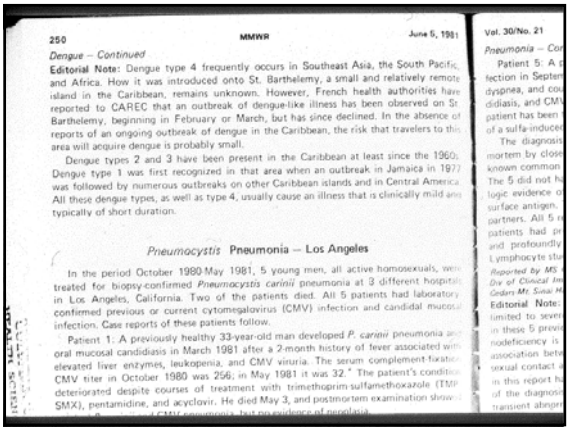
AIDS at 25

Epidemiology and Clinical Management



250 MMWR June 5, 1981 Vol. 30/No. 21

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

Vol. 30/No. 21

Pneumonia – Con

Patient 5: A ... fection in Septem... dyspnea, and cou... didiasis, and CMV... patient has been ... of a sulfa-induced...

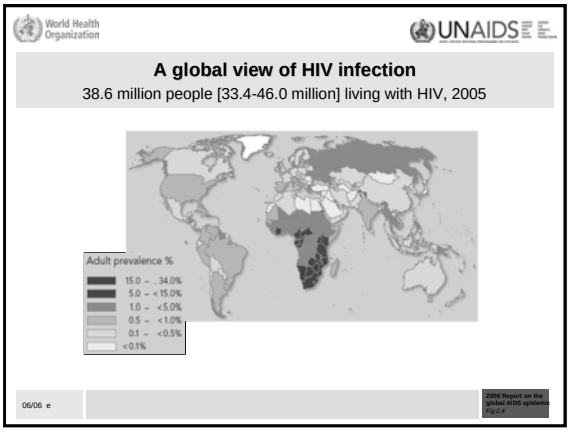
The diagnosis ... mortem by close... known common... The 5 did not ha... logic evidence o... surface antigen... partners. All 5 re... patients had pr... and profoundly ... Lymphocyte stu...

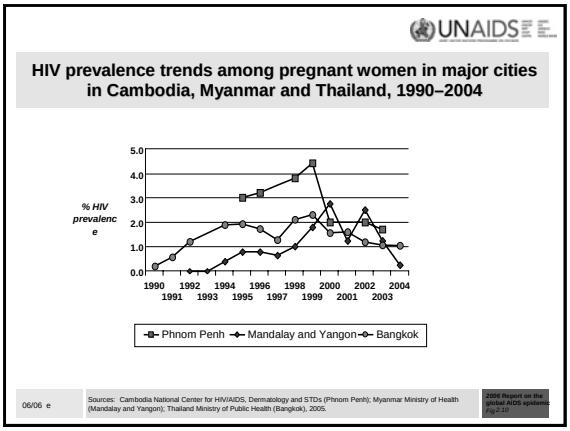
Reported by MS ... Div of Clinical Im... Cedars-Mt. Sinai H...

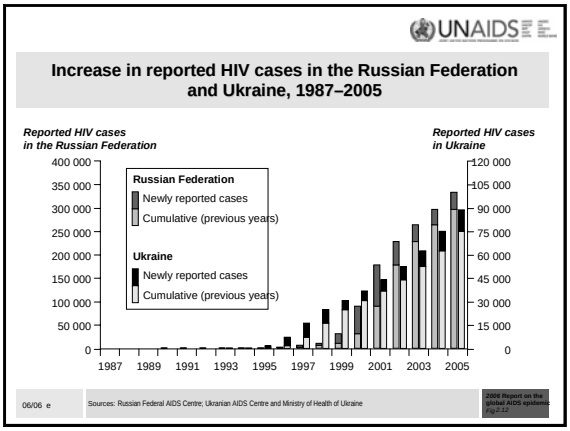
Editorial Note: ... limited to seven... in these 5 previo... nodeficiency is ... association betw... sexual contact a... in this report ha... of the diagnosis ... transient abnorm...

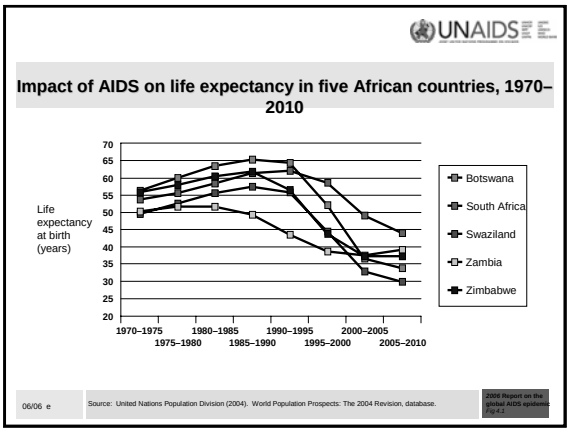
HIV Transmission

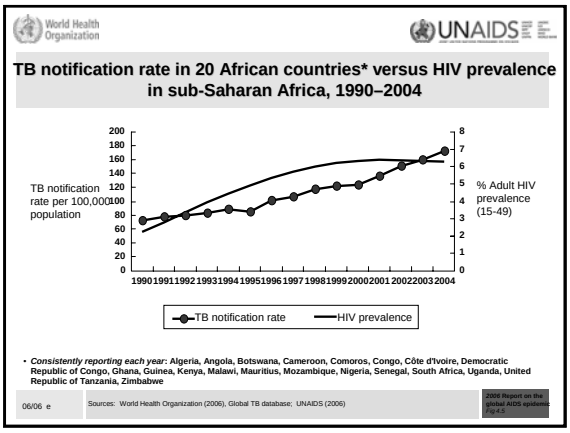
- Blood
  - transfusion
  - injection drug use
- Sexual Intercourse
  - heterosexual
  - male to male
- Perinatal
  - intrapartum
  - breast feeding

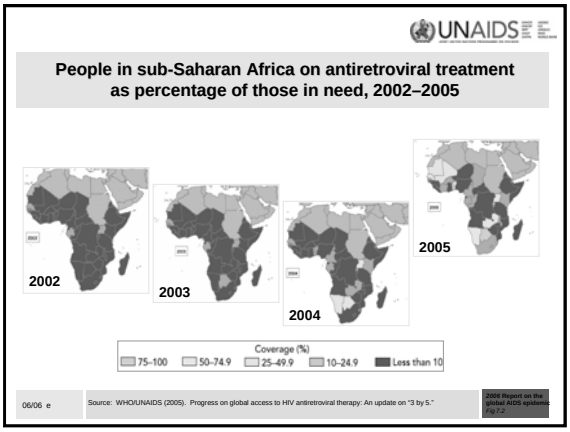


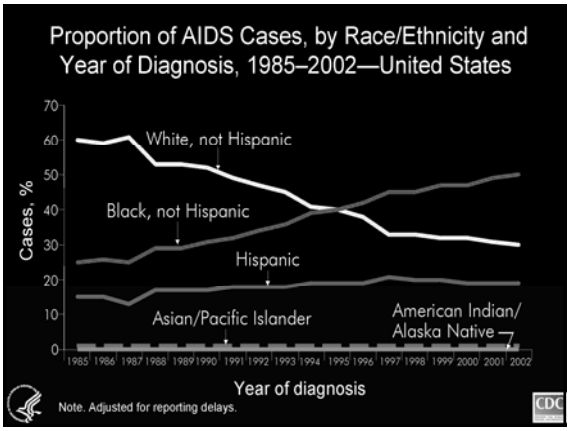


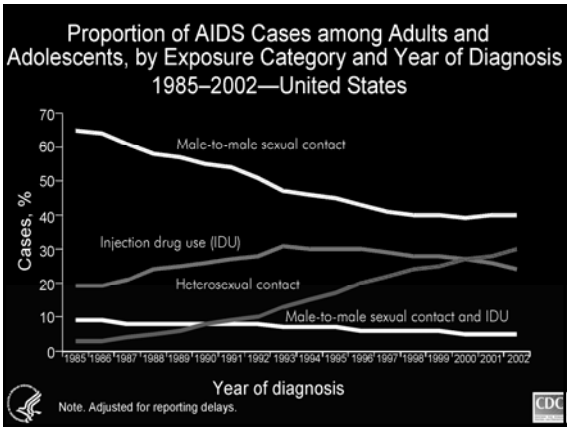


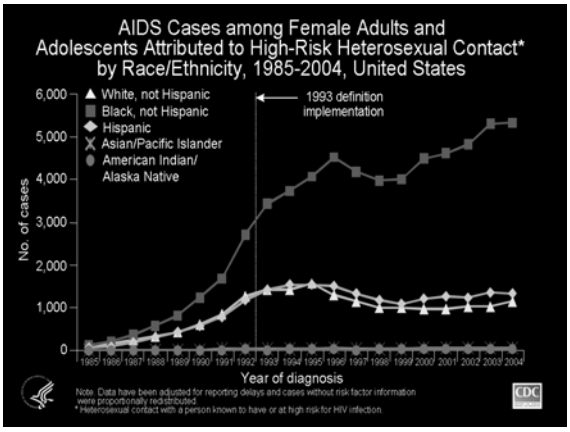

UNAIDS
Impact of AIDS on life expectancy in five African countries, 1970–2010
Life expectancy at birth (years)
70
65
60
55
50
45
40
35
30
25
20
1970–1975
1975–1980
1980–1985
1985–1990
1990–1995
1995–2000
2000–2005
2005–2010
Botswana
South Africa
Swaziland
Zambia
Zimbabwe
06/06 e
Source: United Nations Population Division (2004). World Population Prospects: The 2004 Revision, database.
2006 Report on the global AIDS epidemic Fig 4.1

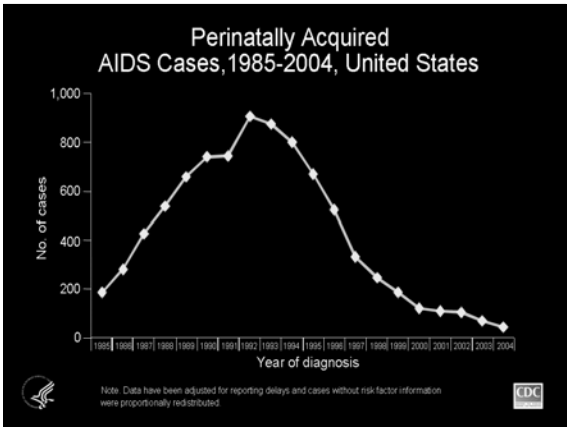

World Health Organization
UNAIDS
TB notification rate in 20 African countries* versus HIV prevalence in sub-Saharan Africa, 1990–2004
TB notification rate per 100,000 population
200
180
160
140
120
100
80
60
40
20
0
% Adult HIV prevalence (15-49)
8
7
6
5
4
3
2
1
0
1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
TB notification rate
HIV prevalence
• 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

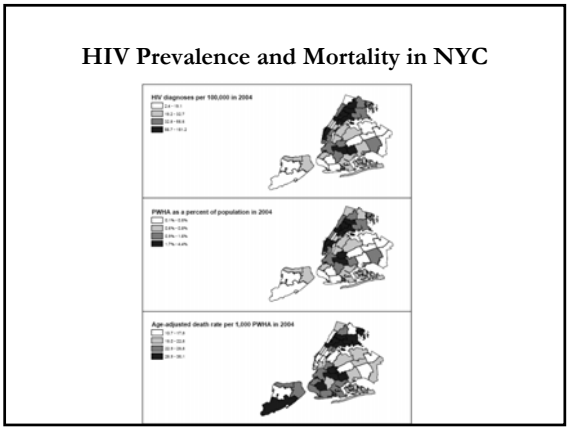

UNAIDS
People in sub-Saharan Africa on antiretroviral treatment as percentage of those in need, 2002–2005
2002
2003
2004
2005
Coverage (%)
75–100
50–74.9
25–49.9
10–24.9
Less than 10
06/06 e
Source: WHO/UNAIDS (2005). Progress on global access to HIV antiretroviral therapy: An update on "3 by 5."
2006 Report on the global AIDS epidemic Fig 7.2

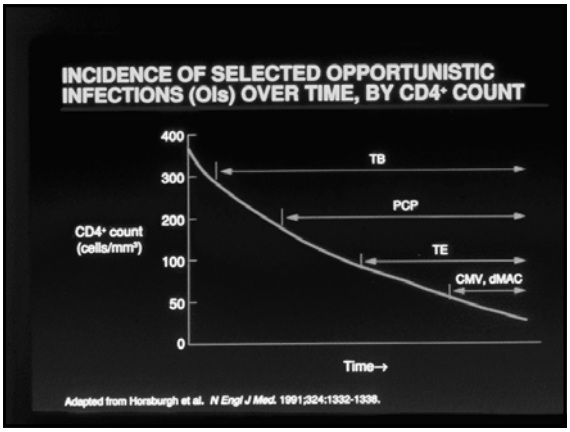

Proportion of AIDS Cases, by Race/Ethnicity and Year of Diagnosis, 1985–2002—United States
Cases, %
70
60
50
40
30
20
10
0
White, not Hispanic
Black, not Hispanic
Hispanic
Asian/Pacific Islander
American Indian/ Alaska Native
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002
Year of diagnosis
Note. Adjusted for reporting delays.
CDC

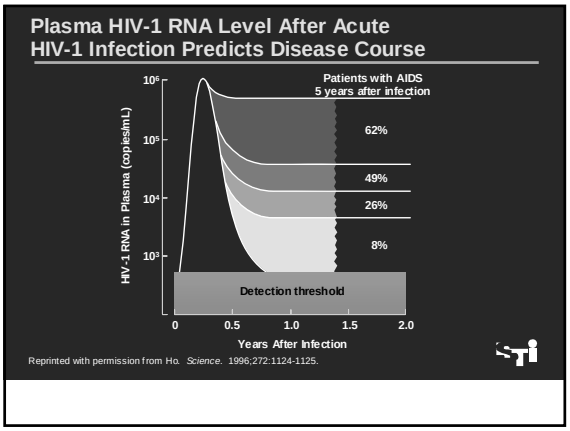

Proportion of AIDS Cases among Adults and Adolescents, by Exposure Category and Year of Diagnosis 1985–2002—United States
Cases, %
70
60
50
40
30
20
10
0
Male-to-male sexual contact
Injection drug use (IDU)
Heterosexual contact
Male-to-male sexual contact and IDU
1985 1986 1987 1988 1989 1990 1991 1992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

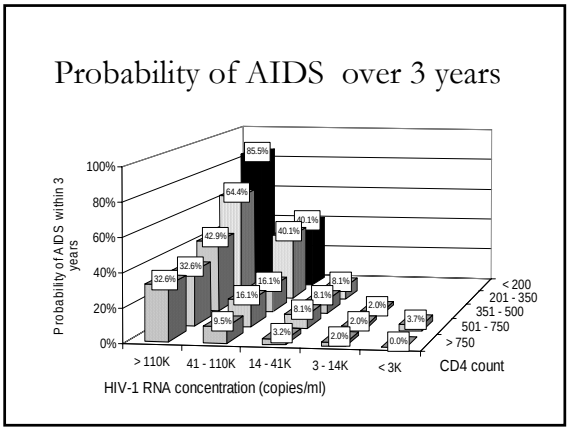

AIDS Cases among Female Adults and Adolescents Attributed to High-Risk Heterosexual Contact* by Race/Ethnicity, 1985-2004, United States
No. of cases
6,000
5,000
4,000
3,000
2,000
1,000
0
White, not Hispanic
Black, not Hispanic
Hispanic
Asian/Pacific Islander
American Indian/ Alaska Native
1993 definition implementation
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.
* Heterosexual contact with a person known to have or at high risk for HIV infection.
CDC

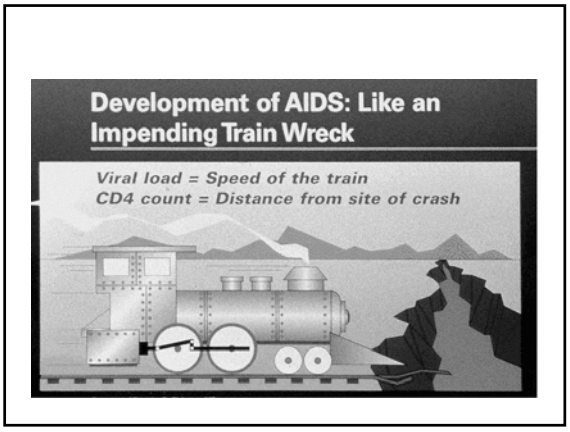

Perinatally Acquired
AIDS Cases,1985-2004, United States
No. of cases
1,000
800
600
400
200
0
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
Year of diagnosis
Note: Data have been adjusted for reporting delays and cases without risk factor information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


HIV Prevalence and Mortality in NYC


INCIDENCE OF SELECTED OPPORTUNISTIC INFECTIONS (OIs) OVER TIME, BY CD4+ COUNT
CD4+ count (cells/mm³)
400
300
200
100
50
0
TB
PCP
TE
CMV, dMAC
Time→
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
Patients with AIDS 5 years after infection
62%
49%
26%
8%
HIV-1 RNA in Plasma (copies/mL)
10⁶
10⁵
10⁴
10³
Detection threshold
0
0.5
1.0
1.5
2.0
Years After Infection
Reprinted with permission from Ho. Science. 1996;272:1124-1125.


Probability of AIDS over 3 years
Probability of AIDS within 3 years
100%
80%
60%
40%
20%
0%
85.5%
64.4%
42.9%
32.6%
40.1%
40.1%
32.6%
16.1%
16.1%
9.5%
8.1%
8.1%
8.1%
3.2%
2.0%
2.0%
2.0%
3.7%
0.0%
> 110K
41 - 110K
14 - 41K
3 - 14K
< 3K
HIV-1 RNA concentration (copies/ml)
< 200
201 - 350
351 - 500
501 - 750
> 750
CD4 count


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%.

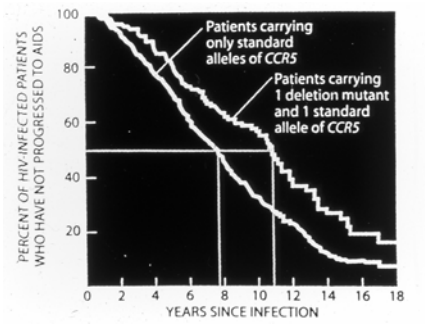
MACS High risk cohort:

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



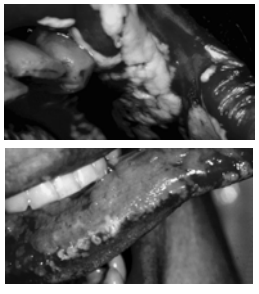
AIDS Restriction Genes

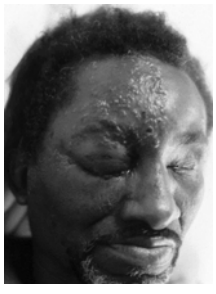
Table 2 Genes that limit AIDS

Gene	Allele	Mode	Effect	Mechanism of action	Reference
HIV entry					
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



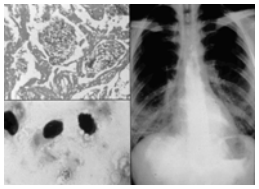


Key features of OIs in AIDS

- 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

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.

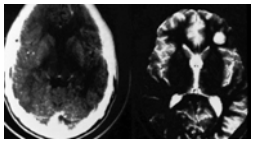


CD4 count predicts risk of PCP

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

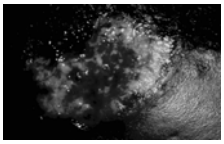
CNS toxoplasmosis

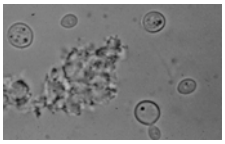


- Protozoon parasite; cats shed oocysts; farm animals incidental hosts; humans infected from cysts, uncooked meat.
- Commonest cause of focal CNS disease in AIDS.
- Serum IgG antibody reliable marker of past infection.
- Reactivation in AIDS associated with CD4<100.

Cryptococcal disease in AIDS

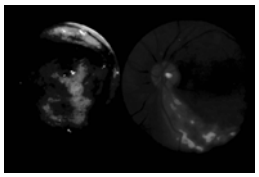
- Ubiquitous soil fungus.
- Initial assymptomatic pneumonia.
- Reactivation in advanced HIV disease (CD4<100).
- Meningitis commonest presentation but wide dissemination frequent.





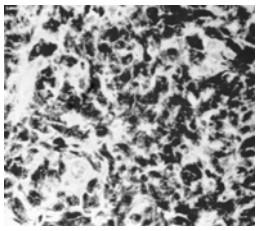
CMV disease in AIDS

- 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)

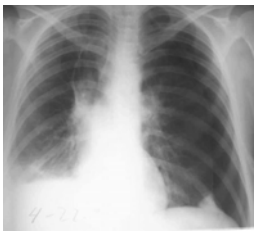
OI Guidelines November, 2001 Comparison of Indications to Discontinue Primary and Secondary Prophylaxis

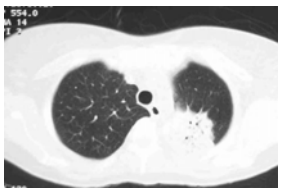
Agent	Recommendation
PCP	1º CD_4 > 200 X 3 months 2º CD_4 > 200 X 3 months
Toxo.	1º CD_4 > 200 X 3 months 2º CD_4 > 200 X 6 months + initial Rx + asymptomatic
MAC	1º CD_4 > 100 X 3 months 2º CD_4 > 100 X 6 months + 12 mo Rx + asymptomatic

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