AIDS at 25

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 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 as oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viraemia. The serum complement-fixing CMV titer in October 1980 was 256; in May 1981 it was 32. He had received trimethoprim-sulfamethoxazole (TMP-SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed CMV pneumonia, but no evidence of malaria.

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Pneumonia — Continued

**Patient 5:** A 37-year-old male with a history of toxoplasmosis, chronic lymphocytic leukemia, and renal transplantation is described. In January 1982 he was admitted to the hospital with a 3-week history of severe headache, malaise, and pancytopenia. 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 CMV pneumonia, but no evidence of malaria.

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**June 5, 1981**

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

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.

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

Sources: Russian Federal AIDS Centre, Ukrainian AIDS Centre and Ministry of Health of Ukraine.

Life expectancy at birth (years)


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

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


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

Note. Adjusted for reporting delays.
Perinatally Acquired AIDS Cases, 1985-2004, United States

HIV Prevalence and Mortality in NYC

Note: Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.
Plasma HIV-1 RNA Level After Acute HIV-1 Infection Predicts Disease Course

Probability of AIDS over 3 years

![Diagram showing the probability of AIDS within 3 years based on HIV-1 RNA concentration and 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.

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**Effect of Co-receptor Heterozygosity**

![Graph showing effect of co-receptor heterozygosity](image)
# AIDS Restriction Genes

## Table 2: Genes that limit AIDS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele</th>
<th>Mode</th>
<th>Effect</th>
<th>Mechanism of action</th>
<th>Reference</th>
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<tbody>
<tr>
<td>CCR5</td>
<td>Δ32</td>
<td>Recessive</td>
<td>Prevent infection</td>
<td>Knockout CCR5 expression</td>
<td>17</td>
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<tr>
<td></td>
<td>Δ32</td>
<td>Dominant</td>
<td>Prevent lymphoma (L)</td>
<td>Knockout CCR5 expression</td>
<td>90</td>
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<tr>
<td></td>
<td>Δ32</td>
<td>Dominant</td>
<td>Delay AIDS</td>
<td>Decrease available CCR5</td>
<td>17</td>
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<tr>
<td>CCR5</td>
<td>F1</td>
<td>Recessive</td>
<td>Accelerate AIDS (E)</td>
<td>Increase CCR5 expression</td>
<td>34</td>
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<tr>
<td>CCR2</td>
<td>H64</td>
<td>Dominant</td>
<td>Delay AIDS</td>
<td>Interact with and reduce CCR4</td>
<td>36,39</td>
</tr>
<tr>
<td>CCR1</td>
<td>H1,1c</td>
<td>Dominant</td>
<td>Accelerate AIDS</td>
<td>Decrease RANTES expression</td>
<td>40</td>
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<tr>
<td>CXCL12</td>
<td>3′A</td>
<td>Recessive</td>
<td>Delay AIDS (L)</td>
<td>Impede CCR5:CXCR4 transition (7)</td>
<td>46</td>
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<tr>
<td>CXCR6</td>
<td>E3A</td>
<td>Dominant</td>
<td>Accelerate PCP (L)</td>
<td>Increase T-cell activations (7)</td>
<td>46</td>
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<tr>
<td>CD152-CD2-CD111</td>
<td>H7</td>
<td>Dominant</td>
<td>Enhance infection</td>
<td>Stimulate immune response (7)</td>
<td>49</td>
</tr>
<tr>
<td>IFNα</td>
<td>5′A</td>
<td>Dominant</td>
<td>Limit infection</td>
<td>Decrease IL10 expression</td>
<td>53</td>
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<tr>
<td></td>
<td>5′A</td>
<td>Dominant</td>
<td>Accurate AIDS</td>
<td>Decrease IL10 expression</td>
<td>53</td>
</tr>
<tr>
<td>IFNG</td>
<td>179F</td>
<td>Dominant</td>
<td>Accurate AIDS (E)</td>
<td>Decrease IL10 expression</td>
<td>55</td>
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<tr>
<td>Acquired immunity, cell mediated HLA</td>
<td>A1, 2, C</td>
<td>Homozygous</td>
<td>Accelerate AIDS</td>
<td>Decrease breadth of HLA class I epitope recognition</td>
<td>52,66</td>
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<td></td>
<td>B27</td>
<td>Codominant</td>
<td>Delay AIDS</td>
<td>Delay HIV-1 escape</td>
<td>9</td>
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<td>Delay AIDS</td>
<td>Delay HIV-1 escape</td>
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<tr>
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<td>B57-Pv</td>
<td>Codominant</td>
<td>Accelerate AIDS</td>
<td>Defect CD4+ T cell clearance of HIV-1</td>
<td>60</td>
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<tr>
<td>Acquired immunity, innate KIR2DS1</td>
<td>3D11 Epistatic with HLA-Bw4</td>
<td>Delay AIDS</td>
<td>Clear HLA+ T-cells (7)</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>


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# 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.

<table>
<thead>
<tr>
<th>CD4+ count at baseline</th>
<th>N</th>
<th>PCP</th>
<th>Percentage with PCP</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 mo.</td>
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<tr>
<td>~ 200</td>
<td>77</td>
<td>19</td>
<td>8.4</td>
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<tr>
<td>201-350</td>
<td>217</td>
<td>47</td>
<td>0.5</td>
</tr>
<tr>
<td>351-500</td>
<td>389</td>
<td>39</td>
<td>0.0</td>
</tr>
<tr>
<td>501-700</td>
<td>483</td>
<td>43</td>
<td>0.0</td>
</tr>
<tr>
<td>~ 700</td>
<td>499</td>
<td>20</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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 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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication</th>
<th>Regimen</th>
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<tr>
<td>PCP</td>
<td>CD4&lt;200</td>
<td>Trimethoprim-sulfa</td>
</tr>
<tr>
<td>Toxo</td>
<td>CD4&lt;100</td>
<td>Trimethoprim-sulfa or Dapsone +Pyrimethamine</td>
</tr>
<tr>
<td></td>
<td>and IgG+</td>
<td></td>
</tr>
<tr>
<td>MAC</td>
<td>CD4&lt;50</td>
<td>Clarithromycin/Azithromycin</td>
</tr>
<tr>
<td>TB</td>
<td>+PPD (5mm)</td>
<td>INH (9 months)</td>
</tr>
</tbody>
</table>
### OI Guidelines November, 2001
Comparison of Indications to Discontinue Primary and Secondary Prophylaxis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| PCP   | 1<sup>st</sup> CD<sub>4</sub> > 200 X 3 months  
2<sup>nd</sup> CD<sub>4</sub> > 200 X 3 months |
| Toxo. | 1<sup>st</sup> CD<sub>4</sub> > 200 X 3 months  
2<sup>nd</sup> CD<sub>4</sub> > 200 X 6 months + initial Rx + asymptomatic |
| MAC   | 1<sup>st</sup> CD<sub>4</sub> > 100 X 3 months  
2<sup>nd</sup> CD<sub>4</sub> > 100 X 6 months + 12 mo Rx + asymptomatic |

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### 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