

HIV Then and Now

Martin S. Hirsch, M.D.

MMWR June 5, 1981

CDC
CENTERS FOR DISEASE CONTROL
AND PREVENTION

MMWRTM MORBIDITY AND MORTALITY WEEKLY REPORT

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

- 249 Dengue Type 4 Infections in U.S. Travelers to the Caribbean
- 250 Pneumocystis Pneumonia — Los Angeles
- 252 Measles — United States, Five Weeks
- 253 Risk-Factor-Prevalence Survey
- 259 Surveillance of Childhood Lead Poisoning — United States
- 261 Quarantine Measures

Pneumocystis Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active homosexuals 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 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 viremia. The serum complement level in October 1980 was 256; in May 1981 it was 32. The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole, amphotericin B, and acyclovir. He died May 3, and postmortem examination showed pneumonia, but no evidence of neoplasia.

Initial Reports of AIDS

- CDC MMWR, June 5, 1981 – report of 5 previously healthy young men in LA with pneumocystis carinii pneumonia (PCP), and cytomegalovirus (CMV) and candida infections
- Editorial note suggested a cellular-immune dysfunction related to a common exposure likely related to sexual contact
- Several MMWR reports of similar syndromes from other cities (NYC, SF) in ensuing weeks

My First AIDS Patient

- In August, 1981, a local internist referred a 29 year old man with Kaposi's sarcoma, CMV infection, and multiple opportunistic infections, asking whether he was the first Boston patient with this new acquired immune deficiency syndrome
- Could CMV be the cause?

Challenger's Men
Take a Space Walk



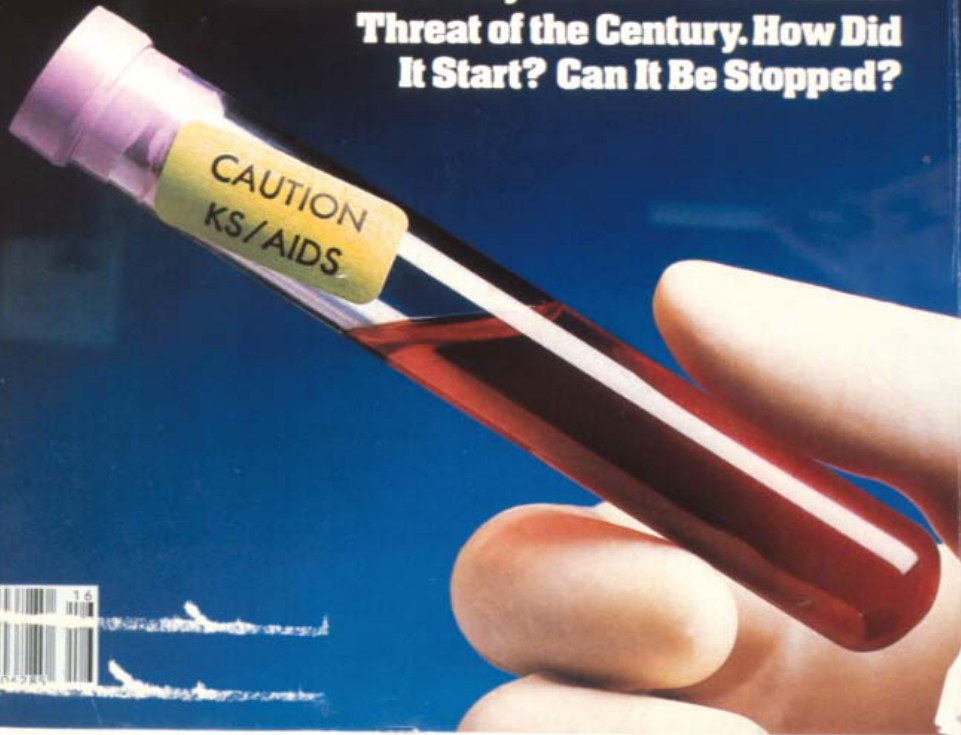
Russia's Spies
Get the Boot

Newsweek

April 18, 1983 / \$1.50

EPIDEMIC

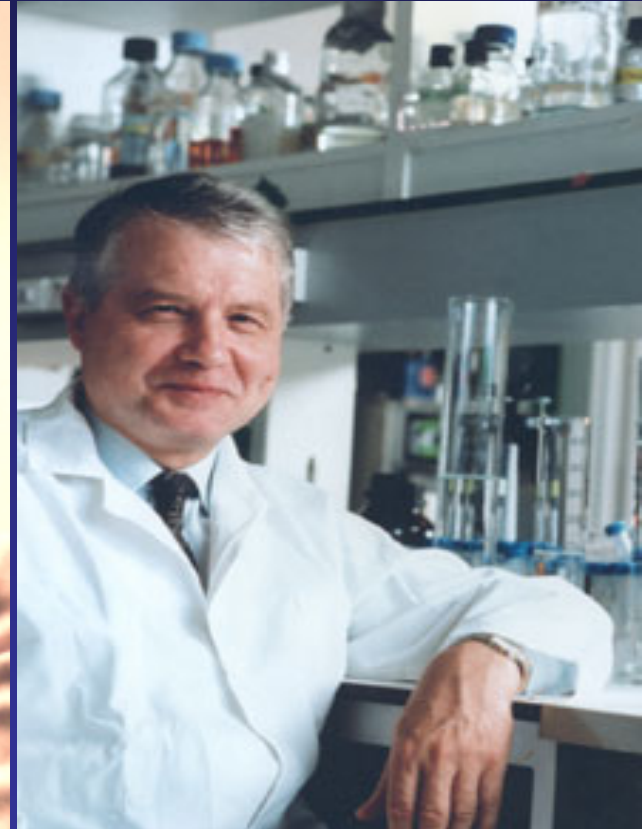
**The Mysterious and Deadly Disease
Called AIDS May Be the Public-Health
Threat of the Century. How Did
It Start? Can It Be Stopped?**



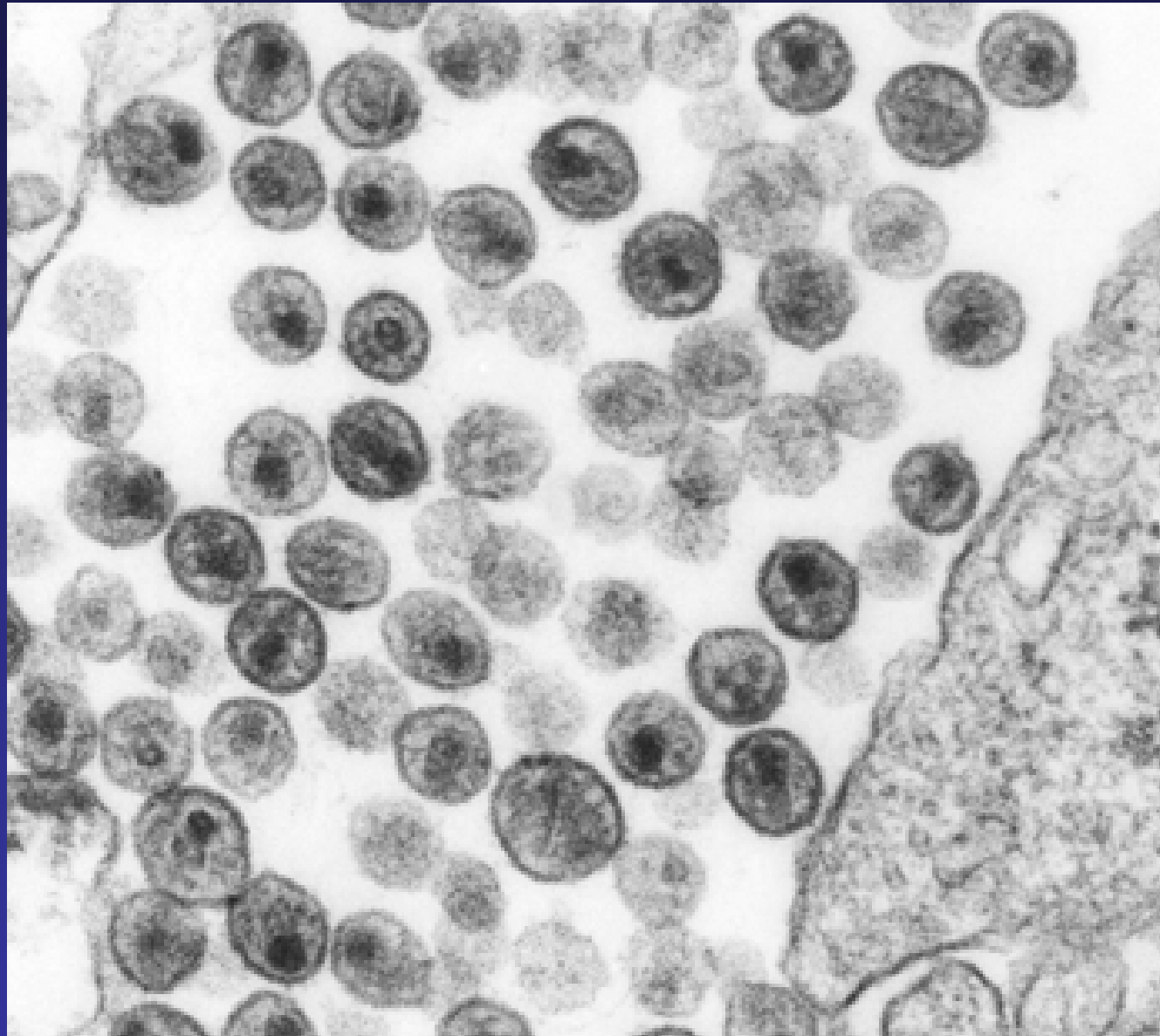
1981-83: Cases of *Pneumocystis pneumonia* and Kaposi's Sarcoma reported in gay men from major urban areas in the USA; shortly thereafter similar cases in women, injection drug users, blood product recipients, and internationally ("no risk factors")

April 18, 1983

Bob Gallo, Francoise Barre-Sinoussi, and Luc Montagnier; discoverers of HIV



HIV



AIDS in the 1980-90s

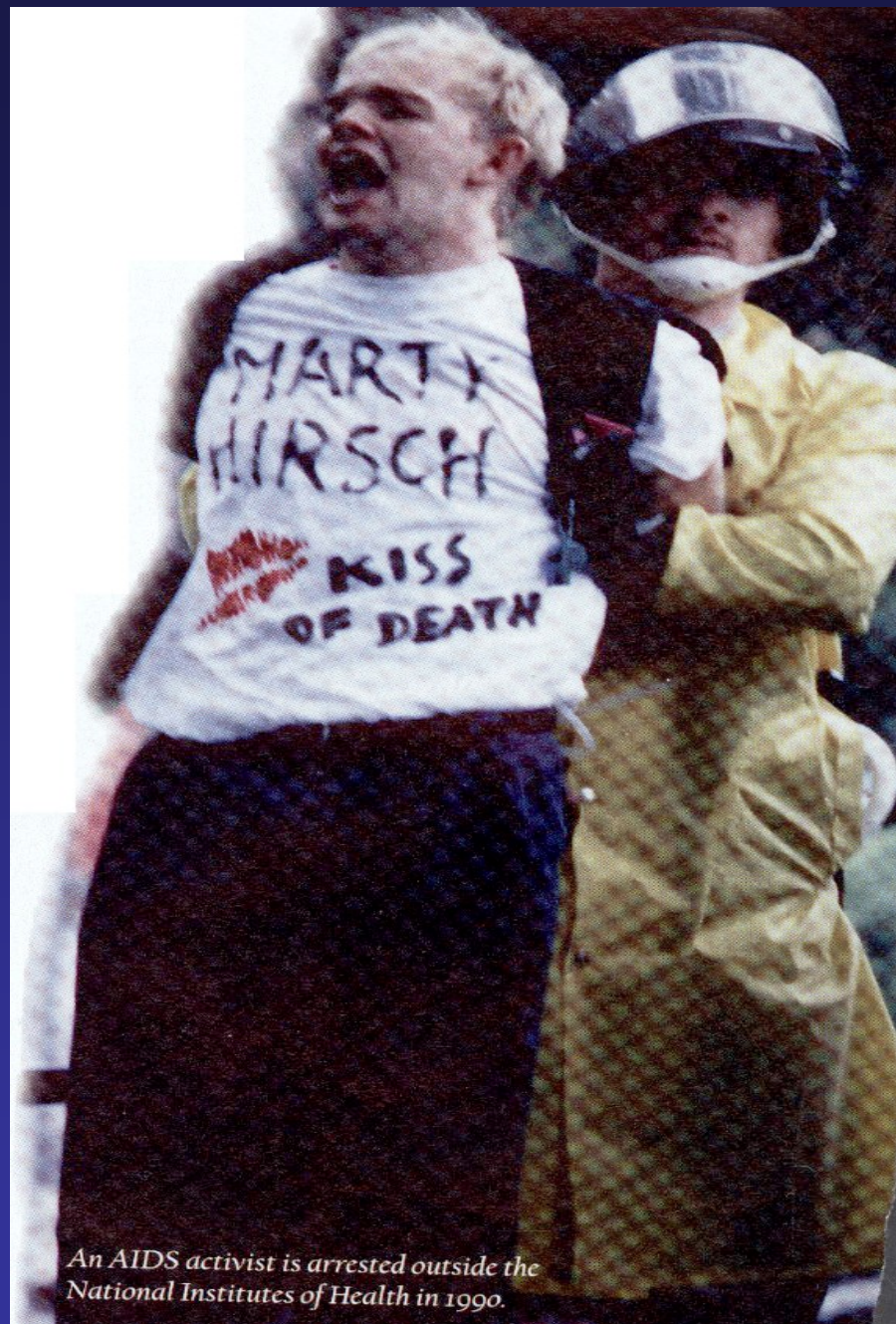
- Characteristics of the Disease
 - Wasting, diarrhea, dementia
 - Near universal death
- Populations Affected Stigmatized
 - MSM
 - IDU
 - Immigrant minorities (e.g., Haitians)
- Fears in Population
 - Contagion

Ryan White



Community Activism

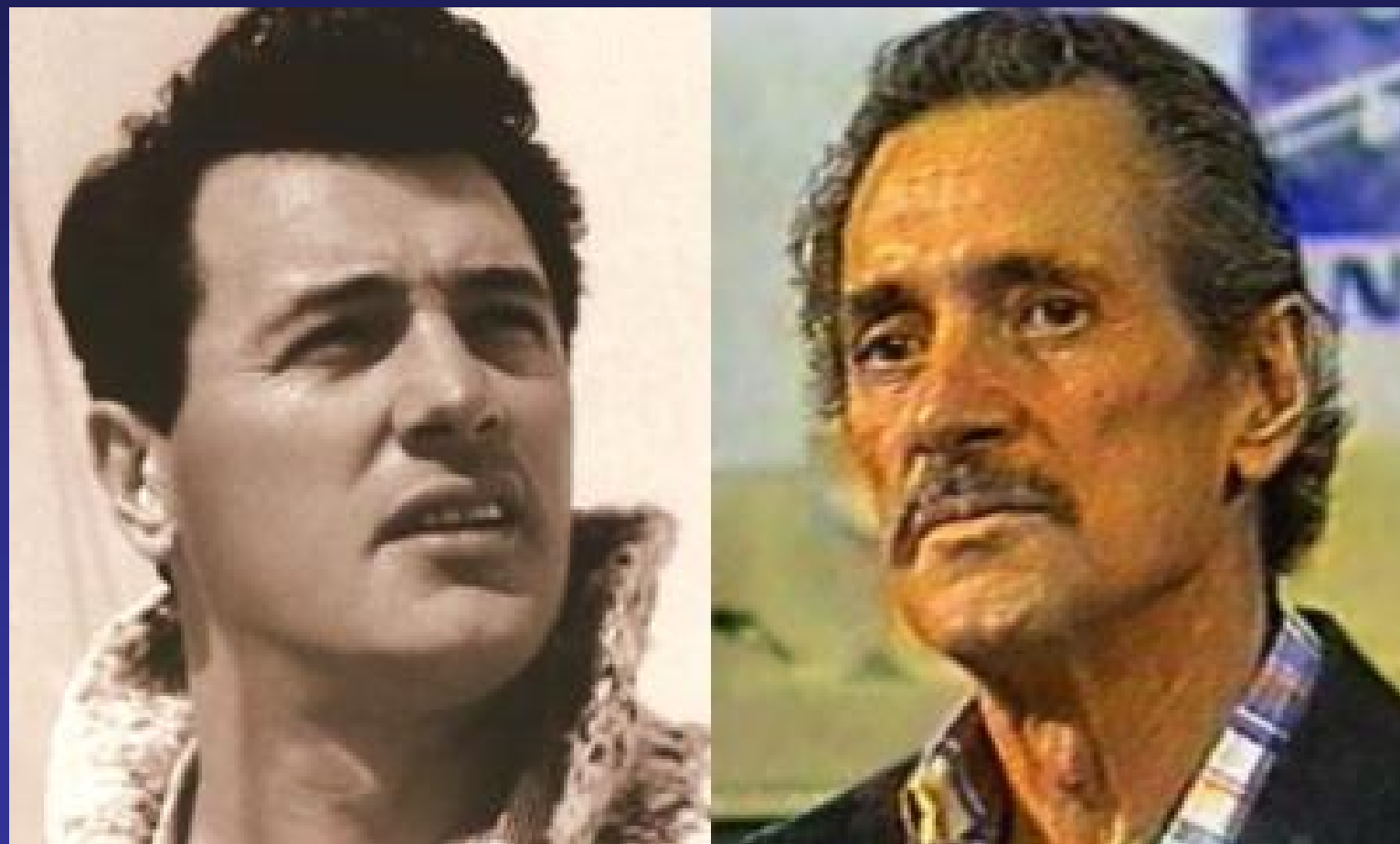




*An AIDS activist is arrested outside the
National Institutes of Health in 1990.*



Rock Hudson – The Face of AIDS



Early HIV Treatment Efforts

- Once HIV discovered in 1984, many candidate drugs proposed, but few good studies performed to demonstrate benefit.
- Meetings 1984-86 among government, academic, pharmaceutical, constituency groups to plan for adequate drug trials
- Formation of a national network, the AIDS Clinical Trials Group (ACTG)

The Promise of Zidovudine (AZT, ZDV)

- AZT a drug that had failed in early cancer trials, shown to have anti-HIV activity and to be tolerated by patients over 6 weeks (1986).
- Controlled trial in 282 subjects with advanced HIV infection (1987)
 - 19 deaths on placebo and 1 on AZT
 - CD4 cell elevations in AZT group
 - Substantial bone marrow toxicity observed in the AZT group

Mid-1980s - New Approaches Needed

- Individual drugs provided only temporary benefit, and resistance could develop
- Sequential single drug therapies not much better, as second responses were usually less sustained
- Would combination drug strategies, as had proven useful in some infections (e.g., tuberculosis) and some cancers be more effective?

Combination Antiretroviral Therapy

COMBINATION ANTIRETROVIRAL THERAPY STUDIES IN VITRO

- 1986-90 – Demonstration that 2 drug combinations may be synergistic, additive or antagonistic in their ability to inhibit HIV-1 replication
- 1991-92 - Demonstration that certain 3 drug combinations are particularly active in inhibiting HIV-1 replication

EARLY ANTI-HIV COMBINATION STUDIES IN PATIENTS

- 1989-95 - Pilot trials of antiretroviral drug combinations in small numbers of patients, suggesting safety and activity
- 1996-98 - Demonstration of the clinical benefits of 2 and 3 drug combinations in large controlled trials

Approved Antiretroviral Agents in 2011

Nucleoside RTIs

- Zidovudine (ZDV)
- Didanosine (ddI)
- ~~Zalcitabine (ddC)~~
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

Nucleotide RTI

- Tenofovir DF (TDF)

N.B.: Seven fixed-dose combinations are approved:

ZDV + 3TC; ZDV + 3TC + ABC; ABC + 3TC;
FTC + TDF; LPV + RTV; TDF + FTC + EFV;
TDF + FTC + RPV

Nonnucleoside RTI

- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFZ)
- Etravirine (ETV)
- Rilpiverine (RPV)

Integrase Inhibitor

- Raltegravir (RAL)

Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- ~~Amprenavir (APV)~~
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

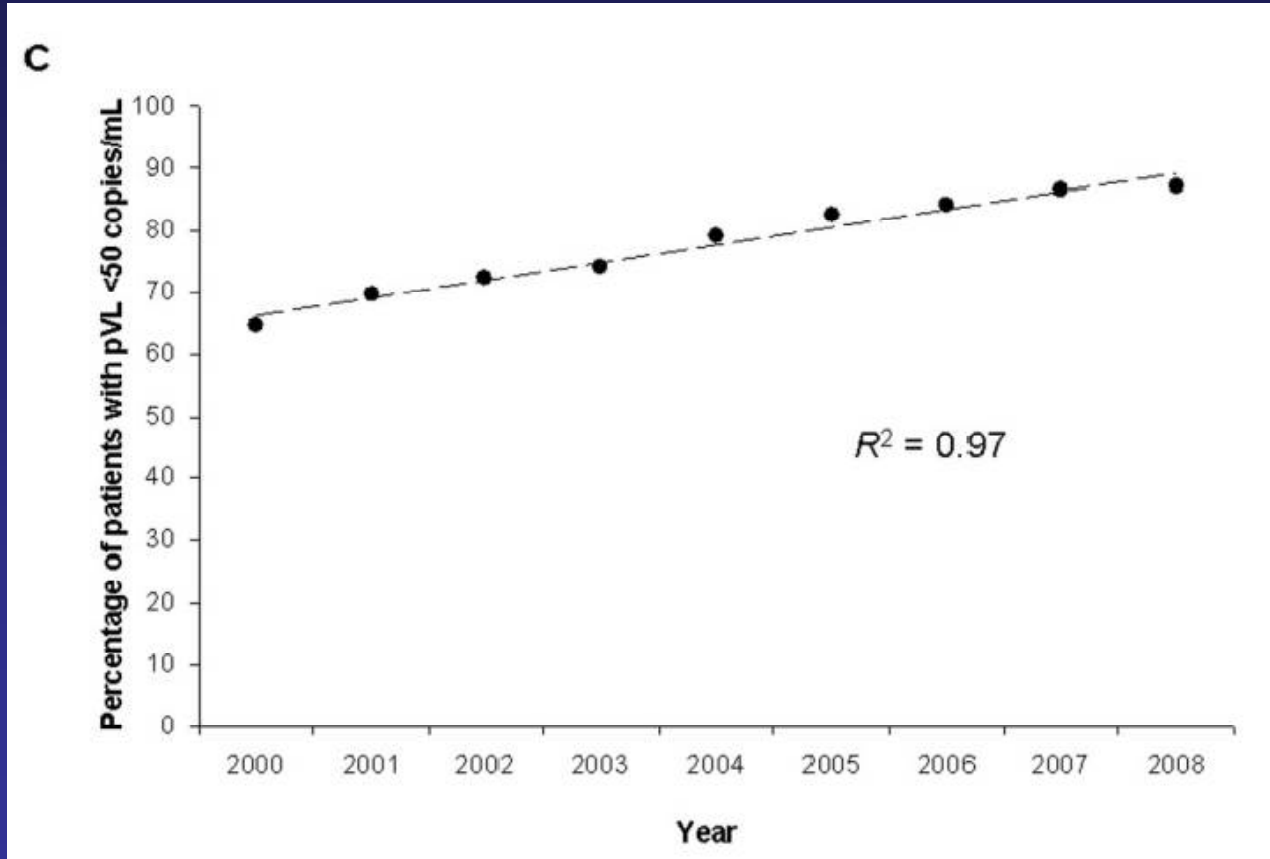
Fusion Inhibitor

- Enfuvirtide (T-20)

CCR5 Antagonist

- Maraviroc (MVC)

Treatment Success is Steadily Increasing



- N= 5422 receiving therapy in British Columbia; 87% now with HIV RNA < 50
- Also noted: 12-fold reduction in new cases of drug resistance

What Have We Accomplished?

- Never in the history of infectious diseases, have we learned so much about a viral disease in so little time
- Over 27 years, the molecular structure of the virus, its replicative pathway, its mechanisms for inducing immune compromise, and approaches to its control have all been elucidated
- We have turned an almost universal death sentence into a manageable infection

Approaches to the Control of HIV

Progress and Pitfalls over 25 Years

- Blood screening
- Prevention of Mother to Child Transmission
- Treatment with Antiretroviral Combinations
- Circumcision
- Pre-exposure prophylaxis (topical, oral)
- Behavioral changes

Future Challenges in HIV/AIDS

- Implementation of antiretroviral pre- and post-exposure prophylaxis
- Increased efforts to test-and-treat, and treat more infected individuals earlier
- Further reductions in worldwide incidence of new infections
- Continued efforts to develop prophylactic and therapeutic vaccines and immunotherapies

Are We Up To The Challenge?