

AIDS at 30

Epidemiology and Clinical Management

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Dengue - Continued

Editorial Note: Dengue type 4 frequently occurs in Southeast Asia, the South Pacific, and Africa. How it was introduced onto St. Barthelemy, a small and relatively remote island in the Caribbean, remains unknown. However, French health authorities have reported to CAREC that an outbreak of dengue-like illness has been observed on St. Barthelemy, beginning in February or March, but has since declined. In the absence of reports of an ongoing outbreak of dengue in the Caribbean, the risk that travelers to this area will acquire dengue is probably small.

Dengue types 2 and 3 have been present in the Caribbean at least since the 1960s. Dengue type 1 was first recognized in that area when an outbreak in Jamaica in 1977 was followed by numerous outbreaks on other Caribbean islands and in Central America. All these dengue types, as well as type 4, usually cause an illness that is clinically mild and typically of short duration.

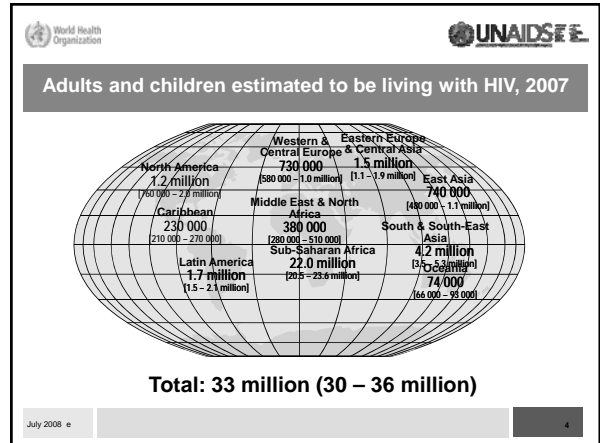
Pneumocystis Pneumonia - Los Angeles

In the period October 1980-May 1991, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

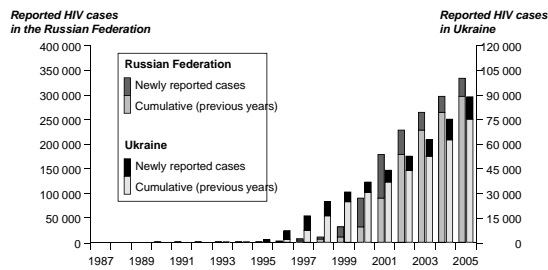
Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viremia. The serum complement-fixable CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP-SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed...

HIV Transmission

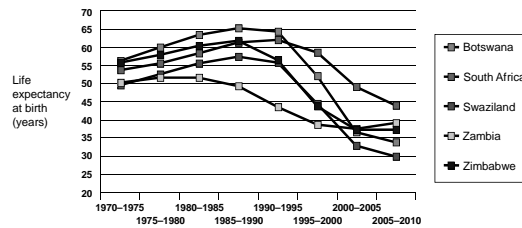
- Blood
 - transfusion
 - injection drug use
- Sexual Intercourse
 - heterosexual
 - male to male
- Perinatal
 - intrapartum
 - breast feeding

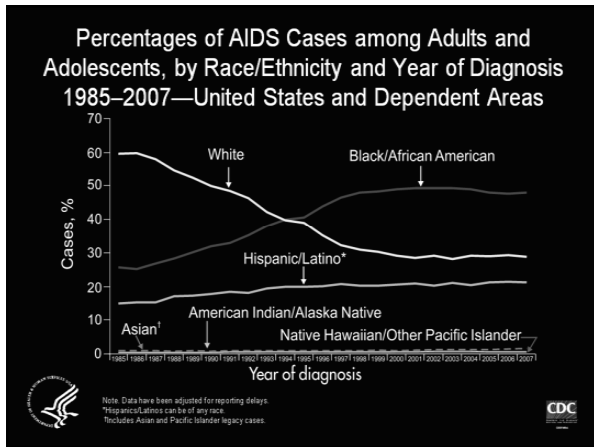
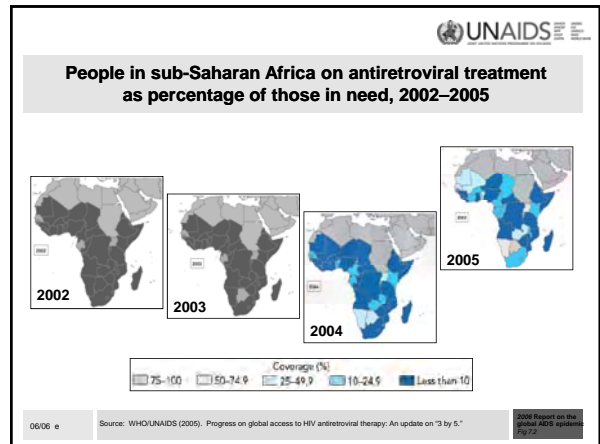
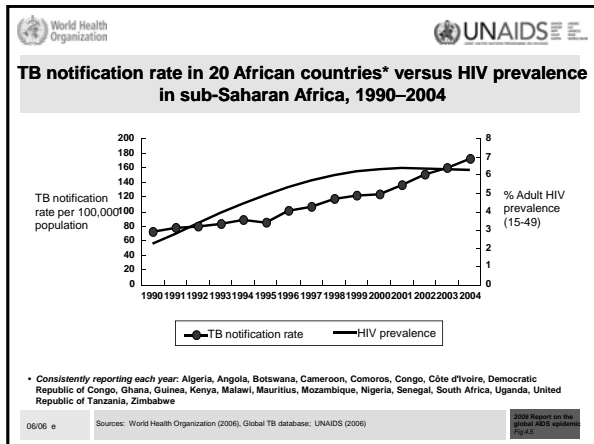


Increase in reported HIV cases in the Russian Federation and Ukraine, 1987-2005



Impact of AIDS on life expectancy in five African countries, 1970-2010





AIDS in Blacks/African Americans

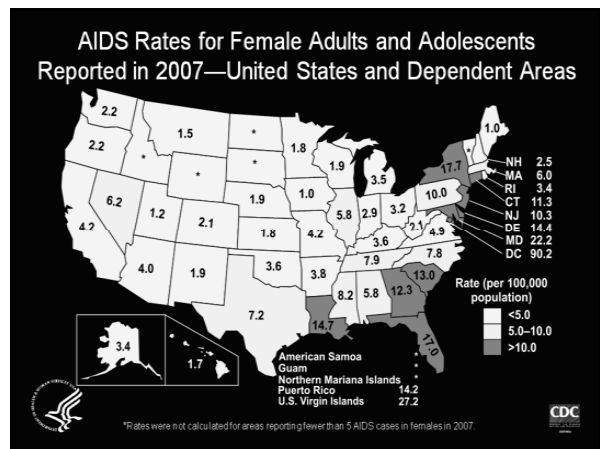
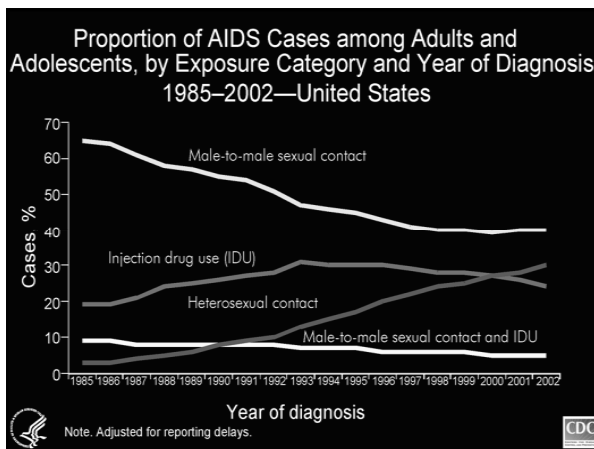
Of the 1,030,832 AIDS cases reported to CDC through 2007, blacks/African Americans accounted for

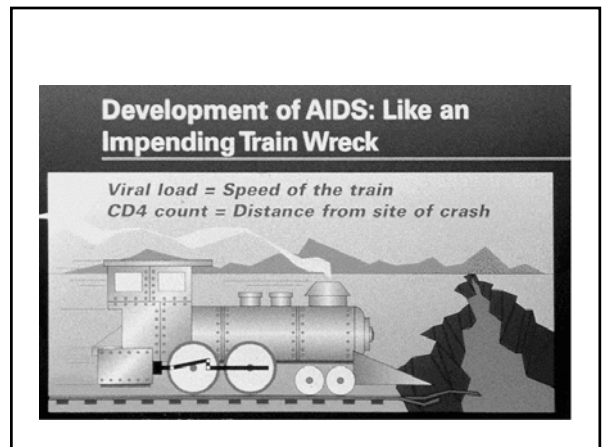
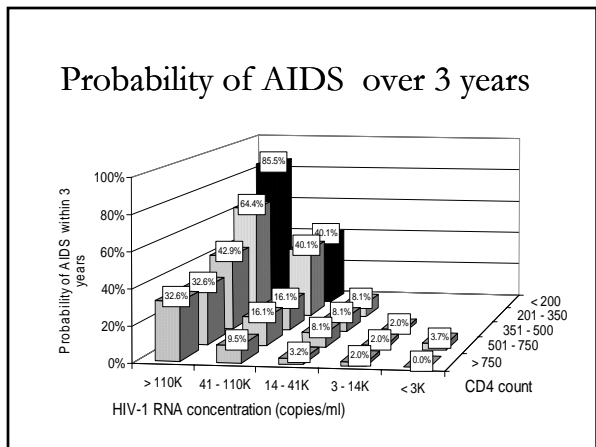
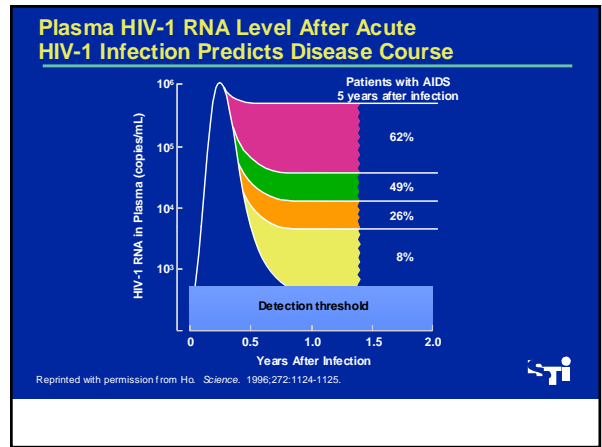
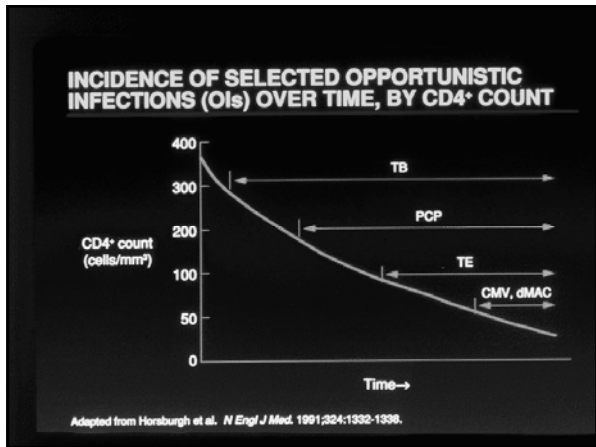
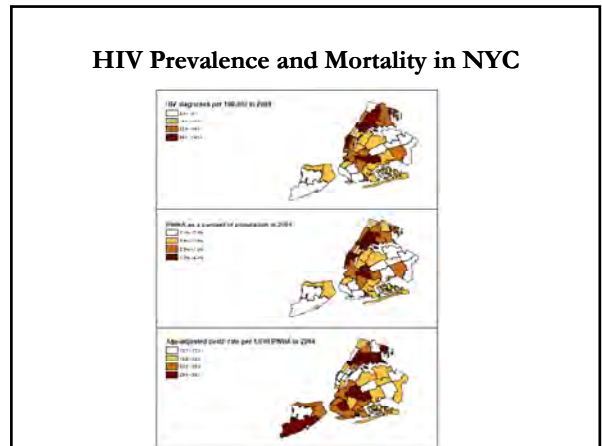
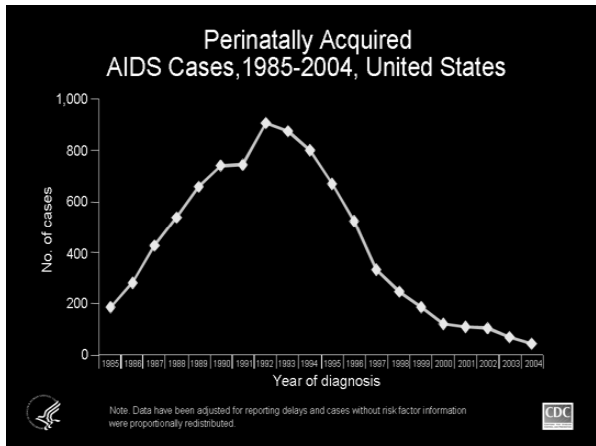
- 41% of total
- 60% of women
- 59% of heterosexual persons at high risk*
- 59% of children aged <13 years

Of AIDS cases reported during 2007, 47% were in black/African American adults and adolescents.

*High-risk/heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

CDC





Frequency of HIV 'Non-Progressors'

- San Francisco City Clinic Cohort
 - 489 HIV+ Gay men with known seroconversion date.
 - 13% developed AIDS by 5 years;
 - 51% developed AIDS by 10 years.
 - 89% had died, developed AIDS or had CD4<500 by 10 years.

[Rutherford et al. BMJ. 1990; 301:1183-8]

Explaining the variability of HIV disease

- Viral Factors
 - Nef deletion
 - Non-clade B subtypes?
- Host Factors
 - Chemokine co-receptors
 - Immune response
 - Gender?
- Environmental Factors
 - Infection, diet?, stress?

HIV Co-receptors

CD4 necessary but not sufficient for infection.
Beta chemokine receptors act as HIV co-receptors.

CXCR4 (lymphocyte) CCR5 (macrophage)

Homozygous CCR5 deletion found in <1%.

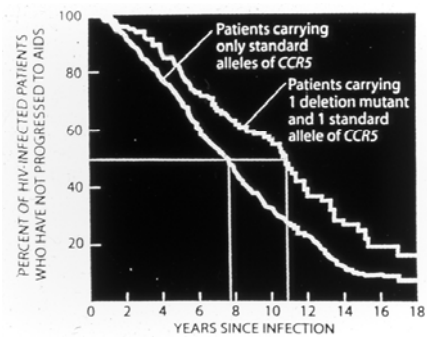
MACS High risk cohort:

No HIV+ among those homozygous for deletion.

3.6% of HIV Negative were homozygous.

Among persistently HIV Neg: up to 33% were homozygous for CCR5 deletion.

Effect of Co-receptor Heterozygosity



AIDS Restriction Genes

Table 2 Genes that limit AIDS

Gene	Allele	Mode	Effect	Mechanism of action	Reference
HIV entry					
CCR5	Δ32	Recessive	Prevent infection	Knockout CCR5 expression	17
	Δ32	Dominant	Prevent symptoms (L)	Decrease available CCR5	90
	Δ32	Dominant	Delay AIDS	Decrease available CCR5	17
CCR5	P1	Recessive	Accelerate AIDS (E)	Increase CCR5 expression	34
CCR2	W4	Dominant	Delay AIDS	Interact with and reduce CXCR4	38,39
CCL5	W11c	Dominant	Accelerate AIDS	Increase RANTES expression	43
CXCL12	J A	Recessive	Delay AIDS (L)	Improve CXCR3-CXCR4 transmembrane (T)	46
CCR6	E3K	Dominant	Accelerate PCP (L)	Alter T-cell activations (T)	48
CCL4-CCL7-CCL11	H7	Dominant	Enhance infection	Stimulate immune response (T)	49
Cytokine anti-HIV					
IL10	5'A	Dominant	Limit infection	Decrease IL10 expression	53
	5'A	Dominant	Accelerate AIDS	Decrease IL10 expression	53
IFNγ	-179T	Dominant	Accelerate AIDS (E)		55
Acquired immunity, cell mediated					
HLA	A,B,C	Homozygous	Accelerate AIDS	Decrease breadth of HLA class I epitope recognition	62,66
	B*27	Codominant	Delay AIDS	Delay HIV-1 escape	9
	B*57	Codominant	Delay AIDS	Delay HIV-1 escape	9
	B*35-Px	Codominant	Accelerate AIDS	Defect CD8-T cell clearance of HIV-1	60
Acquired immunity, innate					
AIR3DS1	3DS1	Epistatic with HLA-B*57	Delay AIDS	Clear HIV*, HLA* cells (T)	70

S. O'Brien, G. Nelson. *Nature Genetics* 2004;36:565

Early indicators of HIV Infection

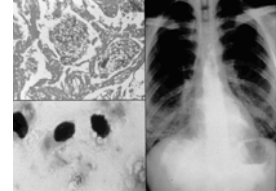


Key features of OIs in AIDS

- HIV causes profound defect mostly restricted to T cell-based immunity (restricted range of pathogens)
- OIs usually reflect reactivation of latent infections.
- Reinfection may occur (eg: tuberculosis)
- Chronic suppression needed after acute treatment.
- Immune reconstitution with anti-retroviral therapy may reverse OI susceptibility (but may also trigger an inflammatory response to active OIs)

Pneumocystis pneumonia in AIDS

- Commonest life threatening complication of AIDS in U.S.
- Subacute illness (fever, cough, dyspnea).
- Diffuse interstitial infiltrate on x-ray.
- Addition of corticosteroids to antimicrobials cuts mortality in severe disease 50%.
- Fully preventable with trimethoprim-sulfa.



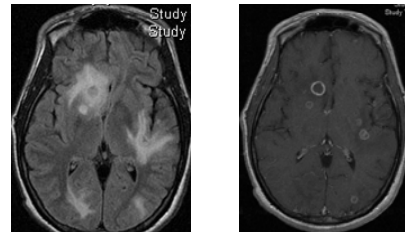
CD4 count predicts risk of PCP

TABLE 1. Cumulative incidence* of *Pneumocystis carinii* pneumonia (PCP) according to CD4+ count at baseline among the MACS seroprevalent cohort†

CD4+ count at baseline	N	PCP	Percentage with PCP		
			6 mo.	12 mo.	36 mo.
< 200	77	19	8.4	18.4	33.3
201-350	217	47	0.5	4.0	22.9
351-500	389	39	0.0	1.4	9.0
501-700	483	43	0.0	0.4	8.3
> 700	499	20	0.0	0.0	3.8

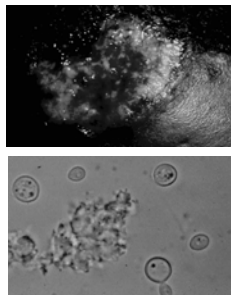
CNS toxoplasmosis

- Protozoan parasite; cats shed oocysts; farm animals incidental hosts; humans infected from cysts, uncooked meat.
- Commonest cause of focal CNS disease in AIDS.
- Serum IgG antibody reliable marker of past infection.
- Reactivation in AIDS associated with CD4<100.



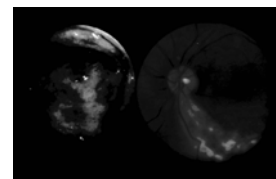
Cryptococcal disease in AIDS

- Ubiquitous soil fungus.
- Initial asymptomatic pneumonia.
- Reactivation in advanced HIV disease (CD4<100).
- Meningitis commonest presentation but wide dissemination frequent.



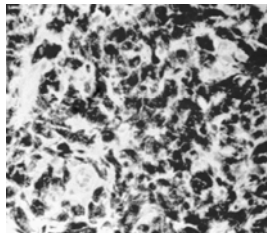
CMV disease in AIDS

- Common viral infection (50% adult seroprevalence).
- Reactivation at CD4<50
- Retinitis commonest.
- Other sites: Colon, CNS.



Disseminated Mycobacterium-avium complex (MAC) disease in AIDS |

- Common in environment (water).
- Local lung disease known prior to AIDS.
- Widespread visceral dissemination in AIDS.
- Diagnosis by blood culture.
- Absence of inflammation in tissue sites.



Prophylaxis of Opportunistic Infections

Pathogen	Indication	Regimen
PCP	CD4<200	Trimethoprim-sulfa
Toxo	CD4<100 and IgG+	Trimethoprim-sulfa or Dapsone +Pyrimethamine
MAC	CD4<50	Clarithro/Azithromycin
TB	+PPD (5mm)	INH (9 months)

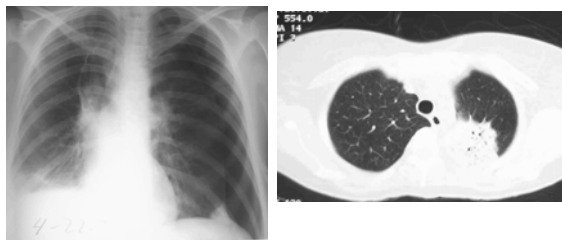
Discontinuation of Prophylactic or Suppressive Regimens

Pathogen	Primary Prophylaxis		Secondary Prophylaxis or suppression: Additional criteria
	CD4 Threshold	CD4 Duration	
PCP	200	3 months	None
Toxo	200	3 months	CD4>200 for 6 months Completed initial Rx.
MAC	100	3 months	CD4>100 for 6 months Completed 12 mo Rx.
Cryptococcus	NA	NA	CD4>200 for 6 mo. Completed initial Rx.
CMV	NA	NA	CD4>100 for 3-6 mo. No active disease

Immune Reconstitution with HIV Therapy

- Focal MAC adenitis
- Inflammatory flare of CMV retinitis
- Worsening of previously stable hepatitis
- Development of cavitary TB

MAC IRIS simulating TB or Lung cancer



HSV IRIS suppressed by thalidomide

