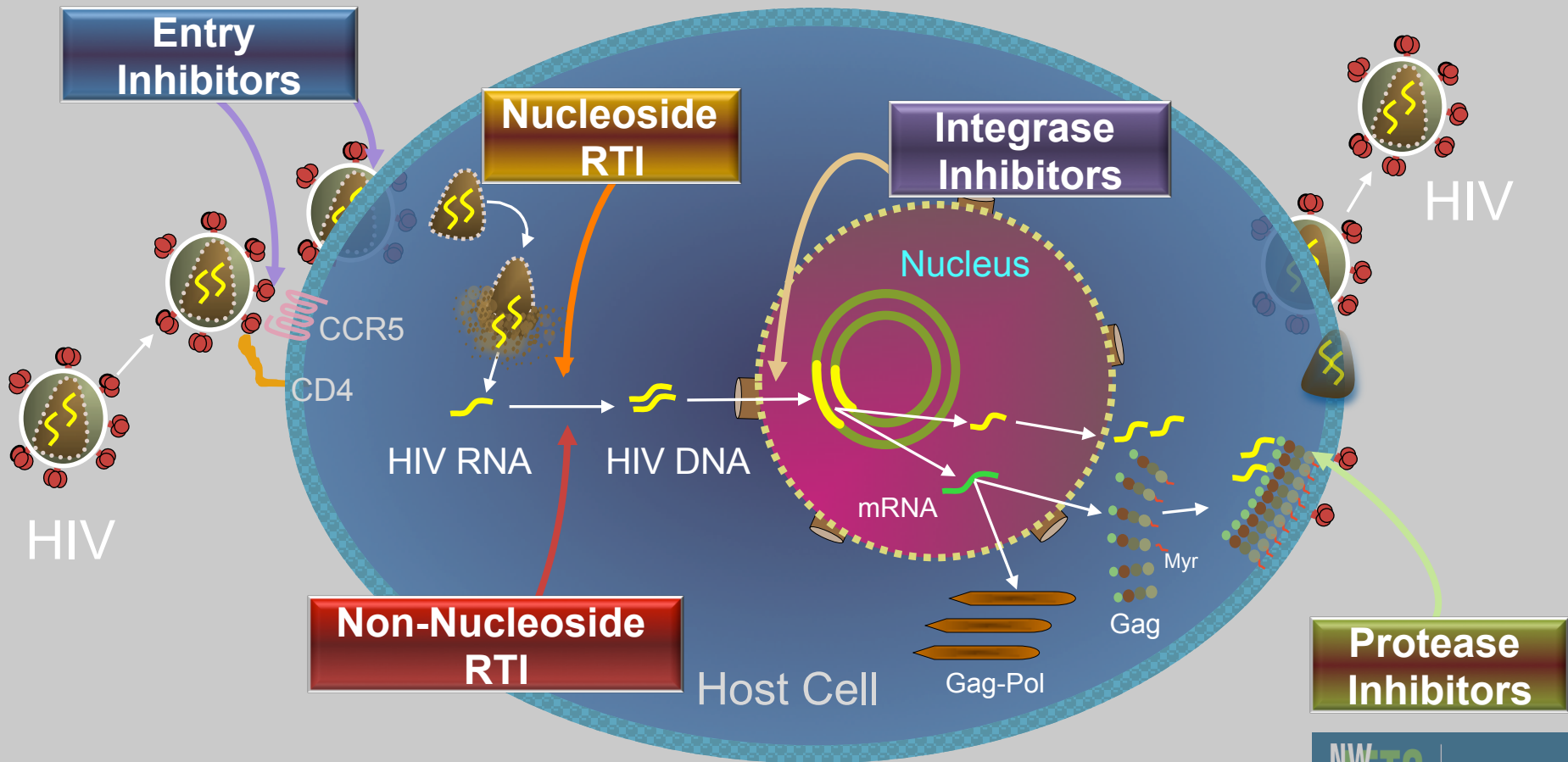
- Current (7/12) enrollment = 2709 (68%)
- Anticipated Duration ~ 6 years

# WHAT TO START



## Regimens for Antiretroviral-Naïve Patients


- New, Alternative, Acceptable Regimens
- Changes to Perinatal ART Guidelines

# Anti-retroviral drug targets














# Anti-retroviral Therapy in 2012




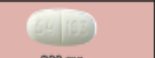
Entry Inhibitors		
<b>Enfuvirtide (ENV)</b> Fuzeon®	 90 mg/ml	Administered dose: 90 mg/ml, subcutaneous (SQ) 2 times a day (106 mg vial diluted with 1.1 ml, sterile water) • Store at controlled room temperature
<b>Maraviroc (MVC)</b> Selzentry®	 150 mg      300 mg	1 x 300 mg tablet 2 times a day (With NRTIs, SpinaVir, rilpivirine, nevirapine, and weak CYP3A4 inhibitors or CYP3A4 inducers) 1 x 150 mg tablet 2 times a day (When given with strong CYP3A4 inhibitors with or without CYP3A4 inducers) 2 x 300 mg tablet 2 times a day (With CYP3A4 inducers including etravirine)

Combination NRTIs + NNRTI		
<b>Tenofovir + Emtricitabine + Efavirenz</b> Atripla®	 TDF 300 mg/FTC 200 mg/ EFV 600 mg	1 tablet once daily at bedtime • Empty stomach recommended

Integrase Inhibitors		
<b>Raltegravir (RAL)</b> Isentress®	 400 mg	1 tablet 2 times a day • May be taken with or without food










Combination NRTIs		
<b>Abacavir + Lamivudine</b> Epizcom®	 ABC 600 mg/3TC 300 mg	1 tablet once daily • May be taken with or without food
<b>Abacavir + Lamivudine + Zidovudine</b> Trizivir®	 ABC 300 mg/3TC 150 mg/ AZT 300 mg	1 tablet 2 times a day • May be taken with or without food
<b>Zidovudine + Lamivudine</b> Combivir®	 AZT 300 mg/3TC 150 mg	1 tablet 2 times a day • May be taken with or without food
<b>Tenofovir + Emtricitabine</b> Truvada®	 TDF 300 mg/FTC 200 mg	1 tablet once daily • May be taken with or without food

Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI)			
<b>Abacavir (ABC)</b> Ziagen®	 300 mg	1 x 300 mg tablet 2 times a day 2 x 300 mg tablets once daily • May be taken with or without food	Hypersensitivity reaction symptoms may include: fever, rash, nausea, vomiting, malaise or fatigue, respiratory difficulties
<b>Didanosine (ddI)</b> Videx®	 250 mg      400 mg	1 x 400 mg capsule once daily • Reduce dose for weight < 65 Kg • Take on an empty stomach. Note: When combined with tenofovir, reduce didanosine to 250 mg once daily; may be taken with food.	Peripheral neuropathy, pancreatitis, nausea, diarrhea
<b>Emtricitabine (FTC)</b> Emtriva®	 200 mg	1 x 200 mg capsule once daily • May be taken with or without food	Headaches, fatigue, nausea
<b>Lamivudine (3TC)</b> Epivir®	 150 mg      300 mg	1 x 150 mg tablet 2 times a day 1 x 300 mg tablet once daily • May be taken with or without food	Headaches, fatigue, nausea
<b>Stavudine (d4T)</b> Zerit®	 30 mg      40 mg	1 x 40 mg capsule 2 times a day • Reduce dose for weight < 65 Kg 1 x 30 mg capsule 2 times a day • May be taken with or without food	Peripheral neuropathy, altered liver function
<b>Tenofovir DF (TDF)</b> Viread®	 300 mg	1 x 300 mg tablet once daily • May be taken with or without food	Renal insufficiency (rare), nausea, upset stomach
<b>Zidovudine (ZDV, AZT)</b> Retrovir®	 100 mg      300 mg	1 x 300 mg tablet 2 times a day • May be taken with or without food	Anemia, neutropenia, headaches, nausea, body aches, insomnia

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
<b>Delavirdine (DLV)</b> Rescriptor®	 200 mg	2 x 200 mg tablets 3 times a day • May be taken with or without food	Rash, headache, altered liver function
<b>Efavirenz (EFV)</b> Sustiva®	 200 mg      600 mg	1 x 600 mg tablet once daily at bedtime 3 x 200 mg capsules once daily at bedtime • Empty stomach recommended	Rash, altered liver function, dizziness, insomnia, impaired concentration, drowsiness
<b>Etravirine (ETR)</b> Intence®	 100 mg	2 x 100 mg tablet 2 times a day • Take with food	Nausea, headache, rash, Stevens-Johnson syndrome, hypersensitivity reaction, erythema
<b>Nevirapine (NVP)</b> Viramune®	 200 mg	1 x 200 mg tablet 2 times a day (start with 200 mg tablet once daily x 14 days) • May be taken with or without food	Rash, headache, altered liver function

New NNRTI: Rilpivirine  
Co-formulated with  
Emtricitabine-Tenofovir as  
**Complera**



Protease Inhibitors (PI)		
<b>Atazanavir (ATV)</b> Reyataz®	 150 mg  200 mg  300 mg	2 x 300 mg capsules once daily 1 x 300 mg capsule with ritonavir 100 mg capsule once daily Note: Use ritonavir boosted dose when combined with efavirenz, nevirapine, or tenofovir • Take with <u>light meal</u> • Consult Reyataz prescribing information for use with antacids, H2-blockers and proton pump inhibitors.
<b>Darunavir (DRV)</b> Prezista®	 400 mg      600 mg	Always use with ritonavir 1 x 600 mg tablet 2 times a day with ritonavir 1 x 100 mg capsule 2 times a day 2 x 400 mg tablet once a day with ritonavir 1 x 100 mg capsule once a day • Take <u>with food</u> .
<b>Fosamprenavir (FPV)</b> Lexiva®	 700 mg	PI-naïve patients: 2 x 700 mg tablets 2 times a day 2 x 700 mg tablets once daily with 1 or 2 x 100 mg ritonavir capsule once daily Note: Use ritonavir boosted dose when combined with efavirenz or nevirapine, use ritonavir 300 mg once daily when combined with NNRTIs. 1 x 700 mg tablet 2 times a day with ritonavir 1 x 100 mg capsule 2 times a day PI-experienced patients: 1 x 700 mg tablet 2 times a day with 1 x 100 mg ritonavir capsule 2 times a day • May be taken with or without food
<b>Indinavir (IDV)</b> Crixivan®	 400 mg	2 x 400 mg capsules 2 times a day with ritonavir 100-200 mg capsules 2 times a day • Take <u>with food</u> • Drink at least 1.5 liters of fluid per day
<b>Lopinavir/Ritonavir (LPV/r)</b> Kaletra®	 LPV 200 mg/RTV 50 mg	PI-naïve patients: 2 tablets 2 times a day 4 tablets once daily PI-experienced patients: 2 tablets 2 times a day Once daily not recommended Note: Use 3 tablets 2 times a day when used with nevirapine or efavirenz
<b>Nelfinavir (NFV)</b> Viracept®	 250 mg      625 mg	2 x 625 mg tablets 2 times a day 5 x 250 mg tablets 2 times a day 3 x 250 mg tablets 3 times a day • Always take <u>with food</u> .
<b>Ritonavir (RTV)</b> Norvir®	 100 mg	Ritonavir is primarily used in low doses to boost drug levels of other protease inhibitors • Keep refrigerated
<b>Saquinavir (SQV)</b> Invirase®	 200 mg  500 mg	Always take at same time with ritonavir 2 x 500 mg tablets 2 times a day with ritonavir 100 mg capsule 2 times a day 5 x 200 mg capsules 2 times a day with ritonavir 100 mg capsule 2 times a day • Always take <u>with food</u> .
<b>Tipranavir (TPV)</b> Aptivus®	 250 mg	Always use with ritonavir PI-experienced patients: 2 x 250 mg capsules 2 times a day with ritonavir 2 x 100 mg capsule 2 times a day • Take <u>with food</u> .

# DHHS Antiretroviral Therapy Guidelines: March 2012

## Preferred Regimens for ARV-Naïve Patients

### Backbone

(2) Nucleoside Reverse  
Transcriptase Inhibitors  
(NRTIs)

+

### Third Agent

Non-Nucleoside Reverse  
Transcriptase Inhibitor  
(NNRTI)

*or*

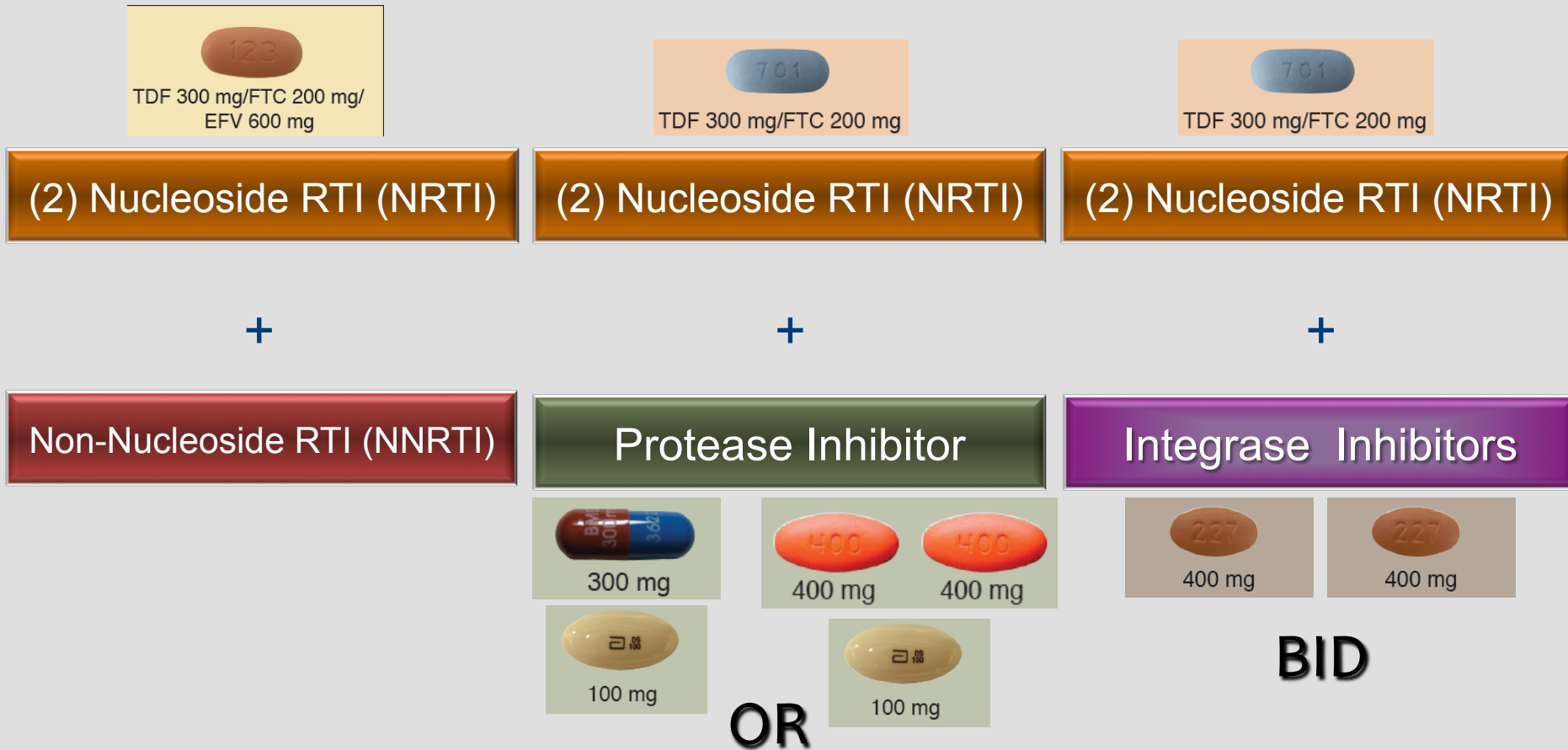
Protease Inhibitor (PI)  
(ritonavir-boosted)

*or*

Integrase Strand  
Transfer Inhibitor (INSTI)

# DHHS Antiretroviral Therapy Guidelines: March 2012

## Preferred Regimens for ARV-Naïve Patients



# DHHS Antiretroviral Therapy Guidelines: March 2012

## Preferred Regimens for ARV-Naïve Patients

Class	Regimen
NNRTI-Based	Efavirenz-Tenofovir-Emtricitabine ( <b>AI</b> )
PI-Based	Atazanavir + Ritonavir + Tenofovir-Emtricitabine ( <b>AI</b> ) Darunavir (qd) + Ritonavir + Tenofovir-Emtricitabine ( <b>AI</b> )
INSTI-Based	Raltegravir + Tenofovir-Emtricitabine ( <b>AI</b> )

# DHHS Antiretroviral Therapy Guidelines: March 2012

## Alternative Regimens for ARV-Naïve Patients

Class	Therapy
NNRTI-Based	Efavirenz + Abacavir-Lamivudine ( <b>BI</b> )
	Rilpivirine + Tenofovir-Emtricitabine ( <b>BI</b> )
	Rilpivirine + Abacavir-Lamivudine ( <b>BIII</b> )
PI-Based	Atazanavir + Ritonavir + Abacavir-Lamivudine ( <b>BI</b> )
	Darunavir + Ritonavir + Abacavir-Lamivudine ( <b>BIII</b> )
	Fosamprenavir (1-2x daily) + Ritonavir + Abacavir-Lamivudine ( <b>BI</b> )
	Fosamprenavir (1-2x daily) + Ritonavir + Tenofovir-Emtricitabine ( <b>BI</b> )
	Lopinavir-Ritonavir (1-2x daily) + Abacavir-Lamivudine ( <b>BI</b> )
Lopinavir-Ritonavir (1-2x daily) + Tenofovir-Emtricitabine ( <b>BI</b> )	
INSTI-Based	Raltegravir + Abacavir-Lamivudine ( <b>BIII</b> )

# DHHS Antiretroviral Therapy Guidelines: March 2012

## Acceptable Regimens for ARV-Naïve Patients

Class	Therapy
NNRTI-Based	Efavirenz + Zidovudine-Lamivudine (CI)
	Nevirapine + Tenofovir-Emtricitabine (CI)
	Nevirapine + Zidovudine-Lamivudine (CI)
	Nevirapine + Abacavir-Lamivudine (CIII)
	Rilpivirine + Zidovudine-Lamivudine (CIII)
PI-Based	Atazanavir + Abacavir-Lamivudine (CI)
	Atazanavir + Zidovudine-Lamivudine (CI)
	Atazanavir + Ritonavir + Zidovudine-Lamivudine (CI)
	Darunavir + Ritonavir + Zidovudine-Lamivudine (CIII)
	Fosamprenavir + Ritonavir + Zidovudine-Lamivudine (CI)
	Lopinavir-Ritonavir + Zidovudine-Lamivudine (CIII)
INSTI-Based	Raltegravir + Zidovudine-Lamivudine (CIII)
CCR5 Antagonist-Based	Maraviroc + Zidovudine-Lamivudine (CI)
	Maraviroc + Tenofovir-Emtricitabine (CIII)
	Maraviroc + Abacavir-Lamivudine (CIII)

## DHHS Antiretroviral Therapy Guidelines: March 2012

### Regimens may be Acceptable but should be used with Caution

Class	Therapy
PI-Based	Saquinavir + Ritonavir + Tenofovir-Emtricitabine ( <b>CI</b> ) Saquinavir + Ritonavir + Abacavir-Lamivudine ( <b>CIII</b> ) Saquinavir + Ritonavir + Zidovudine-Lamivudine ( <b>CIII</b> )

# US Department of Health and Human Services (DHHS) July 31, 2012 Perinatal Antiretroviral Therapy Guidelines



## **Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States**

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 8/2/2012 EST.

Visit the *AIDSinfo* website to access the most up-to-date guideline.

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Downloaded from <http://aidsinfo.nih.gov/guidelines> on 8/2/2012 EST.



# US Department of Health and Human Services (DHHS) July 31, 2012 Perinatal Antiretroviral Therapy Guidelines

## Pre-Conception

- ART recommended for HIV+ partner in sero-discordant couples (**AI** for CD4 < 550 cells/mm<sup>3</sup>, **BIII** for CD4 >550 cells/mm<sup>3</sup>)
- Maximal viral suppression recommended before conception (**AIII**)
- Peri-conception PrEP for HIV- partners may reduce risk (**CIII**)
- Testing for Hepatitis C and Tuberculosis is recommended (**CIII**)

## Intra-Partum

- Intravenous AZT (Zidovudine) no longer required for HIV+ women receiving combination ART who have HIV RNA <400 copies/mL (**BII**)

## Post-Partum

- ART for exposed infants should include AZT (Zidovudine) x 6 weeks with option of adding NVP (Nevirapine) (1<sup>st</sup> dose 0-48 hrs, 2<sup>nd</sup> dose 48 hours after 1<sup>st</sup>, 3<sup>rd</sup> dose 96 hrs after 2<sup>nd</sup>) (**AI**)

# US Department of Health and Human Services (DHHS) July 31, 2012 Perinatal Antiretroviral Therapy Guidelines

## What to Start

- ddl (Didanosine) and d4T (Stavudine): ***alternative → use in special circumstances***
- ATZ/r (Atazanavir): ***alternative → preferred***
- DRV/r (Darunavir): ***insufficient data → alternative***
- RAL (Raltegravir): ***insufficient data → use in special circumstances***
- EFV (Efavirenz): “Because the risk of neural tube defects is restricted to the first 5-6 weeks and pregnancy is rarely diagnosed before 4-6 weeks of pregnancy and unnecessary ARV drug changes during pregnancy may be associated with loss of virologic control and increased risk of perinatal transmission, EFV may be continued in pregnant women receiving an EFV-based regimen who present for care in the 1<sup>st</sup> trimester, provided there is virologic suppression on the regimen”

# Antiretroviral Therapy Guidelines - Summary

## When to Start

- DHHS and IAS-USA Guidelines recommend ART for all HIV-infected individuals; strength of recommendations differs at different CD4 levels

## What to Start

- Starting regimens should use a dual NRTI backbone of Emtricitabine and Tenofovir (FTC/TDF – Truvada) and a third agent such as Efavirenz, Atazanavir/ritonavir, Darunavir/ritonavir, or Raltegravir
- The role of newly approved agents is constantly evolving

## Special Populations

- All pregnant women should start ART to prevent vertical transmission
- ATZ/r is now a ***preferred*** agent, Efavirenz can be used in pregnancy beyond 6<sup>th</sup> week gestation, Raltegravir in pregnancy is discussed by not endorsed...more data needed

# Questions?