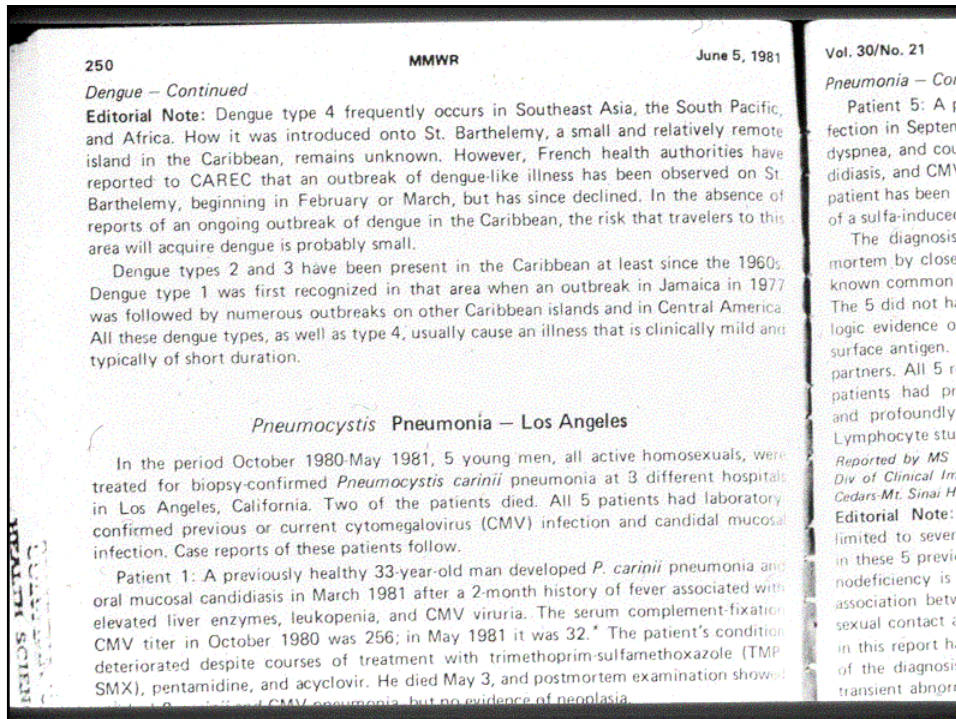


AIDS at 25

Epidemiology and Clinical Management



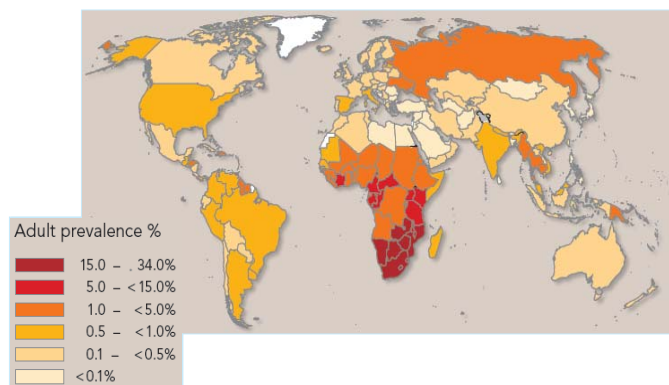
HIV Transmission

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



A global view of HIV infection

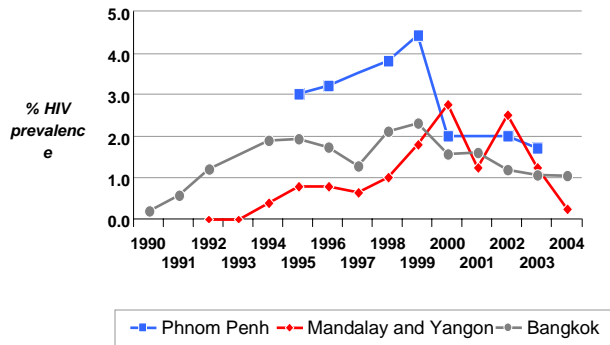
38.6 million people [33.4-46.0 million] living with HIV, 2005



06/06 e

2006 Report on the global AIDS epidemic
Fig 2.4

HIV prevalence trends among pregnant women in major cities in Cambodia, Myanmar and Thailand, 1990–2004



06/06 e

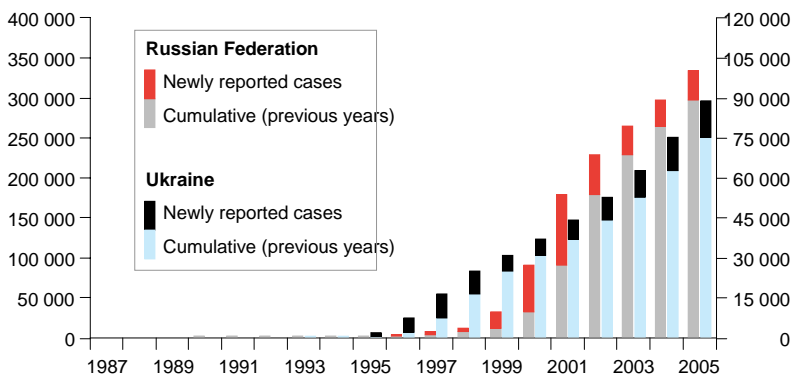
Sources: Cambodia National Center for HIV/AIDS, Dermatology and STDs (Phnom Penh); Myanmar Ministry of Health (Mandalay and Yangon); Thailand Ministry of Public Health (Bangkok), 2005.

2006 Report on the global AIDS epidemic
 Fig 2.10

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

Reported HIV cases in the Russian Federation

Reported HIV cases in Ukraine

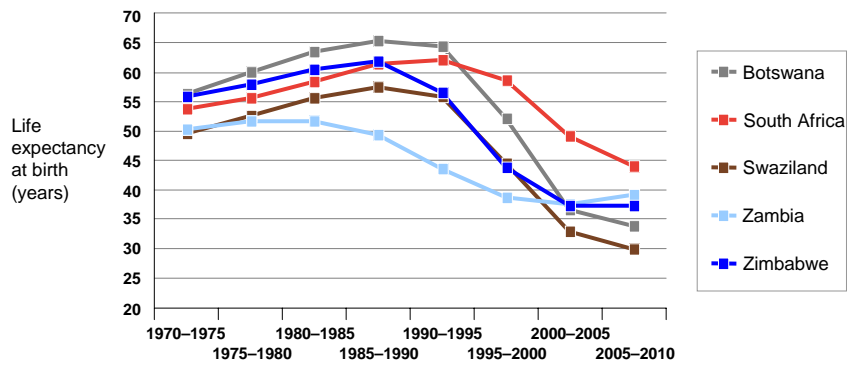


06/06 e

Sources: Russian Federal AIDS Centre; Ukrainian 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

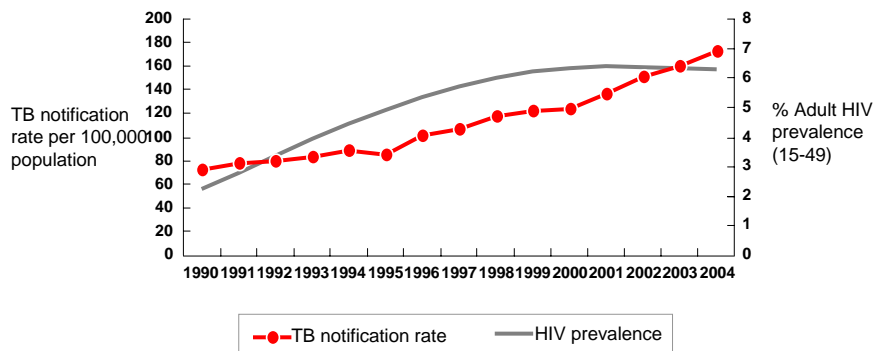


06/06 e

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

2006 Report on the global AIDS epidemic Fig 4.1

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



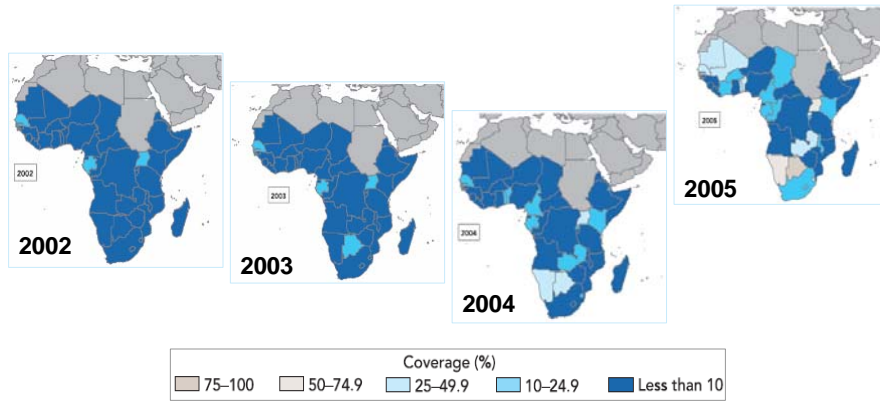
* Consistently reporting each year: Algeria, Angola, Botswana, Cameroon, Comoros, Congo, Côte d'Ivoire, Democratic Republic of Congo, Ghana, Guinea, Kenya, Malawi, Mauritius, Mozambique, Nigeria, Senegal, South Africa, Uganda, United Republic of Tanzania, Zimbabwe

06/06 e

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

2006 Report on the global AIDS epidemic Fig 4.5

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

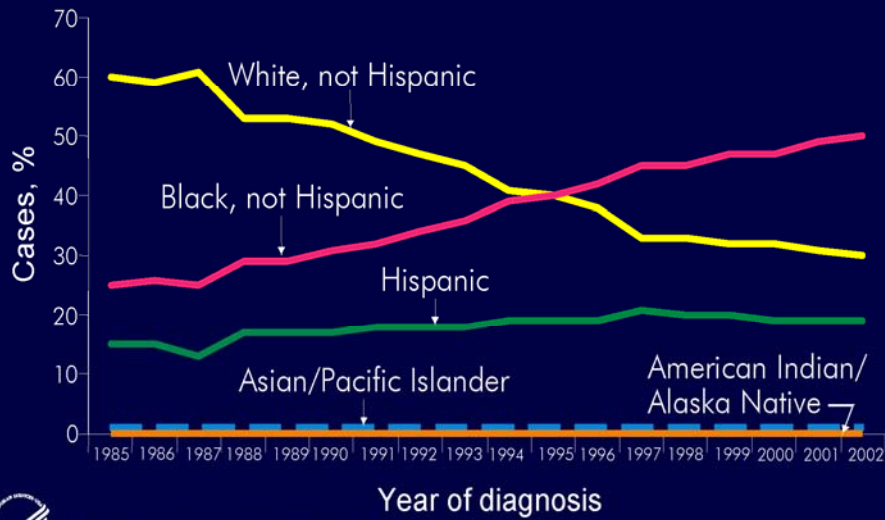


06/06 e

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

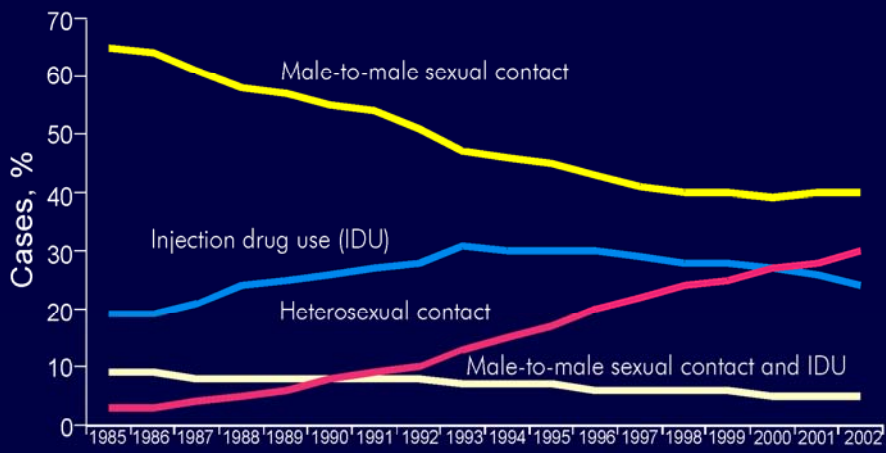
Proportion of AIDS Cases, by Race/Ethnicity and Year of Diagnosis, 1985–2002—United States



Note. Adjusted for reporting delays.



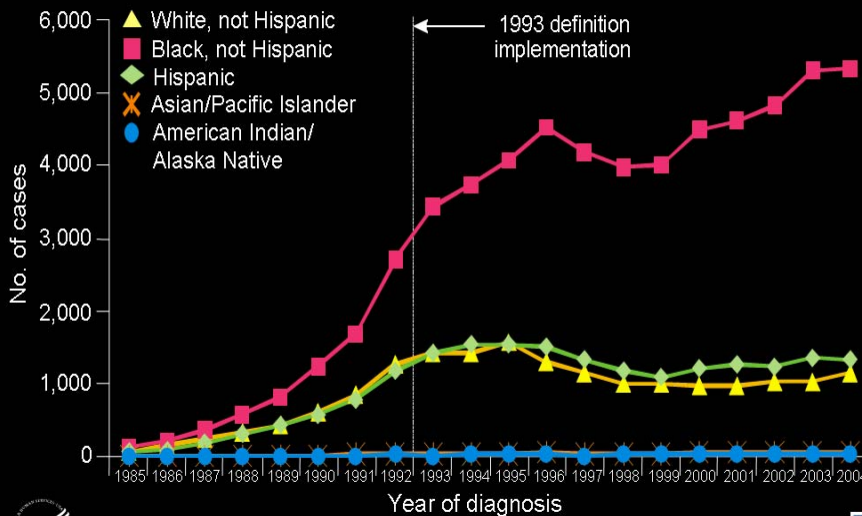
Proportion of AIDS Cases among Adults and Adolescents, by Exposure Category and Year of Diagnosis 1985–2002—United States



Note. Adjusted for reporting delays.



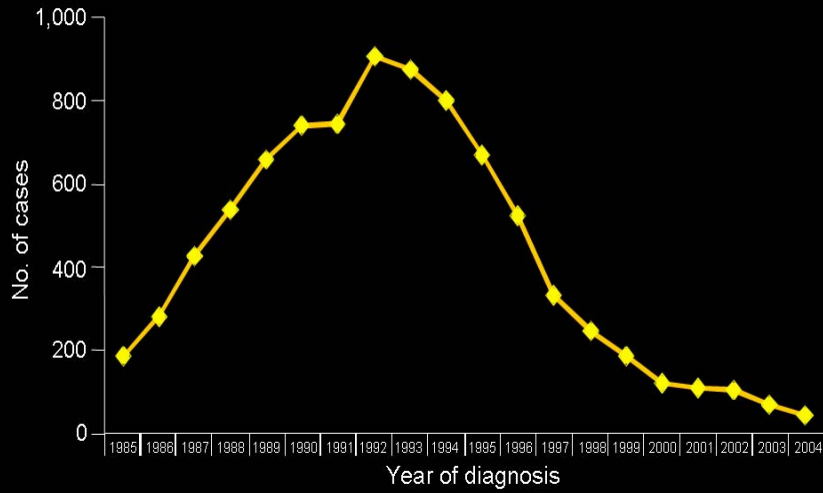
AIDS Cases among Female Adults and Adolescents Attributed to High-Risk Heterosexual Contact* by Race/Ethnicity, 1985-2004, United States



Note. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.
* Heterosexual contact with a person known to have or at high risk for HIV infection.



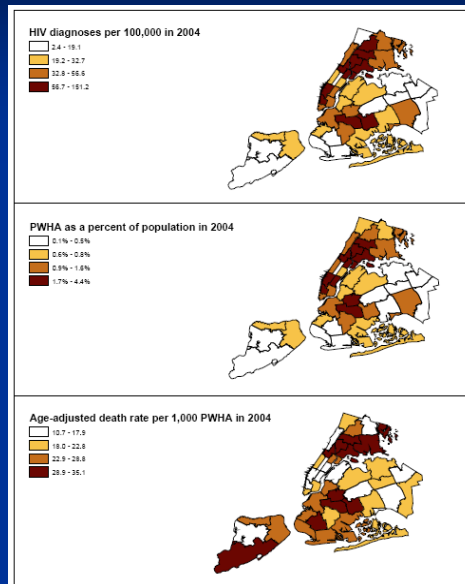
Perinatally Acquired AIDS Cases, 1985-2004, United States



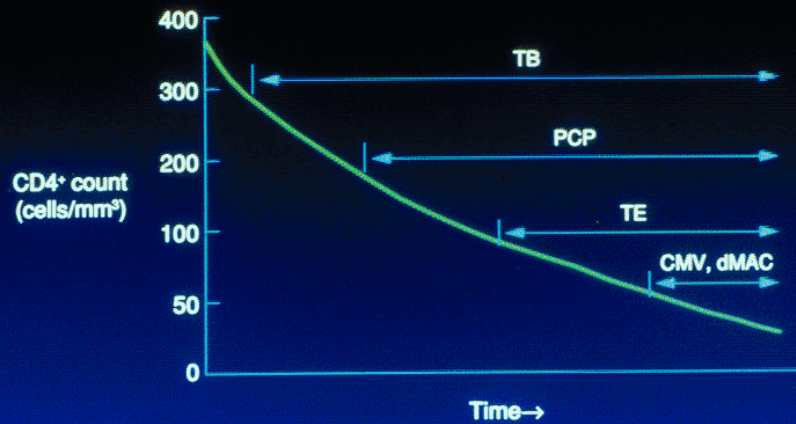
Note. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.



HIV Prevalence and Mortality in NYC

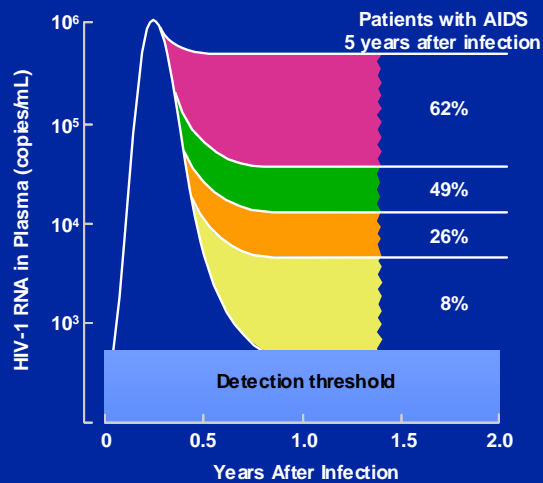


INCIDENCE OF SELECTED OPPORTUNISTIC INFECTIONS (OIs) OVER TIME, BY CD4⁺ COUNT



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

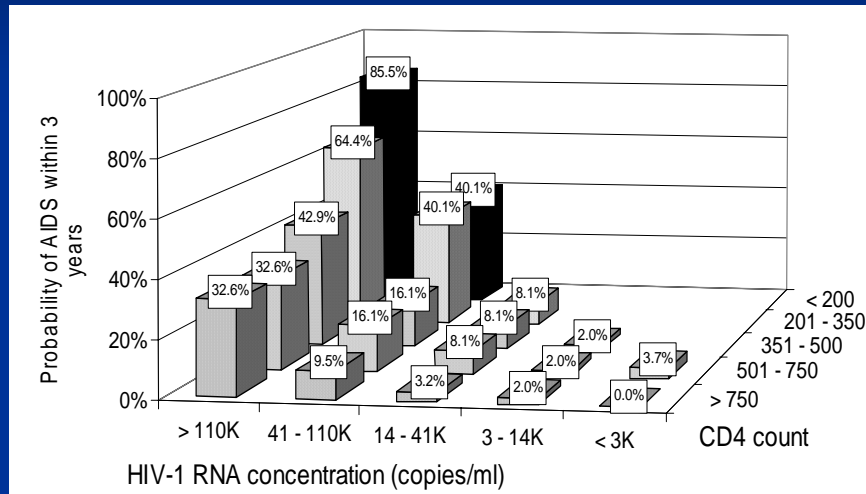
Plasma HIV-1 RNA Level After Acute HIV-1 Infection Predicts Disease Course



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

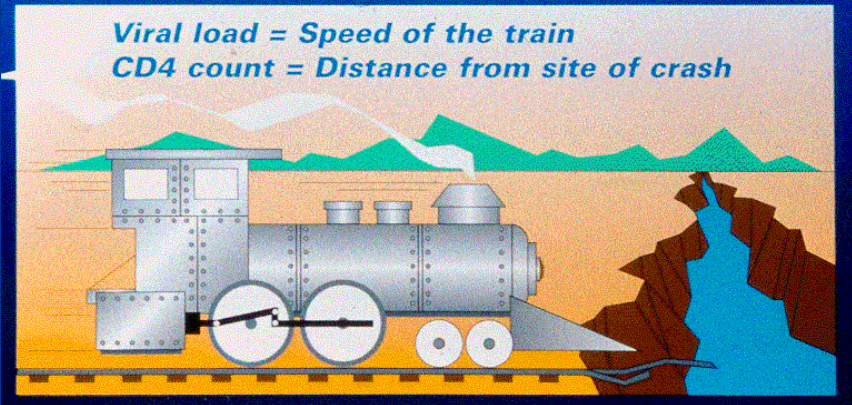


Probability of AIDS over 3 years



Development of AIDS: Like an Impending Train Wreck

Viral load = Speed of the train
CD4 count = Distance from site of crash



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%.

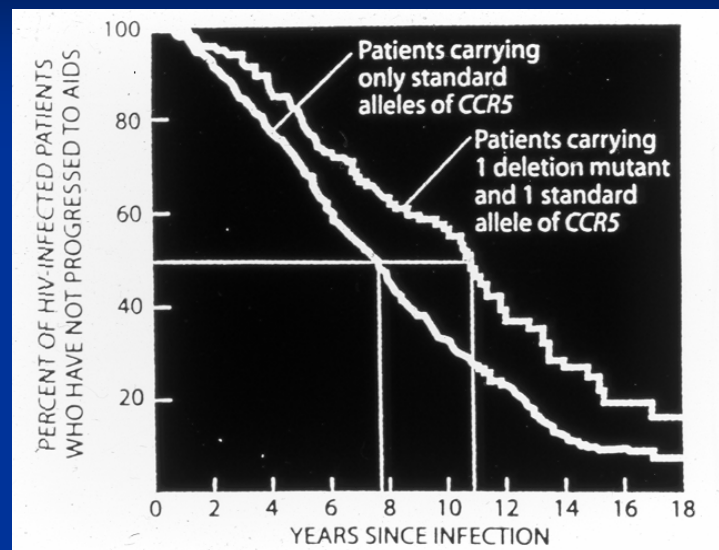
MACS High risk cohort:

No HIV+ among those homozygous for deletion.

3.6% of HIV Negative were homozygous.

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

Effect of Co-receptor Heterozygosity



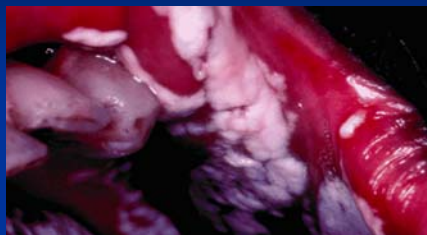
AIDS Restriction Genes

Table 2 Genes that limit AIDS

Gene	Allele	Mode	Effect	Mechanism of action	Reference
HIV entry					
<i>CCR5</i>	$\Delta 32$	Recessive	Prevent infection	Knockout <i>CCR5</i> expression	17
	$\Delta 32$	Dominant	Prevent lymphoma (L)	Decrease available <i>CCR5</i>	90
<i>CCR5</i>	$\Delta 32$	Dominant	Delay AIDS	Decrease available <i>CCR5</i>	17
	P1	Recessive	Accelerate AIDS (E)	Increase <i>CCR5</i> expression	34
<i>CCR2</i>	I64	Dominant	Delay AIDS	Interact with and reduce CXCR4	38,39
<i>CCL5</i>	In1.1c	Dominant	Accelerate AIDS	Decrease RANTES expression	45
<i>CXCL12</i>	3'A	Recessive	Delay AIDS (L)	Impede <i>CCR5</i> -CXCR4 transition (?)	46
<i>CXCR6</i>	E3K	Dominant	Accelerate PCP (L)	Alter T-cell activations (?)	48
<i>CCL2-CCL7-CCL11</i>	H7	Dominant	Enhance infection	Stimulate immune response (?)	49
Cytokine anti-HIV					
<i>IL10</i>	5'A	Dominant	Limit infection	Decrease <i>IL10</i> expression	53
	5'A	Dominant	Accelerate AIDS	Decrease <i>IL10</i> expression	53
<i>IFNG</i>	-179T	Dominant	Accelerate AIDS (E)		55
Acquired Immunity, cell mediated					
<i>HLA</i>	A,B,C	Homozygous	Accelerate AIDS	Decrease breadth of <i>HLA</i> 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					
<i>KIR3DS1</i>	3DS1	Epistatic with <i>HLA-Bw4</i>	Delay AIDS	Clear HIV ⁺ , HLA ⁺ cells (?)	70

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

Early indicators of HIV Infection

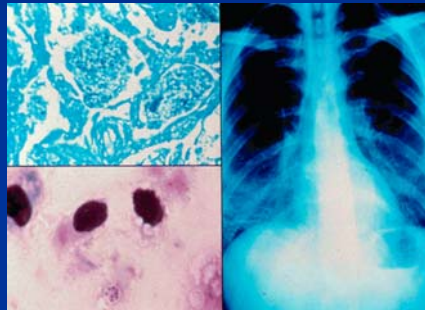


Key features of OIs in AIDS

- 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

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.

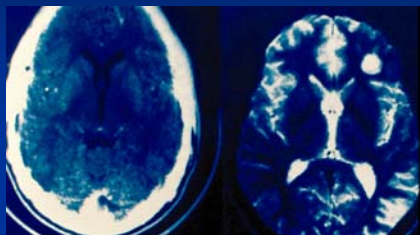


CD4 count predicts risk of PCP

TABLE 1. Cumulative incidence* of *Pneumocystis carinii* pneumonia (PCP) according to CD4+ count at baseline among the MACS seroprevalent cohort¹

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

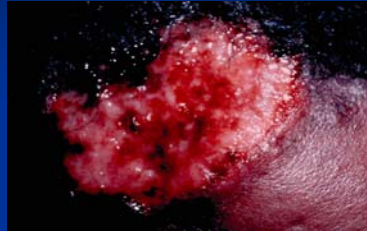
CNS toxoplasmosis



- 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.

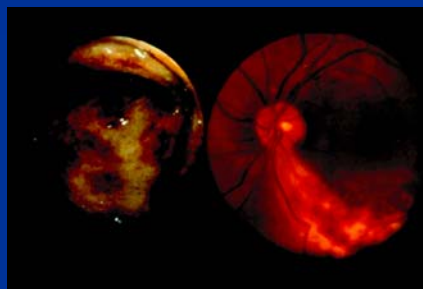
Cryptococcal disease in AIDS

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



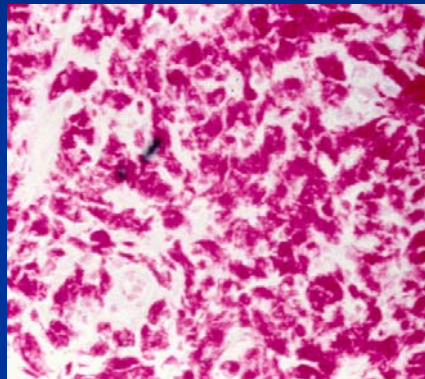
CMV disease in AIDS

- 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)

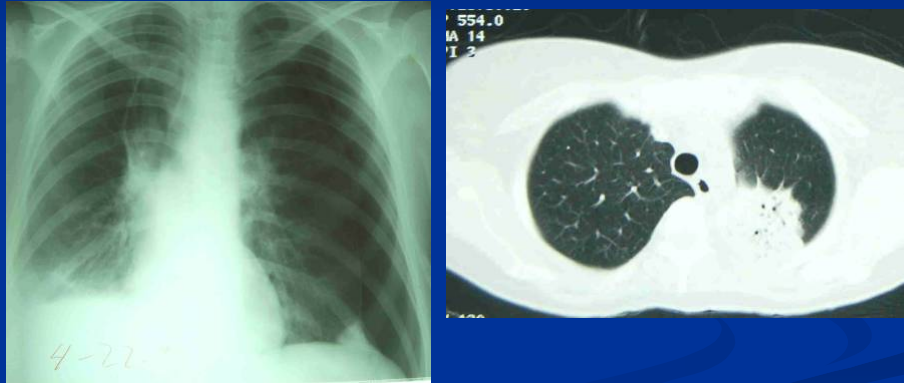
OI Guidelines November, 2001 Comparison of Indications to Discontinue Primary and Secondary Prophylaxis

Agent	Recommendation
PCP	1° CD ₄ > 200 X 3 months 2° CD ₄ > 200 X 3 months
Toxo.	1° CD ₄ > 200 X 3 months 2° CD ₄ > 200 X 6 months + initial Rx + asymptomatic
MAC	1° CD ₄ > 100 X 3 months 2° CD ₄ > 100 X 6 months + 12 mo Rx + asymptomatic

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



CNS crypto IRIS

