HIV Infection – Beginning HAART

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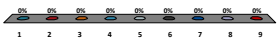
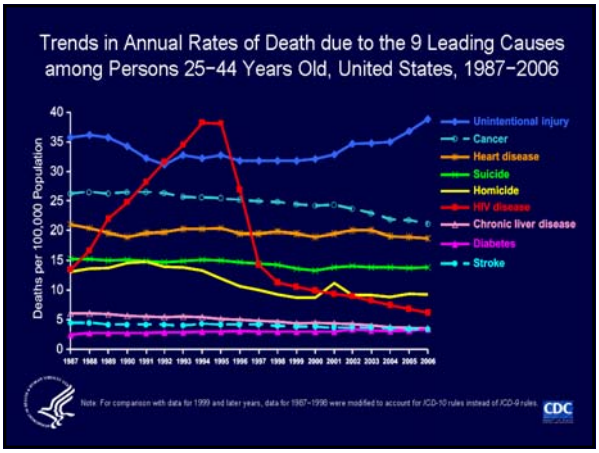
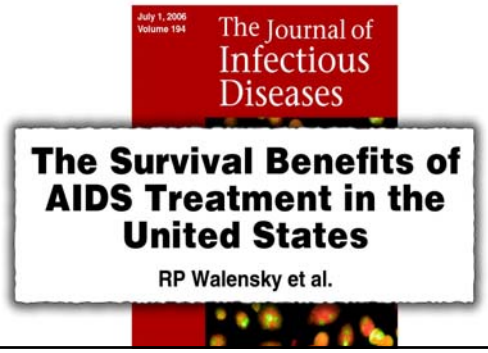
Approximately how many HIV-infected patients do you currently manage?

1. None
2. 1- 4
3. 5 - 10
4. 11 - 20
5. 21 - 50
6. 51 - 100
7. 101 - 250
8. 251 - 350
9. > 350



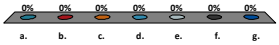


AIDS Drugs Have Saved 3 Million Years of Life in the United States



A 25 y/o male presents with newly diagnosed HIV infection. Besides a complete H&P which of the following tests will you order:

a. CBC with diff and a Chem 18 (includes renal and liver)
b. Lymphocyte subsets (CD4, CD8, etc)
c. Hepatitis (A, B and C) serologies & RPR
d. Tuberculin skin test (TST)
e. Chest x-ray
f. All of the above
g. Only a, b, c & d



Laboratory work-up of the newly diagnosed patient

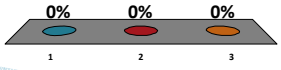
- CD4 count
- HIV RNA
- Hepatitis serologies
  - Hep A Ab
  - Hep BsAg, sAb, cAb
  - Hep C Ab
- Toxoplasmosis IgG
- PAP smear (women)
- G6PD level
- RPR
- Chemistry panel
- CBC with differential
- Urinalysis
- PPD or IGRA
- HLA-B 5701 (if Abacavir is considered)
- ART Resistance testing

Goals of antiretroviral therapy

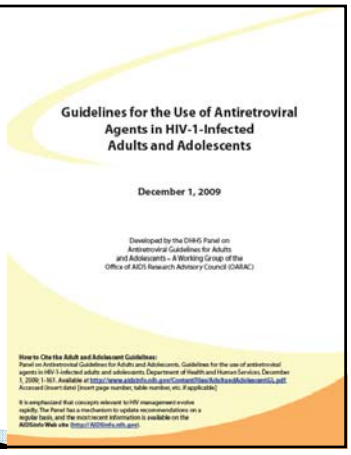
- Maximally and durably suppress plasma HIV viral load
- Reduce HIV-associated morbidity and prolong survival
- Improve quality of life
- Restore and preserve immunologic function
- Prevent HIV transmission

The patient has a CD4 count of 340 cells/mm³ and a VL of 125,000 copies/ml. He is also HBsAg+ and HBeAg+. You would recommend:

1. Starting ARV treatment
2. Starting treatment for Hepatitis B and deferring HIV treatment
3. Not treating for either infection as he is asymptomatic and his transaminases are nl.



Available at:
http://AIDSInfo.nih.gov



Recommendations on when to start HAART DHHS Guidelines Dec 2009

Clinical condition and/or CD4 count	Recommendations
History of AIDS CD4 count <350 cells/mm³ Pregnant women HIV associated nephropathy HBV infected patients about to undergo treatment	Antiretroviral therapy strongly recommended
CD4 350 – 500 cells/mm³ and none of the above conditions	Antiretroviral therapy recommended but 55% of the panel consider this a strong and 45% a moderate recommendation.
CD4 > 500 cells/mm³	The panel was evenly divided between starting therapy or considering it optional

When to start? Comparison to other guidelines

	AIDS or symptoms	CD4 < 200	CD4 201 – 350	CD4 251 – 500	CD4 >500
DHHS 09	YES	YES	YES	YES	YES (optional)
IASUSA 08	YES	YES	YES	Individualize	
UK 08	YES (except TB)	YES	YES	Clinical trial	
EACS 09	YES	YES	YES	Certain patients	Defer
WHO 09	YES	YES	YES	NO	NO

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

- Uncontrolled HIV replication and resultant immune activation associated with 'non-AIDS' illnesses
  - Cardiovascular
  - Hepatic
  - Renal
  - Malignancies
- Patients with CD4 counts >350/µL 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

Recent data supporting the use of earlier ART

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival

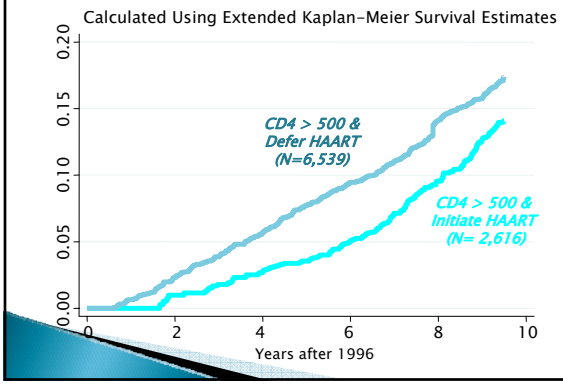
Mari M. Kitahata, M.D., M.P.H., Stephen J. Gange, Ph.D., Alison G. Abraham, Ph.D., Barry Merriman, M.A., Michael S. Saag, M.D., Amy C. Justice, M.D., Ph.D., Robert S. Hogg, Ph.D., Steven G. Deeks, M.D., Joseph J. Eron, M.D., John T. Brooks, M.D., Sean B. Rourke, Ph.D., M. John Gill, M.B., Ch.B., Ronald J. Bosch, Ph.D., Jeffrey N. Martin, M.D., M.P.H., Marina B. Klein, M.D., Lisa P. Jacobson, Sc.D., Benigno Rodriguez, M.D., Timothy R. Sterling, M.D., Gregory D. Kirk, M.D., Ph.D., Sonia Napravnik, Ph.D., Anita R. Rachlis, M.D., Liviana M. Calzavara, Ph.D., Michael A. Horberg, M.D., Michael J. Silverberg, Ph.D., Kelly A. Gebo, M.D., M.P.H., James J. Goedert, M.D., Constance A. Benson, M.D., Ann C. Collier, M.D., Stephen E. Van Rompaey, Ph.D., Heidi M. Crane, M.D., M.P.H., Rosemary G. McKaig, Ph.D., Bryan Lau, Ph.D., Aimee M. Freeman, M.A., and Richard D. Moore, M.D., for the NA-ACCORD Investigators*

HAART Initiation, Regimen, VL Response

	Initiate HAART >500 (N=2,616)	Defer HAART & Initiate <500 (N=945)
Median (IQR) CD4 count cells/mm^3 prior to HAART initiation	674 (579, 831)	390 (300, 451)
Median (IQR) time (mo) from 1st CD4 count in interval to HAART	1 (<1-2)	3 (<1-8)
Median mo/yr HAART initiation (IQR)*	1/00 (4/98, 12/01)	3/00 (4/98, 1/03)
Type of initial HAART Regimen (%)		
PI-based (non-boosted)	51	41
Boosted PI-based	7	9
NNRTI-based	32	40
PI & NNRTI-based	3	2
≥3 NRTIs	6	8
Viral Load <500 within 12 mo HAART	79	73

*Pts initiating HAART >500 by year peaked at 16% in 1998; <10% by 2003

Cumulative Mortality Estimates



ART-CC cohort

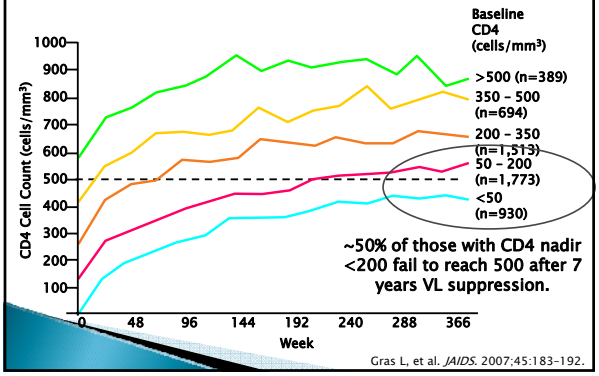
- Collaboration of HIV cohort studies to estimate risk of deferring ART at different CD4 count levels
- ARV-naïve patients (n = 24,444) starting ART after 1997 with CD4 < 550 cells/uL
  - Patients with h/o AIDS or IDU excluded
- Rates of AIDS and death with immediate vs. deferred ART compared in adjacent CD4 ranges of 100 cells/uL
  - Adjusted for lead-time and unseen events in final analysis

Sterne J, et al. 2009 CROI Abst 72LB

Conclusions

- Delaying treatment to below 250 cells/mm^3 is clearly associated with an increased risk of AIDS and death
  - Supports efforts to identify undiagnosed HIV infection
- Delaying treatment to below 350 cells/mm^3 also appears associated with an increased risk of AIDS and death
- For higher CD4 thresholds, differences in absolute risk were relatively small
- These are observational analyses – we cannot exclude confounding

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



Gras L, et al. *JAIDS*. 2007;45:183–192.

CD4 Cell Counts at HIV Diagnosis Among HIV Outpatient Study Participants: 2000–07

- Studied participants in the U.S. HOPS who had a recent HIV diagnosis (≤ 6 months)
- Among 604 patients, 217 (36%) CD4<200 cells/mm³ at diagnosis
- Independent correlates of diagnosis with CD4 <200 cells/mm³ were HIV risk factor not MSM (OR = 1.7, 95% CI 1.1–2.5), non-white race (OR = 1.7, CI 1.0–2.5), and age ≥ 35 years (OR = 2.0, CI 1.4–3.3).

It is hard to benefit from early HIV therapy when you are diagnosed late!

Armon C, 2009 Prevention Abst# 058M

When is ART Started? CD4 Count at Initiation, 2003–5

Since 2000, CD4 count at initiation

- Has increased in Sub-Saharan Africa from 50 to 100
- Has remained stable in developed countries stable at ~150–200,
- Is lower in U.S. than in many other resource-rich nations

Egger M et al. 14th CROI; 2007; Los Angeles. Abstract 62.

Other Reasons to Start ART

Uncontrolled Viremia has Important Negative Consequences

- SMART study
- Numerous reports in many organ systems
- Presumed role of immune activation which is reduced by ARV therapy

Progression of Systemic Disease Accelerated by HIV Viremia

- Renal disease progression fastest in untreated non-controllers. Progression in ARV treated group observed, but faster if viremia recorded.
  - Choi CROI 2009 #38
- Renal function more preserved with continuous than intermittent antiretroviral therapy
  - Beversluis CROI 2009 # 742
- Current level of HIV viremia associated with liver deaths and AIDS deaths in DAD cohort
  - Smith CROI 2009 #145
- Risk of Hodgkin's Lymphoma related to AUC of HIV viremia
  - Zoufaly CROI 2009 #868
- Similar reports in bone loss, cognitive impairment.

Accumulating Data that ART Therapy Reduces HIV Transmission

- Evaluate effect of ART on HIV transmission among HIV serodiscordant, heterosexual couples (2993)
- ARV only if clinically indicated, negative partner tested q3 mo.
  - Not on ARV: 171 linked infections (3.4/100 CY)
  - On ARV: 4 linked infections (0.7/100 CY)
  - Sexual risk behavior lower in those on ARV (19% vs 25%; $p < 0.05$)

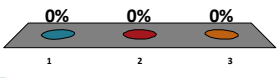
Sullivan P, et al. Abst# 52bLb

Case #2

- 29 y/o man diagnosed as HIV+ during recent a hospitalization for pneumonia which turned out to be PCP.
- Laboratory studies:
  - CD4 = 160 cells/mL
  - HIV RNA 75,000 copies/mL

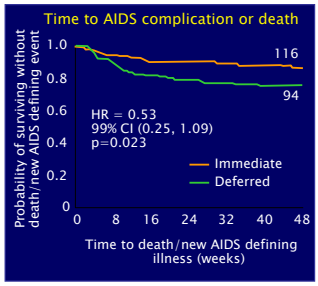
What would you do?

1. Begin Antiretroviral therapy immediately
2. Hold off beginning ART treatment until he completes treatment for PCP
3. Hold off beginning treatment and repeat labs in 3 months



ACTG A5164: Immediate vs delayed ARVs in setting of acute OIs

- Most common OIs: PCP (63%), *Cryptococcus* (12%), BI (12%); *TB excluded*
  - No difference in primary endpoint between groups
  - Immediate treatment had reduced rate of AIDS progression or death (14.2%) vs deferred treatment (24.1%)
  - No differences in IRIS (10 immediate vs 13 deferred)
    - However, 70% of patients with PCP received corticosteroids



Zolopa A, *15th CROI* 2008, #142 & PLoS One 2009

The Sapit Trial– When to start ART in the context of TB treatment?

- Open-label trial in HIV patients with active TB
  - (n = 642)
- Randomized to one of 3 arms
  - Arm 1: ART initiated during intensive phase of TB treatment
  - Arm 2: ART initiated after intensive phase of TB treatment
    - Arm 1 & 2: integrated arm
  - Arm 3: ART initiated after TB treatment completed
    - sequential arm

	Integrated Arm (n = 429)	Sequential Arm (n = 213)
Number of deaths (%)	25 (5%)	27 (13%)
Person-years of f/u	466	222
Mortality rate/100 p-y	5.4	12.1
IRIS	12.1%	3.8%

Abdool Karim S, CROI 2009 Abst# 36a

The Immune Reconstitution Syndrome

Definition– A boosted cellular immune response to a pathogen which has been evading such a response, or a cell –mediated inflammatory disease arising following cessation of immunosuppressant therapy.

Time Course– a delayed response that requires the generation of cellular immunity. Usually peaks 2–6 weeks following generation.

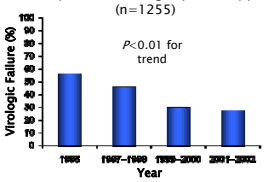
Genesis– may arise soon after removal of immunosuppressive factors, or after beginning therapy for a pathogen which causes immunosuppresion.

Treatment is better and easier

Simplification of therapy 1996 - 2006

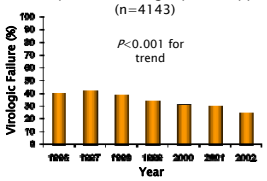
Declining Rates of Virologic Failure of First Regimens

Hopkins HIV Cohort[1]
1996–2002
All patients starting triple therapy
(n=1255)



Virologic failure=HIV RNA >400 c/mL at 6 months

5 Observational Cohorts[2]
1996–2002
All patients starting triple therapy
(n=4143)



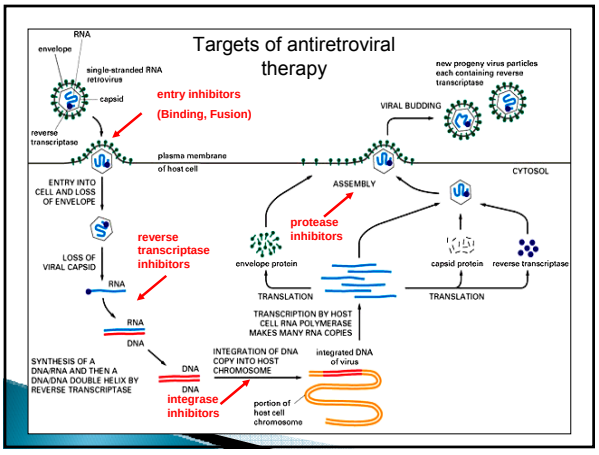
Virologic failure=HIV RNA >500 c/mL at 6–12 months

1. Moore RD, et al. *JAIDS.* 2005;39:195–198.
2. Lampe F, et al. *Arch Intern Med.* 2006;166:521–528.

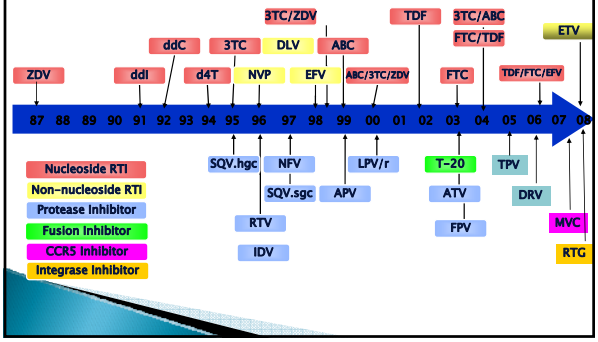
What to Start?

Available ARV Classes

1. Reverse transcriptase inhibitors
   a. Nucleoside reverse transcriptase inhibitors
   b. Non-nucleoside reverse transcriptase inhibitors
2. Protease inhibitors
3. Entry inhibitors
   a. Fusion inhibitor
   b. Co-receptor (CCR5) antagonists
4. Integrase inhibitors



Approved Antiretroviral Agents 1987–2009



Antiretroviral Agents

- **Nucleosides**
  - AZT — zidovudine — Retrovir
  - ddI — didanosine — Videx
  - ddC — zalcitabine — Hivid
  - d4T — stavudine — Zerit
  - 3TC — lamivudine — Epivir
  - ABC — abacavir — Ziagen
  - FTC — emtricitabine — Emtriva
- **Nucleotide**
  - TDF — tenofovir — Viread

Drugs in red not commonly used due to toxicity or dosing

Antiretroviral Agents

- **Combination Nucleosides**
  - AZT/3TC — Combivir
  - AZT/3TC/ABC — Trizivir
  - TDF/FTC — Truvuda
  - 3TC/ABC — Epzicom
- **Combination of two nucleosides and a non-nucleoside**
  - TDF/FTC/EFV — Atripla

Drugs in red not commonly used due to toxicity or dosing

Antiretroviral Agents

- **Non-nucleoside RT inhibitors**
  - delavirdine — Rescriptor
  - nevirapine — Viramune
  - efavirenz — Sustiva
  - Etravirine — Intelence

Drugs in red not commonly used due to toxicity or dosing

Antiretroviral Agents

- **Protease inhibitors**
  - saquinavir — Invirase, Fortovase
  - ritonavir — Norvir
  - indinavir — Crixivan
  - nelfinavir — Viracept
  - lopinavir/ritonavir — Kaletra
  - atazanavir — Reyataz
  - fosamprenavir — Lexiva
  - tipranavir — Aptivus
  - darunavir — Prezista

Drugs in red not commonly used due to toxicity or dosing

Antiretroviral Agents

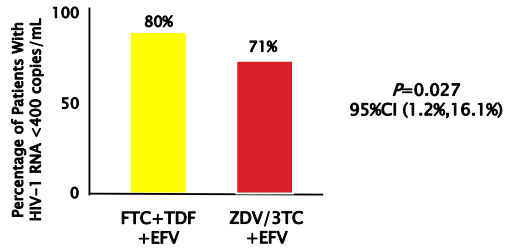
- **CCR5 Inhibitor**
  - Maraviroc — Selzentry
- **Fusion inhibitor**
  - T-20 (enfurvitide) — Fuzeon
- **Integrase Inhibitor**
  - Raltegravir — Isentress

What to start? – Preferred regimens for ARV naïve patients

- NNRTI-based regimen:
  - TDF/FTC + EFV (multiple studies– JAIDS 2008)
    - Nevirapine may be used as an alternative to efavirenz for the initial NNRTI-based regimen in women with CD4 <250 cells/mm3 or in men with CD4 <400 cells/mm3 (BI).
- PI-based regimen:
  - TDF/FTC + ATV/r (CASTLE Study – Lancet 2008)
  - TDF/FTC + DRV/r (ARTEMIS Study – AIDS 2008 & 2009)
- INSTI-based regimen:
  - TDF/FTC + RAL (STARTMRK Study – Lancet 2009)

DHHS ARV Guidelines Dec 1, 2009

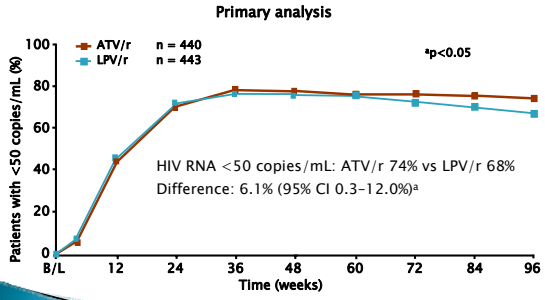
GS-934 48-Week Results (n=487): TLOVR <50 copies/mL



P=0.027
95%CI (1.2%,16.1%)

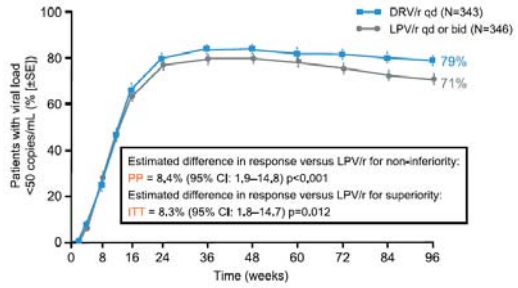
CD4+ cell count +189 +158 P=0.002

CASTLE 96 Weeks: HIV RNA <50 copies/mL (CVR NC=F)



Adapted from: Molina J-M et al, ICAAC/IDSA 2008, Poster H-1250d

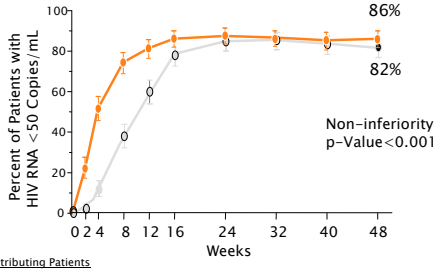
ARTEMIS: HIV-1 RNA < 50 c/mL at Week 96



*Estimated from a logistic regression model including treatment and stratification factors (baseline log_{10} viral load and baseline CD4 cell count)

Mills A, et al. ICAAC 2008. Abstract H-1250C.

STARTMRK – RAL vs EFV both with TDF/FTC

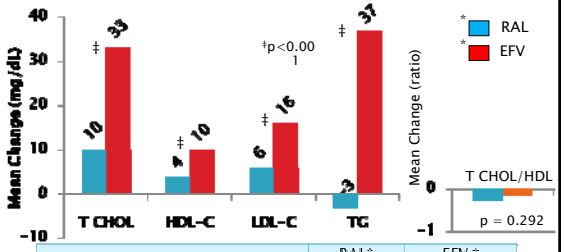


Number of Contributing Patients

Raltegravir 400 mg b.i.d.*	281	279	281	279	281	279	278	280	280
Efavirenz 600 mg q.h.s.*	282	282	282	282	281	282	280	281	281

Lennox, Lancet 2009

STARTMRK – Change From Baseline in Fasting Serum Lipids Week 48



Lipid Lowering Rx	RAL* # (%)	EFV * # (%)
Added Rx	3 (1)	11 (4)
Increased Rx	4 (1)	4 (1)

*In combination with TDF/FTC

What to start?

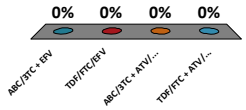
	NNRTI	PI	ISTI*
Dosing	QD	QD or BID	BID
Durability	7 years	7 years	2 years
Side effects	CNS & lipids	GI & lipids	Minimal
Barrier to resistance	low	high	low
Pill burden	1	3 – 4	3

*Integrase Strand Transfer inhibitor

A 34 y/o black male, newly diagnosed has HIV VL = 85,000 copies/ml and CD4 = 280 cells/ul

What combination would you choose for ARV therapy?

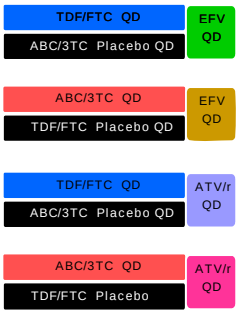
1. ABC/3TC + EFV
2. TDF/FTC/EFV
3. ABC/3TC + ATV/r
4. TDF/FTC + ATV/r



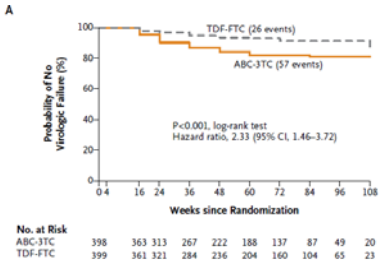
A5202: Study Design

HIV-1 RNA ≥1000 c/mL
Any CD4+ count
≥ 16 years of age

1857 enrolled



A5202 when HIV VL > 100K



Conclusion: risk for VF was higher when ABC+ 3TC was used

NEJM 2009; 361: 2230

A5202– Results in those with HIV RNA $<10^5$ at Baseline

Endpoint	ABC/ 3TC+ EFV	TDF/ FTC+ EFV	p	ABC/ 3TC+ ATVr	TDF/ FTC+ ATVr	p
% No VF at 96Wk	87	89		88	90	
# Safety Endpoint	98	83	.03	80	70	
# Tolerability Endpoint	117	87	.005	100	78	.018

Switches for presumed ABC HSR were greater, but not statistically so, for the ABC/3TC arms

Cohen CROI 2010

A5202– ATV/r vs EFV Results for Entire Study

Endpoint	ABC/3TC +EFV	ABC/3TC +ATVr	TDF/FTC+ EFV	TDF/FTC +ATVr
% No VF at 96Wk	85	83	90	89
# Safety Endpoint	187	170	147	141
# Tolerability Endpoint	186	142	142	126

More NRTI resistance occurred in the EFV arms

No differences in CVD endpoints, renal endpoints

Cohen CROI 2010

A Comparative Study of Three Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Sparing Antiretroviral Regimens for Treatment Naïve HIV-1 Infected Volunteers – A5257

AKA: the ARDENT Study

Atazanavir, Raltegravir or Darunavir with Emtricitabine/tenofovir for Naïve Treatment

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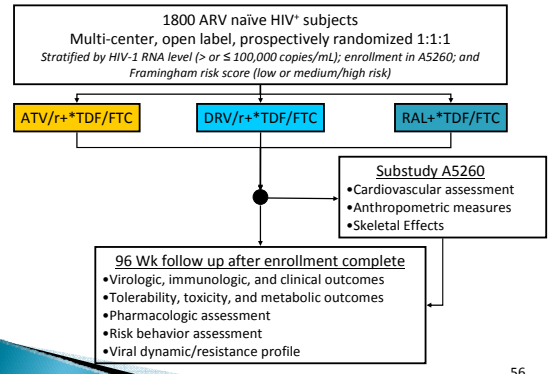
A5257 Study Schema



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*NRTIs flexibility allowed in case of intolerance/resistance

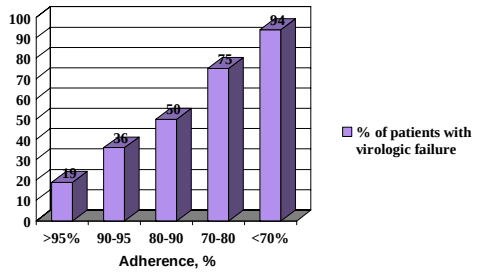
How is successful antiretroviral therapy defined?

1. Improvement in CD4+ T-cells
2. Suppression of HIV RNA to below 50 copies/ml of plasma

Why does treatment fail?

- Adherence
- Baseline resistance
- Prior use of ART
- Drug levels and drug interactions
- Tissue reservoir penetration
- Provider inexperience
- Other causes (unknown)

Correlation between Adherence and Virologic Failure



Paterson DL et al, Ann Int Med 2000;133:21.

Transmission of Resistant Virus: 2006

- 0%–14% of new infections are AZT-resistant
- 0%–10% PI resistant
- 2%–14% resistance to NNRTIs
- Reports of transmission of HIV resistance to all ARVs
- Most HIV transmission is by persons who know that they are infected

International AIDS Society–USA* Drug Resistance Mutations Group

Update of the Drug Resistance Mutations in HIV-1: December 2008

Victoria A. Johnson, MD, Françoise Brun-Vézinet, MD, PhD, Bonaventura Clotet, MD, PhD, Huldrych F. Günthard, MD, Daniel R. Kuritzkes, MD, Deenan Pillay, MD, PhD, Jonathan M. Schapiro, MD, and Douglas D. Richman, MD

Topics HIV Med. 16(5):138–145. Updates available at www.iasusa.org

Virologic Criteria for Changing Therapy

- Inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/ml)
  - Incomplete virologic response: two consecutive plasma HIV RNA > 400 copies/ml after 24 weeks or > 50 copies/ml by 48 weeks of ART
  - Virologic rebound: after virologic suppression repeated detection above the limit of the assay (50 copies/ml) . Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance
    - Persistent low level viremia (50 – 200 copies/ml) does not necessarily indicate virologic failure or the need to change treatment

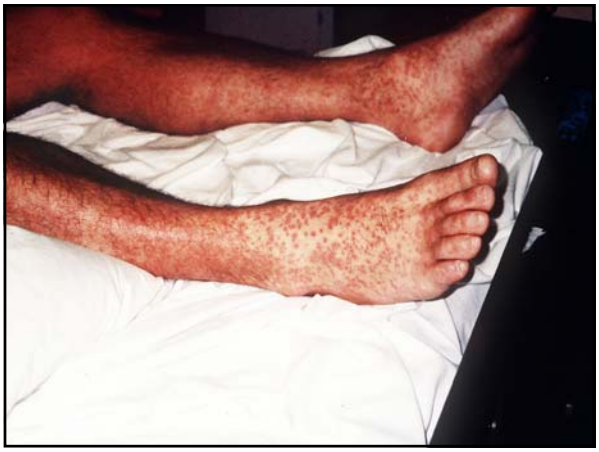
DHHS Guidelines, 20019

Antiretroviral Treatment Toxicities

- Immediate
  - Headaches, GI intolerance (PI's), rash, hypersensitivity reactions (ABV), vivid dreams (EFV)
- Short term
  - Immune reconstitution syndrome
- Long term
  - Lipid and cardiovascular disorders
  - Lipodystrophy
  - Hyperglycemia
  - Osteopenia
  - Cancer?

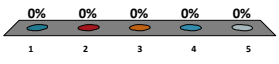
Rash after Initiating ARV Therapy

- 37 WM complaining of rash, myalgias, sore throat and fever
- HIV positive; CD4 311; VL- 40K
- Recently started ABC/3TC/ABC/r
  - Denies GI or respiratory symptoms
  - History of depression, on Wellbrutin, Paxil



What would you recommend:

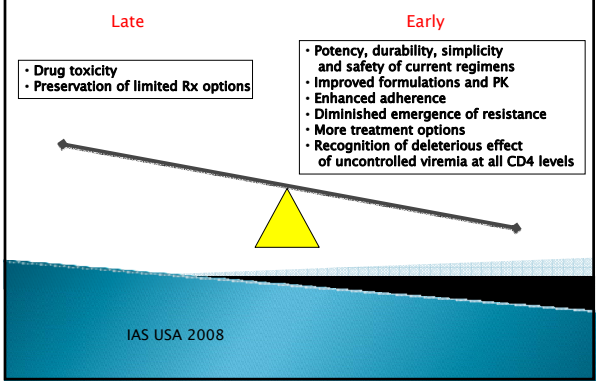
1. Starting prednisone 1 mg/kg/d
2. Obtaining a skin biopsy
3. Starting benadryl
4. Stopping ART
5. Stopping ABC but continuing other ARV's



Abacavir Hypersensitivity

- Observed in ~5% of patients receiving ABC. Almost always in patients who are HLA-B5701+.
- Incidence is near 0% if ABC given to patients who are screened first for HLA type.
- Median onset- 11 days; 93% within 6 weeks
- Most common symptoms include fever, rash, fatigue, and gastrointestinal symptoms
- Can have respiratory symptoms, musculoskeletal symptoms
- Often involves multi-organ systems
- Symptoms improve after discontinuation of ABC
- Rechallange with ABC is fatal

When to Start Therapy in 2010



IAS USA 2008