Morbidity and Mortality Weekly Report (MMWR)

**Pneumocystis Pneumonia — Los Angeles**

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for 8 pneumonia-confirmed Pneumocystis carini 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.

**Global HIV epidemic, 1990-2008**

- 33+ million living with HIV
- ~2.5 million new infections/year
- ~2 million deaths/year
- 23 million in sub-Saharan Africa

**Changes in life expectancy in selected African countries with high HIV prevalence — 1950 to 2000**

*Source: United Nations Population Division, 1998*
Over 6800 new HIV infections a day in 2007

- >96% are in low-middle income countries
- ~1200 are in children <15 years of age
- ~5800 are in adults 15 years and older:
  - ~50% are among women
  - ~40% are among young people (ages 15-24)

Early History of AIDS

- 1981: reports of gay men with PCP, KS, CD4 depletion
- then injection drug users, hemophiliacs, transfusion recipients
- blood-borne; sexually transmitted
- 1983-84: isolation of HIV-1
- 1985: HIV-1 antibody testing available
- 1986: isolation of HIV-2
- 1987: first antiretroviral drug approved (AZT)
  - 25,000 Americans dead
(Later) Early History of HIV/AIDS

- 1988: PCP prophylaxis with Bactrim
- 1994: AZT prophylaxis for perinatal transmission; 2-drug ART introduced into clinical practice
- 1996: 3-drug ART introduced into clinical practice
- 2000: Durban conference, move to bring ART to developing world gains momentum

HIV-1 Virions

Gelderblom, Human Retroviruses and AIDS 1997

Human Immunodeficiency Virus

- formerly HTLV-III; isolated 1983
- human retrovirus – outer glycoprotein coat, inner protein coat and genetic material: RNA (2 strands)
- types: HIV-1 and HIV-2
- subtypes (clades): B most common in North America and Europe
- target cell: CD4+ lymphocyte

Origin of HIV

- Evidence for zoonosis
  - similarity of genomes, phylogenetic relationships, prevalence in normal host, geographic coincidence, plausible route of transmission
- SIVsm (sooty mangabey) --- HIV-2
- SIVcpz (chimpanzee) --- HIV-1 (~1930)
- ? Skin/mucous membrane exposure to infected animals (pets, food)

Hahn et al. Science 2000;287:607

HIV Testing

- HIV antibody testing (indirect)
  - Window period ~3 months
  - Screening test: HIV antibody by ELISA
  - If repeatedly positive, proceed to confirmatory test
  - Confirmatory test: HIV antibody by Western Blot
  - 20-minute oral test now available
- HIV viral testing (direct)
  - p24 antigen
  - viral culture
  - HIV RNA (viral load)

HIV Transmission Routes

- Sexual transmission
  - Low efficiency (~1% per contact)
- Injection drug use
  - High efficiency (~10% per contact)
- Blood, blood products, tissue
  - Very high efficiency (~90% per transfusion)
- Perinatal transmission (~25% per birth)
- Needlestick injury (~1/300 exposures)
Viral Dynamics -- Summary

- 10 billion new virions created and cleared daily
- 2 billion CD4 cells destroyed daily (twice the rate of replacement by the hematopoietic system)
- Mechanism of CD4 cell destruction is poorly understood

Ho, Nature 1995;373:123
Wei, Nature 1995;373:117
Perelson, Science 1996;271:1582

Time Course of HIV Infection

CDC Adult AIDS Case Definition

- 1982: “AIDS” -- list of diseases (definitive diagnosis) and disqualifying conditions
- 1985: HIV antibody testing added to definition
- 1987: presumptive diagnoses with a positive HIV antibody added
- 1993: CD4 <200 (without symptoms) and other diagnoses added

Opportunistic Infection (OI): Definition

- Infection caused by an organism capable of causing disease only in a host whose resistance is lowered (by other diseases or by drugs)

Examples of Common OIs/Malignancies

- Developed world
  - Pneumocystis carinii (fungus)
  - Cytomegalovirus (virus)
  - Toxoplasma gondii (parasite)
  - Mycobacterium avium complex (bacterium)
  - Kaposi’s sarcoma (malignancy)

- Developing world
  - Cryptococcus (fungus)
  - Mycobacterium tuberculosis (bacterium)
  - Wasting disease

Annual Rates of Death from Leading Causes of Death Among Persons 25-44 Years Old, USA, 1982-1998

- Unintentional injury
- Cancer
- Heart disease
- Suicide
- HIV infection
- Homicide
- Chronic liver disease
- Stroke
- Diabetes

ART in U.S.: 3 million life-years saved!

HIV Survival: Denmark

Figure: Survival from age 25 years.

Walensky, J Infect Dis 2006;194:11-19

Africans on ART (% of those in need)

ART scale up: Uganda

DART \( (n=1015) \) mortality (vs historical cohort 1995–2000)
- 17-fold reduction in mortality with ART
- 94% 2-year survival

Munderi P, IAC 2006, #THLB0208

ART Scale-up: Haiti

Historically:
1-year survival without ART: 30%

No. at Risk 100 755 503
Severe, NEJM 2005;353:2325-2334

Progress in ART Scale Up

Achievements
- 1.6 M people on ART
- 24% of 6.8 M in need; male=female
- 21 countries treating >50% in need; capacity growing
- Favorable outcomes in large cohorts
- $8.3 B mobilized
- G-8 commitment: Universal access by 2010

Challenges
- 10–20% ART mortality in 1st year
- 73% present with CD4+ <100
- <5% of HIV+ children on ART
- <10% of HIV+ pregnant women receive PMTCT
- Less access and ART for IDUs
- Human resource, skill deficits
- Labs, toxicities, costs
- Sustainability – $25 B needed

UNAIDS 2006 Report

Antiretroviral Drug Approval: 1987 - 2008

Goal of Antiretroviral Therapy

- to suppress HIV RNA (viral load level) as low as possible, for as long as possible
- to preserve or enhance immune function
- to delay clinical progression of HIV disease
Antiretroviral Activity: 1987-1997

Fischl, NEJM, 1987
Eron, NEJM, 1995;
Hammer, NEJM, 1995;
Gulick, NEJM, 1997;
Cameron, Lancet, 1998

Antiretroviral Drugs: 2008

**nucleoside/tide RTIs (NRTIs)**
- zidovudine (ZDV, AZT)
- didanosine (ddI)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TDF)

**protease inhibitors (PIs)**
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NVP)
- lopinavir/ritonavir (LPV/r)
- atazanavir (ATV)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

**NNRTIs**
- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETR)

**chemokine receptor inhibitors**
- enfuvirtide (T-20, fusion inh)
- maraviroc (MVC, CCR5 inh)

**integrase inhibitors (IIs)**
- raltegravir (RAL)

What to start?

DHHS Treatment Guidelines

Recommended regimens:
- 2 nucs + NNRTI
  - preferred and alternative choices
- 2 nucs + PI (+/- RTV)
  - preferred and alternative choices

DHHS Guidelines, 12/1/07
Evidence for Immune Reconstitution with ART

- Decreased mortality
- Decreased morbidity
  - fewer opportunistic infections (OI)
  - discontinuation of OI prophylaxes possible
  - resolution of chronic OI without maintenance therapy
- Resolution of “untreatable” diseases
  - e.g. cryptosporidiosis, microsporidiosis, PML, malignancies
- Expansion of CD4 populations
- Improved lymph node architecture and immune function (e.g., DTH responses).

Life Cycle of HIV

HIV prevention efforts

Abstain, Be faithful, Condoms, Counseling & testing
Conclusions

- HIV/AIDS is a worldwide pandemic.
- Worldwide, the most common mode of transmission is sexual contact.
- HIV RNA levels and CD4 cell counts predict disease progression.
- Antiretroviral therapy (ART) decreases HIV RNA and increases CD4 cell count, and thus prevents disease progression.
- Current ART consists of 3-drug therapy and is increasingly available worldwide.
- Prevention of HIV infection continues to be a key strategy.

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