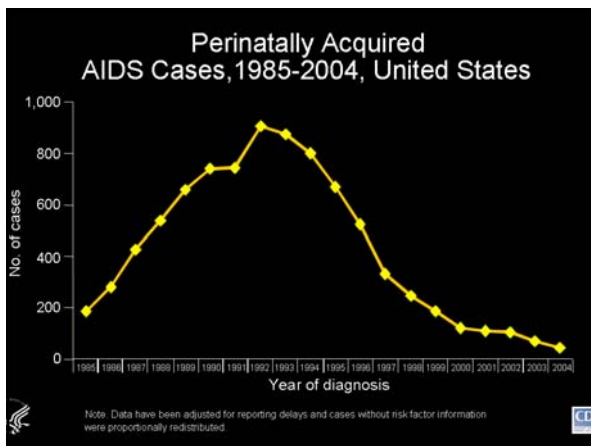
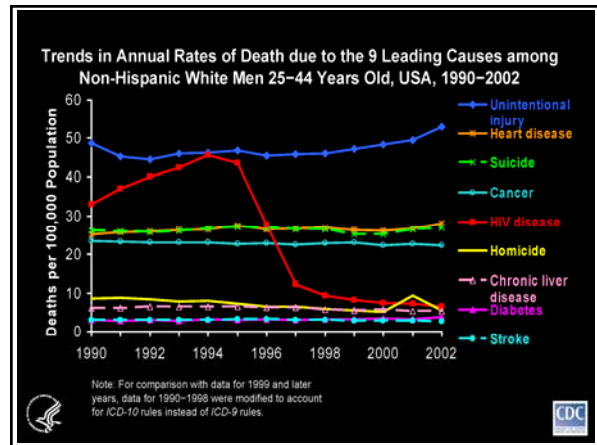
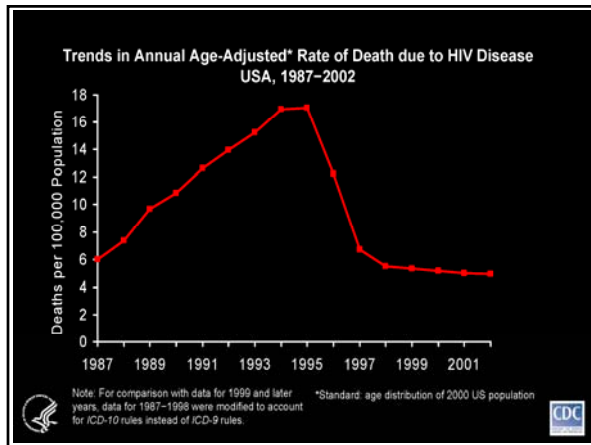


HIV Management What Remains?

Paul Volberding, MD
UCSF

Fine Tuning and Unfinished Business

- Remember how far we've come



HIV/AIDS Care Has Saved 3 Million Life Years in the US

The Survival Benefits of AIDS Treatment in the United States

Richard P. Wainwright, A. David Paltiel, Ellen Laine, Laura M. Merino-Cabrera, Bruce R. Schackman, Paul E. Sax, Milton C. Weinstein, and Kenneth A. Freedberg

Division of Infectious Diseases and General Medicine, Department of Medicine, Massachusetts General Hospital, and Center for AIDS Research, Harvard Medical School, and Department of Health Policy and Management, Harvard School of Public Health, Department of Biostatistics and Epidemiology, Boston University School of Public Health, and Division of Infectious Diseases, Brigham and Women's Hospital, Boston; Division of Health Policy and Administration, Yale School of Medicine, New Haven, Connecticut; Department of Public Health, Yale Medical College of Connecticut, New Haven, Connecticut.

See the editorial commentary by Vernon on pages 1-6.

Background: As widespread adoption of potent combination antiretroviral therapy (ART) reaches its third year, our objective was to quantify the cumulative survival benefits of acquired immunodeficiency syndrome (AIDS) care in the United States.

Methods: We defined care corresponding to advances in standards of human immunodeficiency virus (HIV) disease care, including opportunistic infection prophylaxis, treatment with ART, and the prevention of mother-to-child transmission (PMTCT) of HIV. For person survival benefits for each era were determined using a multi-structural simulation model. Published estimates provided the number of adult patients with new diagnosis of AIDS who were receiving care in the United States from 1989 to 2005.

Results: Compared with survival associated with untreated HIV disease, per-person survival increased 6.26 years with zidovudine versus zalcitabine prophylaxis alone. Four years of increasingly effective ART in addition to prophylaxis resulted in per-person survival increases of 7.61, 10.06, 11.17, and 11.19 years, compared with the absence of treatment. Treatment for patients with AIDS in care in the United States since 1989 yielded a total survival benefit of 2.8 million years (95%CI 2.6 million to 3.0 million), equivalent to 117,000 additional years of survival benefit.

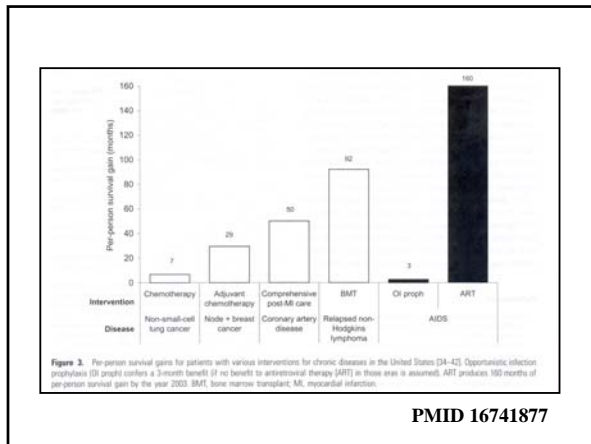
Conclusions: At least 1.8 million years of life have been saved in the United States as a direct result of care of patients with AIDS, highlighting the significant advances made in HIV disease treatment.

Substantially more life years saved than other accepted therapies of chronic illnesses

91% of AIDS cases in 2000-2002 survived to next "treatment era"

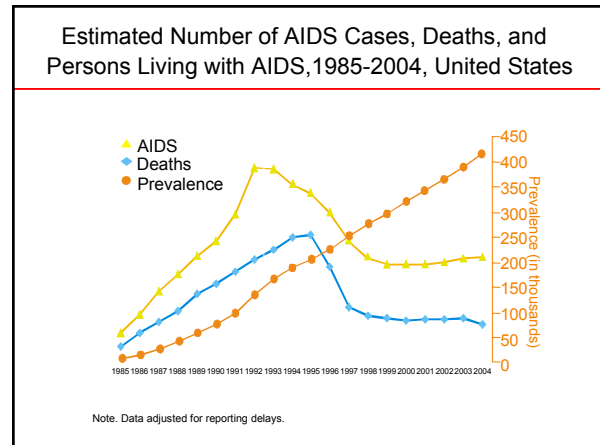
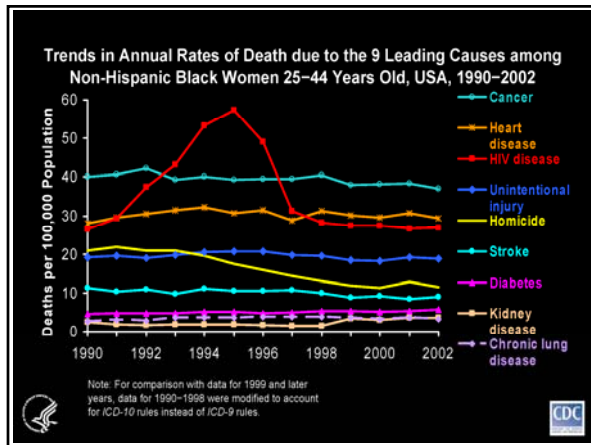
ARV averted 2900 HIV infected infants

PMID 16741877



Fine Tuning and Unfinished Business

- Remember how far we've come
- Without forgetting those left behind



Why Can't We All Get Along?

- We can still have a good argument:
 - When to start?
 - What to use first?
- But the fact that we argue itself suggests something
 - HIV therapy used “too early” is probably not that bad
 - Even when used “late” therapy has striking benefits
- Some regimens may be better than others
- But the range of difference is so slight that proof is very difficult

What Might We Do Tonight?

- Ask what questions in HIV care are still open
- Consider research approaches
- Speculate on where all this might take us
- Summarize research areas of concentration
- Predict the future (!)

When Should Antiretroviral Therapy Be Initiated?

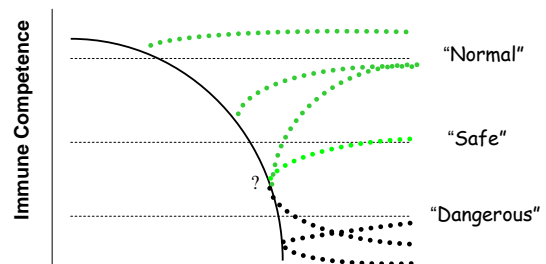
Probably the Hottest Question of the Moment

- Framing the issue:
 - Starting at optimal time maximizes clinical benefit while controlling cost and toxicity
 - Those least impressed by benefits and most concerned about costs/risks biased to delay
 - Those impressed by benefits and discount downsides biased to initiate
 - “Proving” best approach through prospective randomized trial really hard and expensive
 - “Supporting” best approach by cohorts inexpensive and essentially done
 - Those with support for clinical trial or cohort have predictable preference
 - Pharmaceuticals mostly on the sidelines but obviously lean to early initiation

When to Start HIV Therapy? Why Are Trials Hard?

- Outcome of therapy started late very good at least in mid-term
- Small expected differences require very large, very long period of study
- Most potential subjects either:
 - Already in care
 - Don't want care
 - Are not ideal trial subjects
 - May not be representative of “typical” chronic infection
- Treatment paradigm may well change during trial (integrase as first line?) making results suspect
- Treatment guidelines may anticipate “answer” and make trial impossible/unethical

Immune Recovery With Potent Antiretroviral Therapy

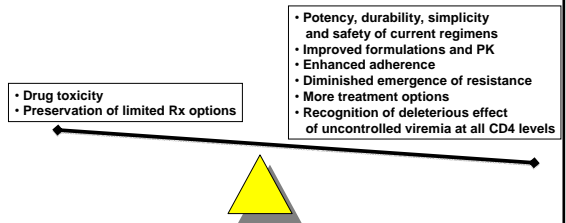


Rationale for Initiation of Therapy Before CD4 Cell Counts Fall to 350/ μ L

- Uncontrolled HIV replication and resultant immune activation associated with 'non-AIDS' illnesses
 - Cardiovascular
 - Hepatic
 - Renal
 - Malignancies
- Patients with CD4 counts >350/ μ L and HIV-1 RNA levels >400 copies/mL have greater morbidity and mortality than those with viral suppression
 - Definition of HIV-related disease progression should be revisited
- Potential for decreased horizontal HIV-1 transmission

IAS USA 2008

When to Start Therapy: Balance Tipping in Favor of Earlier Initiation



IAS USA 2008

When to Start Antiretroviral Therapy

Measure	Recommendation	Comments
Symptomatic HIV disease	Therapy recommended	
Asymptomatic HIV disease		
CD4 <350/ μ L	Therapy recommended	Recommendation strengthened since 2006
CD4 \geq 350/ μ L	Therapy should be considered and decision individualized	<p><u>Correlates of faster HIV disease progression:</u></p> <ul style="list-style-type: none"> • High viral load (>100,000 RNA copies/mL) • Rapidly declining CD4 (>100/μL per year) <p><u>Coexistent conditions influenced by uncontrolled viremia:</u></p> <ul style="list-style-type: none"> • Presence of, or high risk for, cardiovascular disease • Active HBV or HCV coinfection • HIV-associated nephropathy

IAS-USA 2008

Examples →

When to Start ART

- Potent ART may improve and preserve immune function in most patients with virologic suppression, regardless of baseline CD4 count
 - ART indicated for all with low CD4 count or symptoms
 - Earlier ART may result in better immunologic responses and better clinical outcomes
 - Recommended ARV combinations are considered to be durable and tolerable
 - Exact CD4 count at which to initiate therapy not known, but evidence points to starting at higher counts
 - Current recommendation: ART for all patients with CD4 count of <350 cells/ μ L, certain others regardless of count

DHHS 2008

Potential Benefits of Early Therapy (CD4 count >350 cells/ μ L)

- Maintain higher CD4 count; prevent irreversible immune system damage
- Decrease risk of HIV-associated complications
 - eg, TB, NHL, KS, peripheral neuropathy, HPV-associated malignancies, HIV-associated cognitive impairment
- Decrease risk of nonopportunistic conditions and non-AIDS-associated conditions
 - eg, CV, renal, and liver disease; malignancies; infections
- Decrease risk of HIV transmission

DHHS 2008

Potential Risks of Early Therapy (2) (CD4 count >350 cells/ μ L)

- ARV-related side effects and toxicities
- Drug resistance (attributable to ART failure)
- Inadequate time to learn about HIV, treatment, and adherence
- Increase in total time on ART; greater chance of treatment fatigue
- Current ART may be less effective or more toxic than future therapies
- Transmission of ARV-resistant virus, if incomplete virologic suppression

DHHS 2008

Indications for Initiating ART: Chronic Infection

Clinical Category or CD4 Count	Recommendation
<ul style="list-style-type: none"> • History of AIDS-defining illness • CD4 count <350 cells/μL • Pregnant women • HIV-associated nephropathy • Hepatitis B coinfection, when HBV treatment is indicated* 	Initiate ART

* Treatment with fully suppressive drugs active against both HIV and HBV is recommended.

DHHS 2008

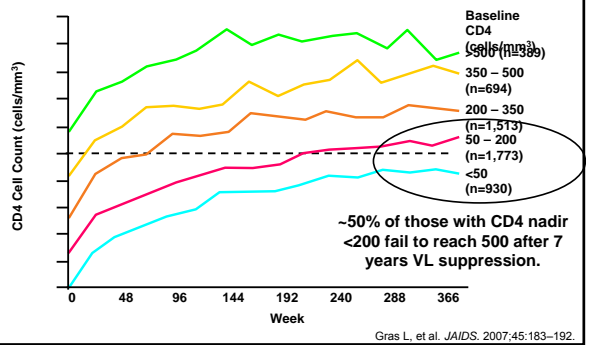
Indications for Initiating ART: Chronic Infection (2)

Clinical Category or CD4 Count	Recommendation
CD4 count of >350 cells/ μ L, asymptomatic, without conditions listed above	Optimal time to initiate ART is not well defined. Consider individual patient characteristics and comorbidities.

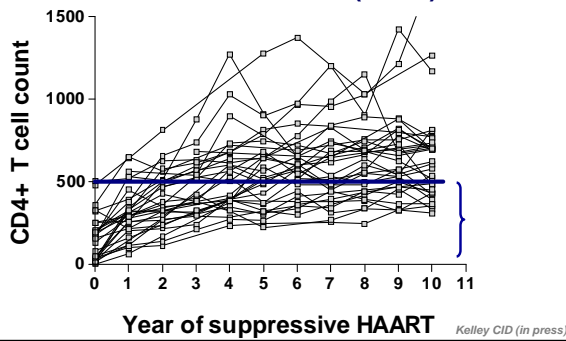
DHHS 2008

Outcome of ARV Therapy Better When Started at an Earlier Disease Stage as Measured by Baseline CD4

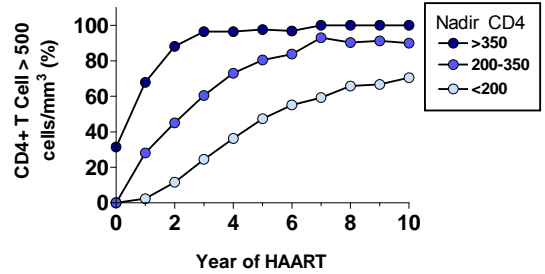
Suboptimal CD4 T Cell Gains are Common Among Patients who Initiate HAART Late (ATHENA)



SCOPE: Even after 10 years of fully suppressive HAART, many patients fail to obtain normal CD4 (n= 32)



CNICS: ~ 40% of patients with a nadir CD4 < 200 fail to achieve a normal CD4+ cell count, even after 10 years of viral suppression (n=300)



The NA-Accord Bombshell

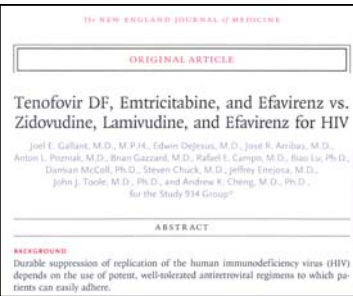
- Combined cohort collection from US and Canada
- 8,400 started ARV with CD4 351-500 (median CD4=432)
- 16,600 started later (median CD4=275)
- Mortality increased by 70% in delayed ARV group although absolute difference small.

What Drugs Should Be Included in Initial Regimen?

Current ARV Medications

<p>NRTI</p> <ul style="list-style-type: none"> • Abacavir (ABC) • Didanosine (ddI) • Emtricitabine (FTC) • Lamivudine (3TC) • Stavudine (d4T) • Tenofovir (TDF) • Zidovudine (AZT, ZDV) <p>NNRTI</p> <ul style="list-style-type: none"> • Efavirenz (EFV) • Etravirine (ETR) • Nevirapine (NVP) 	<p>PI</p> <ul style="list-style-type: none"> • Atazanavir (ATV) • Darunavir (DRV) • Fosamprenavir (FPV) • Indinavir (IDV) • Lopinavir (LPV) • Nelfinavir (NFV) • Ritonavir (RTV) • Saquinavir (SQV) • Tipranavir (TPV) 	<p>Fusion Inhibitor</p> <ul style="list-style-type: none"> • Enfuvirtide (ENF, T-20) <p>CCR5 Antagonist</p> <ul style="list-style-type: none"> • Maraviroc (MVC) <p>Integrase Inhibitor</p> <ul style="list-style-type: none"> • Raltegravir (RAL)
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No Surprise: Simple, Potent Regimens Raising the Bar For Newer Drugs



PMID 16421366

(I criticized the release of preliminary 24 week trial data in 2004 What's Hot)

48 week final data show non-inferiority to prior standard regimen and superior viral suppression

International AIDS Society – USA Guidelines: Update Highlights

When to Start	<ul style="list-style-type: none"> • Recommendation strengthened to start before CD4 falls below 350/μL in asymptomatic persons • Strong consideration of treatment at CD4 counts higher than 350/μL (with no upper threshold) in a number of circumstances
Options for Initial Therapy	<ul style="list-style-type: none"> • EFV or PI/r plus TDF/FTC or ABC/3TC in persons with drug susceptible virus
Patient Monitoring	<ul style="list-style-type: none"> • HLA-B*5701 screening when ABC being considered • Viral tropism when MVC being considered
When to Change	<ul style="list-style-type: none"> • Intolerance, toxicity or failure
What to Change	<ul style="list-style-type: none"> • Options improved to achieve goal of HIV-1 RNA level <50 copies/mL even in highly treatment-experienced patients with MDR virus • Approval of RAL, MVC, ETV in past 2 yrs

2008

Choice of Initial Regimen (cont'd)

Component	Recommended Drugs	Comments
NNRTI component	efavirenz	EFV: teratogenic in 1 st trimester NVP (alternative): increased risk of hepatotoxicity in women with CD4 >250/μL and men with CD4 >400/μL
PI/r component	lopinavir/r, atazanavir/r, fosamprenavir/r, darunavir/r, or saquinavir/r	ATV/r: diminished hyperlipidemic potential; care with antacids DRV/r: important role in Tx-exp pts (reserve?)
Dual nRTI component	tenofovir/emtricitabine or abacavir/lamivudine	ZDV/3TC: alternative ABC: Screen for HLA-B*5701 to ↓ HSR risk; ↑ risk of CVD? ABC/3TC: ?efficacy when viral load >100,000 c/mL

Components of Initial ART: DHHS Categories

- Preferred
 - Clinical data show optimal efficacy and durability
 - Acceptable tolerability and ease of use
- Alternative
 - Clinical trial data show efficacy but also show disadvantages in ARV activity, durability, tolerability, or ease of use (compared with "preferred" components)
 - May be best option in select individual patients
- Other options
 - Inferior efficacy or greater or more serious toxicities

Initial Treatment: Preferred Components

NNRTI Option

• EFV¹

+

NRTI Option¹

• TDF + FTC²

OR

PI Options (alphabetical order)

- ATV + RTV
- DRV + RTV (QD)
- FPV + RTV (BID)
- LPV/r (QD or BID)³

+

NRTI Option¹

• TDF + FTC²

¹ Avoid in pregnant women and women with high pregnancy potential

² FTC can be used in place of 3TC and vice versa

³ Do not use QD LPV/r in pregnant women

DHHS 2008

Initial Treatment: Alternative Components

NRTI Options (in alphabetical order)

- ABC¹ + 3TC²
- ddI + (FTC or 3TC)
- ZDV + 3TC¹

¹ For patients who have tested negative for HLA-B*5701
² FTC can be used in place of 3TC and vice versa

Will Antiretrovirals Have a Role in Prevention?

PEP
PREP

Will PEPFAR Continue and Expand Given a New Administration? A Collapsing Global Economy?

How Can we Find the Infected, Out of Care Population?

HIV Testing Should Become Routine in Health Care Setting Voluntary Opt-Out Without Written Consent

1: MMWR Recomm Rep. 2006 Sep 22;55(RR-14):1-17

Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings.

Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, Clark JE; Centers for Disease Control and Prevention (CDC).

Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (proposed), Atlanta, GA 30333, USA. bbranson@cdc.gov

These recommendations for human immunodeficiency virus (HIV) testing are intended for all health-care providers in the public and private sectors, including those working in hospital emergency departments, urgent care clinics, inpatient services, substance abuse treatment clinics, public health clinics, community clinics,

PMID 16988643

Arguably most important paper of 2006

Will increase diagnosis, adding to burden on facilities and providers

Will allow earlier treatment and may decrease transmission

Awareness of HIV Status among Persons with HIV, United States

Number HIV infected	1,039,000 – 1,185,000
Number unaware of their HIV infection	252,000 - 312,000 (24%-27%)
Estimated new infections annually	40,000

Glynn M, Rhodes P. 2005 HIV Prevention Conference

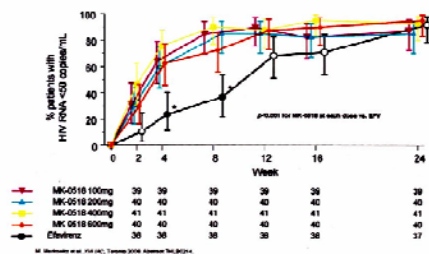
How Can We Bring the Most Marginalized Population into Care?

How Can We Retain Them?

How Long Will the “nRTI Backbone” Survive?

What Might Replace It?

Protocol 004: Percent (95% CI) of patients with HIV RNA <50 copies/ml (NC=F)



Does a “Narrow Resistance Barrier” Matter?

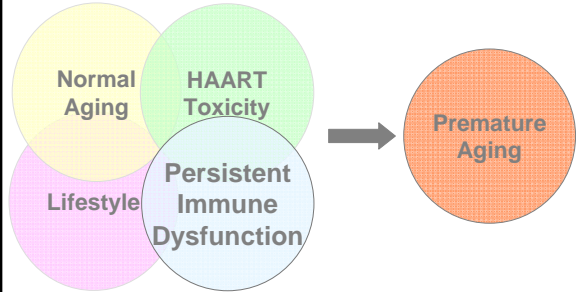
Is it Trumped by Potency, Long Half Life?

What is the Role for PI's given nRTI and Integrase Options?

HIV and Aging Real or Memorex?

HIV,
immunosenescence
and “aging”

Non-AIDS events are more common in HIV disease, even after attempts are made to adjust for age, HAART exposure and traditional risk factors



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

	CD4 Nadir		
	< 100	100-200	>200
Potential years of life lost before age of 65 (per 1000 person-yrs)	461	265	138
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

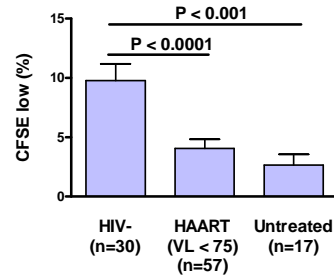
ART-CC; Lancet 2008 (see also Lohse AIM 2007 and Bhaskaran JAMA 2008)

Inflammatory markers are associated with mortality during stable HAART in SMART study

Biomarker	All-Cause Mortality	
	OR	P-value
hs-CRP	2.7	0.08
IL-6	2.4	0.03
Amyloid A	1.50	0.40
Amyloid P	0.7	0.46
D-dimer	7.1	0.08
F1.2	0.7	0.55

Kuller L, et al. Plos Medicine 2008

While T cell activation may remain elevated during HAART (compared to HIV negatives), T cell proliferation defects persist



Some similarities between HAART treated patients (nadir < 200) and the elderly

- Low CD4/CD8 ratio
- Low naïve/memory T cell ratio
- High levels of T cell activation
- Clonal expansion of CD8 T cell subsets
 - High levels of CMV specific T cell responses
- Reduced T cell proliferation
- Lower telomere lengths (CD8 subset)
- Reduced humoral responses to novel antigens
- Increased lymphoid fibrosis/involution
- Reduced thymic function/stem cell numbers?

Linton and Dorshkind, Nature Immunology 04

What Explains Variability in Progression Rate?
Can This Lead to Treatment Strategies?

Predictive Value of Plasma HIV RNA Level on Rate of CD4 T-Cell Decline in Untreated HIV Infection

Benigno Rodriguez, MD, MS
 Ayes K. Sethi, PhD, MHS
 Vinay K. Cherven, MS, MS
 Wilma Markov, MS
 Ronald J. Bock, PhD
 Mark Kraliana, MD, MPH
 Stephen L. Bozzoff, MD
 W. Christopher Mathews, MD, MSPH
 David B. Bangsberg, MD
 Jeffrey Martin, MD
 Christopher C. Whalen, MD, MS
 Scott Sieg, PhD
 Sabrina Yalowitz, MSM-DS
 Steven G. Deeks, MD
 Michael M. Lederman, MD

Context: Plasma human immunodeficiency virus (HIV) RNA level predicts HIV disease progression, but the extent to which it explains the variability in rate of CD4 cell depletion is poorly characterized.

Objective: To estimate the proportion of variability in rate of CD4 cell loss predicted by presenting plasma HIV RNA levels in untreated HIV-infected persons.

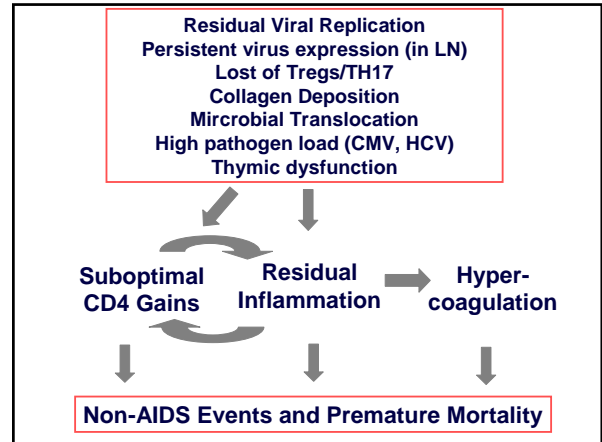
Design: Repeated-measures analysis of 2 multicenter cohorts, comprising observations beginning on May 12, 1984, and ending on August 26, 2004. Analyses were conducted between August 2004 and March 2006.

Setting: Two cohorts of HIV-infected persons: patients followed up at 4 US teaching medical institutions or participating in either the Research in Access to Care for the Homeless Cohort (REACH) or the San Francisco Men's Health Study (SFAMHS) cohorts and participants in the Multicenter AIDS Cohort Study (MACS) cohort.

Participants: Antiretroviral treatment-naïve, chronically HIV-infected persons (n = 1289 and n = 1512 for each of the 2 cohorts) untreated during the observation period (16 months) and with at least 1 HIV RNA level and 2 CD4 cell counts available. Approximately 35% were men who have sex with men, and 35% had risk factors other than male-to-male sexual contact.

Main Outcome Measures: The extent to which presenting plasma HIV RNA level could explain the rate of model-derived yearly CD4 cell loss, as estimated by the coefficient of determination (R²).

PMID 17003398



Is CCR5 a Viable Therapy Target Given Tropism Assay Limitations?

Physicians and Pharmaceuticals Will HIV Lead or Follow?

Does HIV Care Have a Political Voice?

Thanks!

- Veronica Miller
- Steve Deeks