NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Antiretroviral Therapy Guidelines

Christian B. Ramers, MD, MPH
Medical Director, NW AETC ECHO
Assistant Professor of Medicine & Global Health, University of Washington

Presentation Prepared by:
Christian B. Ramers, MD, MPH and David Spach, MD
Last Updated: February 22, 2012

NW AETC | echo

When To Start

- October 2011 DHHS Guidelines
- July 2010 IAS-USA Guidelines
- Supporting Evidence Base

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

October 14, 2011

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

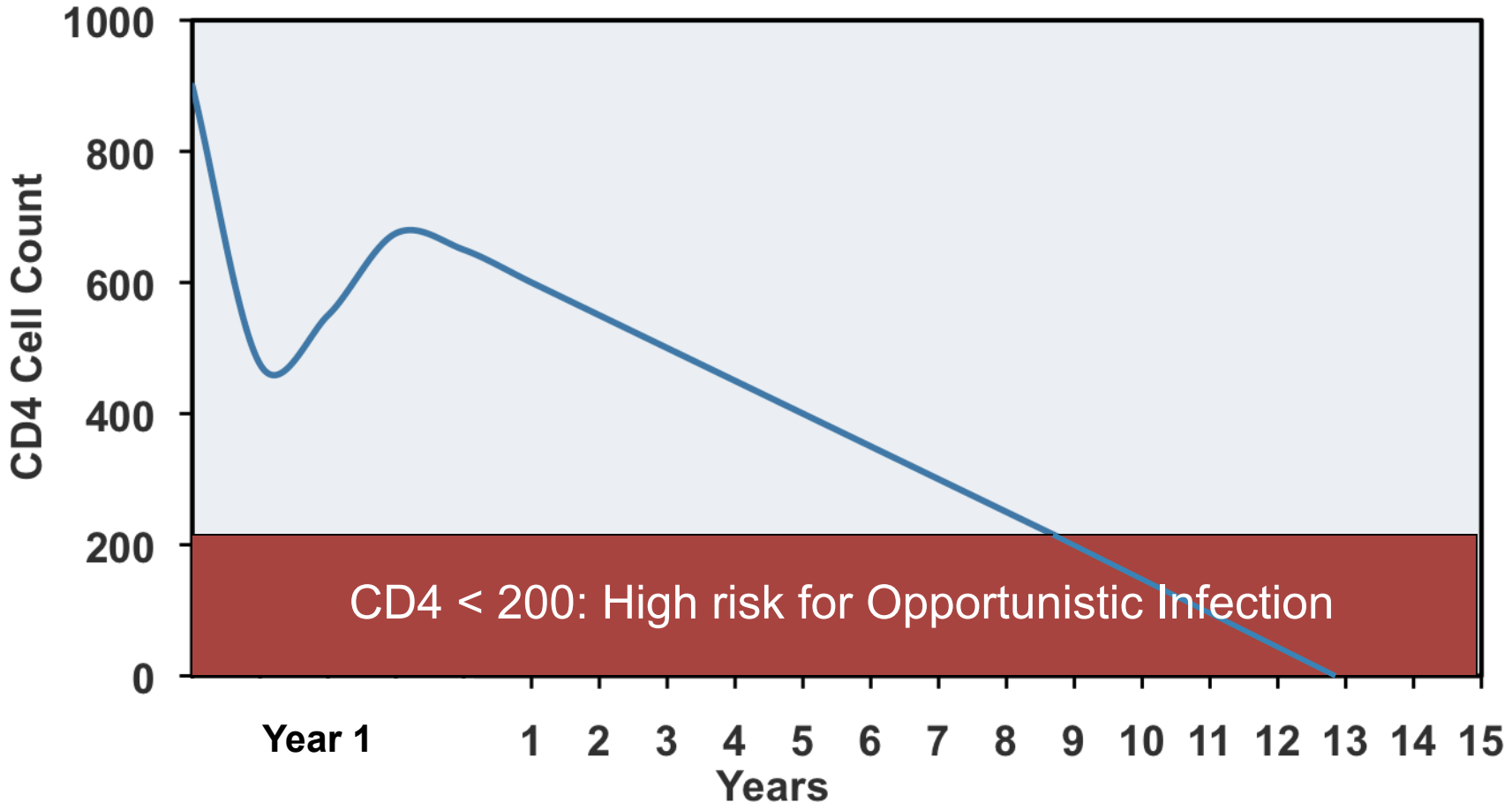
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 14, 2011; 1–167. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).

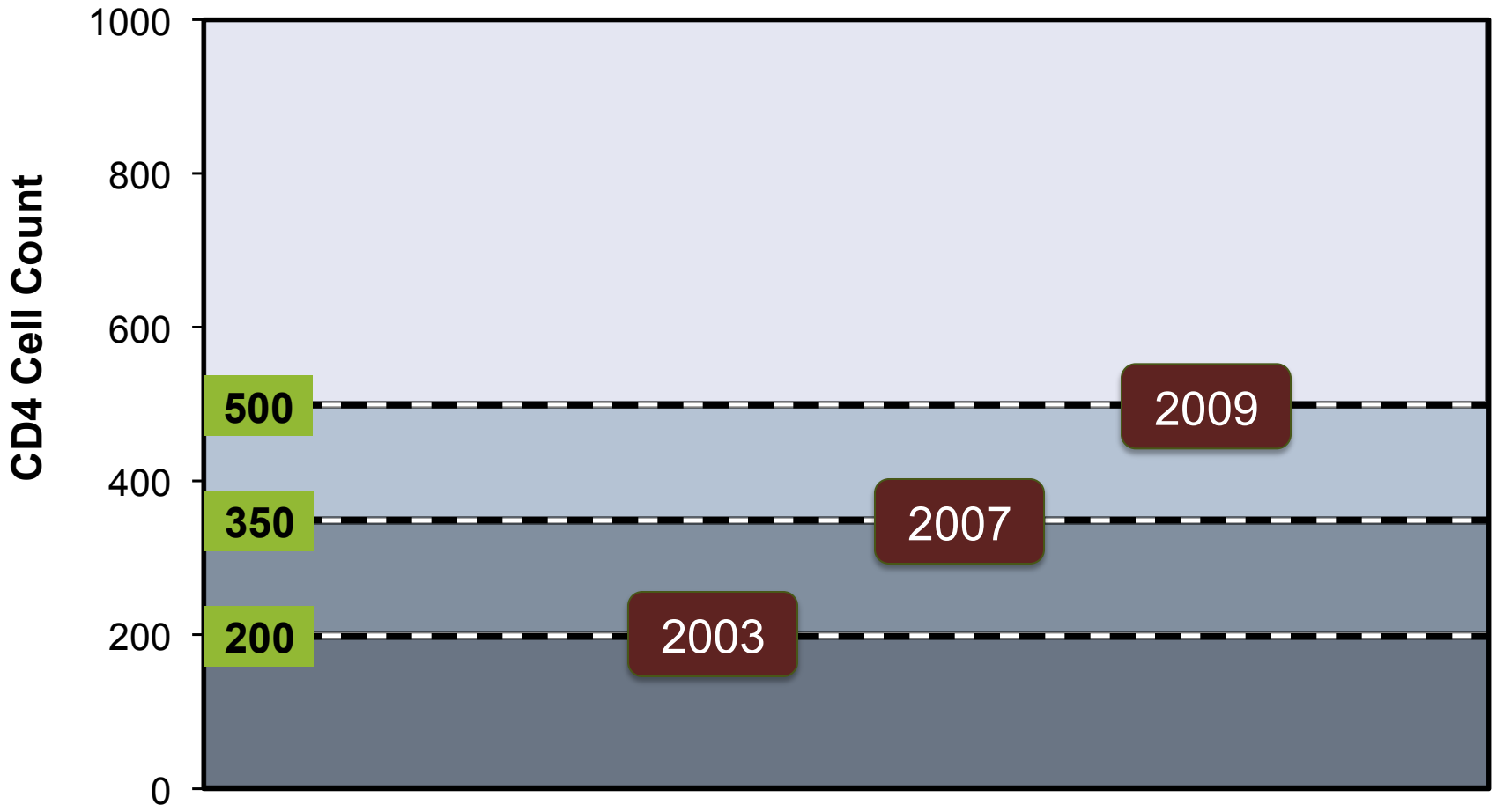
access AIDS*info* mobile site

Source: 2011 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

Natural History of Untreated HIV Infection

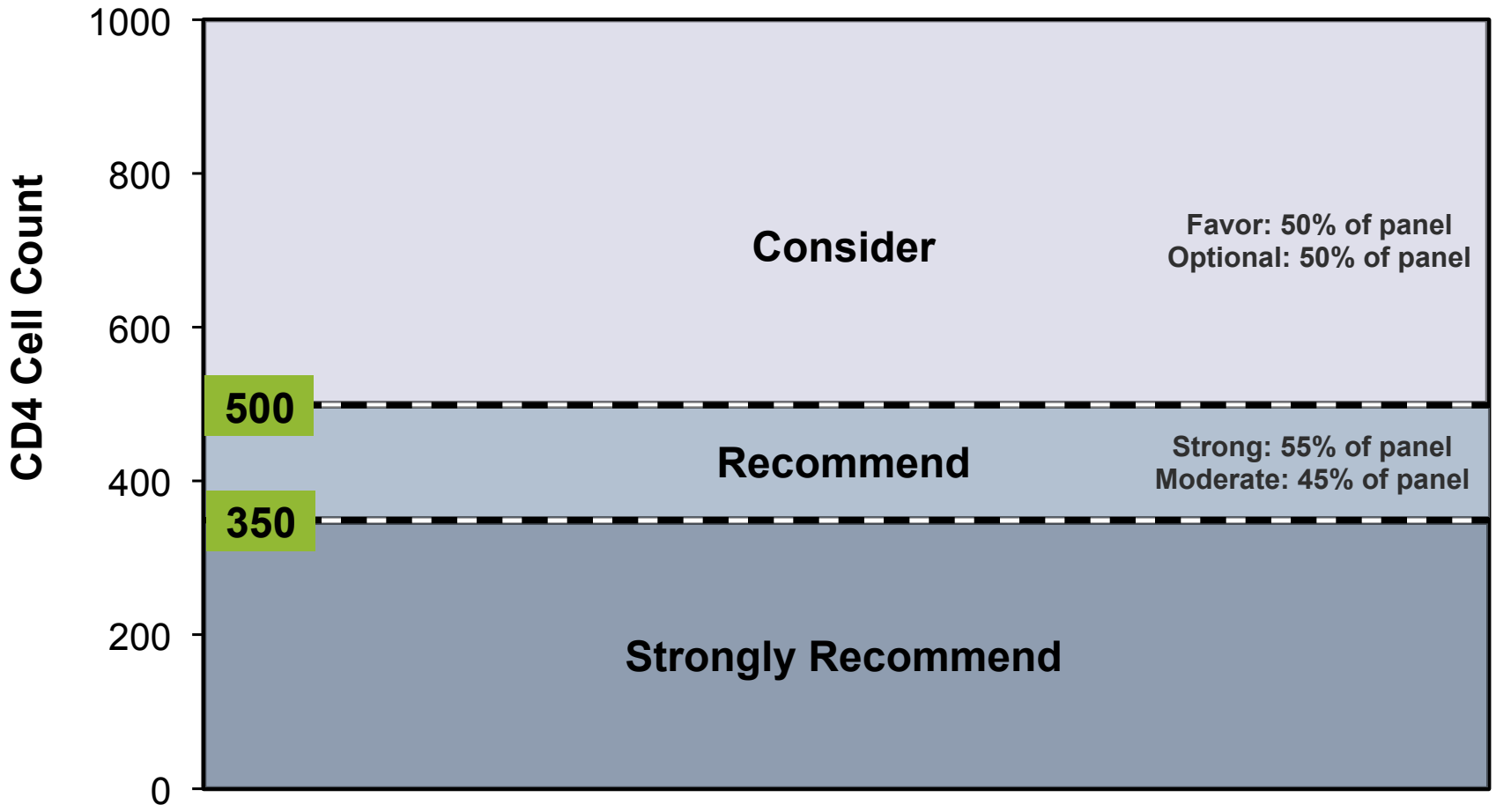


Initiating Antiretroviral Therapy in Treatment-Naïve Patients
Change in CD4 Threshold in DHHS Guidelines



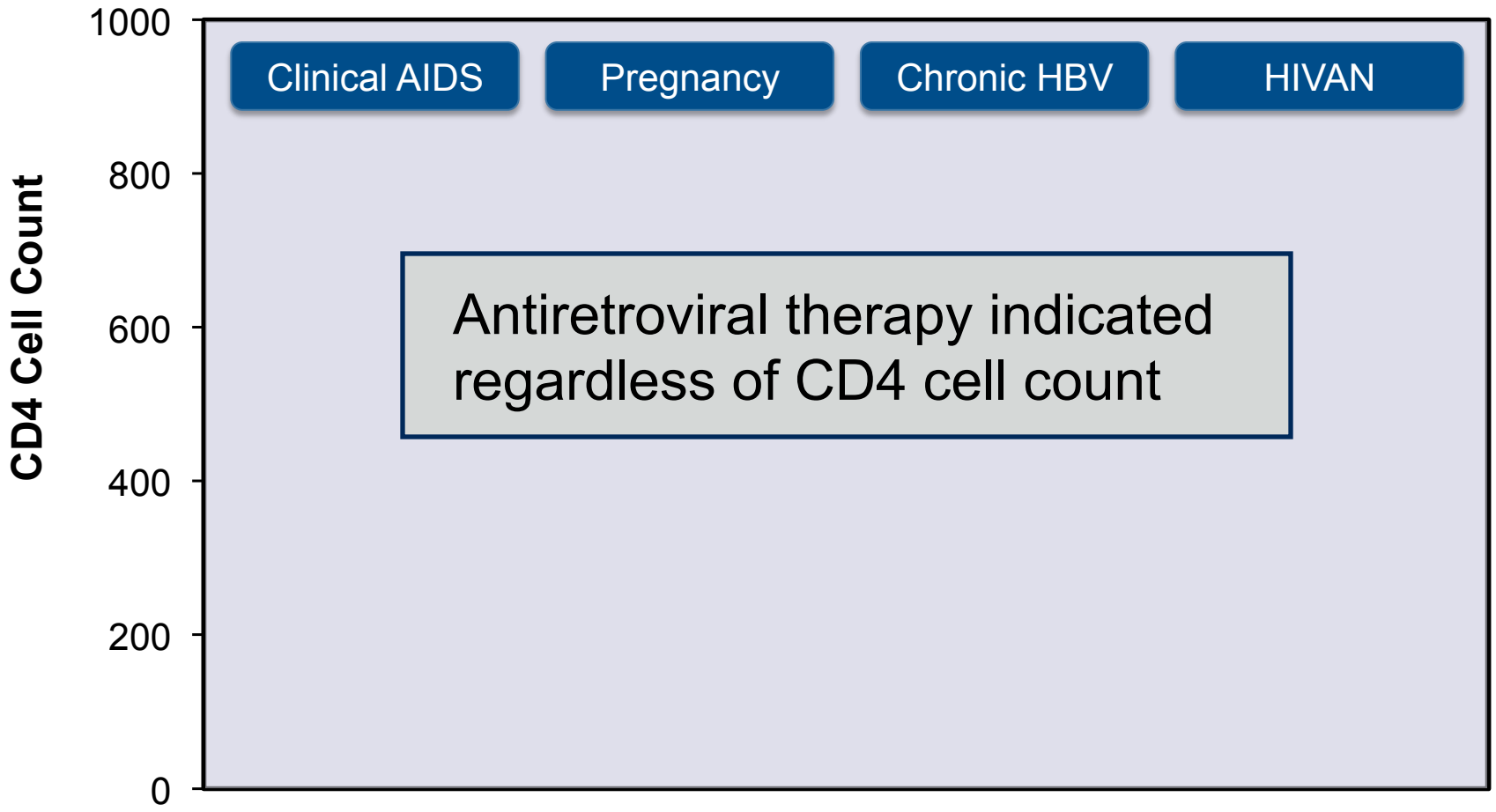
Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

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



Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

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



Source: 2011 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

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

CD4 Cell Count	Recommendation for Antiretroviral Therapy
<350 cells/mm^3	**Strongly Recommend** Initiating Therapy (**AI**)
350-500 cells/mm^3	**Recommend** Initiating Therapy (**A/B-II**): -55% of panel voted for strong recommendation (**A**) -45% of panel voted for moderate recommendation (**B**)
>500 cells/mm^3	**Consider** Initiating Therapy (**B/C-III**): -50% of panel favor starting antiretroviral therapy (**B**) -50% of panel view treatment is optional (**C**)

Initiating Antiretroviral Therapy Regardless of CD4 Cell Count

- History of AIDS-defining illness **(AI)**
- Pregnancy **(AI)**
- Hepatitis B virus (HBV) co-infection when treatment of HBV is indicated **(AIII)**
- HIV associated nephropathy **(AII)**

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

Antiretroviral Treatment of Adult HIV Infection

2010 Recommendations of the International AIDS Society–USA Panel

Melanie A. Thompson, MD
Judith A. Aberg, MD
Pedro Cahn, MD
Julio S. G. Montaner, MD
Giuliano Rizzardini, MD
Amalio Telenti, MD, PhD
José M. Gatell, MD, PhD
Huldrych F. Günthard, MD
Scott M. Hammer, MD
Martin S. Hirsch, MD
Donna M. Jacobsen, BS
Peter Reiss, MD, PhD
Douglas D. Richman, MD
Paul A. Volberding, MD
Patrick Yeni, MD
Robert T. Schooley, MD

Context Recent data regarding the consequences of untreated human immunodeficiency virus (HIV) infection and the expansion of treatment choices for antiretroviral-naive and antiretroviral-experienced patients warrant an update of the International AIDS Society–USA guidelines for the use of antiretroviral therapy in adults with HIV infection.

Objectives To provide updated recommendations for management of HIV-infected adults, using antiretroviral drugs and laboratory monitoring tools available in the international, developed-world setting. This report provides guidelines for when to initiate antiretroviral therapy, selection of appropriate initial regimens, patient monitoring, when to change therapy, and what regimens to use when changing.

Data Sources and Study Selection A panel with expertise in HIV research and clinical care reviewed relevant data published or presented at selected scientific conferences since the last panel report through April 2010. Data were identified through a PubMed search, review of scientific conference abstracts, and requests to antiretroviral drug manufacturers for updated clinical trials and adverse event data.

Data Extraction and Synthesis New evidence was reviewed by the panel. Recommendations were drafted by section writing committees and reviewed and edited by the entire panel. The quality and strength of the evidence were rated and recommendations were made by full panel consensus.

Conclusions Patient readiness for treatment should be confirmed before initiation of antiretroviral treatment. Therapy is recommended for asymptomatic patients with a CD4 cell count ≤500/μL, for all symptomatic patients, and those with specific conditions and comorbidities. Therapy should be considered for asymptomatic patients with CD4 cell count >500/μL. Components of the initial and subsequent regimens must be individualized, particularly in the context of concurrent conditions. Patients receiving antiretroviral treatment should be monitored regularly; treatment failure should be detected and managed early, with the goal of therapy, even in heavily pretreated patients, being HIV-1 RNA suppression below commercially available assay quantification limits.

JAMA. 2010;304(3):321-333 www.jama.com

SUCCESSFUL ANTIRETROVIRAL therapy (ART) is associated with dramatic decreases in AIDS-defining conditions and their associated mortality. Expansion of treatment options and evolving knowledge require revision of guidelines for the initiation and long-term management of ART in adults with HIV infection.

Since the 2008 International AIDS Society–USA ART guidelines,[1] new data have emerged regarding timing of therapy, optimal regimen choices, and monitoring. There are also issues of special relevance to circumstances such as pregnancy, hepatitis virus coinfections, kidney disease, cardiovascular disease, and primary HIV infection.

CME available online at www.jamaarchivescme.com and questions on p 357.

Analyses of clinical trials and epidemiologic cohorts have shed light on the role of ART in mitigating serious non-AIDS events associated with uncontrolled HIV replication. Newer drugs are better understood in terms of efficacy, toxicity, and potential uses. New data also suggest a role for ART in the prevention of HIV transmission.

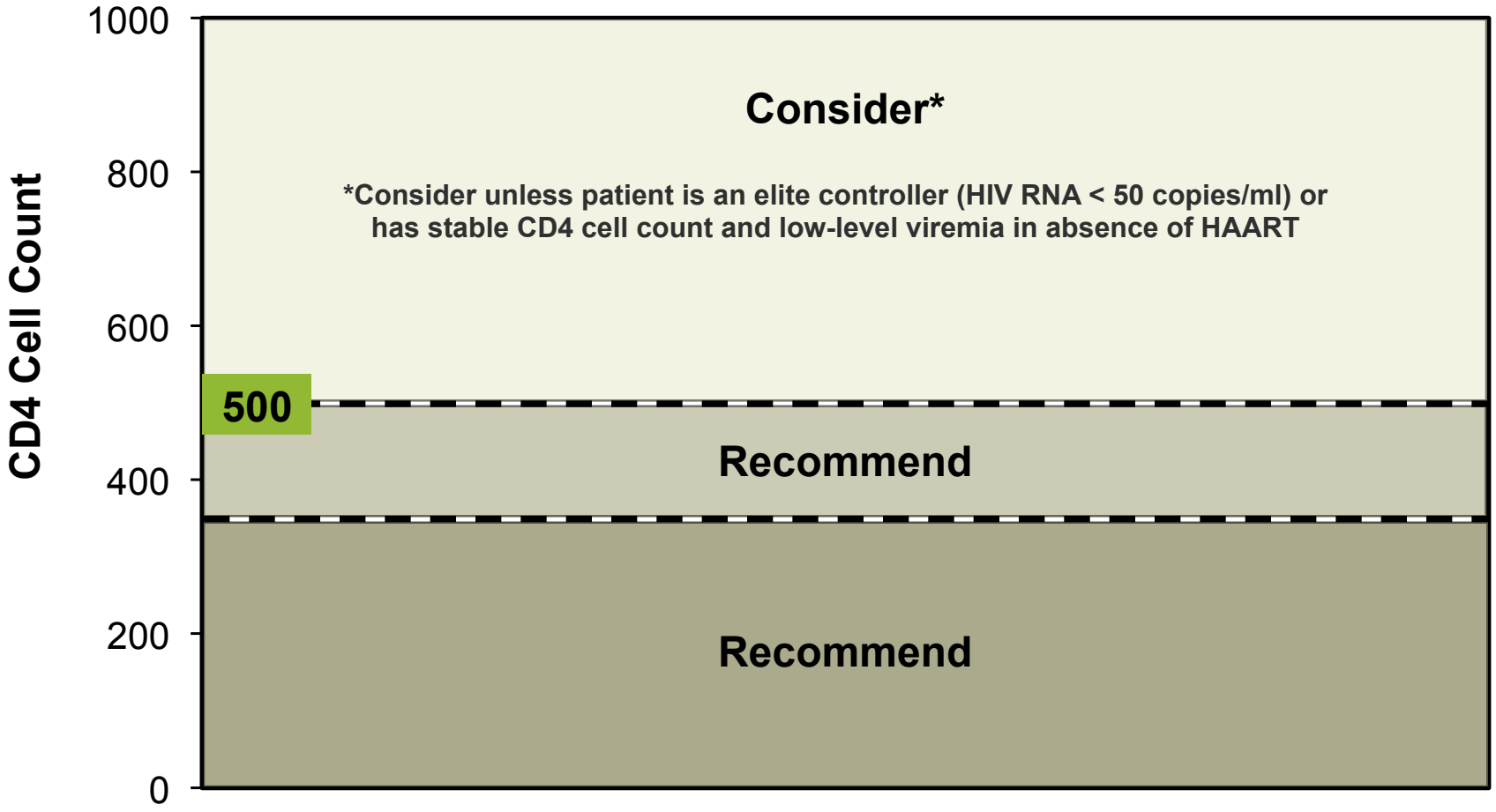
METHODS

The panel was convened in 1995 to develop evidence-based recommendations for ART for HIV-infected adults in developed-world settings.[2] Members are appointed by International AIDS Society–USA according to clinical and research expertise. Current panel members do not participate in pharmaceutical marketing or promotional activities (eg, speakers' bureaus, industry satellites) during tenure on the panel. The current panel convened in January 2010 and met weekly in person or by teleconference. Data published or presented in specific scientific meetings since the last report[1]

Author Affiliations are listed at the end of this article.
Corresponding Author: Melanie A. Thompson, MD, 131 Ponce de Leon Ave NE, Ste 130, Atlanta, GA 30308 (drmt@mindspring.com).

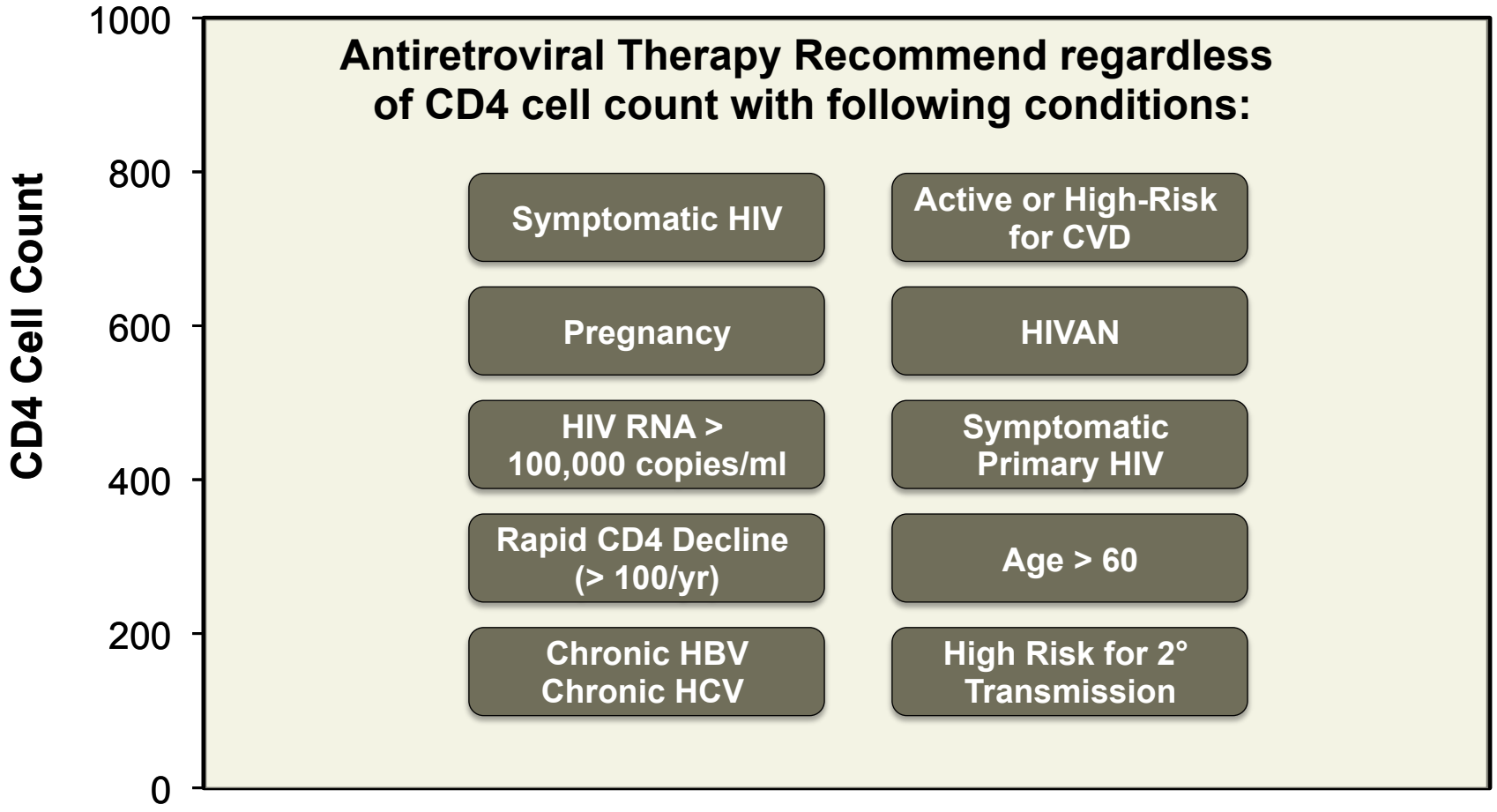
Source: Thompson MA, et al. JAMA. 2010;304:321-33.

IAS-USA Antiretroviral Therapy Guidelines: July 2010 Recommendations for Initiating Therapy in Treatment-Naive



Source: Thompson MA, et al. JAMA. 2010;304:321-33.

IAS-USA Antiretroviral Therapy Guidelines: July 2010 Recommendations for Initiating Therapy in Treatment-Naive



Source: Thompson MA, et al. JAMA. 2010;304:321-33.

IAS-USA Antiretroviral Therapy Guidelines: July 2010 Recommendations for Initiating Therapy in Treatment-Naive

2010 IAS-USA Recommendations: Initiating ARV Therapy in Treatment-Naive HIV-1 Infected Adults*		
Measure	**Antiretroviral Therapy Recommendation**	**Rating**
Specific Conditions		
Symptomatic HIV Disease	Antiretroviral Therapy Recommended Regardless of CD4 cell Count	AIa
Pregnant women		AIa
HIV-1 RNA > 100,000 copies/ml		AIIa
Rapid decline in CD4 count, > 100/µl per year		AIIa
Active HBV or HCV coinfection		BIIa, AIIa
Active or high risk for cardiovascular disease		BIIa
HIV-associated nephropathy		BIIa
Symptomatic primary HIV infection		BIIa
High risk for secondary HIV transmission		BIIa
Asymptomatic		
CD4 cell count < 350/µl	Recommended	AIa
CD4 count 350-500/µl	Recommended	AIIa
CD4 count >500/µl	Consider	CIII

Source: Thompson MA, et al. JAMA. 2010;304:321-33.

Mounting Evidence supporting Earlier HAART

Study	Type	Setting	Main Findings
CIPRA HT 001	RCT	Haiti	Deferring ART until CD4<200 associated with higher mortality than starting when CD4 between 200 and 350
SMART substudy	RCT	Europe, Australia	Deferring ART until CD4<250 associated with higher mortality than starting when CD4 between 350 and 250
ART-CC	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^3 compared to earlier treatment.
NA-ACCORD	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
HPTN 052	RCT	Africa, 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

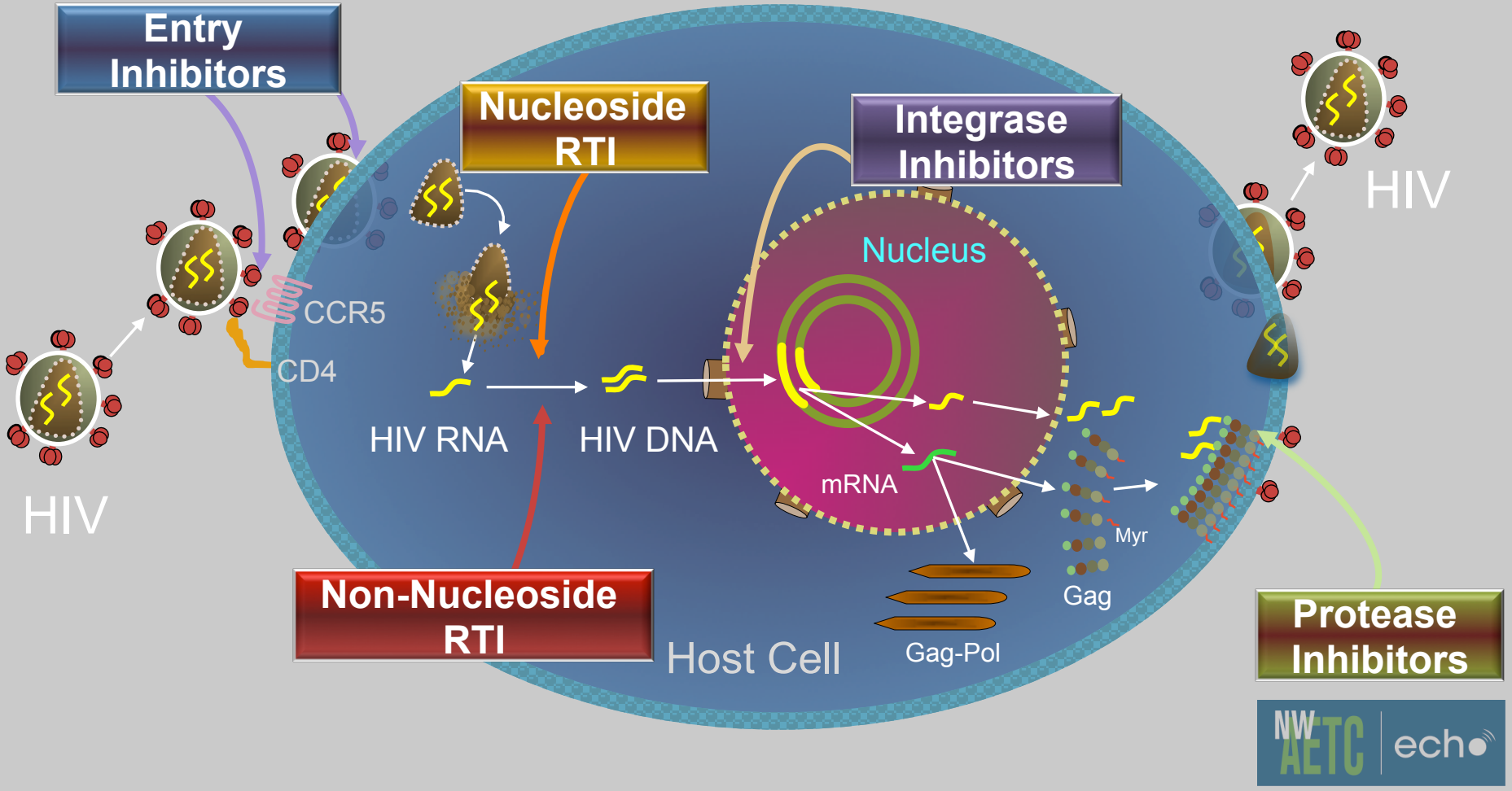
CID. 2009 Apr 15;48(8):1138-51; 16th CROI, 2009 Abs 72LB; JID 2008;197:1133–1144; NEJM 2009;360:1815

NW AETC | echo

What to Start

- Regimens for ART Naïve Patients
- New, Alternative, and Acceptable Agents

Anti-retroviral drug targets



Anti-retroviral Therapy in 2012

Entry Inhibitors

Enfuvirtide (ENV) Fuzeon®	 90 mg/ml	Administered dose: 90 mg/mL subcutaneously (SQ) 2 times a day (108 mg vial diluted with 1.1 mL sterile water) • Store at controlled room temperature
Maraviroc (MVC) Selzentry®	 150 mg 300 mg	1 x 300 mg tablet 2 times a day (With NRTIs, tipranavir/ritonavir, nevirapine, and weak CYP3A inhibitors or CYP3A inducers) 1 x 150 mg tablet 2 times a day (When given with strong CYP3A inhibitors with or without CYP3A inducers) 2 x 300 mg tablet 2 times a day (With CYP3A inducers including efa-

Combination NRTIs + NNRTI

Tenofovir + Emtricitibine + Efavirenz Atripla®	 TDF 300 mg/FTC 200 mg/ EFV 600 mg	1 tablet once daily at bedtime • Empty stomach recommended

Integrase Inhibitors

Raltegravir (RAL) Isentress®	 400 mg	1 tablet 2 times a day • May be taken with or without food

Combination NRTIs

Abacavir + Lamivudine Epzicom®	 ABC 600 mg/3TC 300 mg	1 tablet once daily • May be taken with or without food
Abacavir + Lamivudine + Zidovudine Trizivir®	 ABC 300 mg/3TC 150 mg/ AZT 300 mg	1 tablet 2 times a day • May be taken with or without food
Zidovudine + Lamivudine Combivir®	 AZT 300 mg/3TC 150 mg	1 tablet 2 times a day • May be taken with or without food
Tenofovir + Emtricitibine 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)

Abacavir (ABC) 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
Didanosine (ddI) Videx®	 250 mg 400 mg	1 x 400 mg capsule once daily • Reduce dose for weight < 60 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
Emtricitabine (FTC) Emtriva®	 200 mg	1 x 200 mg capsule once daily • May be taken with or without food	Headaches, fatigue, nausea
Lamivudine (3TC) 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
Stavudine (d4T) Zerit®	 30 mg 40 mg	1 x 40 mg capsule 2 times a day • Reduce dose for weight < 60 Kg 1 x 30 mg capsule 2 times a day • May be taken with or without food	Peripheral neuropathy, altered liver function
Tenofovir DF (TDF) Viread®	 300 mg	1 x 300 mg tablet once daily • May be taken with or without food	Renal insufficiency (rare), nausea, upset stomach
Zidovudine (ZDV, AZT) 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)

Delavirdine (DLV) Rescriptor®	 200 mg	2 x 200 mg tablets 3 times a day • May be taken with or without food	Rash, headache, altered liver function
Efavirenz (EFV) 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
Etravirine (ETR) Intelence®	 100 mg	2 x 100 mg tablet 2 times a day • Take with food	Nausea, headache, rash, Stevens-Johnson syndrome, hypersensitivity reaction, erythema
Nevirapine (NVP) 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)

Atazanavir (ATV) Reyataz®	 150 mg 200 mg 300 mg	2 x 200 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 light meal • Consult Reyataz prescribing information for use with antacids, H2-blockers and proton pump inhibitors.
Darunavir (DRV) 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 with food
Fosamprenavir (FPV) 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 capsules 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
Indinavir (IDV) Crixivan®	 400 mg	2 x 400 mg capsules 2 times a day with ritonavir 100-200 mg capsule(s) 2 times a day • Take with food • Drink at least 1.5 liters of fluid per day
Lopinavir/ Ritonavir (LPV/r) 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
Nelfinavir (NFV) 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 with food
Ritonavir (RTV) Norvir®	 100 mg	Ritonavir is primarily used in low doses to boost drug levels of other protease inhibitors • Keep refrigerated
Saquinavir (SQV) 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 with food
Tipranavir (TPV) 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 capsules 2 times a day • Take with food

Source: www.nwaetc.org

NW AETC | echo

DHHS Antiretroviral Therapy Guidelines: October 2011 Preferred Regimens for ARV-Naïve Patients

Backbone

(2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

+

Third Agent

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

or

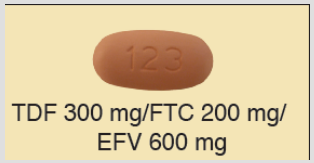
Protease Inhibitor (PI) (ritonavir-boosted)

or

Integrase Strand Transfer Inhibitor (INSTI)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

DHHS Antiretroviral Therapy Guidelines: October 2011
Preferred Regimens for ARV-Naïve Patients

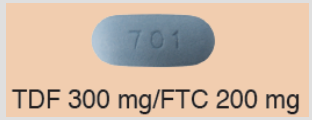


TDF 300 mg/FTC 200 mg/
EFV 600 mg

(2) Nucleoside RTI (NRTI)

+

Non-Nucleoside RTI (NNRTI)

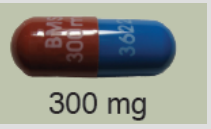


TDF 300 mg/FTC 200 mg

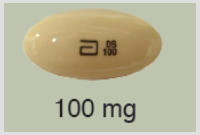
(2) Nucleoside RTI (NRTI)

+

Protease Inhibitor

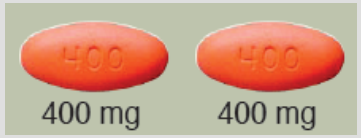


300 mg

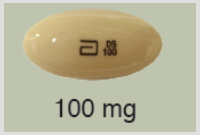


100 mg

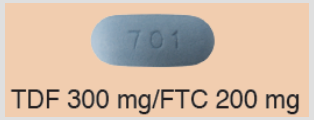
OR



400 mg 400 mg



100 mg



TDF 300 mg/FTC 200 mg

(2) Nucleoside RTI (NRTI)

+

Integrase Inhibitors

400 mg 400 mg

BID

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

DHHS Antiretroviral Therapy Guidelines: October 2011
Preferred Regimens for ARV-Naïve Patients

Class	Therapy
NNRTI-Based Regimen	Efavirenz-Tenofovir-Emtricitabine (**AI**)
PI-Based Regimen	Atazanavir + Ritonavir + Tenofovir-Emtricitabine (**AI**) Darunavir (qd) + Ritonavir + Tenofovir-Emtricitabine (**AI**)
INSTI-Based Regimen	Raltegravir + Tenofovir-Emtricitabine (**AI**)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

DHHS Antiretroviral Therapy Guidelines: October 2011
Alternative Regimens for ARV-Naïve Patients

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

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

DHHS Antiretroviral Therapy Guidelines: October 2011
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**)
	Darunavir + Ritonavir + Zidovudine-Lamivudine (**CIII**)
	Fosamprenavir + Ritonavir + Zidovudine-Lamivudine (**CI**)
	Lopinavir-Ritonavir + Zidovudine-Lamivudine (**CI**)
INSTI-Based	Raltegravir + Zidovudine-Lamivudine (**CIII**)
CCR5 Antagonist-Based	Maraviroc + Zidovudine-Lamivudine (**CI**)
	Maraviroc + Tenofovir-Emtricitabine (**CIII**)
	Maraviroc + Abacavir-Lamivudine (**CIII**)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

Special Populations

- Acute HIV Infection
- Pregnancy
- Opportunistic Infections
- Tuberculosis

ART in Special Populations: Acute HIV & Pregnancy

Acute HIV Infection

- Benefit unknown for treatment of acute HIV infection; treatment should be considered optional (**CIII**) *except in pregnant women* **(AI)**.
- A ritonavir (RTV)-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available (**AIII**).

Pregnancy

- Antiretroviral therapy (ART) is recommended for all pregnant women, regardless of CD4 count with the goal to prevent perinatal transmission **(AI)**
- The preferred regimen for pregnant women is Lopinavir/ritonavir (Kaletra) + Zidovudine/Lamivudine (Combivir) twice daily

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

ART in Special Populations: OI's & Tuberculosis

Opportunistic Infections

- In OI's with no effective therapy (Cryptosporidiosis, Microsporidiosis, PML). Initiate ART as soon as possible (**AIII**)
- In OI's with a high potential for IRIS (Cryptococcus, MAC). A short delay may be warranted before initiating ARV treatment (**CIII**)
- In OI's known to have better survival with early ART (*Pneumocystis* pneumonia). ART should not be delayed **(AI)**

Tuberculosis

CD4 Cell Count	Recommendations for TB Therapy and ART
All	Start TB therapy immediately (**AI**)
< 200 cells/mm^3	Initiate ART within 2-4 weeks of starting TB treatment (**AI**)
200-500 cells/mm^3	Initiate ART within 2-4 weeks, or at least by 8 weeks, after starting TB treatment (**AIII**)
> 500 cells/mm^3	Initiate ART within 8 weeks of starting TB treatment (**BIII**)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

Antiretroviral Therapy Guidelines - Summary

When to Start

- DHHS and IAS-USA Guidelines recommend starting ART at or below a CD4 count threshold of 500 cells/mm^3. Treatment above this level is considered optional.

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
- ART in the setting of Primary HIV and/or acute OI or TB is complex and evolving based on current evidence