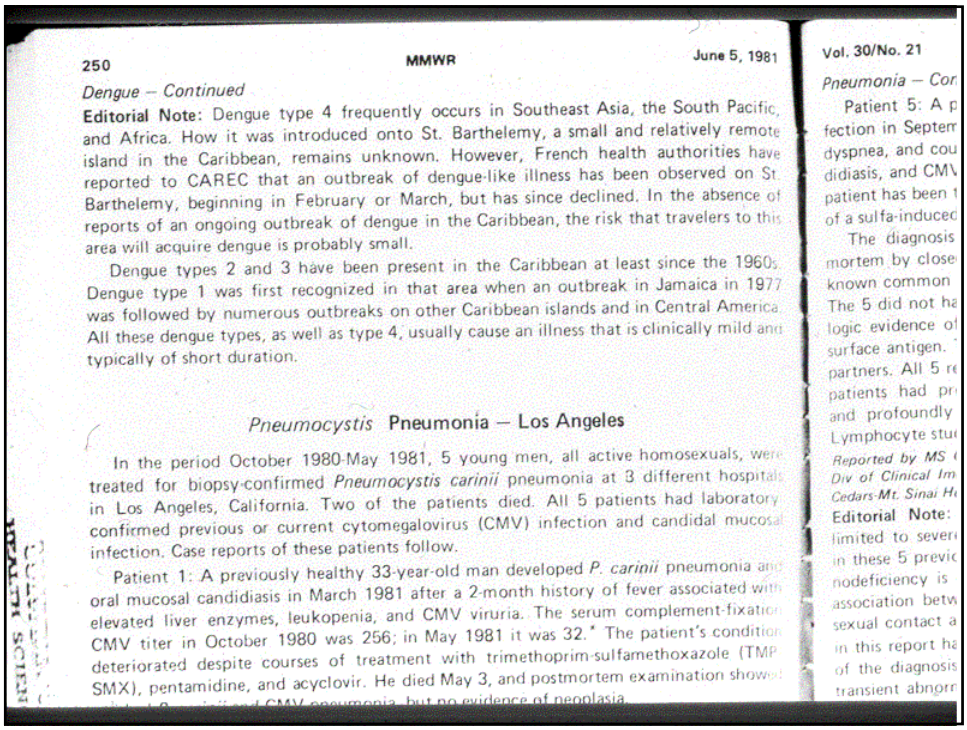
AIDS at 30

Epidemiology and Clinical Management



250 MMWR June 5, 1981

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 1981, 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 viruria. The serum complement-fixation 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

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Pneumonia – Cor

Patient 5: A p
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Editorial Note:
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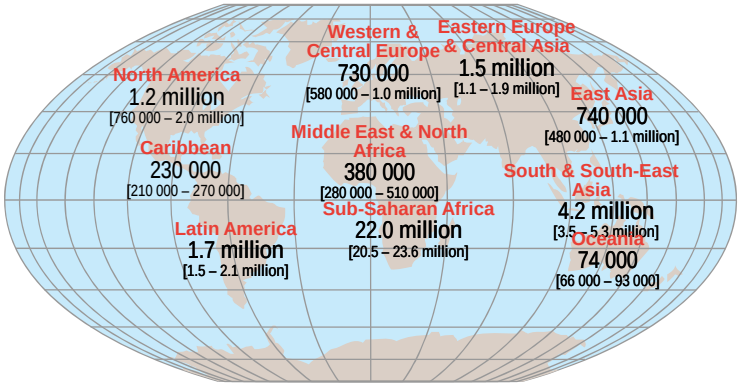
HIV Transmission

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

World Health Organization

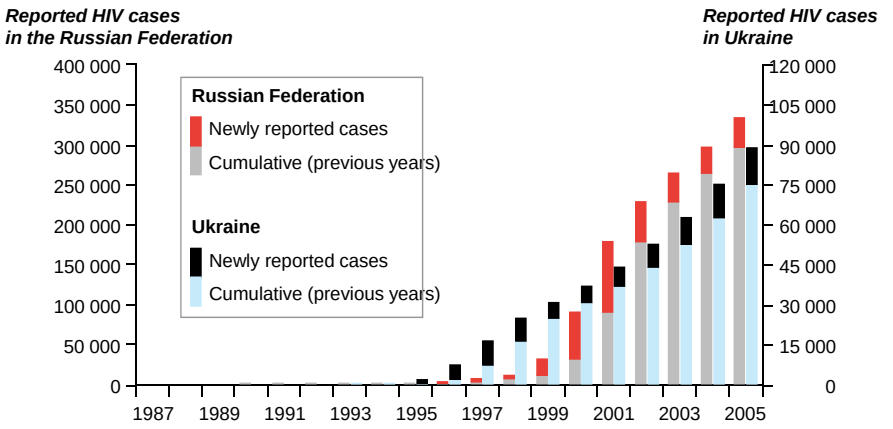
UNAIDS

Adults and children estimated to be living with HIV, 2007



Total: 33 million (30 – 36 million)

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

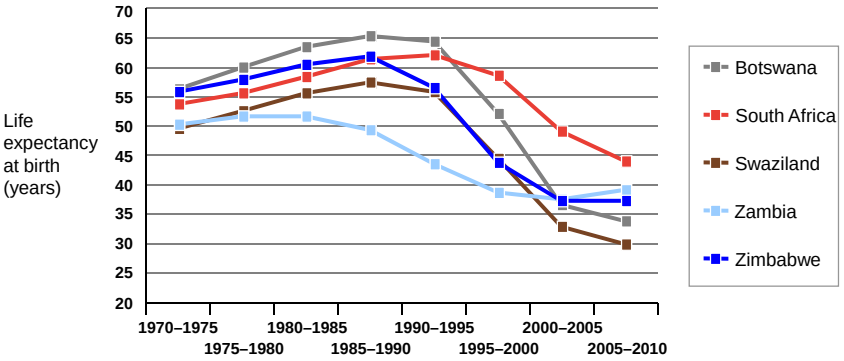


06/06 e

Sources: Russian Federal AIDS Centre; Ukranian AIDS Centre and Ministry of Health of Ukraine

2006 Report on the global AIDS epidemic
Fig 2.12

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



06/06 e

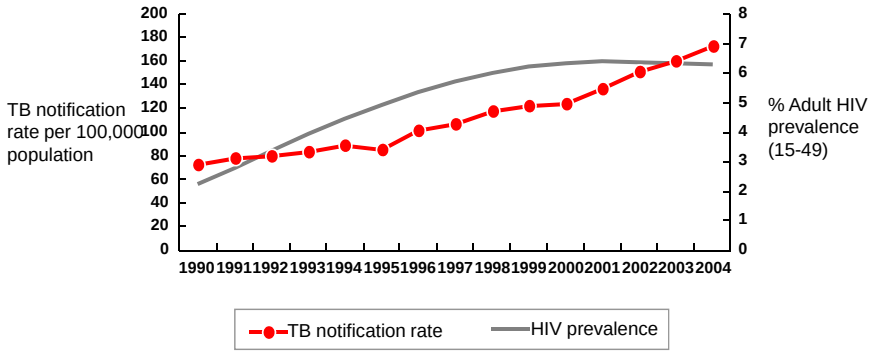
Source: United Nations Population Division (2004). World Population Prospects: The 2004 Revision, database.

2006 Report on the global AIDS epidemic
Fig 4.1

World Health Organization

UNAIDS

TB notification rate in 20 African countries* versus HIV prevalence in sub-Saharan Africa, 1990–2004



- ***Consistently reporting each year*: Algeria, Angola, Botswana, Cameroon, Comoros, Congo, Côte d'Ivoire, Democratic Republic of Congo, Ghana, Guinea, Kenya, Malawi, Mauritius, Mozambique, Nigeria, Senegal, South Africa, Uganda, United Republic of Tanzania, Zimbabwe**

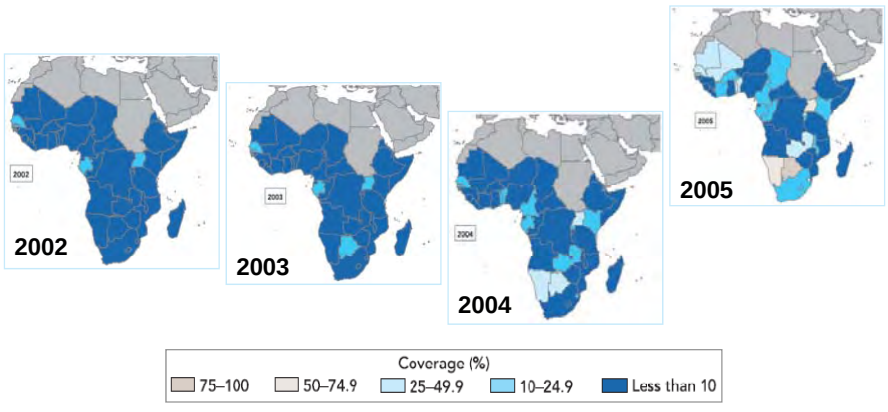
06/06 e

Sources: World Health Organization (2006), Global TB database; UNAIDS (2006)

2006 Report on the global AIDS epidemic *Fig 4.5*

UNAIDS

People in sub-Saharan Africa on antiretroviral treatment as percentage of those in need, 2002–2005



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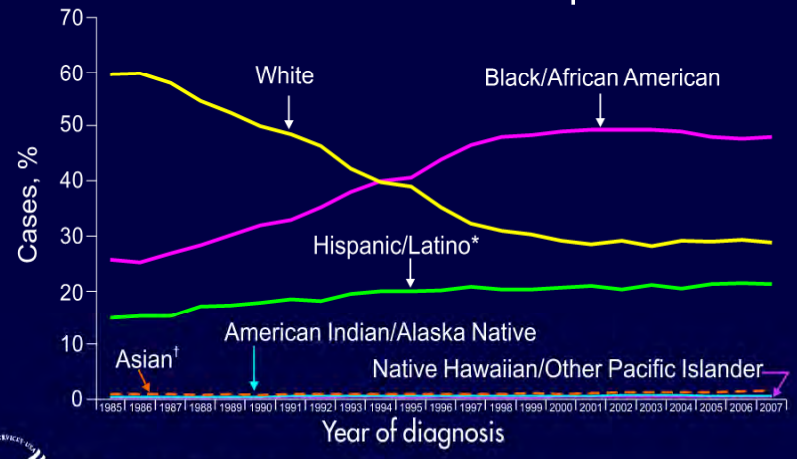
Source: WHO/UNAIDS (2005). Progress on global access to HIV antiretroviral therapy: An update on "3 by 5."

2006 Report on the global AIDS epidemic *Fig 7.2*

Percentages of AIDS Cases among Adults and Adolescents, by Race/Ethnicity and Year of Diagnosis 1985–2007—United States and Dependent Areas



Note. Data have been adjusted for reporting delays.
*Hispanics/Latinos can be of any race.
†Includes Asian and Pacific Islander legacy cases.

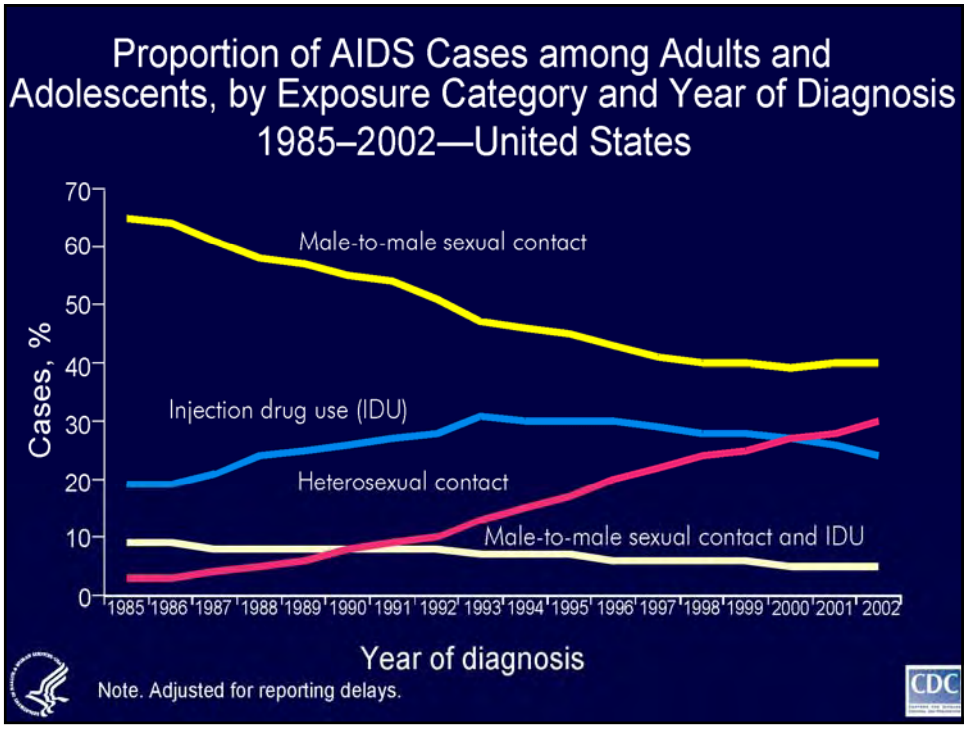
AIDS in Blacks/African Americans

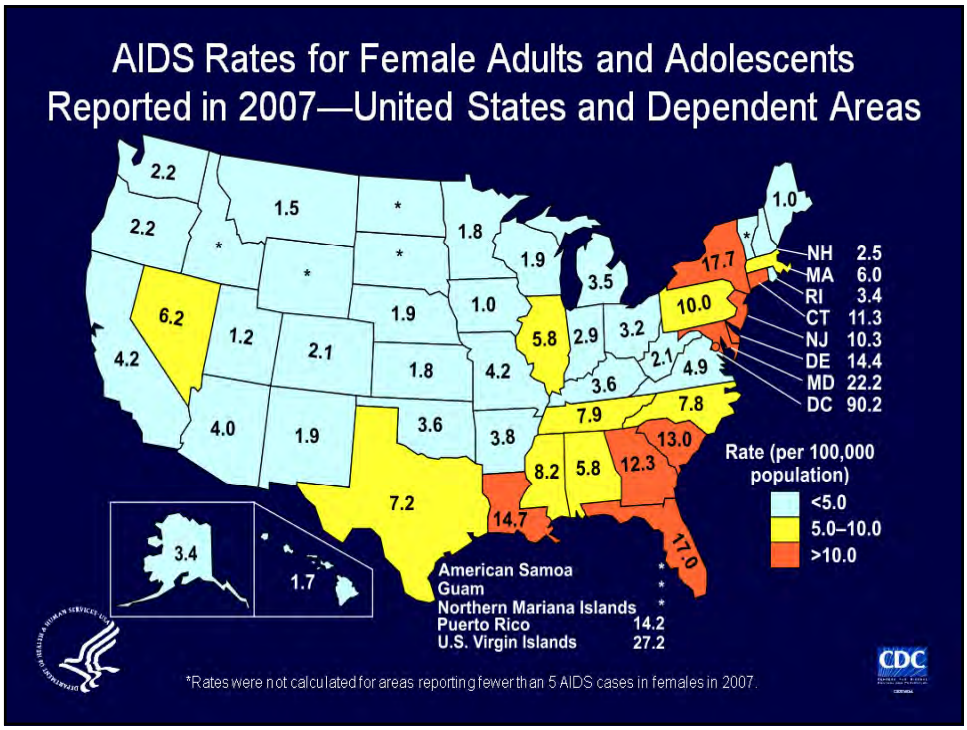
Of the 1,030,832 AIDS cases reported to CDC through 2007, blacks/African Americans accounted for

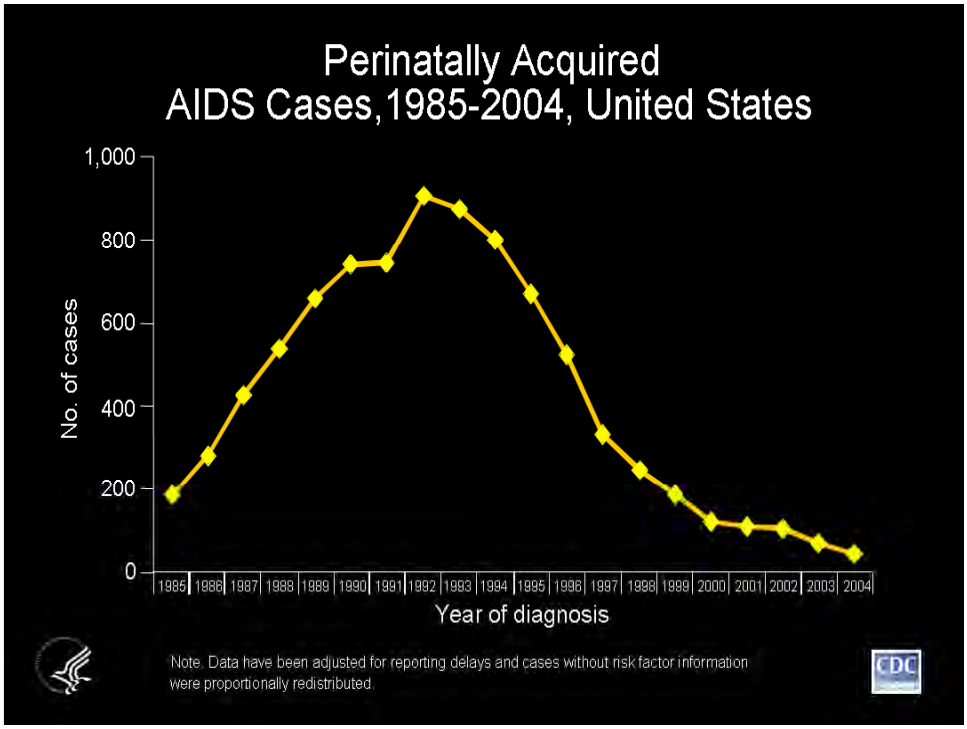
- 41% of total
- 60% of women
- 59% of heterosexual persons at high risk*
- 59% of children aged <13 years

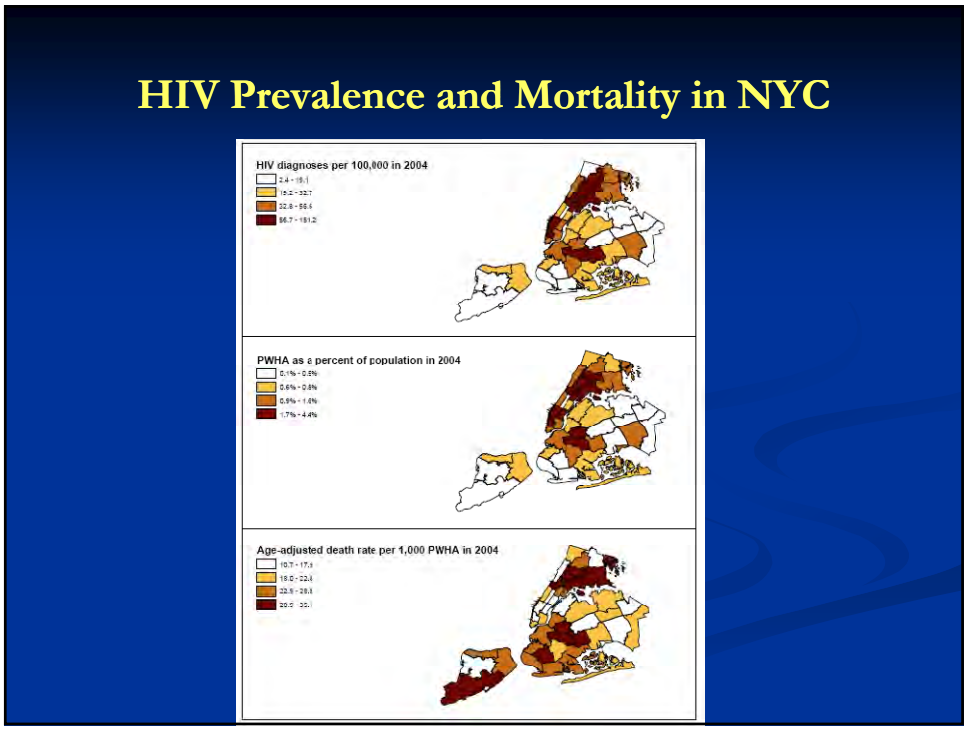
Of AIDS cases reported during 2007, 47% were in black/African American adults and adolescents.

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

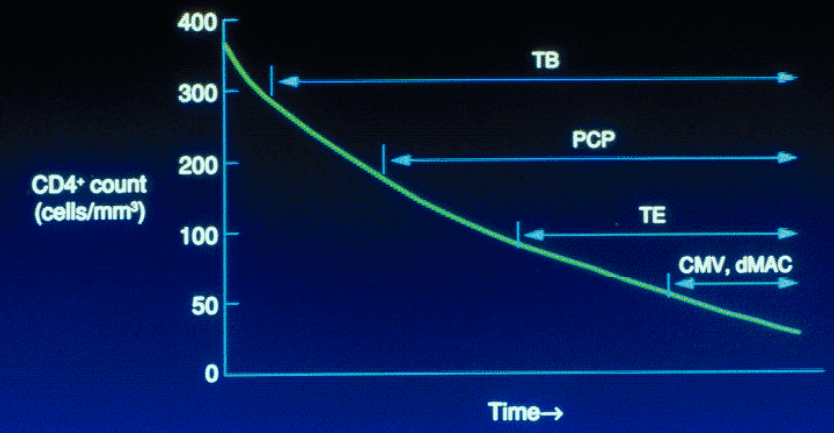

Proportion of AIDS Cases among Adults and Adolescents, by Exposure Category and Year of Diagnosis 1985–2002—United States
Cases, %
70
60
50
40
30
20
10
0
Male-to-male sexual contact
Injection drug use (IDU)
Heterosexual contact
Male-to-male sexual contact and IDU
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002
Year of diagnosis
Note. Adjusted for reporting delays.
CDC


AIDS Rates for Female Adults and Adolescents Reported in 2007—United States and Dependent Areas
NH 2.5
MA 6.0
RI 3.4
CT 11.3
NJ 10.3
DE 14.4
MD 22.2
DC 90.2
Rate (per 100,000 population)
<5.0
5.0–10.0
>10.0
American Samoa *
Guam *
Northern Mariana Islands *
Puerto Rico 14.2
U.S. Virgin Islands 27.2
*Rates were not calculated for areas reporting fewer than 5 AIDS cases in females in 2007.
CDC


Perinatally Acquired
AIDS Cases,1985-2004, United States
No. of cases
1,000
800
600
400
200
0
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
Year of diagnosis
Note. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.
CDC

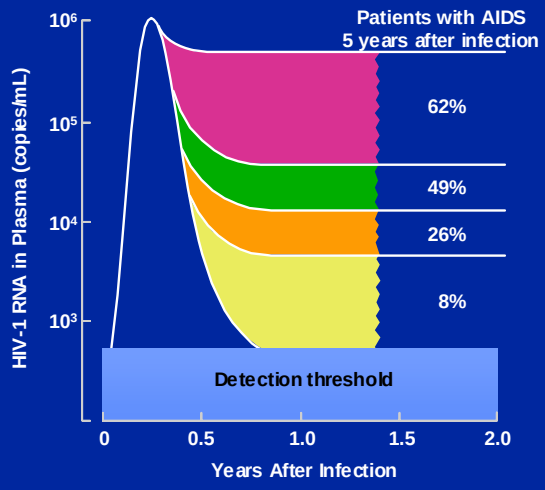

HIV Prevalence and Mortality in NYC
HIV diagnoses per 100,000 in 2004
PWHA as a percent of population in 2004
Age-adjusted death rate per 1,000 PWHA in 2004

INCIDENCE OF SELECTED OPPORTUNISTIC INFECTIONS (OIs) OVER TIME, BY CD4+ COUNT



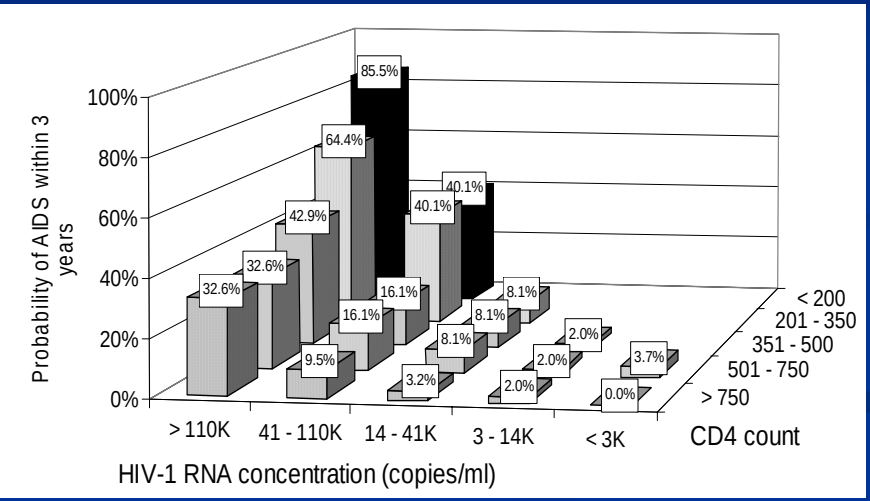
Adapted from Horsburgh et al. *N Engl J Med.* 1991;324:1332-1338.

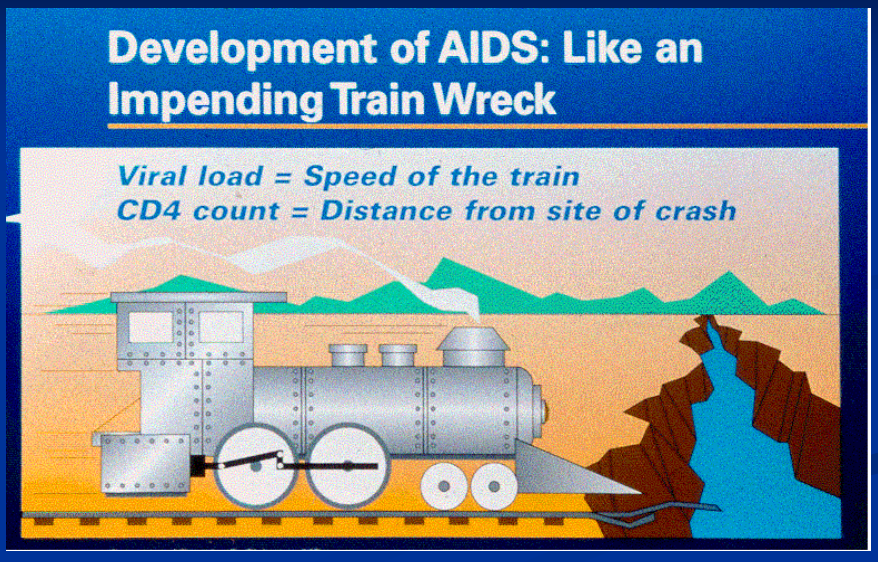
Plasma HIV-1 RNA Level After Acute HIV-1 Infection Predicts Disease Course



Reprinted with permission from Ho. *Science.* 1996;272:1124-1125.

Probability of AIDS over 3 years





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.

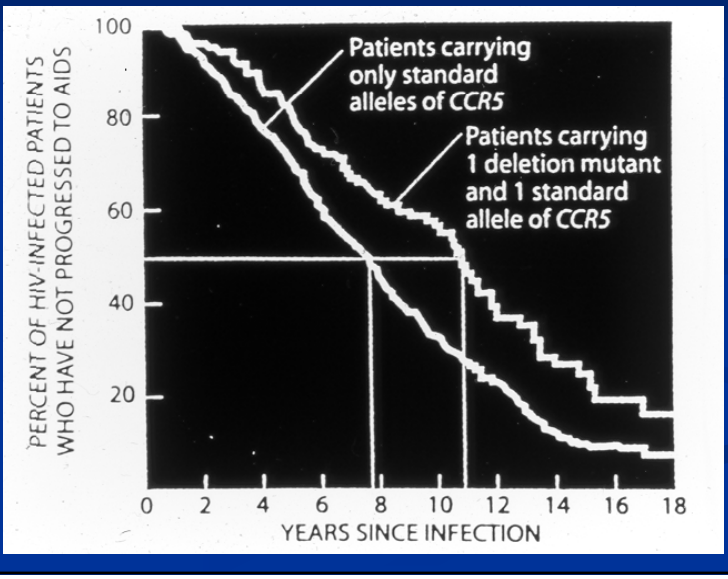
- CXCR4 (lymphocyte) CCR5 (macrophage)

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



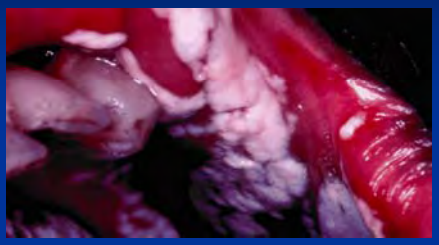
AIDS Restriction Genes

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 lymphoma (L)	Decrease available CCR5	90
	Δ32	Dominant	Delay AIDS	Decrease available CCR5	17
CCR5	P1	Recessive	Accelerate AIDS (E)	Increase *CCR5* expression	34
CCR2	I64	Dominant	Delay AIDS	Interact with and reduce CXCR4	38,39
CCL5	In1.1c	Dominant	Accelerate AIDS	Decrease RANTES expression	45
CXCL12	3′A	Recessive	Delay AIDS (L)	Impede CCR5-CXCR4 transition (?)	46
CXCR6	E3K	Dominant	Accelerate PCP (L)	Alter T-cell activations (?)	48
CCL2-CCL7-CCL11	H7	Dominant	Enhance infection	Stimulate immune response (?)	49
Cytokine anti-HIV					
IL10	5′A	Dominant	Limit infection	Decrease IL10 expression	53
	5′A	Dominant	Accelerate AIDS	Decrease IL10 expression	53
IFNG	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	Deflect CD8-T cell clearance of HIV-1	60
Acquired immunity, innate					
KIR3DS1	3DS1	Epistatic with *HLA-Bw4*	Delay AIDS	Clear HIV^+, HLA^- cells (?)	70

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

Early indicators of HIV Infection

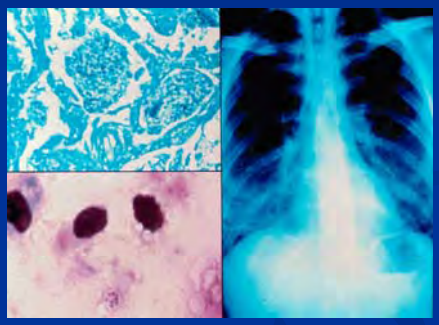


Key features of OIs in AIDS

- 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.



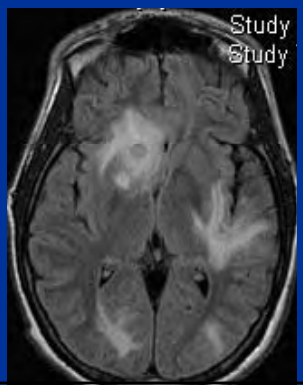
CD4 count predicts risk of PCP

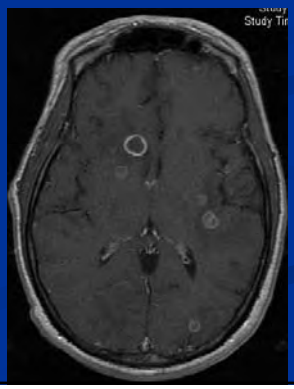
TABLE 1. Cumulative incidence* of *Pneumocystis carinii* pneumonia (PCP) according to CD4+ count at baseline among the MACS seroprevalent cohort†

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

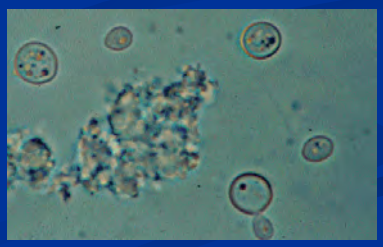
- Protozoon parasite; cats shed oocysts; farm animals incidental hosts; humans infected from cysts, uncooked meat.
- Commonest cause of focal CNS disease in AIDS.
- Serum IgG antibody reliable marker of past infection.
- Reactivation in AIDS associated with CD4<100.





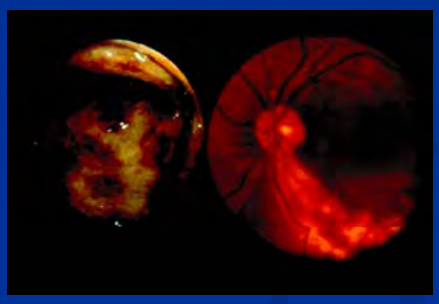
Cryptococcal disease in AIDS

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



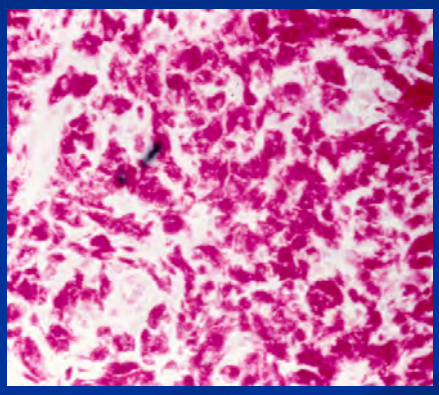
CMV disease in AIDS

- 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)

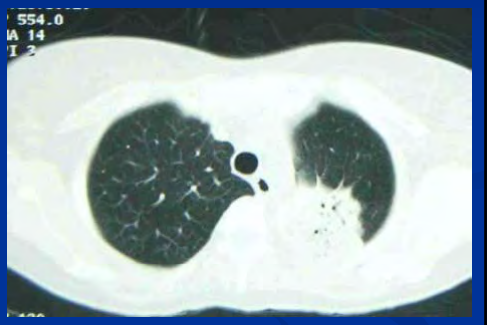
Discontinuation of Prophylactic or Suppressive Regimens

Pathogen	Primary Prophylaxis CD4 Threshold	Primary Prophylaxis CD4 Duration	Secondary Prophylaxis or suppression: Additional criteria
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