HIV/AIDS: recenti acquisizioni in terapia antiretrovirale

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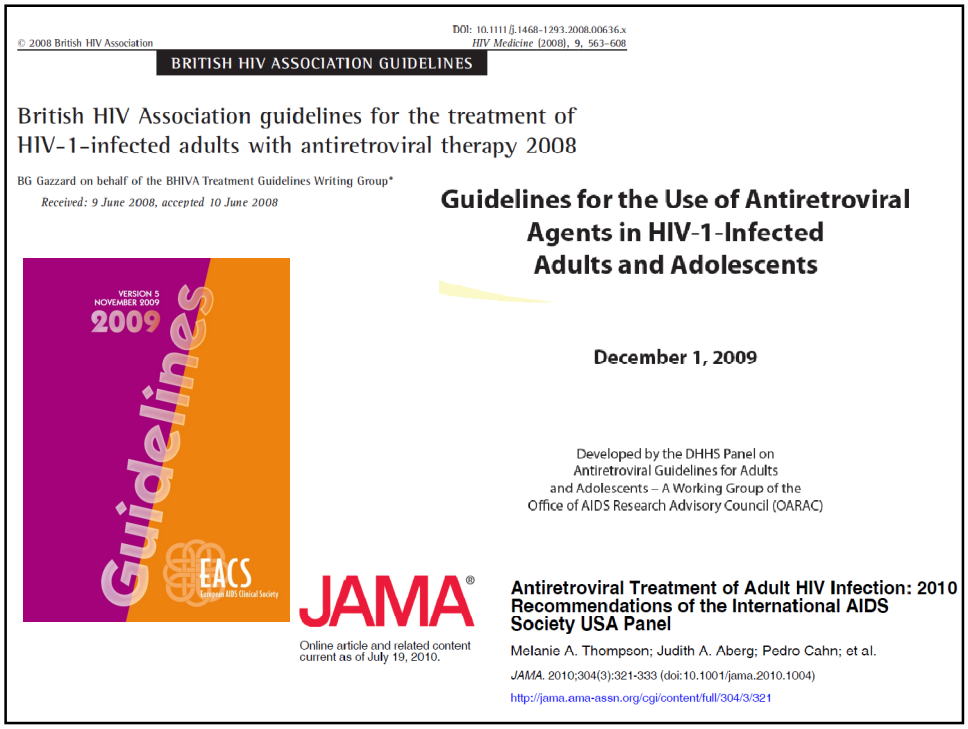


DOI: 10.1111/j.1468-1293.2008.00636.x
HIV Medicine (2008), 9, 563–608

BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008

BG Gazzard on behalf of the BHIVA Treatment Guidelines Writing Group*

Received: 9 June 2008, accepted 10 June 2008

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

December 1, 2009

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

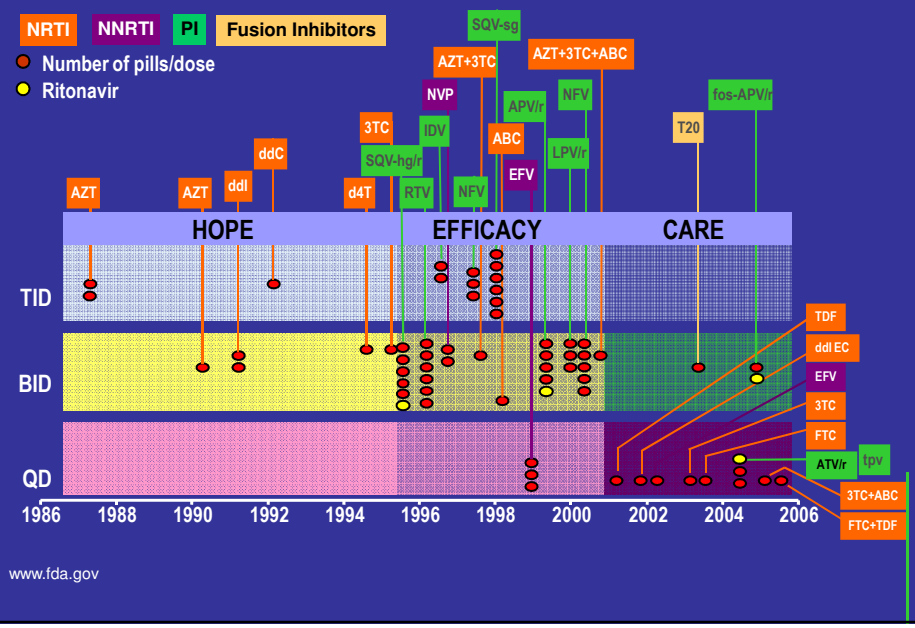
Antiretroviral Treatment of Adult HIV Infection: 2010 Recommendations of the International AIDS Society USA Panel

Melanie A. Thompson; Judith A. Aberg; Pedro Cahn; et al.

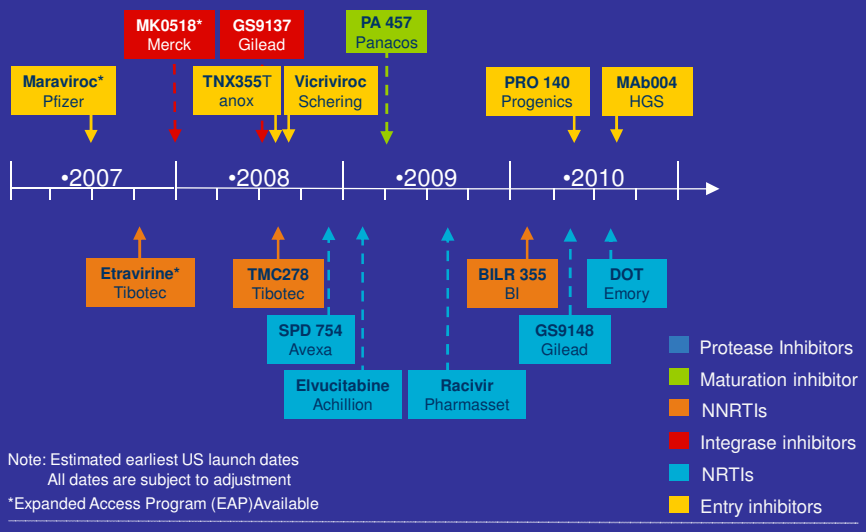
JAMA. 2010;304(3):321-333 (doi:10.1001/jama.2010.1004)
http://jama.ama-assn.org/cgi/content/full/304/3/321

Vancouver 1996…una cura è possibile!!

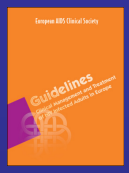
History of antiretroviral therapy



The ARV Pipeline: 2007–2010

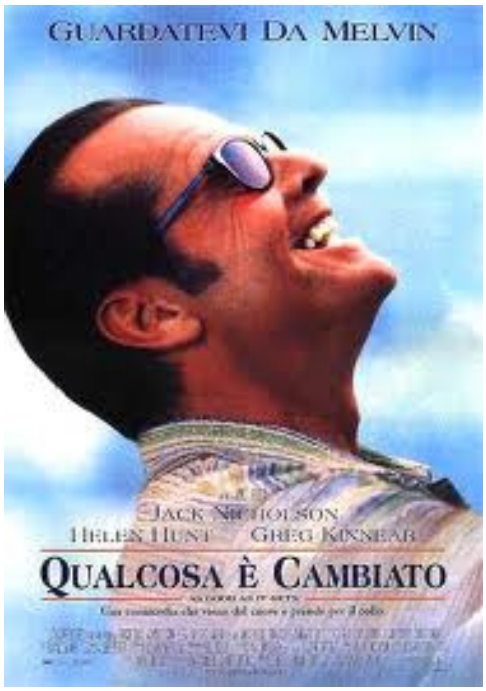


Note: Estimated earliest US launch dates
All dates are subject to adjustment
*Expanded Access Program (EAP)Available



The Guidelines : An evolving matter

- *When to start ?*
- *Which first line drugs ?*
- *When and How to switch ?*



Recommendations from guidelines today

Clinical Category	CD4 cells/mm^3	HIV RNA copies/mL	BHIVA[2]	DHHS 09[3]
AIDS-defining or symptoms	Any value	Any value	Treat	Treat
Asymptomatic	<200	Any value	Treat	Treat
Asymptomatic	200–350	Any value	Treat as soon as possible when patient ready	Offer treatment
Asymptomatic	350–500	Any value	Individual basis*	Offer treatment
Asymptomatic	>500	Any value	Consider enrolment into 'when to start' trial*	Panel were divided 50/50

http://www.sm.ee/fileadmin/meedia/Dokumendid/Tervisevaldkond/Tervishoid/Ravijuhis_HIV.pdf.
2. Gazzard B et al. HIV Medicine 2008; 9:563–608; 3. DHHS Guidelines 2008.
http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

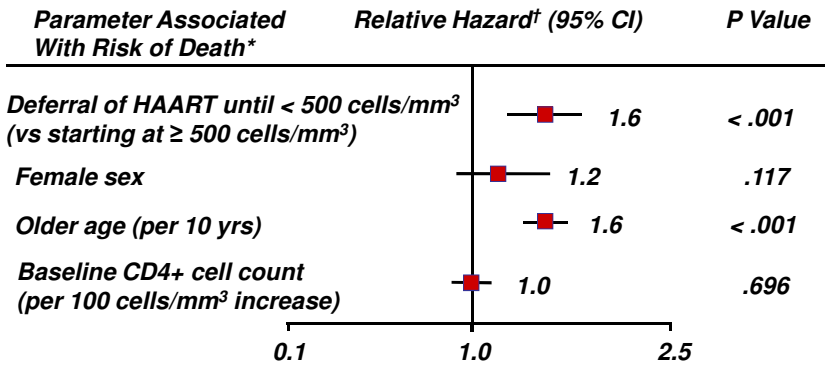
DHHS Guidelines 2010: When to Start

Asymptomatic Infection	Recommendation
• CD4+ cell count < 350 cells/mm^3	• Start HAART
• CD4+ cell count 350-500 cells/mm^3	• Start HAART
• CD4+ cell count > 500 cells/mm^3	• Panel divided
Clinical Conditions Favoring Initiation of Therapy Regardless of CD4+ Cell Count	
• History of AIDS-defining illness • Certain acute opportunistic infections • Pregnancy • HIVAN • HBV coinfection when HBV treatment is indicated • CD4+ count decline > 100 cells/mm^3/yr • HIV-1 RNA > 100,000 copies/mL • Serodiscordant relationships	

DHHS Guidelines. December 1, 2009.

START EARLIER – HOW DID WE GET THERE?

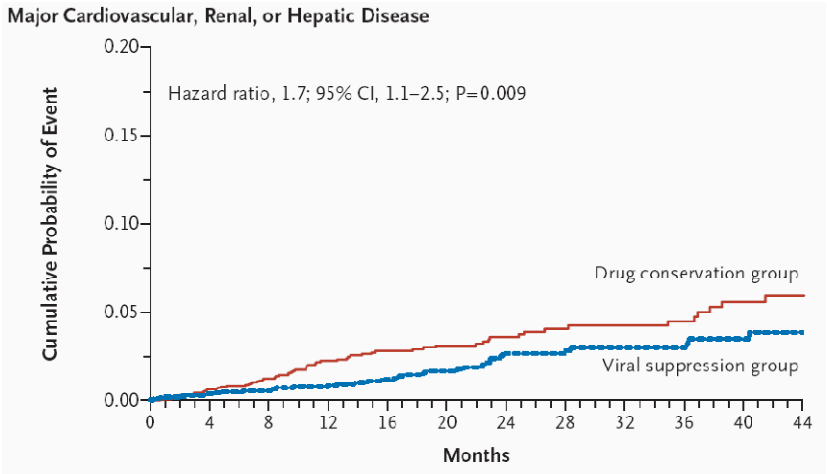
NA-ACCORD: Survival Benefit of Earlier HAART by Baseline Factor



*All causes of death unspecified. †Stratified by cohort and calendar year.

Kitahata MM, et al. CROI 2009. Abstract 71.

SMART Trial: Drug conservation vs viral suppression



SMART Study Group, NEJM 2006

SMART: Immediate Therapy Reduces Risk of OD, Serious Non-AIDS Events

- Immediate group experienced substantially fewer events compared with deferred group
  - Excess risk associated with deferring therapy: 5.4 events/100 person-yrs

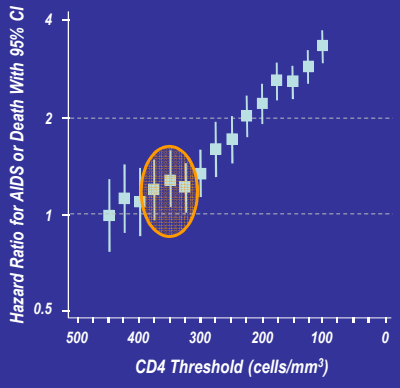
Event, n (Rate per 100 Person-Yrs)	Deferred Arm (n = 228)	Immediate Arm (n = 249)	HR (DC/VS)	95% CI	*P* Value
OD/death	15 (4.8)	5 (1.3)	3.5	1.3-9.6	.02
OD only	11 (3.5)	4 (1.1)	3.3	1.0-10.3	.04
Serious non-AIDS events	12 (3.9)	2 (0.5)	7.0	1.6-31.4	.01
Composite*	21 (7.0)	6 (1.6)	4.2	1.7-10.4	.002

*Fatal and nonfatal OD plus serious non-AIDS events.

Emery S, et al. J Infect Dis. 2008;197:1133-1144.

Data From Antiretroviral Therapy Cohort Collaboration (ART-CC)

Delaying ART to a CD4 count < 350 (but not < 375) cells/mm^3 is associated with an increased risk of AIDS or death



Comparison	Hazard Ratio (95% CI)*
276–375 vs 376–475	1.19 (0.96 to 1.47)
251–350 vs 351–450	1.28 (1.04 to 1.57)
226–325 vs 326–425	1.21 (1.01 to 1.46)

*Adjusted for lead times and unseen events

Sterne J, et al. Lancet. 2009;373:1352-1363.

Many non-AIDS events appear to be higher in HIV patients than controls

- Cardiovascular disease[1-4]
- Cancer (non-AIDS)
- Bone fractures/osteopenia [5,6]
- Left ventricular dysfunction
- Liver failure[7]
- Kidney failure
- Cognitive decline (controversial)[8]
- Frailty[9]

1. Klein D, et al. J Acquir Immune Defic Syndr. 2002;30:471-477. 2. Hsue P, et al. Circulation. 2004;109:316-319. 3. Mary-Kraus M, et al. AIDS. 2003;17:2479-2486. 4. Grinspoon SK, et al. Circulation. 2008;118:198-210. 5. Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504. 6. Arnsten JH, et al. AIDS. 2007 ;21:617-623. 7. Odden MC, et al. Arch Intern Med. 2007;167:2213-2219. 8. McCutchan JA, et a. AIDS. 2007 ;21:1109-1117. 9. Desquilbet L, et al. J Gerontol A Biol Sci Med Sci. 2007;62:1279-1286

Impact of Current CD4+ on Non-AIDS–Defining Cancer Risk

- Retrospective database analysis of 19,280 HIV-infected patients; 202,313 HIV-uninfected patients

Adjusted HR*	HIV Infected CD4+ Cell Count, cells/mm^3			
	< 200	201-499	≥ 500	*P* Value
Any infection related	12.8†	5.9†	3.2†	< .001
Anal	164.2†	83.1†	34.2†	< .001
Hodgkin's lymphoma	55.0†	11.0†	11.6†	< .001
Oral/pharyngeal	3.1†	1.9‡	0.8	.030
Any infection unrelated	1.8†	1.2	1.1	.002
Lung	2.1‡	1.0	1.2	.083
Colorectal	2.2‡	1.0	0.9	.050

*Adjusted for age, sex, smoking, overweight, alcohol/drug abuse, viral hepatitis; reference = uninfected cohort. †$P < .001$ relative to uninfected. ‡$P < .05$ relative to uninfected.

Silverberg M, et al. CROI 2010. Abstract 28. Table reproduced with permission.

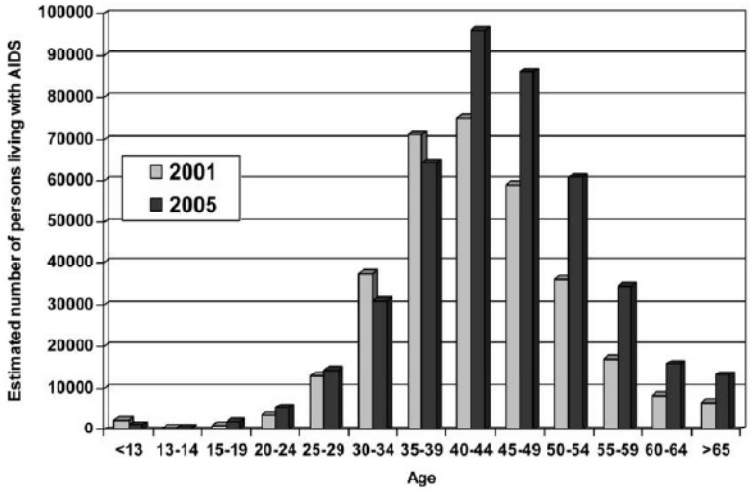
Potential Benefits of Early Therapy (CD4 count >500 cells/µL)

- Potential decrease in risk of many complications, including:
  - HIV-associated nephropathy
  - Liver diease progression from hepatitis B or hepatitis C
  - Cardiovascular disease
  - Malignancies (AIDS defining and non-AIDS defining)
  - Neurocognitive decline
  - Blunted immunological response due to ART initiation at older age
  - Persistent T-cell activation and inflammation
- Prevention of sexual and bloodborne transmission of HIV
  - Studies of heterosexual discordant couples observed no transmission in patients treated with ART and with viral load below 400 copies/mL, but data were compatible with one transmission per 79 person-years
- Prevention of mother-to-child transmission of HIV

Many non-AIDS events appear to be higher in HIV patients than controls

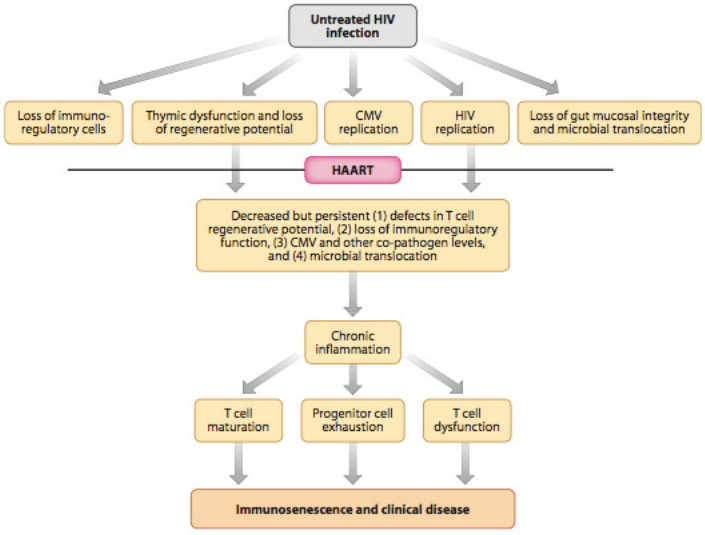
WHY IS THIS HAPPENING?

The age of the epidemic in the US is increasing

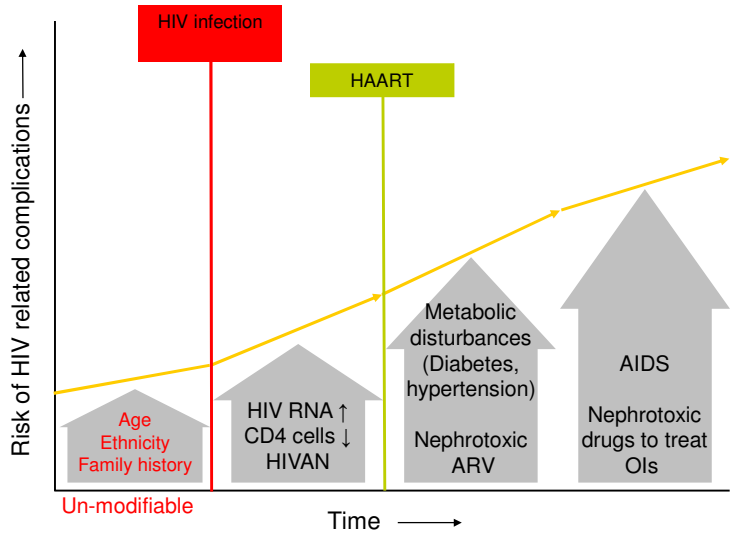


Effros RB, et al. Clin Infect Dis. 2008;47:542-553.

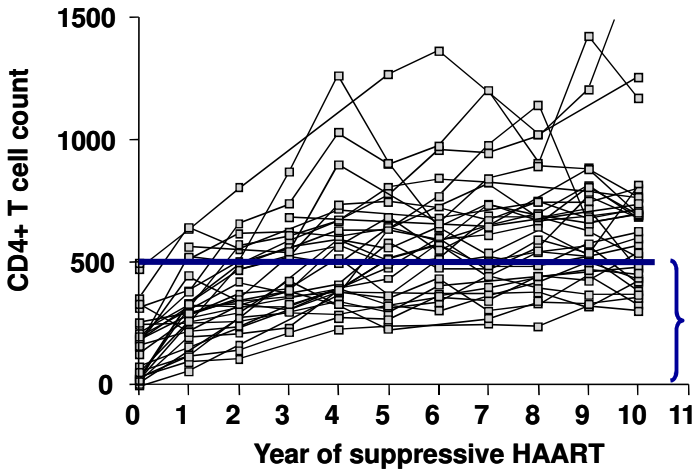
HIV infection and INFLAMMAGING



Hypothetical acquisition of risk of HIV-related dysfunsions

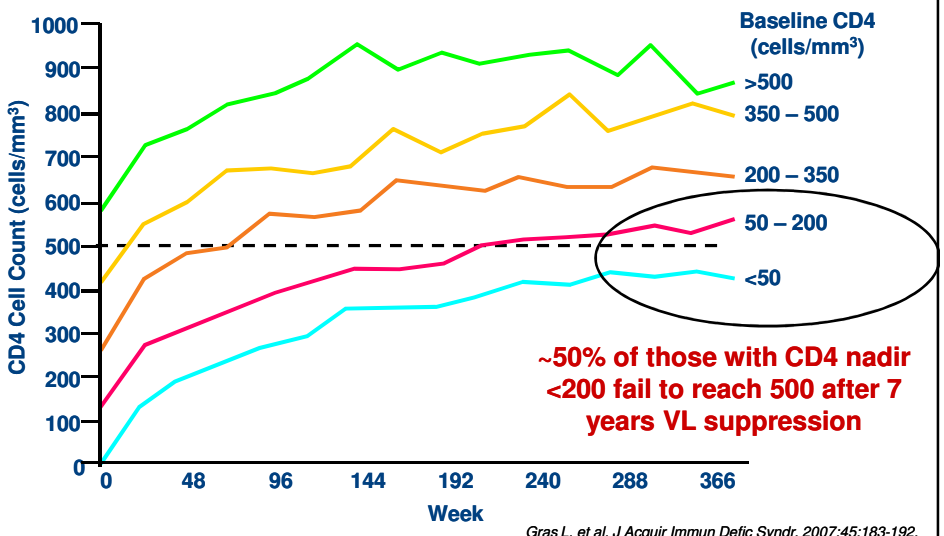


CNICS: ~ 40% of patients with a nadir CD4 < 200 fail to achieve a normal CD4+



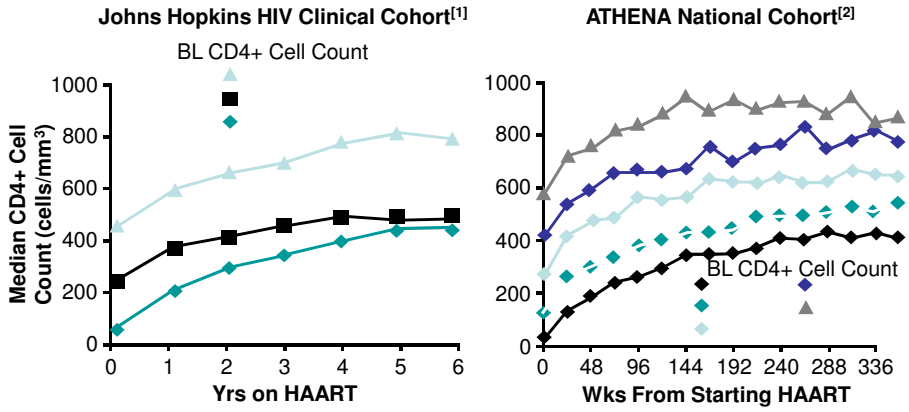
Kelley CF, et al. Clin Infect Dis 2009;48:787-794.

Suboptimal CD4 T Cell Gains Are Common Among Patients Who Initiate HAART Late



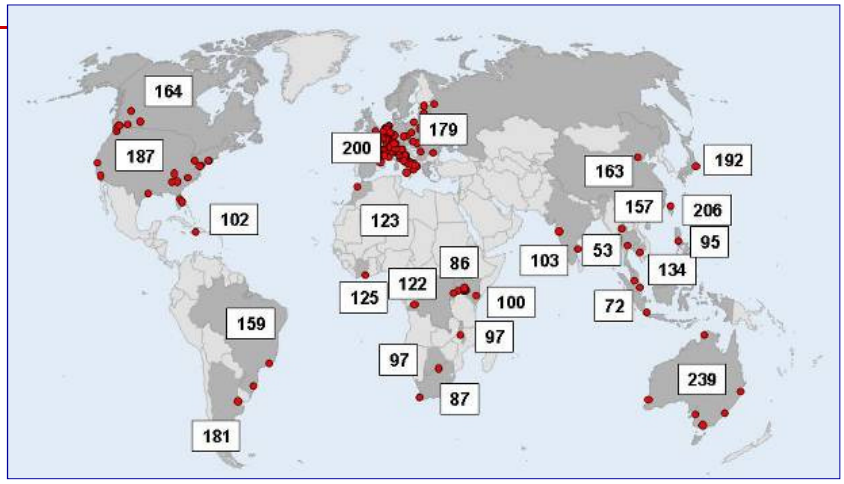
Gras L, et al. J Acquir Immun Defic Syndr. 2007;45:183-192.

Likelihood of Achieving Normal CD4+ Cell Count on ART Depends on BL Level



1. Moore RD, et al. Clin Infect Dis. 2007;44:441-446. Published by The University of Chicago Press. Copyright ©2009. University of Chicago Press. All rights reserved. http://www.journals.uchicago.edu/toc/cid/current.
2. Gras L, et al. J Acquir Immune Defic Syndr. 2007;45:183-192. Reproduced with permission.

CD4 count at start of HAART (2003-2005)

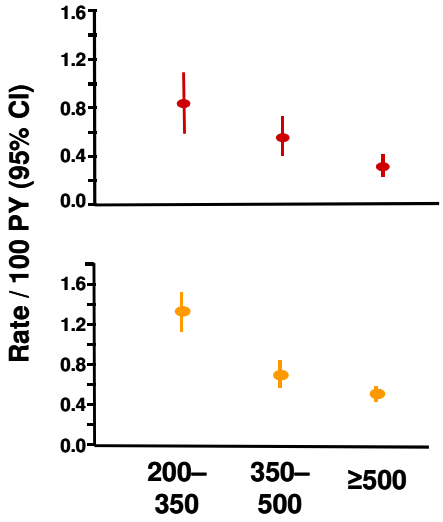


Since 2000, CD4+ cell count at initiation has increased in Sub-Saharan Africa from 50 to 100 cells/mm^3; in developed countries it has remained ~150–200 cells/mm^3

Egger M, et al. CROI 2007. Abstract 62.

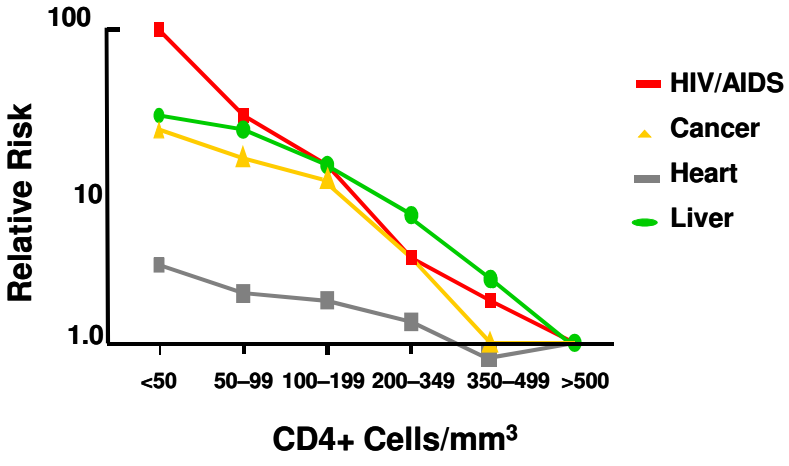
Hey Doc, …what about my life span?

Risk of death due to Non-AIDS causes is predicted by CD4 on therapy



Phillips A . CROI 2008. Abstract 8.

Low CD4 on therapy predicts risk of AIDS and more importantly of non-AIDS events



Weber R, et al. CROI 2005. Abstract 595.

HIV-patients do not have a normal life span, particularly those with a low CD4 nadir

	CD4 Nadir		
	< 100	100-200	>200
Life expectancy, years (at age 20)	32	42	50

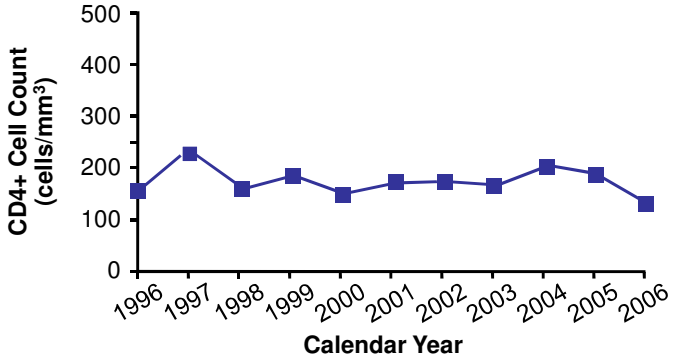
Depending on when HAART is started, life expectancy during modern HAART era is 10 to 30 years less than that in uninfected patients

ART-Cohort Collaboration. Lancet. 2008;372:293-299

Earlier Treatment Initiation Requires Earlier Diagnosis

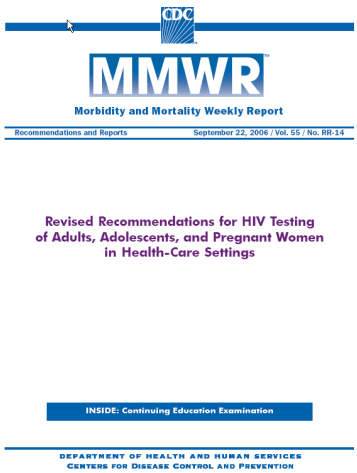
The Problem of Late Diagnosis

- CD4+ cell counts typically low among treatment-naive patients first presenting for HIV care



Moore RD, et al. CROI 2008. Abstract 805. Graphic reproduced with permission.

September 22, 2006, Recommendations From CDC: Routine Testing for HIV-1

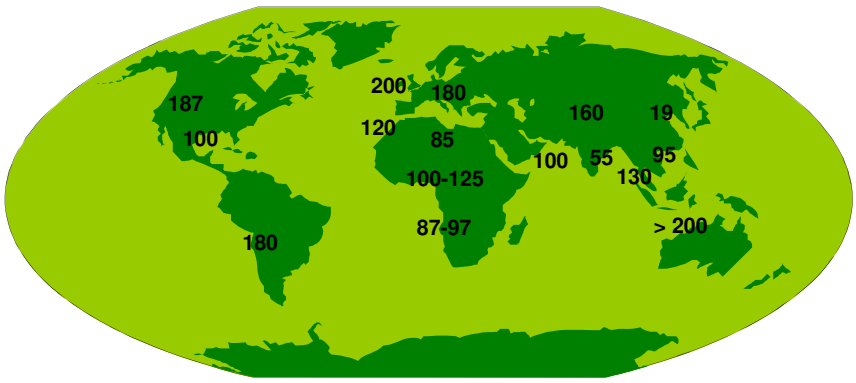


- Routine voluntary testing for patients aged 13-64 yrs in healthcare settings—not based on patient risk
- Opt-out testing
- No separate consent for HIV
- Pretest counseling not required
- Repeat HIV testing at discretion of provider, based on patient risk

Branson BM, et al. MMWR Recomm Rep. 2006;55(RR-14):1-17.

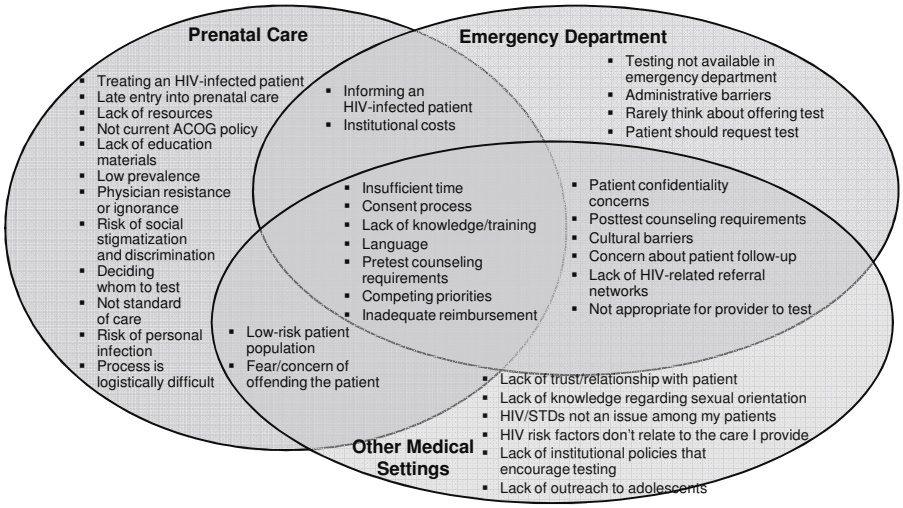
When Is Antiretroviral Therapy Started?

- Review of data from 2003-2005 from 176 sites in 42 countries
- Since 2000, CD4+ cell count at initiation in developed countries stable at approximately 150-200 cells/mm^3, increasing in sub-Saharan Africa from 50-100 cells/mm^3



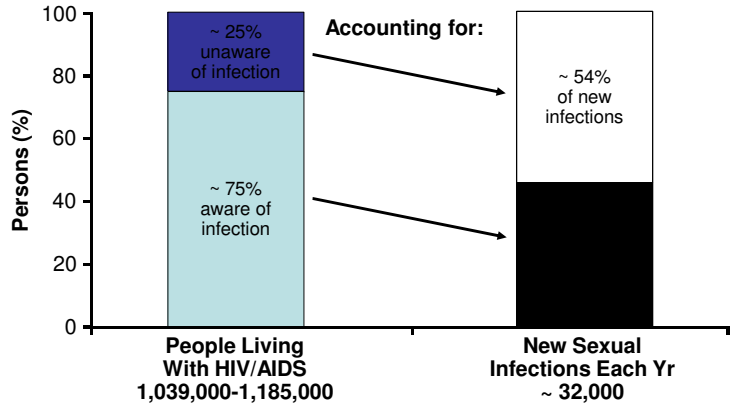
Egger M, et al. CROI 2007. Abstract 62.

Barriers to HIV Testing Cited by US Physicians



Burke RC, et al. AIDS. 2007;21(12):1617-1624. Why don't physicians test for HIV? A review of the US literature.

Scope of the Problem: Burden of HIV Infection in the United States



Marks G, et al. AIDS. 2006;20:1447-1450.
Campsmith ML, et al. J Acquir Immune Defic Syndr. 2010;53:619-624.

San Francisco Chronicle

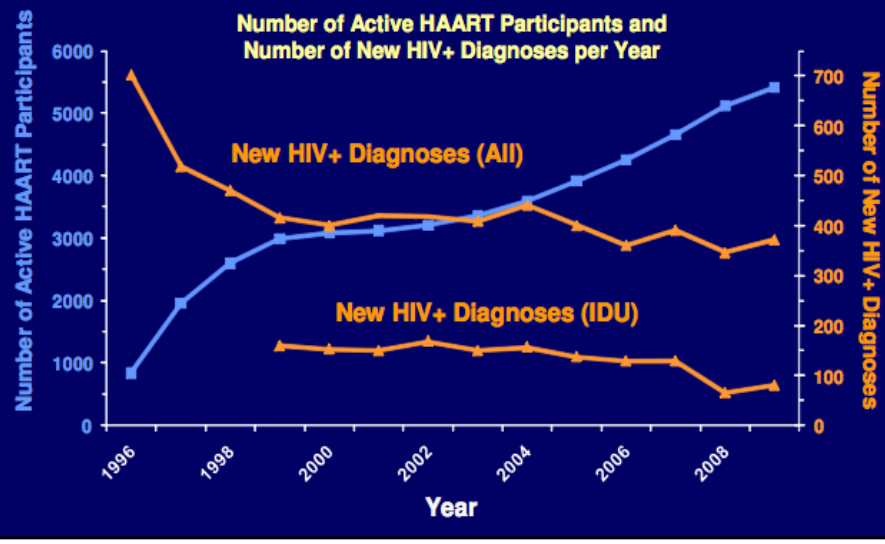
NORTHERN CALIFORNIA'S LARGEST NEWSPAPER

May 9, 2007

"Treatment is not going to stop this epidemic. In 2005, there were six new infections for every person put into treatment. That is not sustainable. That means we are losing the battle."

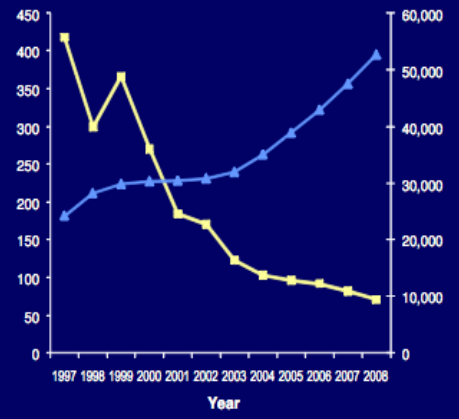
--Dr. Peter Piot, UNAIDS Executive Director

Montaner British Columbia Study
Number of Active HAART Participants & Number of New HIV+ Diagnoses, by Year

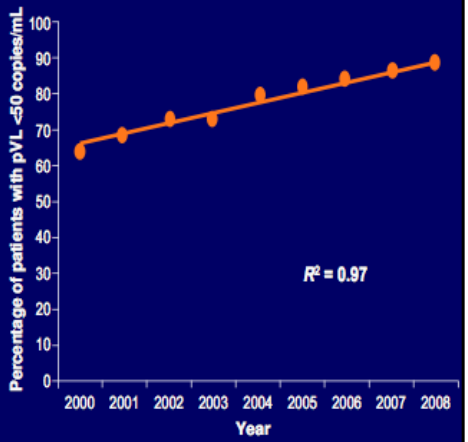


Montaner British Columbia Study
Improved Virologic Outcomes in British Columbia, Concomitant with Decreasing Incidence of Drug Resistance

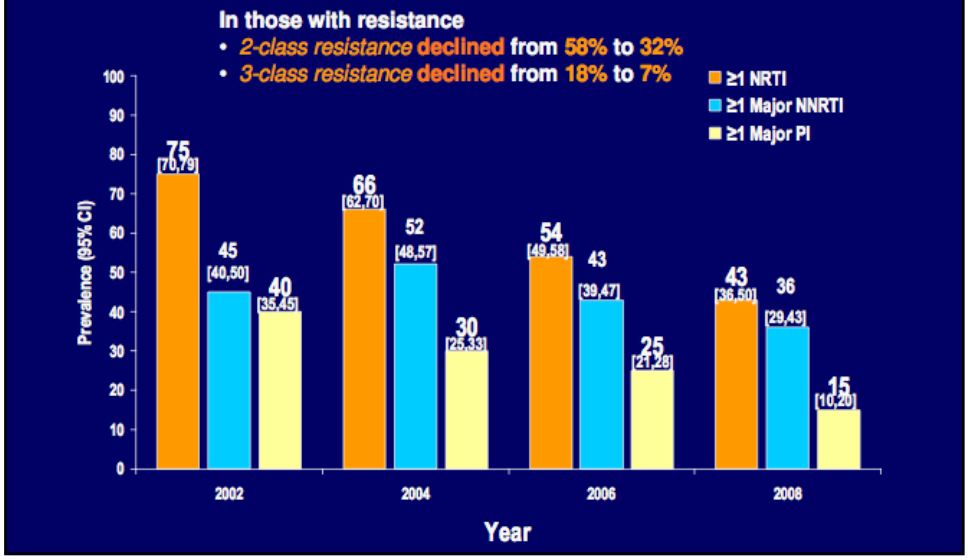
Decreasing resistance despite increased ARV exposure in BC, 1997-2008



Increasing proportion of VL levels <50 c/mL in BC, 2000-2008

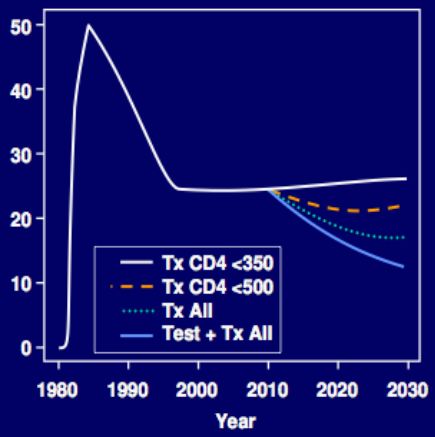


CNICS
Decreasing Prevalence of Resistance Mutations at Failure, by ARV Class over a 7-Year Period



San Francisco: Predicted HIV Prevalence and Percent Reduction in New HIV Infections Among MSM, by Specific Test & Treat Strategy

Predicted HIV Prevalence by ART Strategy



Reduction in New HIV Infections, %

	Tx <500	Tx All	Test & Tx All
2014	42%*	59%	76%
2029	33%*	55%	81%

*Implementing the current DHHS Guidelines of treating patients with CD4 <500 is predicted to result in 1,554 less HIV infections in five years and 4,940 less over 20 years.

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Giovanni Fioni

Benefits and Risks of Earlier Initiation of Antiretroviral Therapy

Immunoreconstitution

Why do T cells remain low despite effective HAART?

Mechanisms associated to the persistence of low CD4+ cell count levels

- Residual HIV replication
- Persistent high level T cell activation even during HAART
- Accellerated turnover and immunologic exhaustion
- T cell dysfunction, proliferation defects, loss of thymus
- High prevalence and burnen of other co-infections
- Persistent microbial translocation

HIV, Cancer, and Predictive Factors FHDH-ANRS CO4 Study

Cancer	Predictive Factors
Hodgkin's lymphoma; lung and liver cancer	**Current CD4 cell count**
Kaposi's sarcoma; non-Hodgkin's lymphoma	**Current CD4 cell count,** current VL, and absence of cART
Cervical cancer	**Current CD4 cell count** and absence of cART
Anal cancer	**Time to CD4 count < 200 cells/µL** and VL > 5 $\log_{10}$ copies/mL

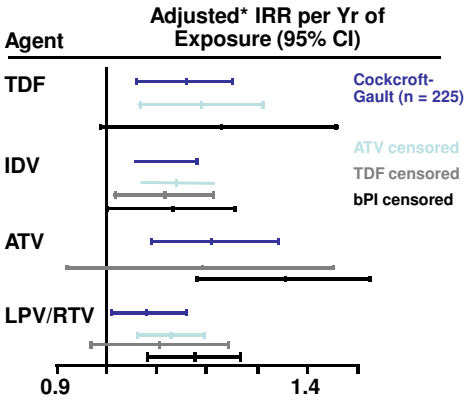
Guiguet M, et al. Lancet Oncol. 2009 October 7;.

Potential Patient Risks of Earlier Antiretroviral Therapy Initiation

- Potential for poor adherence leading to drug resistance in patients who are not psychologically ready to begin therapy
- Potentially reduced quality of life resulting from adverse events associated with antiretroviral therapy
- Potential adverse effects of prolonged antiretroviral exposure
  - eg, peripheral neuropathy, renal complications, lipoatrophy, dyslipidemia, insulin resistance, anemia, BMD loss
- Increased monetary costs from longer overall treatment duration
  - Drug costs/copays
  - Follow-up monitoring expenses/copays

Cumulative ARV Exposure and Risk of Chronic Kidney Disease in EuroSIDA

- 6843 HIV-infected pts with ≥ 3 serum creatinine measures and corresponding body weight measures from EuroSIDA study
  - 21,482 pt-yrs follow-up
- Cumulative exposure to TDF, ATV, LPV/RTV, or IDV each associated with increased risk of CKD
- Risk of CKD after stopping TDF remained elevated for 1 yr
  - Within 12 mos: IRR 4.05 (2.51-6.53)
  - After 12 mos: IRR 1.12 (0.63-1.99)
- Risk of CKD after stopping ATV or LPV/RTV similar to pts never exposed



Kirk O, et al. CROI 2010. Abstract 107LB. Permission received by CCO for use of this graphic.

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- High prevalence and burnen of other co-infections
- Persistent microbial translocation

Immunopathogenesis of immunoactivation

Virus Induced

- Residual HIV replication in reservoirs
- Residual HIV replication in latent infected cells
- Low level viremia

Microbial Translocation Induced

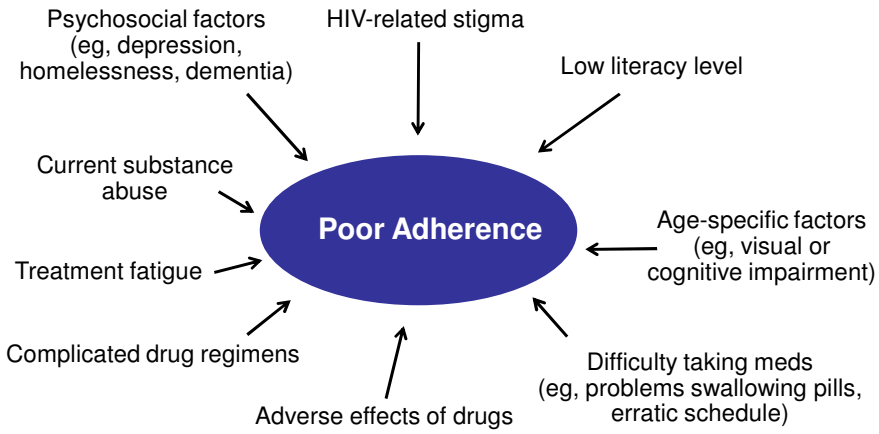
- GALT CD4+CCR5+ T cell depletion
- Damage and impairement of Mucosal Immunity
- Persistent microbial translocation

Conditions Favoring Delay of Therapy

- Significant barriers to adherence
- Presence of comorbidities that complicate or prohibit antiretroviral therapy (eg, scheduled surgery that might force treatment interruption or other medications that may have interactions with antiretroviral medications)
- Elite controllers or long-term nonprogressors
- ***Delay of antiretroviral initiation suggested only for patients with higher CD4+ cell counts***

DHHS. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.

Factors Associated With Poor Adherence



DHHS. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.

Factors Other Than CD4+ Cell Count to Consider When Initiating Antiretroviral Therapy Initiation

Factors Relevant to Regimen Selection

- Baseline HIV-1 RNA level
- Comorbid conditions (CV disease, chemical dependency, liver disease, psychiatric disease, renal diseases, TB)
- Potential adverse drug effects
- Potential drug interactions with other medications
- Pregnancy or pregnancy potential
- Results of genotypic resistance testing
- Patient sex and pretreatment CD4+ cell count if considering nevirapine
- HLA-B*5701 testing if considering abacavir
- Coreceptor tropism assay if considering maraviroc
- Patient adherence potential
- Convenience (pill burden, dosing frequency, and food and fluid considerations)

Patient Factors/Comorbidities That Impact Timing of Antiretroviral Therapy

- Certain conditions favoring initiation regardless of CD4+ cell count
  - History of AIDS-defining illness
  - Certain acute opportunistic infections
  - Pregnancy
  - HIV-associated nephropathy
  - HBV coinfection when HBV treatment is indicated
  - CD4+ cell count decline > 100 cells/mm3 per yr
  - HIV-1 RNA > 100,000 copies/mL
- Other potential reasons for starting therapy earlier
  - Decreased rates of transmission in serodiscordant couples
  - Decrease in new HIV diagnoses within the community

DHHS. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.

Additional Factors to Consider

- Patient age
- Patient readiness
- Likelihood of treatment adherence
- Potential impact of antiretrovirals on patient quality of life
- Additional comorbidities that could impact success of therapy including depression
- Concurrent drugs not compatible with antiretroviral agents
- Long-term nonprogressors or elite controllers

DHHS. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.