Merle A. Sande, M.D.
September 2, 1939 - November 14, 2007

With much appreciation for all of your contributions

You will be dearly missed

Top Ten Stories in HIV Medicine in 2007

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Meg Newman, M.D.
UCSF – Positive Health Program at San Francisco General Hospital

Top 10 Stories in HIV Medicine in 2007

- Out of the Pipeline
- Pharmacogenomics Comes of Age
- Mythbusters take on HIV Re-Infection
- Vaccines: the Setback
- The Global epidemic – better or worse?

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Out of the Pipeline

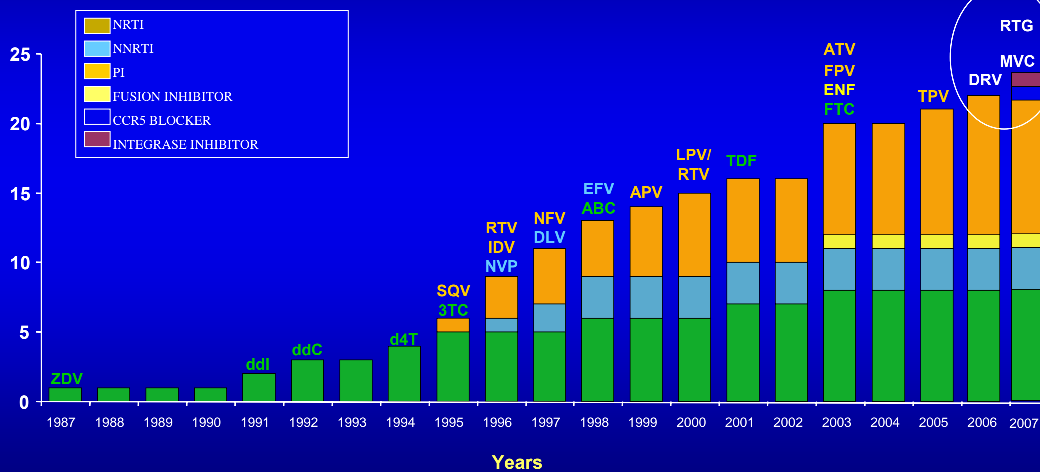
Darunavir

Raltegravir

Maraviroc

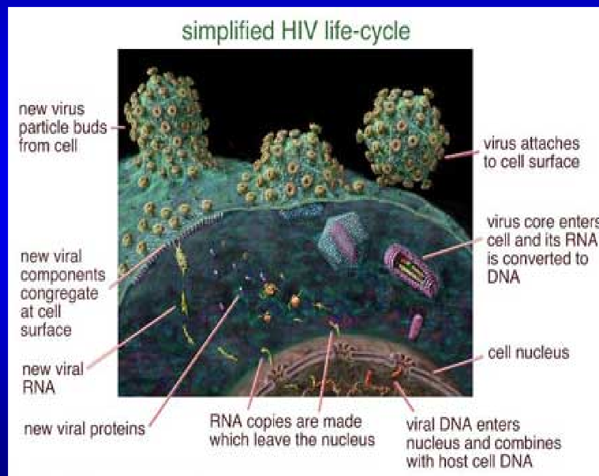
UCSF, S49

Approval of Antiretrovirals: 1987-2007



Adapted from clincaloptions.com/hiv (Oct, 2007) UCSF, S49

Darunavir (Prezista)



- Inhibits HIV protease
- Orally twice daily dosing
- Requires ritonavir boosting
- Approved for “treatment-experienced” patients

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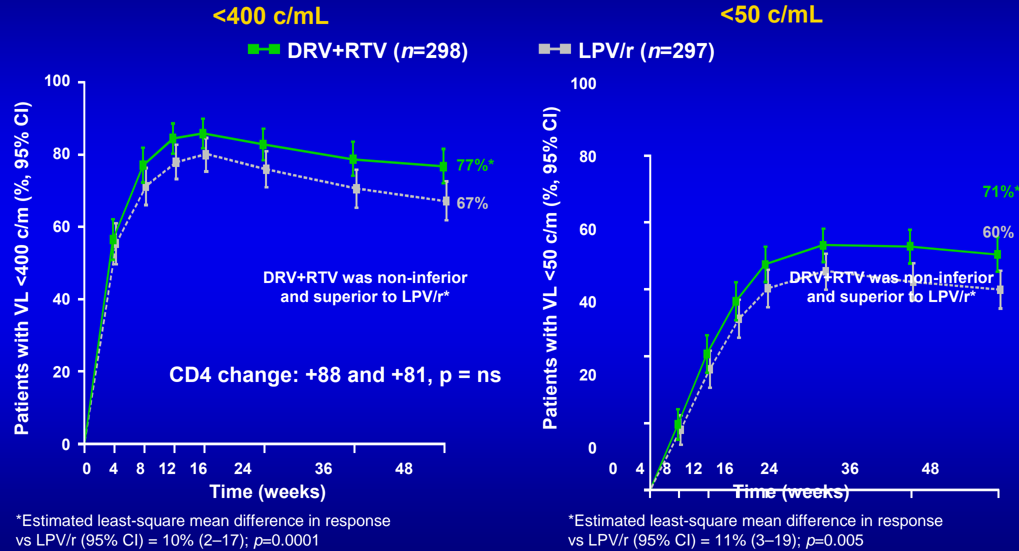
TITAN: Virologic efficacy at Week 48



Valdez-Madruga J, *et al.* 4th *IAS*, Sydney 2007, #TUAB101

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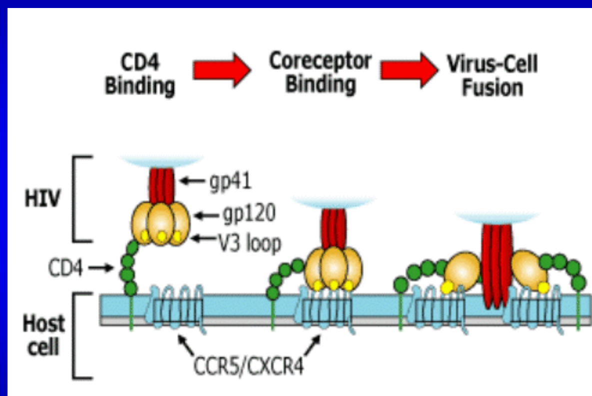
Maraviroc (Selzentry)



- Oral Entry Inhibitor
- Blocks CCR5
- Requires assessment of viral tropism
- Twice daily dosing
- Approved for “treatment-experienced” patients

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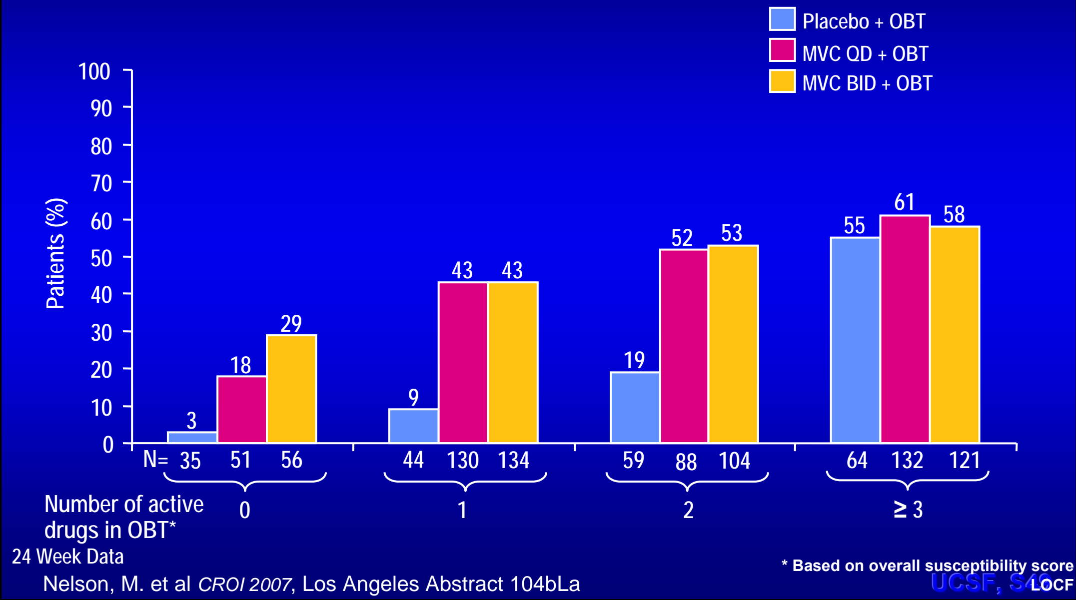
MOTIVATE 1 and 2: Percentage of Patients with HIV-1 RNA < 50 copies/mL by Number of Active Drugs in OBT*



Nelson, M. et al *CROI 2007*, Los Angeles Abstract 104bLa

UCSF, S48

Raltegravir (Isentress)

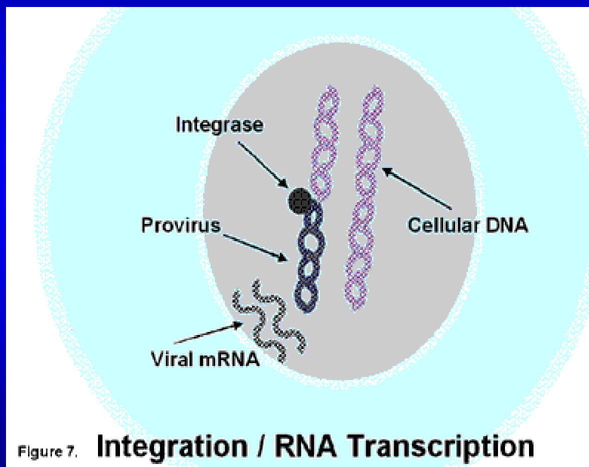


Figure 7. **Integration / RNA Transcription**

- Novel class
- Inhibits HIV integrase
- Orally twice daily dosing
- No ritonavir boosting
- Approved for “treatment-experienced” patients

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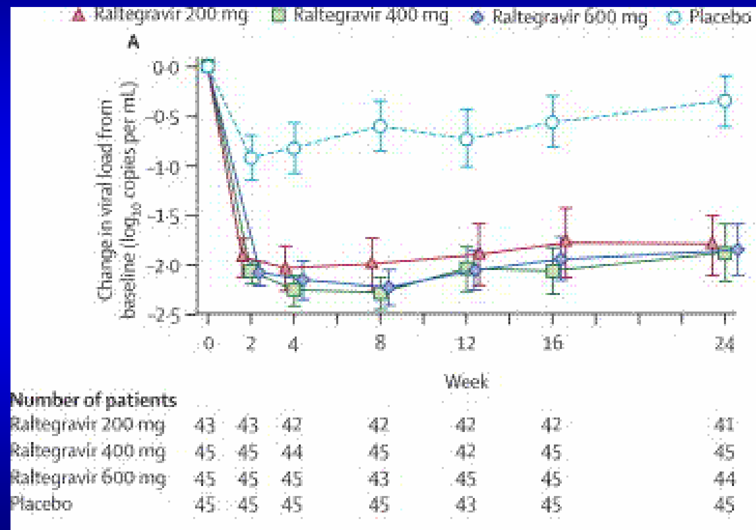
Raltegravir: Activity in Treatment Experienced Patients



Lancet, 2007

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The New Paradigm

- **Availability of 2 new classes of drugs for the first time in the HIV epidemic provides the opportunity for highly treatment -experienced patients to achieve virologic suppression and sustained benefits**
- **"Virologic suppression for all"**

WARNING: RESISTANCE CAN DEVELOP TO THESE AGENTS REQUIRING STRATEGIC USAGE

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Pharmacogenomics Comes of Age

- **Host genetics contribute to heterogeneity in drug disposition and toxicity**
- **Pharmacogenomics correlates gene expression or polymorphisms with clinical outcomes**
- **Goal is to use knowledge of host genetics to maximize efficacy and minimize toxicity therapy**
- **Represents new era of "personalized medicine"**

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HIV Drugs and Disorders

NRTI		
Abacavir	HLA-B*5701	Abacavir hypersensitivity
Zidovudine and lamivudine	MRP4	↑ efflux intracellular levels
NNRTI		
Efavirenz	CYP2B6 516G>T	↑ efavirenz exposure/ toxicity
Nevirapine	CYP2B6 516G>T HLA-DRB*0101	↑ nevirapine exposure Nevirapine hypersensitivity
Protease inhibitors		
Indinavir	UGT1A1	hyperbilirubinemia
Atazanavir	UGT1A1 ABCB1 3435C>T	hyperbilirubinemia atazanavir exposure
Metabolic disorders		
Lipoatrophy	TNF-α 238 allele ABCB1 3435C>T	Increased lipoatrophy Less lipoatrophy
Hyperlipidemia	APOE APOC3	hyperlipidemia

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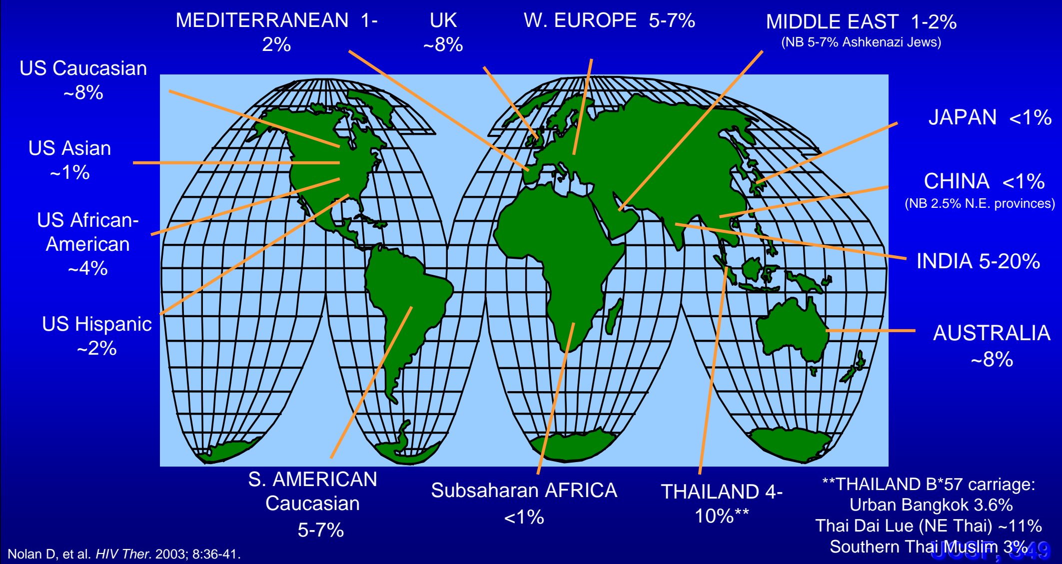
Carriage Rates of *HLA-B*5701* Vary Around the World



Nolan D, et al. *HIV Ther.* 2003; 8:36-41.

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HLA-B57*01 as Predictor of Abacavir Hypersensitivity Reaction (HSR)

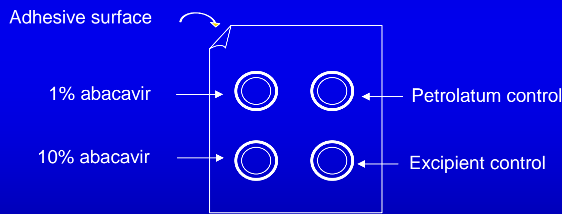
- **PREDICT-1**
  - **Prospective, randomized, blinded study of HLA-B57*01 screening to predict HSR**
- **SHAPE**
  - **Retrospective case-control study of the sensitivity of HLA-B57*01 to predict HSR in both white and black patients**

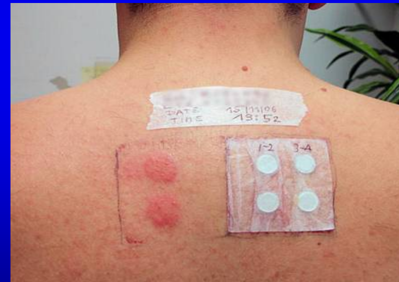
Saag M, *et al. 4th IAS*, Sydney 2007, #WEAB305
Mallal S, *et al. 4th IAS*, Sydney 2007, #WESS101

UCSF, S49

Abacavir HSR Skin Patch Testing (SPT)

- **Immune cell-mediated reaction**
- **Research tool used to identify patients with immune-mediated ABC HSR**





Phillips E, *et al.* 4th *IAS*, Sydney 2007, #MOPEB001;
Phillips EJ, *et al. AIDS* 2002;16:2223–5; Phillips EJ, *et al. AIDS* 2005;19:979–81

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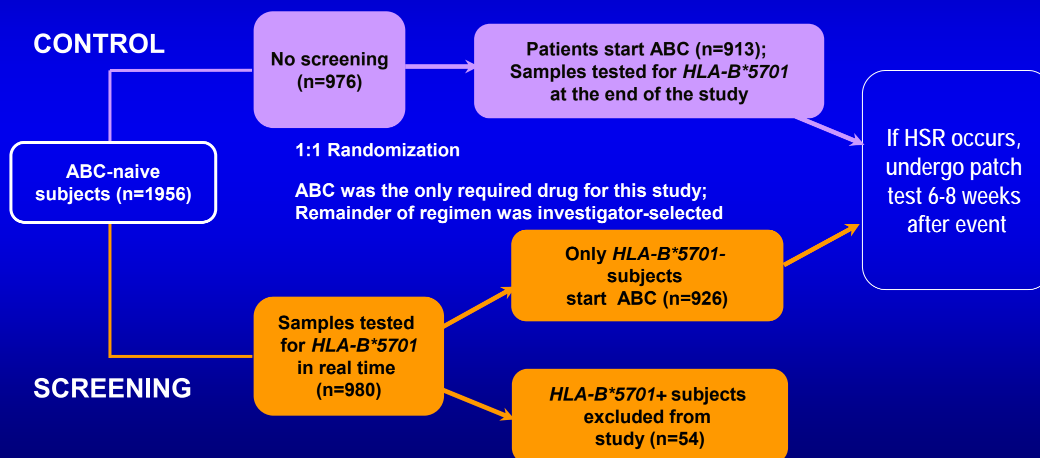
PREDICT-1: Study Design

Prospective, randomized (1:1), double-blind, multi-center study with 6-week observation period (>90% of HSR cases)



Mallal S, et al. 4th IAS 2007: Oral WESS101.

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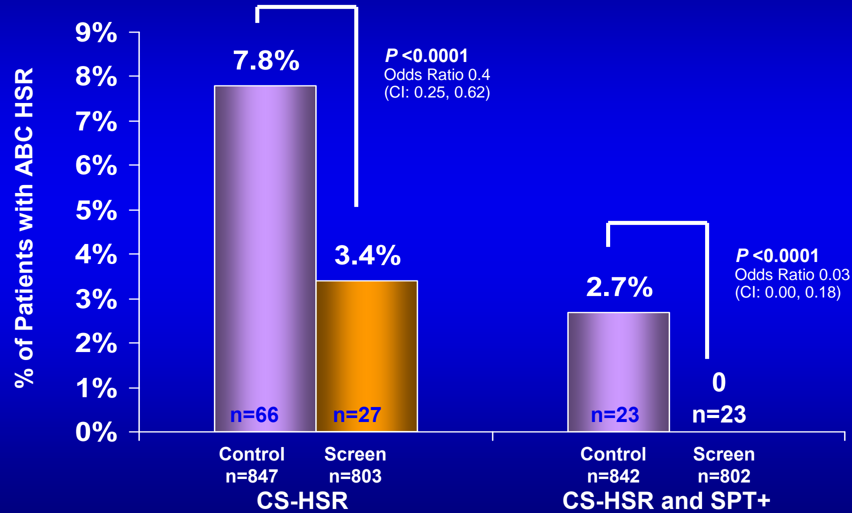

PREDICT-1

Clinically Suspected HSR (CS-HSR) in Control Arm

	HSR	No HSR	
*HLA-B*5701+*	30	19	PPV = 61% (30/49)
*HLA-B*5701-*	36	762	NPV = 96% (762/798)
	Sensitivity = 46% (30/66)	Specificity = 98% (762/781)	

Mallal S, et al. 4th IAS 2007. Oral WESS101

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PREDICT-1

CS-HSR and Skin Patch Test Positive (CS-HSR and SPT+) in Control Arm

	HSR	No HSR	
*HLA-B*5701+*	23	25	PPV = 48% (23/48)
*HLA-B*5701-*	0	794	NPV = 100% (794/794)
	Sensitivity = 100% (23/23)	Specificity = 97% (794/819)	

Mallal S, et al. 4th IAS 2007: Oral WESS101.

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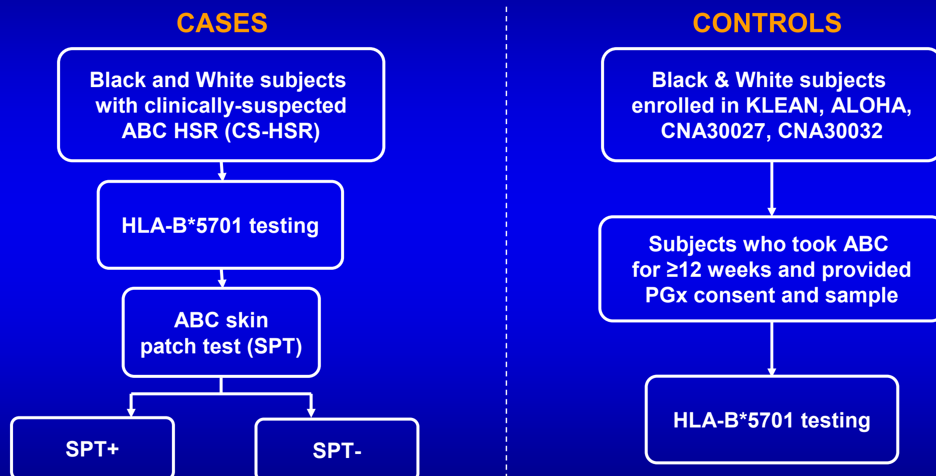
SHAPE

SHAPE: Study Design



*HLA-B*5701* results available for all but one case
Skin patch test results unavailable for 3 Whites, 1 Black

*HLA-B*5701* results available for all control subjects

Saag M, *et al.* *4th IAS*, Sydney 2007, #WEAB305

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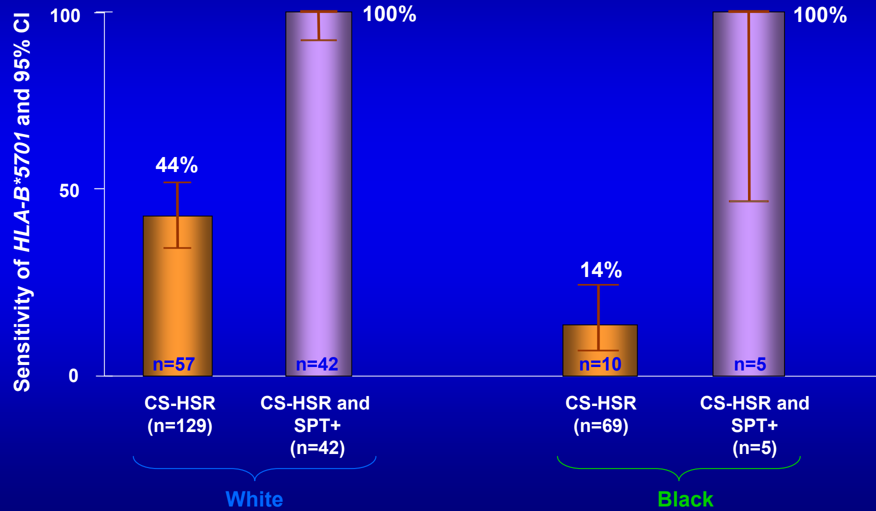
SHAPE

Sensitivity of *HLA-B*5701* Based on HSR Classification



Saag M, *et al.* *4th IAS*, Sydney 2007, #WEAB305

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SHAPE

Results in Whites

Whites	CS-HSR and SPT+ n = 42	CS-HSR n = 129*	Controls n = 202
*HLA-B*5701+*	42 (100%)	57 (44%)	8 (4%)
*HLA-B*5701-*	0	72 (56%)	194 (96%)
Odds ratio (95% CI)	1945 (110, 34352)	19 (8, 48)	referent

**HLA-B*5701* results were not available for one subject

Saag M, *et al.* *4th IAS*, Sydney 2007, #WEAB305

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SHAPE

Results in Blacks

Blacks	CS-HSR and SPT+ n = 5	CS-HSR n = 69	Controls n = 206
*HLA-B*5701+*	5 (100%)	10 (14%)	2 (<1%)
*HLA-B*5701-*	0	59 (86%)	204 (99%)
Odds ratio (95% CI)	900 (38, 21045)	17 (3, 164)	referent

Saag M, *et al. 4th IAS,* Sydney 2007, #WEAB305

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Summary and Conclusions

- The use of *HLA-B*5701* allele for HSR screening reduced the persons who had HSR (clinical or skin test confirmed)
- The positive predictive value of *HLA-B*5701* allele for HSR is approximately 50%-- not all patients with this genotype will have HSR
- *HLA-B*5701* predicts HSR in whites and blacks: HSR is less common in black populations
- *HLA-B*5701* is now recommended for screening in persons starting abacavir in the new DHSS guidelines
- Vigilance and education for patients still required!

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HIV Superinfection

- Circulating recombinant forms comprise nearly one third of all HIV infections
- Most compelling indirect evidence of co-infection or super-infection
- 20 confirmed cases of superinfection in the literature
- Risk higher during primary infection

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HIV Subtypes: Global and Evolving Diversity

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HIV: Co-Infection and Superinfection– Injection drug users

- Epidemic of subtype B and CRF11
- Injection drug users in Switzerland
- 2 of 156 subjections with chronic subtype B had superinfection with CRF11
- Superinfection associated with increase in HIV RNA and decrease in CD4

Yerly, AIDS, 2004

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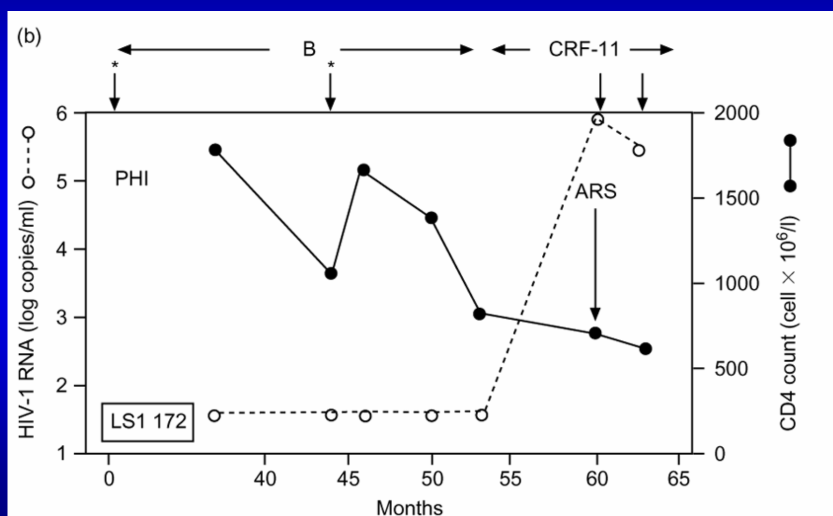
Superinfection with CRF-11



Yerly, AIDS, 2004

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Recent Report from PLOS

- 36 HIV + Kenyan female sex workers (subtype A)
- Analyzed at 4 months and 5 years
- 7 women had evidence of superinfection
- 5 of these occurred after first year
- 3 of these were subtype A

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Superinfection Conclusions

- Natural HIV-1 does not always produce a protective immune response
- Superinfection occurs with “same clade” virus
- Concern for vaccine development
- Undermines “serosorting” premise

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Vaccines- The Setback

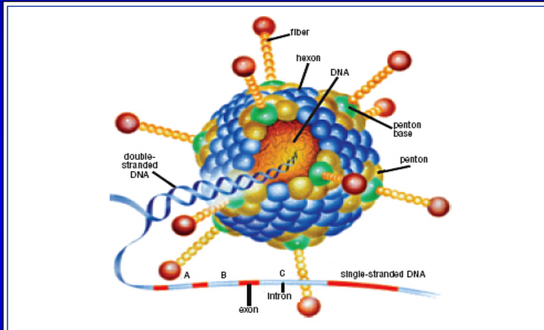

Figure 1. Adenovirus particle. *Adenoviruses are non-enveloped, double-stranded DNA viruses with icosahedral symmetry. The viral capsid is composed of 240 hexon proteins (shown in blue) and 12 penton base proteins (shown in green). The fiber spike associated with each penton base allows the virus to attach to human cells using the coxsackie-adenovirus receptor. There are 51 serotypes of human adenoviruses identified so far, three of which are currently in or soon to enter clinical trials as AIDS vaccine vectors (Ad5, Ad35, and Ad26). To circumvent pre-existing immunity to these vectors, Dan Barouch and colleagues have constructed a chimeric Ad5/Ad48 virus where the hexon proteins, the primary target of antibodies, are substituted with the corresponding proteins from Ad48.*

Adenovirus

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STEP TRIAL: Phase 2B Adenovirus Based Vaccine

- **Vaccine: 3 recombinant adenovirus serotype 5 (rAd5) vectors expressing HIV-1 gag, pol, and nef (Merck)**
- **Mechanism: CD8 T cells would become programmed to recognize and kill HIV- infected cells**
- **Study Design: 3000 HIV - adults at high risk for HIV randomized to receive 3 doses of vaccine or placebo over 6 months**

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STEP TRIAL: Phase 2B
Adenovirus Based Vaccine

- Interim analysis performed on approximately 1500 participants (average follow-up 13 months)
- Evaluation: HIV acquisition and viral load setpoint
- Stratification by baseline adenovirus antibody titers (AD5)

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STEP TRIAL: Phase 2B
Adenovirus Based Vaccine

- Vaccine was well tolerated in subjects with Ad5 ≤ 200 but ***no significant decrease in risk of HIV acquisition or set point viral load was found among vaccinees***
- Rates of HIV acquisition: 3.2% in vaccinated; 2.8% in the placebo group
- Mean VL : 41K in the vaccinated group and 26K in the placebo group after 8 -12 weeks

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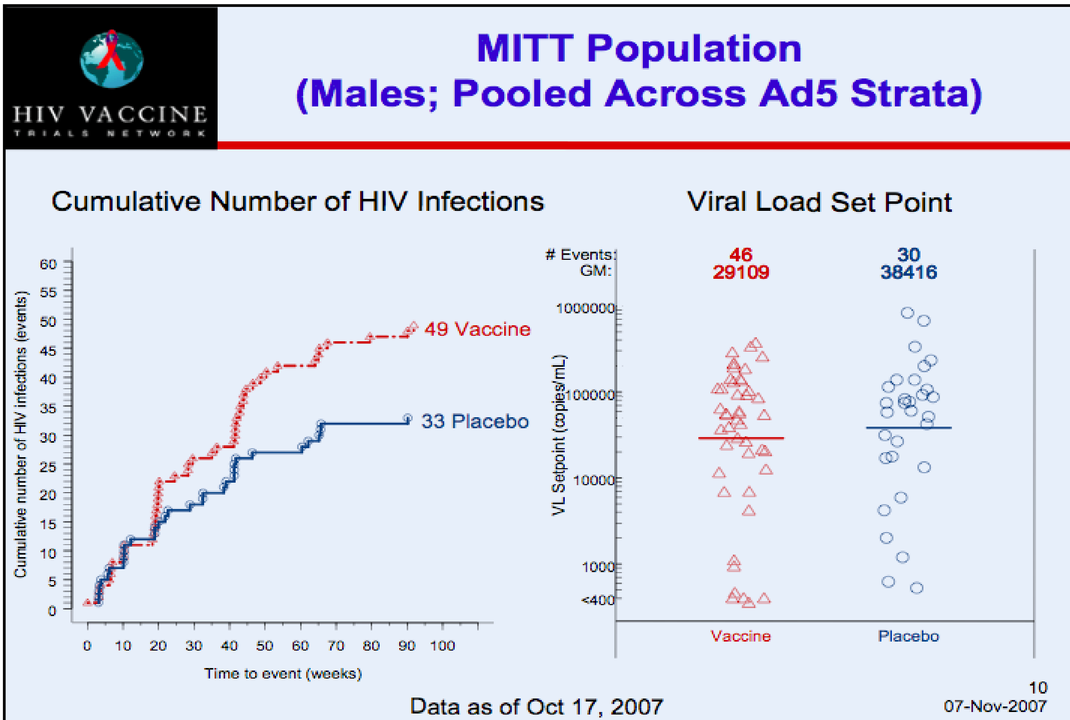
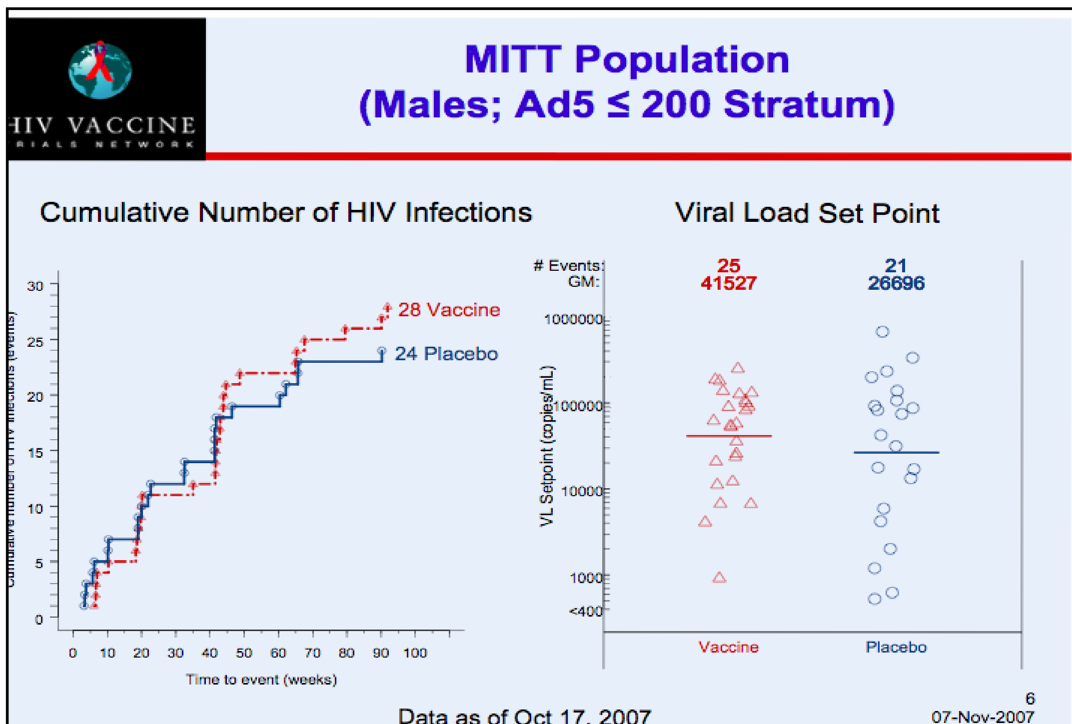
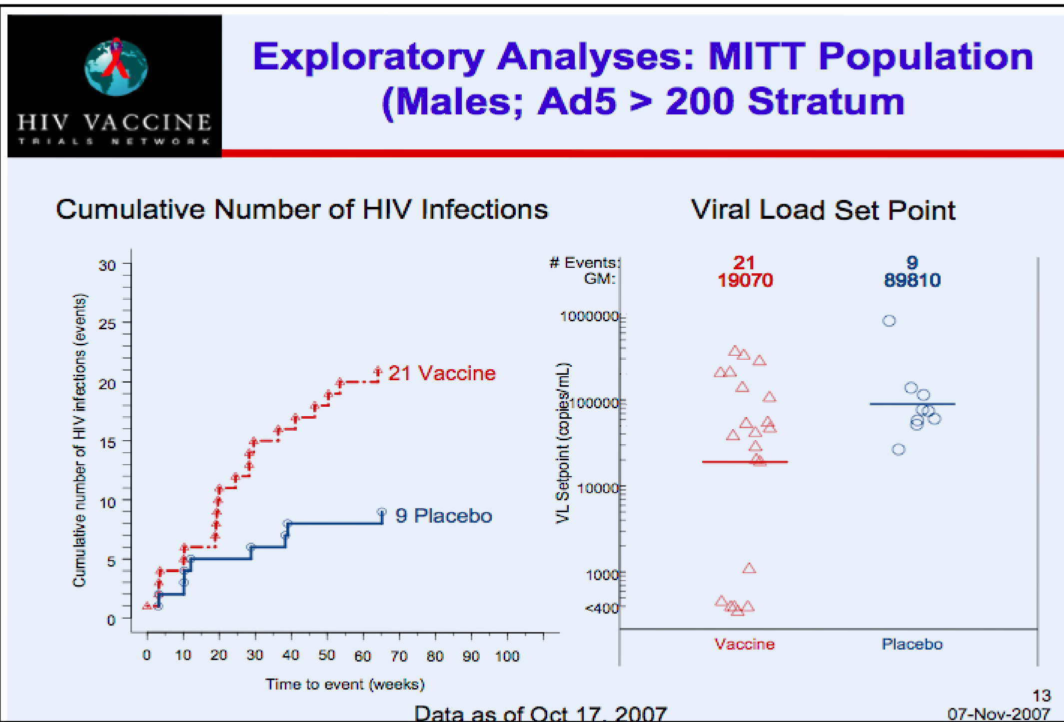

MITT Population
(Males; Pooled Across Ad5 Strata)
HIV VACCINE
TRIALS NETWORK
Cumulative Number of HIV Infections
Viral Load Set Point
49 Vaccine
33 Placebo
Cumulative number of HIV infections (events)
Time to event (weeks)
Events:
GM:
46
29109
30
38416
VL Setpoint (copies/mL)
Vaccine
Placebo
Data as of Oct 17, 2007
10
07-Nov-2007


MITT Population
(Males; Ad5 ≤ 200 Stratum)
HIV VACCINE
TRIALS NETWORK
Cumulative Number of HIV Infections
Viral Load Set Point
28 Vaccine
24 Placebo
Time to event (weeks)
Events:
GM:
25
41527
21
26696
VL Setpoint (copies/mL)
Vaccine
Placebo
Data as of Oct 17, 2007
6
07-Nov-2007



STEP Trial: Stratum of Subjects with Ad5 > 200

- **The vaccine was well tolerated**
- **A trend for *increased risk of HIV acquisition and increased viral load set point was appreciated in those vaccinated***
- **Increased HIV acquisition rates were a surprise in this subgroup**
- **Potential confounders such as age, risk behaviors, region or circumcision status, did not "explain" the trend**

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Vaccine Conclusions

- Multiple mechanisms may explain the observed trend in the > 200 Ad5 group including
  - Biological effect of vaccination
  - Confounding factors unrelated to vaccination
  - Chance
- Alternate strategies are being actively pursued
  - Modified adenovirus vectors
  - “Prime boost” with different vectors

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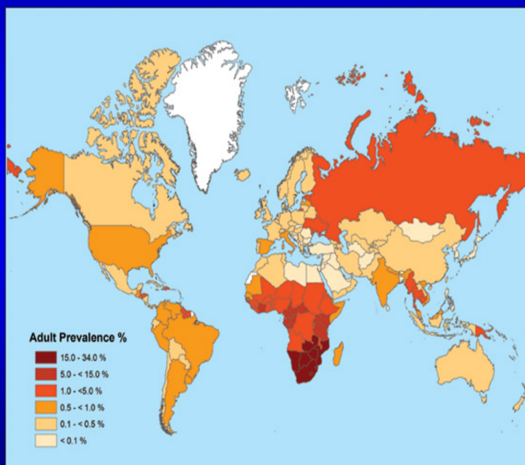
The Global Epidemic: Better or Worse?



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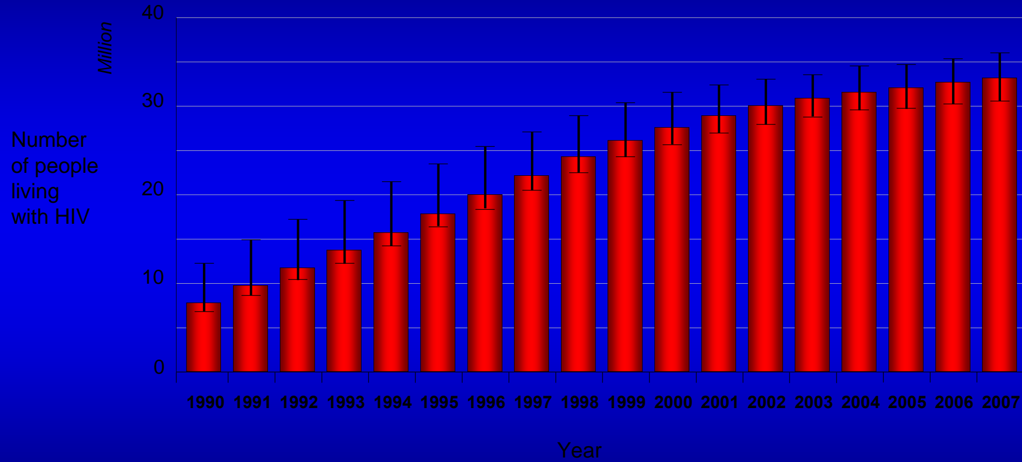
Estimated Number of People Living with HIV globally, 1990–2007
Million
40
30
20
10
0
Number of people living with HIV
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007
Year
This bar indicates the range
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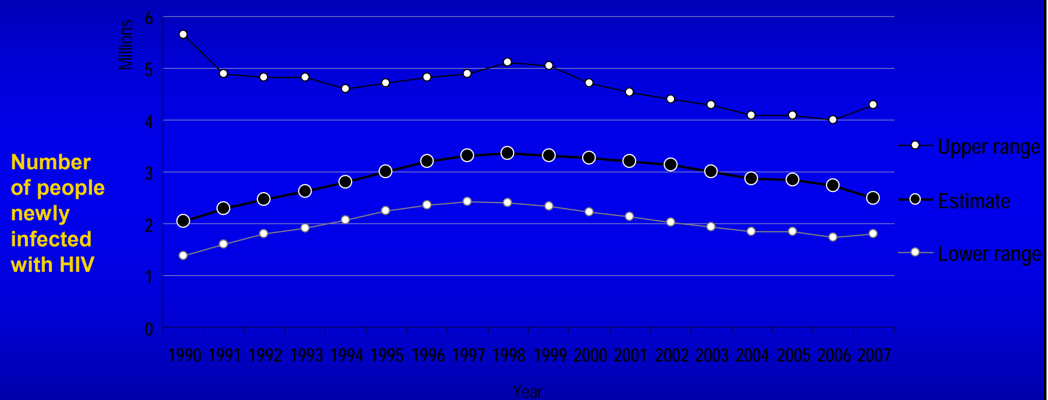
Estimated Number of People Newly Infected with HIV Globally 1990–2007
Millions
6
5
4
3
2
1
0
Number of people newly infected with HIV
Upper range
Estimate
Lower range
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007
Year
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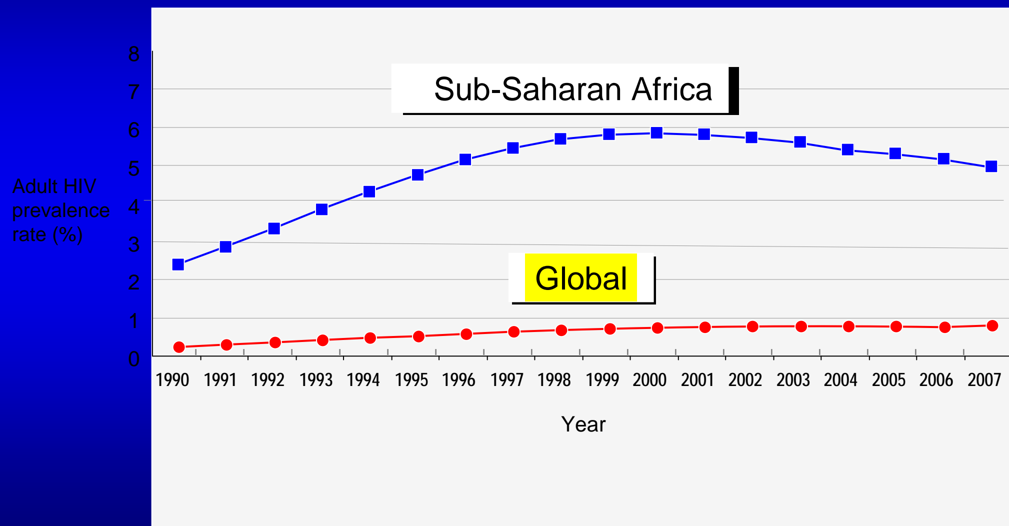
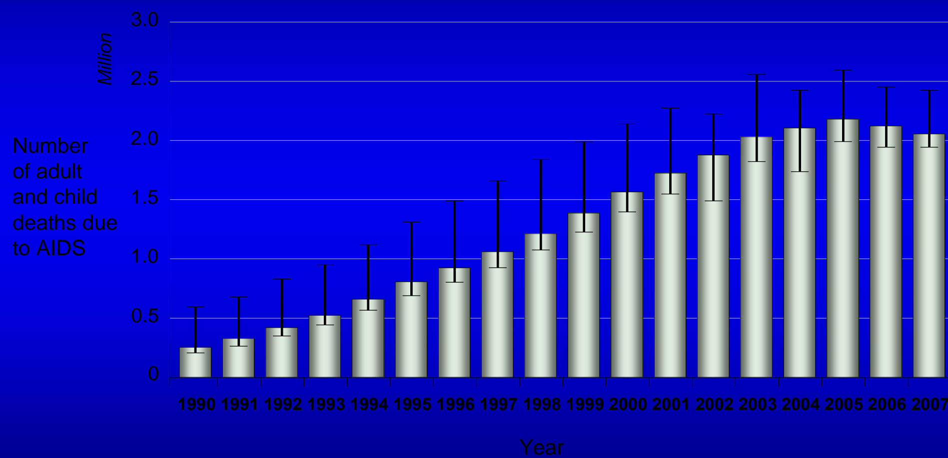


Estimated Adult (15–49 years) HIV Prevalence Rate (%)
Globally and in Sub-Saharan Africa, 1990–2007
Sub-Saharan Africa
Global
Adult HIV prevalence rate (%)
8
7
6
5
4
3
2
1
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007
Year
UCSF, S49



Estimated Number of Adult and Child Deaths
Due to AIDS Globally, 1990–2007
Million
Number of adult and child deaths due to AIDS
3.0
2.5
2.0
1.5
1.0
0.5
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007
Year
This bar indicates the range
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Global Epidemic Summary

- Peak of epidemic in 1998
- Still 2.5 million new cases and 2 million deaths
- Concentrated epidemics in certain areas– Eastern Europe with rapid upward trajectories (150% increase)
- Behavioral risk trends worrisome in some areas
- HIV represents most important global public health challenge and requires increase, not decrease in efforts to prevent and treat

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Top 10 Stories in HIV Medicine in 2007

- Think Globally and Test Locally: Expanded HIV Testing…Has Anything Changed?
- Wonder Drugs Have Us Wondering
- Quick Update on HBV Vaccine and When Not to Use Entecavir
- Still Dating: Osteopenia/Osteoporosis and HIV
- The Graying of AIDS

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Think Globally and Test Locally

- September 22, 2006, U.S. Urges H.I.V. Tests for Adults and Teenagers
- **The Centers for Disease Control and Prevention recommended that all adults and teenagers (ages 13-64) have HIV tests as part of routine medical care**
- The agency also urged the removal of two major testing barriers: ***separate signed consent forms and lengthy counseling before each test.***

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ARS QUESTION

- 1. My hospital requires written consent for all screening of patients for HIV
- 2. My hospital now does routine screening of patients for HIV as an opt out procedure
- 3. My hospital does not do testing except for high risk patients
- 4. My hospital does not have rapid testing
- 5. I don't know what my hospital does

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Detecting Undiagnosed HIV Infection in an Urban emergency department (ED).

- HIV screening with rapid tests was offered to ED patients regardless of risks or symptoms. ED providers could also refer patients for diagnostic testing.
- 4849 eligible patients approached for screening, 2824 (58%) accepted and were tested
- 414 (95%) of 436 provider-referred patients accepted and were tested.
- 35 (1.2%) screened patients & 48 (11.6%) provider-referred patients were infected with HIV ($P < 0.001$). 18 (51%) screened patients and 24 (50%) referred patients reported <u>*no traditional risk factors*</u>
- 27 (77%) screened patients and 38 (79%) referred patients entered HIV care.
- 45% of HIV-infected screened patients and 82% of provider-referred patients had <200 cells/[mu]L ($P < 0.001$)
- Conclusions: *ED screening detects HIV infection and links to care patients who may not be tested through risk- or symptom-based strategies.*
- ***Results c/w accruing SFGH results- (unpublished personal communication with Brad Hare)***
- *JAIDS Journal of Acquired Immune Deficiency Syndromes. 44(4):435-442, April 1, 2007.*

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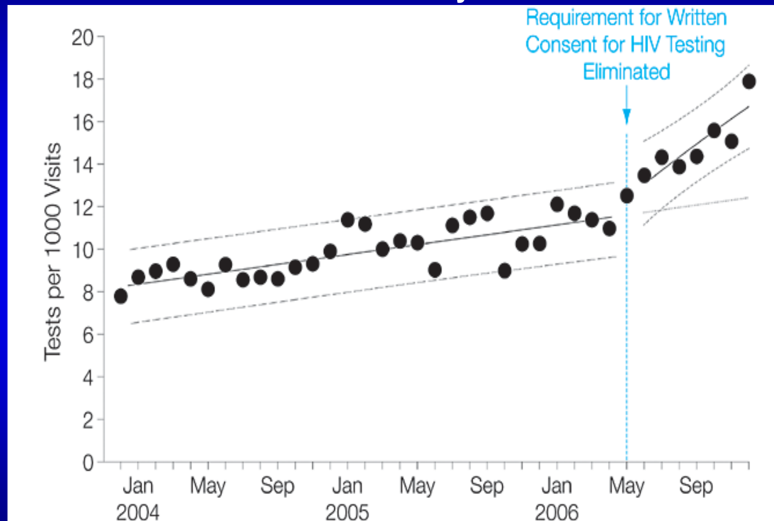
Mean Rate of HIV Tests per 1000 Patient-Visits in Persons Aged 18 Years or Older (December 2003-December 2006), San Francisco Department of Public Health Medical Care System



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Zetola JAMA 2007

JAMA 9

Expanded HIV Testing

- **As a federal agency the CDC made recommendations but *state laws govern HIV testing in each state***
- **Systematic review of the legal literature found that most states have very specific consent requirements**
- **In 14 states oral consent is okay, in 5 states oral consent must be accompanied by written documentation, and 12 states require explicit written consent**
- **24 states oversee the specific information that is required during the consent process**

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Expanded HIV Testing?

- Survey of state HIV testing laws demonstrates that the majority of states have HIV testing requirements that are inconsistent with the CDC's recommendations
- ***States that have recently amended their laws have not eased the requirements for pretest counseling and informed consent***
- The reasons for the persistence of these legal requirements must be understood to effect policy changes to increase HIV testing

Wolf LE, Donoghoe A, Lane T (2007) Implementing Routine HIV Testing: The Role of State Law. PLoS ONE 2(10): e1005. doi:10.1371/journal.pone.0001005

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What Would Hippocrates Do?

- We should be advocating for reaching undiagnosed HIV infected individuals through HIV Testing that should :
  - focus on routine health care settings AND
  - focus on high risk settings (prisons, drug treatment programs, etc)
  - ***most importantly, be linked to integration with longitudinal care***
- Insured patients with access to care are more likely to test, therefore:
  - providing health insurance coverage for all is part of the route to the control of HIV disease and increased health for the entire nation

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ARS Question

- You and or your clinic have made:

1. No changes in nelfinavir use
2. Have stopped using it all together
3. Have stopped using it only in pregnant women
4. Have stopped using it in women of child-bearing potential and pregnant women

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Nelfinavir…No Longer a Trusted Medicine

- Pfizer issued a warning letter on September 10, 2007 informing clinicians that nelfinavir has been found to contain a manufacturing impurity *Ethyl Methanesulfonate (EMS)*
- This is a process-related chemical that is potentially carcinogenic in humans
- Nelfinavir has 2 manufacturers, Roche and Pfizer, and the EMS in the Roche drug is higher than the Pfizer brand

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Nelfinavir…No Longer a Trusted Medicine

- **Roche, which supplies the European market, has recalled all the nelfinavir from Europe**
- **The FDA, Pfizer and the DHHS agree**
  - **Pregnant women and children who are starting ART should not be offered nelfinavir-containing regimens "until further notice"**
  - **Children who are stable on the drug can continue to receive it**
  - **Pregnant women with alternative treatments options should be switched to alternate therapy**

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Nelfinavir…No Longer a Trusted Medicine

- **The FDA, Pfizer and the DHHS agree**
  - **Nelfinavir should be avoided in HIV-infected women who are planning to become pregnant. (Remember most pregnancies are *UNPLANNED*)**
  - **Pregnant women and children who are starting ART should not be offered nelfinavir-containing regimens "until further notice"**
  - **This includes nelfinavir mesylate 250 mg, 625 mg, and powder for oral suspension**
- ***DHHS Panel on Antiretroviral Therapy Guidelines for Adults and Adolescents-Notice on Nelfinavir FDA- Pfizer Letter 9/13/2007, Pfizer, Important information for Prescribers 9/10/2007***

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Now…Some Bad News

- Multiple cases of new-onset depressed mood, suicidal ideation, and changes in emotion and behavior *within days to weeks of initiating varenicline/ (Chantix) treatment.*
- The role of varenicline/chantix in these cases is not clear because smoking cessation is associated with nicotine withdrawal symptoms and *has also been associated with the exacerbation of underlying psychiatric illness*.
- Careful consideration should go into initiating this medicine *despite its great success with smoking cessation*. Monitor patients taking Varenicline (Chantix) for behavioral and mood changes.

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FDA Website to Register a Potential Case of Varenicline (Chantix) Side Effects

- The complete MedWatch safety summary, including a link to the FDA Early Communication Sheet about the ongoing safety review on this issue, can be found at http://www.fda.gov/medwatch/safety/2007/safety07.htm#Chantix.
- Adverse events related to varenicline therapy should be reported to the FDA's MedWatch reporting program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, online at http://www.fda.gov/medwatch, or by mail to 5600 Fishers Lane, Rockville, MD 20852-9787.

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Safety of Rosiglitazone What about Pioglitazone?

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Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs

Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

Comparator Drug	Odds Ratio (95% CI)	P Value
Myocardial infarction		
Metformin	1.14 (0.70–1.86)	0.59
Sulfonylurea	1.24 (0.78–1.98)	0.36
Insulin	2.78 (0.58–13.3)	0.20
Placebo	1.80 (0.95–3.39)	0.07
Combined comparator drugs	1.43 (1.03–1.98)	0.03
Death from cardiovascular causes		
Metformin	1.13 (0.34–3.71)	0.84
Sulfonylurea	1.42 (0.60–3.33)	0.43
Insulin	5.37 (0.51–56.52)	0.16
Placebo	1.22 (0.64–2.34)	0.55
Combined comparator drugs	1.64 (0.98–2.74)	0.06

Nissen S and Wolski K. N Engl J Med 2007;10.1056/NEJMoa072761

The NEW ENGLAND JOURNAL of MEDICINE

Rates of Myocardial Infarction and Death from Cardiovascular Causes

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,280 (0.43)	22/6105 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.44)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,557 (0.38)	7/3700 (0.19)	2.40 (1.17–4.91)	0.02
DREAM	12/2,365 (0.51)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2854 (0.18)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

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What Do We Know?

- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared *Rosiglitazone* (R) to placebo, showed *R* to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction
- Three other studies (mean duration 41 months; 14,067 total patients) comparing *R* to some other approved oral antidiabetic agents or placebo *have not confirmed or excluded this risk*. *In their entirety, the available data on the risk of myocardial ischemia are inconclusive*.
- Data from the short-term trials suggest an increased risk of myocardial ischemia, particularly in patients who take *R with insulin or nitrates.* However, the long-term trials with *R* do not show an increase in these events compared to other commonly used medications.
- (ADOPT) shows no increased myocardial ischemic risk compared to metformin or sulfonylurea.

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What Do We Know?

- The interim results of a second long-term trial (RECORD) also show no increased risk of major cardiovascular events (death, heart attack, stroke) between *Rosiglitazone* and other medications; however, *firm conclusions cannot be drawn because the trial has not yet been completed*
- A long-term trial in prediabetic patients (DREAM) shows there was no increased risk of *Rosiglitazone* over comparators with regard to myocardial infarction, mortality, or other *non-heart-failure cardiovascular events*
- FDA : No oral antidiabetes drug (OAD) has been conclusively shown to reduce cardiovascular risk
- The FDA will request that labeling of all approved OADs contain language describing the lack of data showing this benefit

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What Would Hippocrates Do?

- *Patients receiving R and either insulin or nitrates were at greater risk of reporting myocardial ischemia, so do not use R with insulin or nitrates*
- *Thiazolidinediones, including rosiglitazone, can cause or exacerbate congestive heart failure in some patients. This can occur with pioglitazone too.*
- *For sure do not give to patients with symptomatic heart failure, and find another drug for those with asymptomatic heart failure*
- *Watch for heart failure in anyone given a thiazolidinedione*
- *Initiation of rosiglitazone is not recommended for patients experiencing an acute coronary event*

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Entecavir (E)… Not for Primary HBV Therapy in Co-infected Patients

- Initial in vitro studies suggested E had no activity against human immunodeficiency virus type 1 (HIV-1); thus, it *was* recommended as primary therapy for HBV in persons with HIV-1 and HBV coinfection who did not require HIV-1 antiviral therapy
- McMahon et al show that E *is an effective inhibitor of HBV and HIV in vitro and in vivo and may select for M184V or other mutations in HIV-1 reverse transcriptase. HIV inhibition is potent but partial.*

N EJM Vol 356(25):2614-2621
June 21, 2007

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Entecavir (E)

- Prior reports showing no anti-HIV-1 activity of E used an older assay which relies on cytopathic effect, resulting in cell death as a surrogate measure of infection. The McMahon report used a *quantitative infectivity assay*
- This new assay allows for a more direct measure of drug inhibition during the early steps in HIV replication (virus attachment) and includes virus gene expression
- Drug inhibition is also measured in *primary CD4+ lymphoblasts which are the in vivo target cells of HIV-1 vs. transformed cell lines* (older assay) *which may metabolize E differently*

N EJM
Vol 356(25):2614-2621
June 21, 2007

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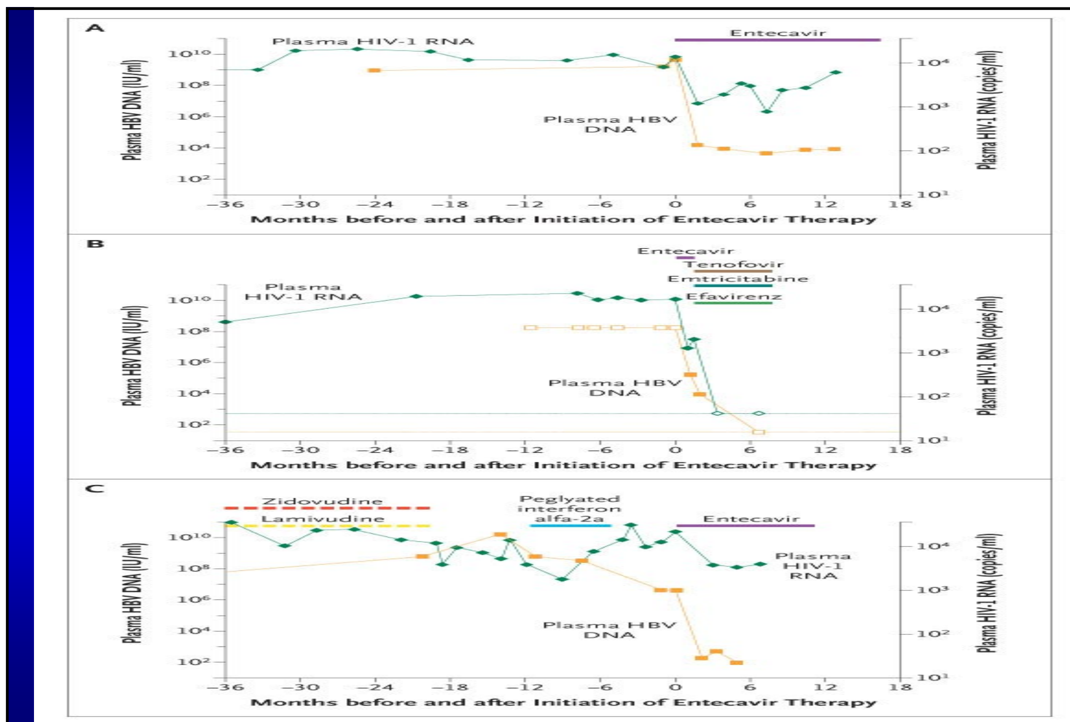

Entecavir (E)

- **DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents *no longer recommends entecavir for HIV co-infected patients who are not simultaneously receiving HIV therapy***
- **Options for those patients include**
  - **pegylated Interferon alfa or adefovir**
  - **or to begin combination HIV therapy with tenofovir and emtricitabine or lamivudine + a third HIV agent**

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New DHHS/IDSA OI Recommendations on Hepatitis B Vaccine

- The guidelines will be recommending a new Hepatitis B vaccine dosage
- All HIV positive patients should receive the 40 mcg formulation at 0, 1 and 6 months vs. the 10mcg formulation
- For patients who fail to seroconvert 1 month after receipt of the complete primary series, the entire series should be repeated again with the 40 mcg formulation
- This recommendation is based on several references that show that the seroconversion rates can be improved from about 34% to 47% in most HIV+ patients

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ARS Question

In my clinical practice:

1. Over 10% of men and women below 65 have premature osteoporosis or osteopenia
2. I wouldn’t know because I don’t test unless patients are over 65 or have a premature fracture
3. I test patients who have been underweight, bed-bound, had more than 2 weeks of steroids and have been heavy drinkers or smokers regardless of age
4. Numbers 1 and 3

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Relationship Between HIV Disease and Bone

- Multiple cohort studies show ↑ rates of osteopenia (OP) and osteoporosis (OPO) in HIV-positive patients
- As a cohort of people, many HIV infected people have moderate to long periods of *low BMI, immobility, low intake of calcium and vitamin D, and some have moderate to heavy alcohol, opiate and tobacco use*
- HIV/AIDS patients often begin ARVs late in disease
- These days many patients are in their 5th or 6th decade when they start ART
- *Conclusion: Traditional risk factors for OP and OPO are common in HIV+ pts.*

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Multiple Studies: Relationship Between HIV Disease OP and OPO

- Initiation of ART is associated with *increased rates of bone metabolism, particularly resorption.* These increases occur during the first 1-3 months of ARV tx
- No progression was seen during 9 months - 3 years of f/up. These and other studies suggest that this ↑ in bone metabolism is *not progressive. Note: BMD improved in some studies.*
- Currently there are no long-term studies *examining fracture risk, which is the most meaningful outcome of OP or OPO*
- *Tebas CROI 07/ Bonnet 9th IW Adverse Drug Reactions and Lipodystrophy in HIV 2007/Bolland 2007 Clinical Endocrinology*

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SUN Cohort: Osteopenia/Osteoporosis

Total Cohort Osteopenia 47%	Total Cohort Osteoporosis 11%	Statistical Significance
Low BMD was associated with ⇨	Age > 45, male gender, lower BMI, unemployment, d4T use	Yes
Osteoporosis was associated with ⇨ CROI 2007	Older age, nonwhite-race, lower BMI, longer duration since HIV dx, unemployment	Yes

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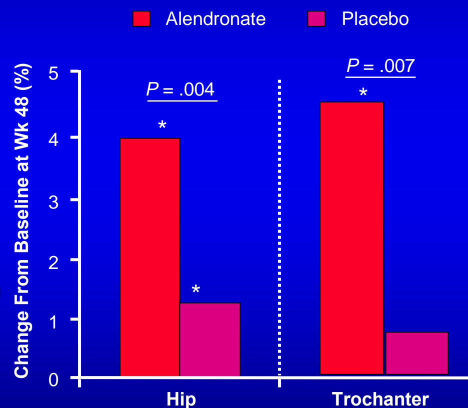
ACTG 5163: Alendronate + Vit D + CA^{++} VS. Vit D and CA^{++} on BMD

- RCT, phase II, Osteopenic (lumbar T-score < -1.5) 71% men
- Safe, effective in hip and trochanter but *not in the femoral neck*
- Black race associated with smaller change from BL with alendronate (*P* = .003)



*Significant change from BL.

McComsey G, et al. CROI 2007. Abstract 42.

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Key Points

- Vitamin D_3 levels are chronically low in many patients who are HIV uninfected and HIV infected
- May 2007 recommendations from the Osteoporosis Society for those > 50 years of age! *Most of us in this room should have in our diets or in supplements*
  - Calcium 1400 mg per day
  - Vitamin D_3 1200 mg per day
- *Traditional risk factors for OP and OPO are common in HIV+ pts; it is likely that is the HIV connection. More data is accruing… stay tuned*

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ARS Question

- 1. Approximately 9% of those living with AIDS in the US are > 50 years; older adults may present with dementia as the sentinel event that establishes a diagnosis of AIDS/HIV
- 2. It is anticipated that 20% of people with AIDS will be over 65 in 2015
- 3. In 2004, 18.6% of newly dx AIDS cases were in those > 50 years of age
- 4. HIV infection, per se, lowers the threshold for other age-related neurodegenerative disorders to occur

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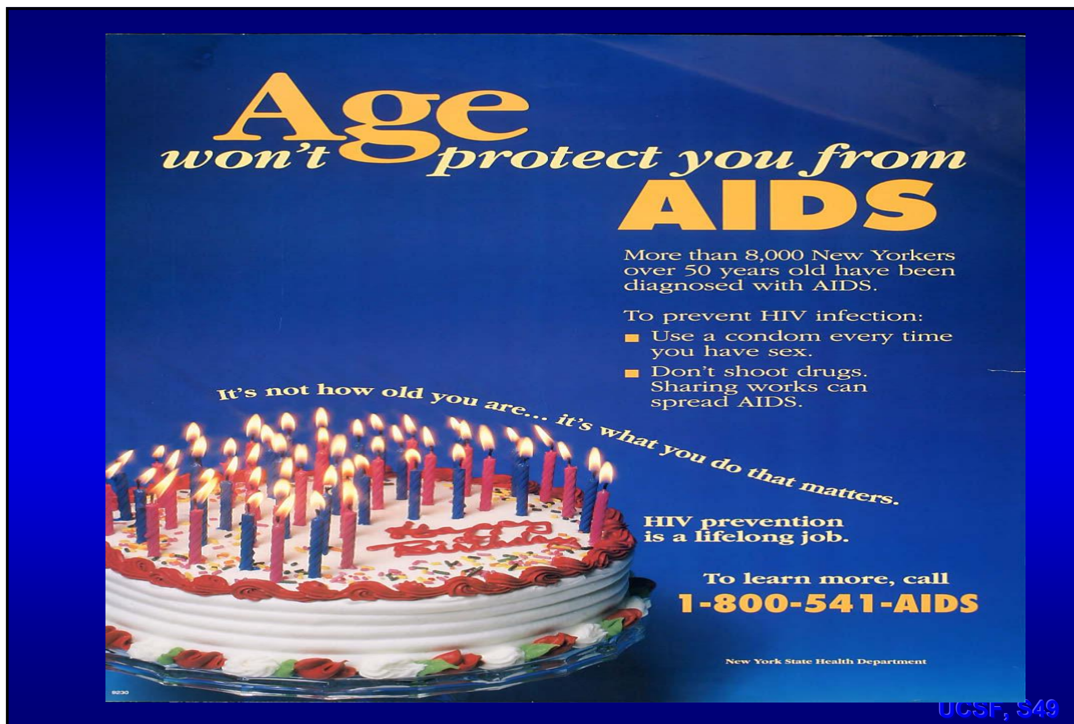
Age
won't protect you from
AIDS
More than 8,000 New Yorkers over 50 years old have been diagnosed with AIDS.
To prevent HIV infection:
Use a condom every time you have sex.
Don't shoot drugs. Sharing works can spread AIDS.
It's not how old you are... it's what you do that matters.
HIV prevention is a lifelong job.
To learn more, call
1-800-541-AIDS
New York State Health Department
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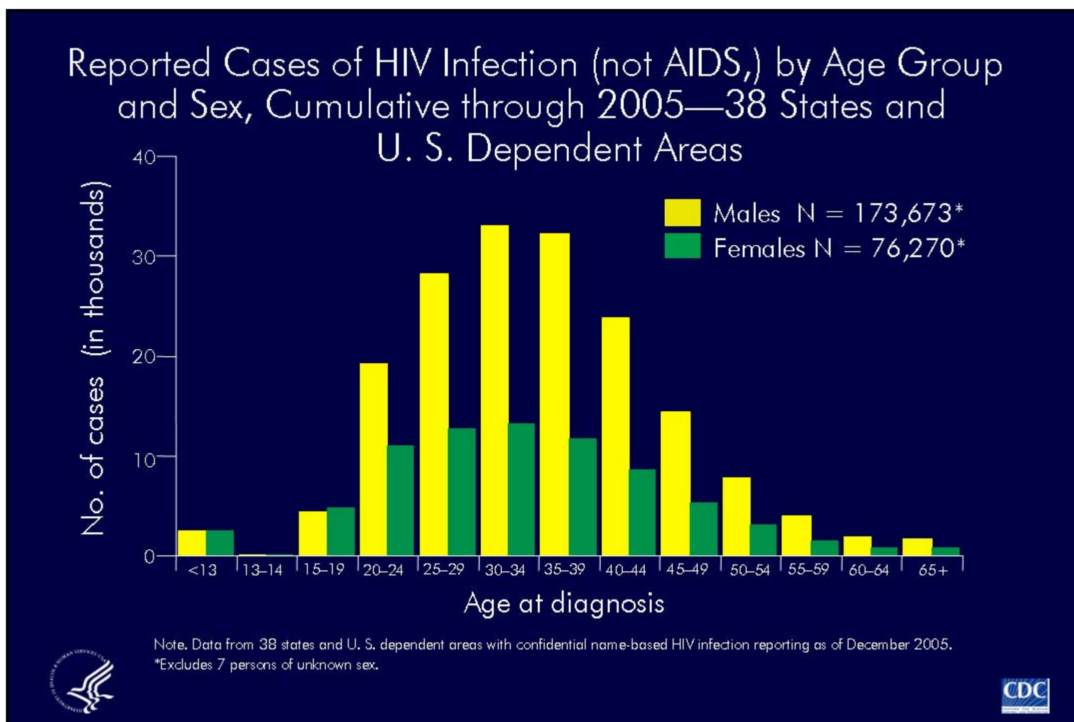
Reported Cases of HIV Infection (not AIDS,) by Age Group and Sex, Cumulative through 2005—38 States and U. S. Dependent Areas
No. of cases (in thousands)
40
30
20
10
0
Males N = 173,673*
Females N = 76,270*
<13
13–14
15–19
20–24
25–29
30–34
35–39
40–44
45–49
50–54
55–59
60–64
65+
Age at diagnosis
Note. Data from 38 states and U. S. dependent areas with confidential name-based HIV infection reporting as of December 2005.
*Excludes 7 persons of unknown sex.
CDC

HIV/AIDS in Those > 50 Years Old

In the U.S.

- Between 1994 and 2000 the number of adults aged 50 and older living with AIDS increased by 213.7% *accounting for 18.9% of persons living with AIDS in 2000.*
- *In 2004, 18.6% of newly dx AIDS cases were in those > 50 years old*
- US Senate Special Committee on Aging predicts a 50% prevalence of *HIV/AIDS patients > 50 by 2015*

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HIV/AIDS in Those > 50

- In the U.S., HIV/AIDS prevention and education efforts are not geared for older adults
  - We don't explore risk behaviors among older patients, especially sex and drug use
  - *Many sx of HIV/AIDS can be misinterpreted by providers and patients as relating to "old age"*

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Aging and HIV

- The incidence and prevalence of HIV infection in older adults is rising, with disproportionate increases in women and minorities.
  - *70% of cases in older women are in women of color*
- Older patients who have HIV often are diagnosed later in the course of the disease and *may have an accelerated decline in immune function due to their age*
- Although the prognosis for older adults has improved with the initiation of highly active antiretroviral therapy, there remains *a higher risk for comorbid illness and drug interactions*
- Additional efforts to diagnose and prevent HIV infection in this older age group are necessary to decrease the transmission of HIV and to reduce the morbidity and mortality associated with this infection
- *JAIDS (August 2007)*

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Glossary for Dementia in HIV-Infected Patients

- HIV-associated dementia (HAD): an acquired abnormality in 2 or more cognitive domains with an additional abnl finding in either motor function or motivation and/or emotional control
- Minor cognitive motor disorder (MCMD) is a milder impairment with 2 or more cognitive and/or behavioral symptoms and an objective finding of 1 acquired cognitive or motor abnormality
- Both require that the cognitive problems reduce ability to completely ADL's or work

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Important Questions About Aging and HIV

- Older adults may present with ***dementia as the sentinel*** event that establishes a diagnosis of AIDS/HIV
- Whether there is an additive or synergistic relationship between aging and HIV is still not known
- Does HIV infection, per se, lower the threshold for other age-related neurodegenerative disorders to occur?
- Is immunosenenesence ***entirely*** mitigated by ART?

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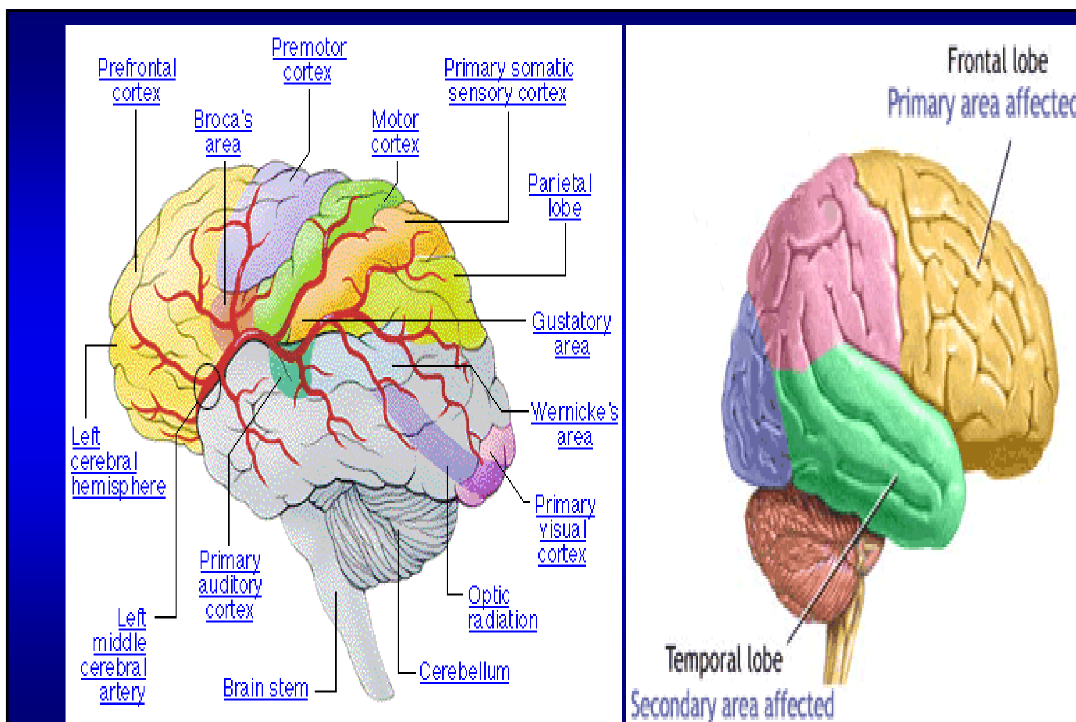

HIV/AIDS and Aging

- The brain remains vulnerable despite ART and peripheral viral loads below the level of detection
  - Especially for those who started with a low nadir
- CNS compartmentalization of the virus occurs and plasma HIV RNA levels are not always equated with brain parenchymal exposure, injury and inflammation
- *Neurotoxicity of ART, lipid abnormalities and metabolic syndromes, not uncommon in our patients, can be precursors to cerebrovascular disease and cognitive impairment*
- Cerebral endothelial changes have been found in some with lipodystrophy and diabetes and HAD

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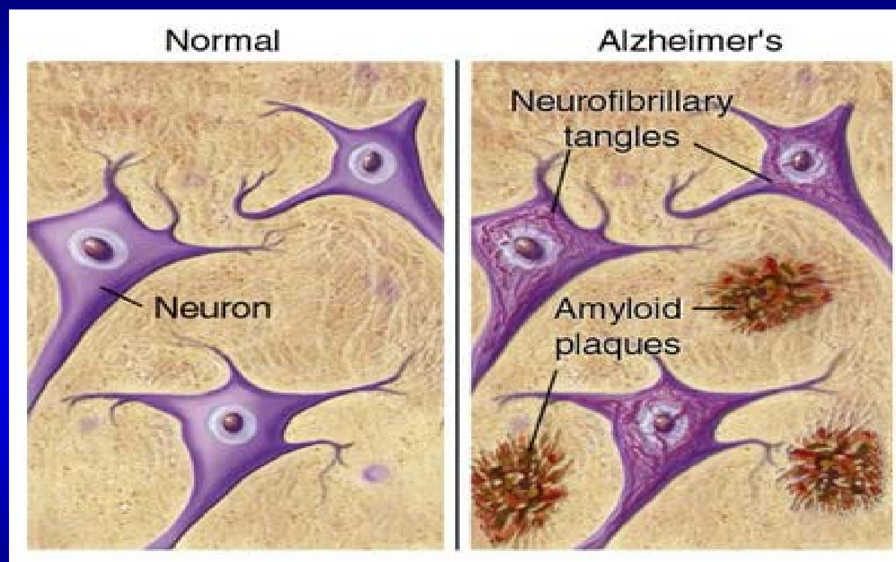

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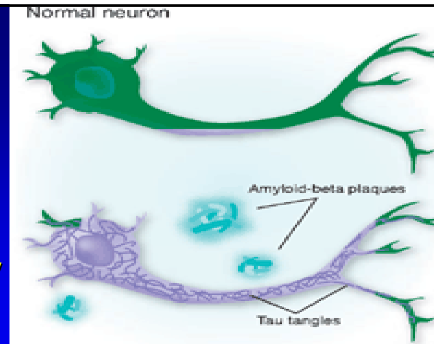
HIV/AIDS and Aging



- New data suggest that an overlap in Alzheimer's neuropathology and HIV dementia should be addressed
  - Increased brain *B*-amyloid deposition and extracellular amyloid plaques have now been reported in HIV infected patients
  - Neprolysin, an enzyme responsible for amyloid degradation, is inhibited by Tat
  - The existence of apolipoprotein *E*4 allele correlates to HAD
- *Many complexities beset the older HIV infected patient*

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Top 10 Conclusions

- Advocate for routine and high risk HIV testing
  - State and local governments are the rate limiting step
- Use caution with nelfinavir, varenicline, entecavir, rosiglitazone and pioglitazone and more.
  - Always watch for drug interactions
- Understand the cohort effect of HIV and OPO and that ARV's initially increase bone resorption
  - Adequate Vit D_3 and CA++ are recommended esp. if > 50
  - Consider early DEXA screening if risk factors for OPO are present

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Top 10 Conclusions

- **Stay tuned as our patients age and:**
  - **When routine testing is in place and we are able to diagnose HIV early in the course of the infection and determine *if earlier tx with ART is neuroprotective esp. in older people***
  - **We learn how to mitigate neurodegenerative diseases in HIV infected and uninfected individuals**
  - **Note: This is another example of how much of HIV research continues to be generalizable to non-HIV infected patients**
  - ***mnewman@php.ucsf.edu***

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HIV/AIDS Resources for Those over 50

- ***Publication from the HIV/AIDS Bureau of the U.S. Health Resources and Services Administration (HRSA)***
  ftp://ftp.hrsa.gov/hab/hrsa2-01.pdf
- **Special Needs of Elderly HIV Positive African Americans**
  Abstract from the 2003 National HIV Prevention Conference
  http://gateway.nlm.nih.gov/robot_pages/MeetingAbstracts/102261991.html
- **HIV, AIDS, and Older People**
  Fact sheet from the National Institute on Aging
  http://www.niapublications.org/agepages/aids.asp
  En Español

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HIV/AIDS Resources for Those over 50

- *From Center for AIDS Prevention Studies, University of California at San Francisco*
  http://www.caps.ucsf.edu/pubs/FS/over50.php En Español
- Tip Sheet - HIV/AIDS and Older Adults
  Fact sheet from the National Association on HIV Over Fifty (NAHOF) http://www.hivoverfifty.org/tip.html
- HIV in Elderly Presents Unique Challenges
  News article from UPI, provided by the AIDS Education Global Information System (AEGIS)
  http://www.aegis.com/news/upi/2002/UP020305.html
- The Elderly, HIV/AIDS and Sustainable Rural Development

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