Looking Back and Looking Forward at HIV Care

Michael Saag, MD,
University of Alabama, Birmingham
Director, Center for AIDS Research

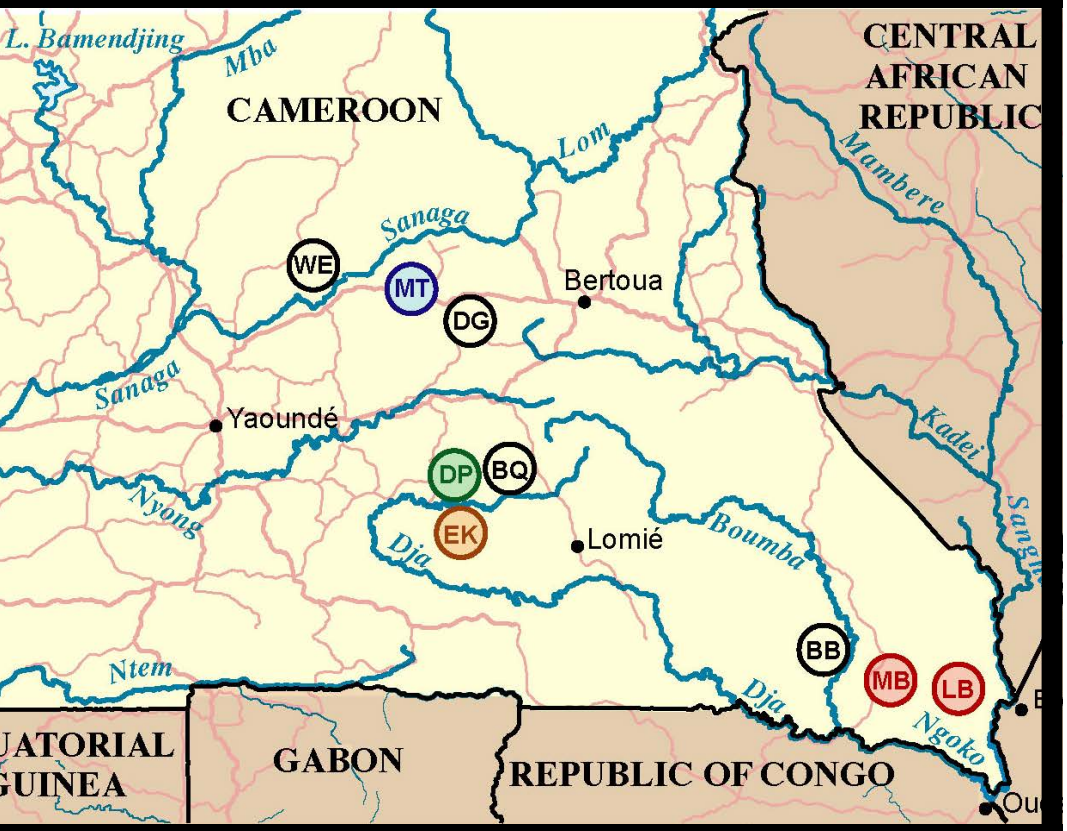
CFAR
CENTER FOR AIDS RESEARCH
University of Alabama at Birmingham

Circa 1900 - 1920


1920
© Magdalena Lukasik (JGI)

Chimpanzee Reservoirs of HIV-1

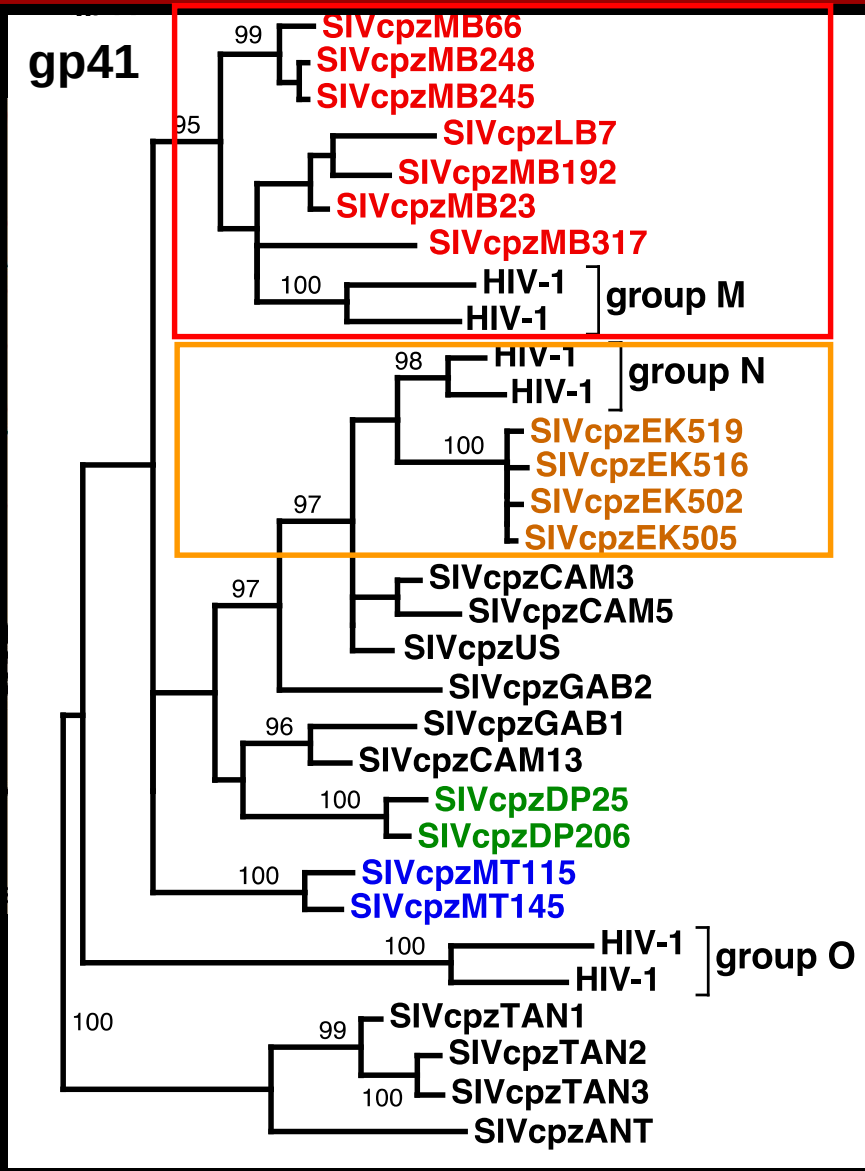
1920



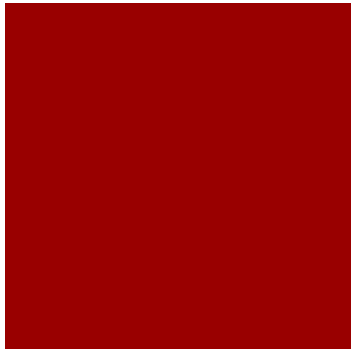
MB+LB closest relatives of HIV-1 M

EK closest relatives of HIV-1 N

also sites with highest prevalence

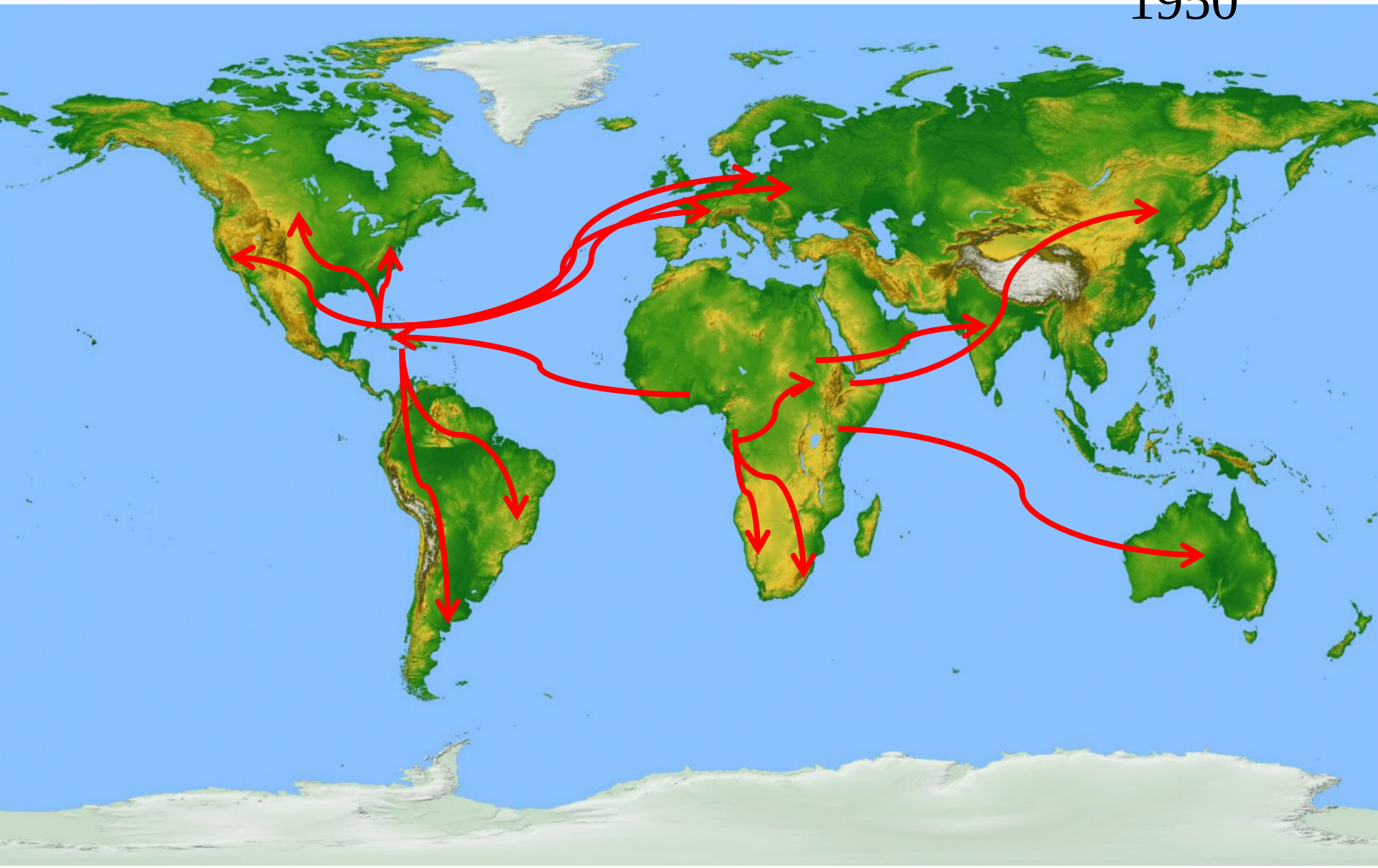


1950 - 1980




to Europe
Tunisia
Morocco
to Middle East
Algeria
Libya
Egypt
Western Sahara
Cape Verde
Mauritania
Mali
Niger
Chad
Sudan
Eritrea
Djibouti
Senegal
Burkina
Guinea
Nigeria
Cote d'Ivoire
Ethiopia
Cent Afr Rep
Ghana
Togo
Benin
Cameroon
Somalia
Uganda
Kenya
Gabon
Sao Tome & Principe
Equatorial Guinea
Congo
D.R. of Congo
Rwanda
Burundi
Tanzania
Seychelles
Liberia
Sierra Leone
Guinea-Bissau
The Gambia
Comoro Is.
Angola
Malawi
Zambia
St. Helena
Mozambique
Zimbabwe
Namibia
Madagascar
Botswana
Reunion
Swaziland
Mauritius
South Africa
Lesotho

1940


1950

Intestinal Cryptosporidiosis Complicated by Disseminated Cytomegalovirus Infection

1980

LOUIS WEINSTEIN, S. MIGUEL EDELSTEIN, JAMES L. MADARA, KENNETH R. FALCHUK, BRUCE M. McMANUS, and JERRY S. TRIER

The Divisions of Infectious Disease and Gastroenterology of the Department of Medicine and the Department of Pathology, Peter Bent Brigham Division of the Brigham and Women's Hospital, and the Departments of Medicine and Pathology, Harvard Medical School, Boston, Massachusetts

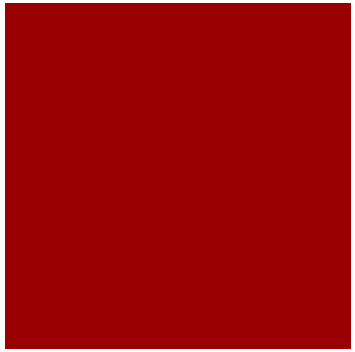
"Although no clear-cut evidence of immuno-deficiency could be demonstrated in our patient, this could not be ruled out completely."

Received November 10, 1980. Accepted April 22, 1981.

Address requests for reprints to: Louis Weinstein, M.D., Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115.

0016-5085/81/090584-08$02.50

1981



CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 2

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

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 residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed,

*Paired specimens not run in parallel.

CENTERS FOR DISEASE CONTROL

July 3, 1981 / Vol. 30 / No. 25

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

Skin or mucous membrane lesions, often dark blue to violaceous plaques or nodules, were present in most of the patients on their initial physician visit. However, these lesions were not always present and often were considered benign by the patient and his physician.

A review of the New York University Coordinated Cancer Registry for KS in men under age 50 revealed no cases from 1970-1979 at Bellevue Hospital and 3 cases in this age group at the New York University Hospital from 1961-1979.

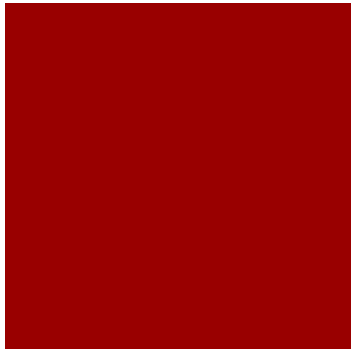
Seven KS patients had serious infections diagnosed after their initial physician visit. Six patients had pneumonia (4 biopsy confirmed as due to *Pneumocystis carinii* [PC]), and one had necrotizing toxoplasmosis of the central nervous system. One of the patients with *Pneumocystis* pneumonia also experienced severe, recurrent, herpes simplex infection; extensive candidiasis; and cryptococcal meningitis. The results of tests for cytomegalovirus (CMV) infection were available for 12 patients. All 12 had serological evidence of past or present CMV infection. In 3 patients for whom culture results were available, CMV was isolated from blood, urine and/or lung of all 3. Past infections with amebiasis and hepatitis were commonly reported.

TABLE 1. Presenting complaints in 20 patients with Kaposi's sarcoma

Presenting complaint	Number (percentage) of patients
Skin lesion(s) only	10 (50%)
Skin lesions plus lymphadenopathy	4 (20%)
Oral mucosal lesion only	1 (5%)
Inguinal adenopathy plus perirectal abscess	1 (5%)
Weight loss and fever	2 (10%)
Weight loss, fever, and pneumonia (one due to *Pneumocystis carinii*)	2 (10%)

1981

1981 - 1987



DEATH WATCH

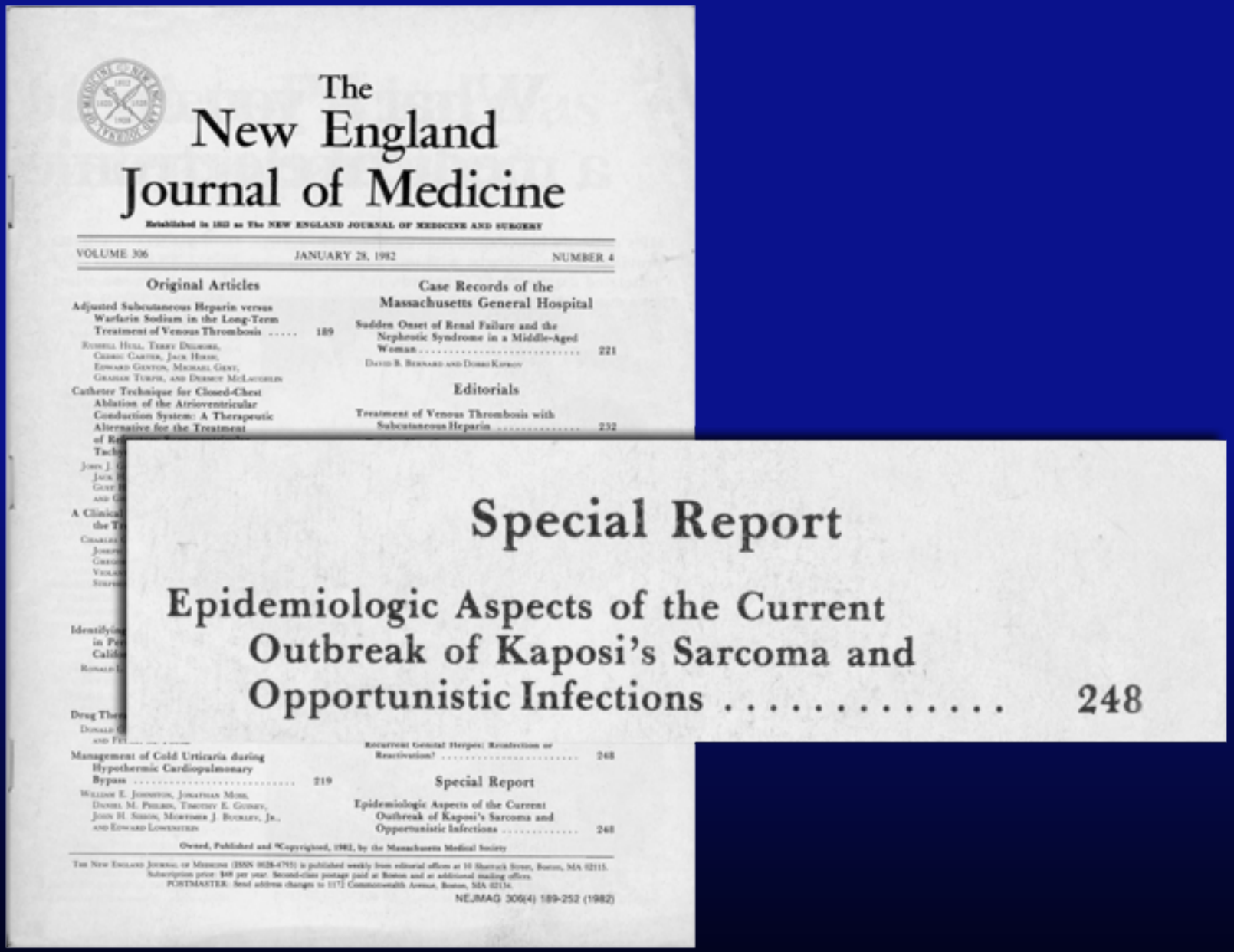
In 1981 a small band of CDC researchers first glimpsed the AIDS epidemic. Their lives would never be the same.

Atlanta, spring 1981. *It began quietly. The first alarm did not shrill from maximum biocontainment laboratories or flash from the screens of whirring computers. It began slowly, the greatest epidemiological chase in history, tracking a disease so horrible and relentless that medical historians would have to reach back to the terrors of the 14th century's Black Death for comparisons. In just eight years AIDS would kill more than 50,000 Americans and doom millions more around the globe. Doctors armed with medicines and magic bullets culled from technology's cutting edge would stand as helpless as their medieval counterparts before the plague. Those eight years would affect the members of a tiny task force of medical researchers as nothing before in their lives.*

BY VINCENT COPPOLA

"Hot stuff" was scribbled by Dr. James Curran across the first report Dr. Wayne Shandera and Dr. Mary Guinan (front) filed on a mysterious new disease. Soon, doctors (back row, from left) Thomas Spira, Curran, Harold Jaffe, Dennis Ceranek and William Darrow would be involved with the AIDS epidemic.

1981



The New England Journal of Medicine

Established in 1812 as The NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 306 JANUARY 28, 1982 NUMBER 4

Original Articles

Case Records of the Massachusetts General Hospital

Editorials

Special Report

Epidemiologic Aspects of the Current Outbreak of Kaposi's Sarcoma and Opportunistic Infections 248

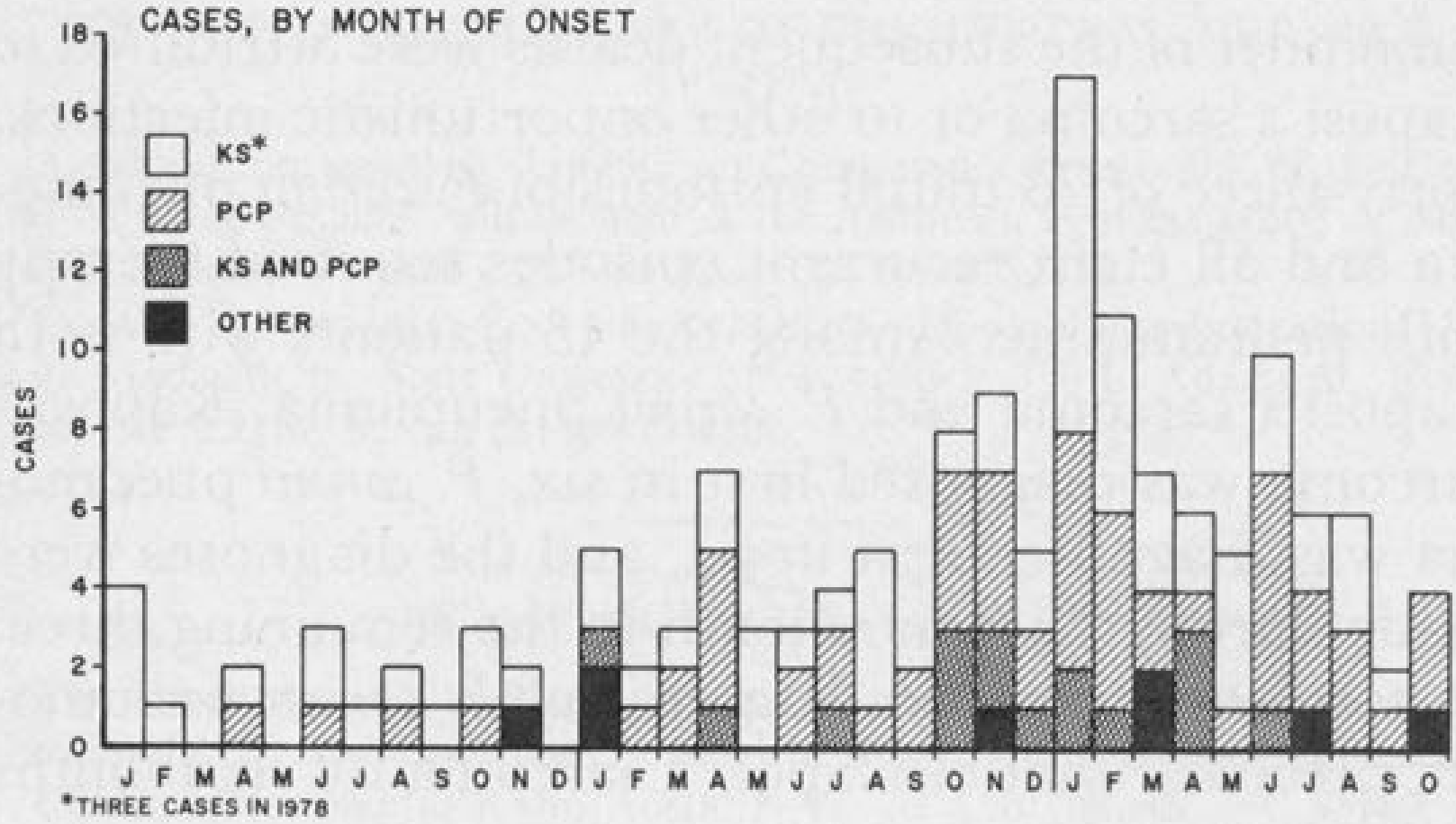
Special Report

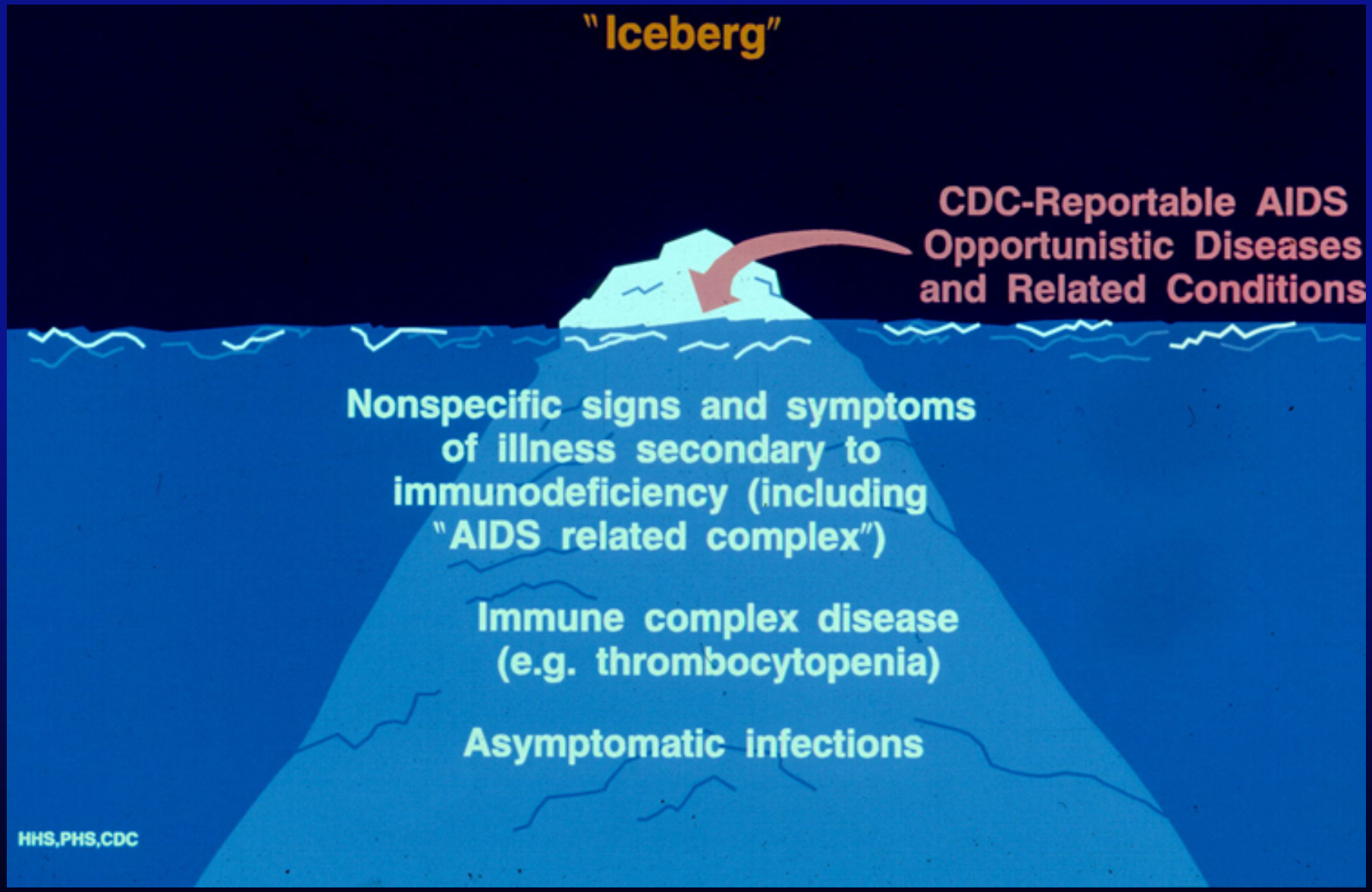
The New England Journal of Medicine (ISSN 0028-4793) is published weekly from editorial offices at 10 Shattuck Street, Boston, MA 02115. Subscription price: $48 per year. Second-class postage paid at Boston and at additional mailing offices. POSTMASTER: Send address changes to 1172 Commonwealth Avenue, Boston, MA 02134.

NEJMAQ 306(4) 189-252 (1982)

1982

THE NEW ENGLAND JOURNAL OF MEDICINE Jan. 28, 1982



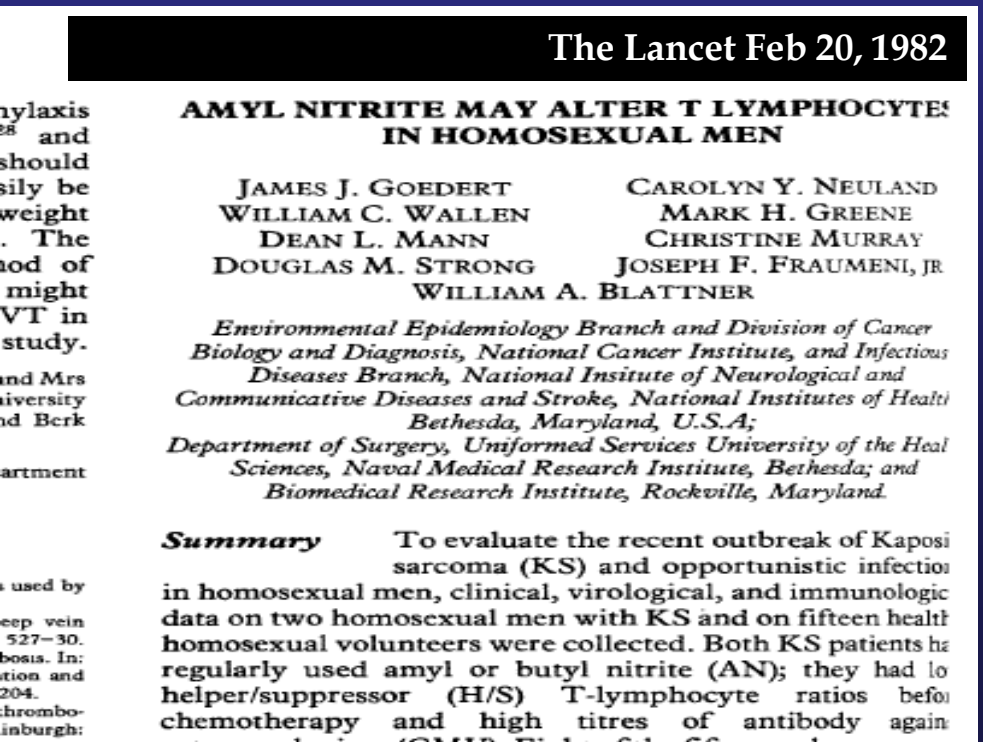

"Iceberg"
CDC-Reportable AIDS
Opportunistic Diseases
and Related Conditions
Nonspecific signs and symptoms
of illness secondary to
immunodeficiency (including
"AIDS related complex")
Immune complex disease
(e.g. thrombocytopenia)
Asymptomatic infections
HHS,PHS,CDC

1982

1982

Alternative Theories

- Drugs – e.g., Amyl Nitrites (“Poppers”)
- Fungi
- Allogeneic semen as immunosuppressant



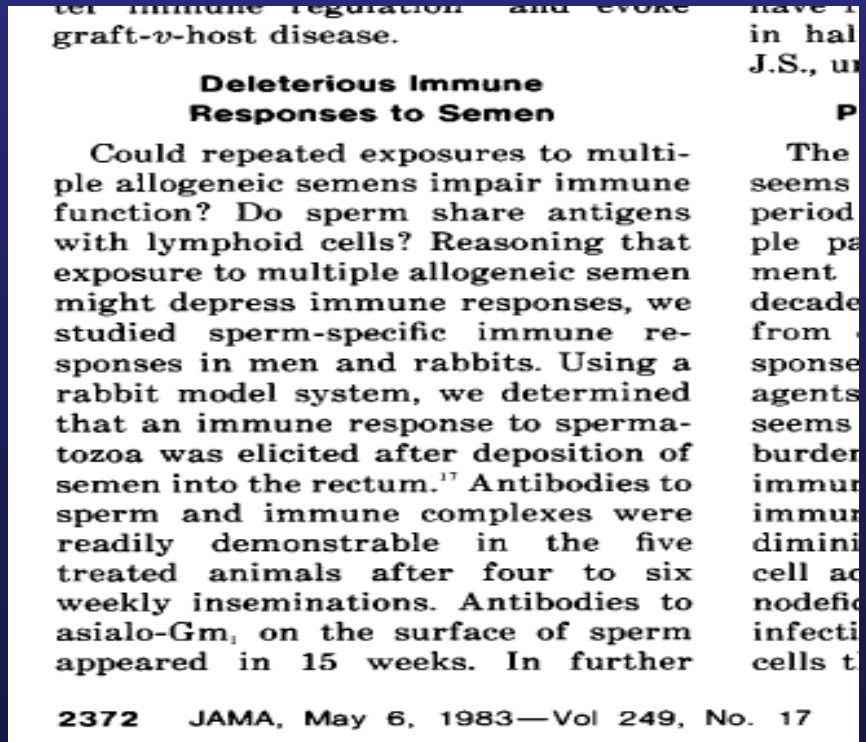
The Lancet Feb 20, 1982

AMYL NITRITE MAY ALTER T LYMPHOCYTES IN HOMOSEXUAL MEN

JAMES J. GOEDERT, CAROLYN Y. NEULAND, WILLIAM C. WALLEN, MARK H. GREENE, DEAN L. MANN, CHRISTINE MURRAY, DOUGLAS M. STRONG, JOSEPH F. FRAUMENI, JR, WILLIAM A. BLATTNER

Environmental Epidemiology Branch and Division of Cancer Biology and Diagnosis, National Cancer Institute, and Infectious Diseases Branch, National Insitute of Neurological and Communicative Diseases and Stroke, National Institutes of Healti Bethesda, Maryland, U.S.A;
Department of Surgery, Uniformed Services University of the Heal Sciences, Naval Medical Research Institute, Bethesda; and Biomedical Research Institute, Rockville, Maryland.

Summary To evaluate the recent outbreak of Kaposi sarcoma (KS) and opportunistic infectio in homosexual men, clinical, virological, and immunologic data on two homosexual men with KS and on fifteen health homosexual volunteers were collected. Both KS patients ha regularly used amyl or butyl nitrite (AN); they had lo helper/suppressor (H/S) T-lymphocyte ratios befo chemotherapy and high titres of antibody again



graft-*v*-host disease.

Deleterious Immune Responses to Semen

Could repeated exposures to multiple allogeneic semens impair immune function? Do sperm share antigens with lymphoid cells? Reasoning that exposure to multiple allogeneic semen might depress immune responses, we studied sperm-specific immune responses in men and rabbits. Using a rabbit model system, we determined that an immune response to spermatozoa was elicited after deposition of semen into the rectum.[17] Antibodies to sperm and immune complexes were readily demonstrable in the five treated animals after four to six weekly inseminations. Antibodies to asialo-GM_1 on the surface of sperm appeared in 15 weeks. In further

ONE STEP BEHIND A

KILLER

Medicine's best and brightest have not yet solved the puzzle of Acquired Immune Deficiency Syndrome. But that's not for want of trying.

by Susan West

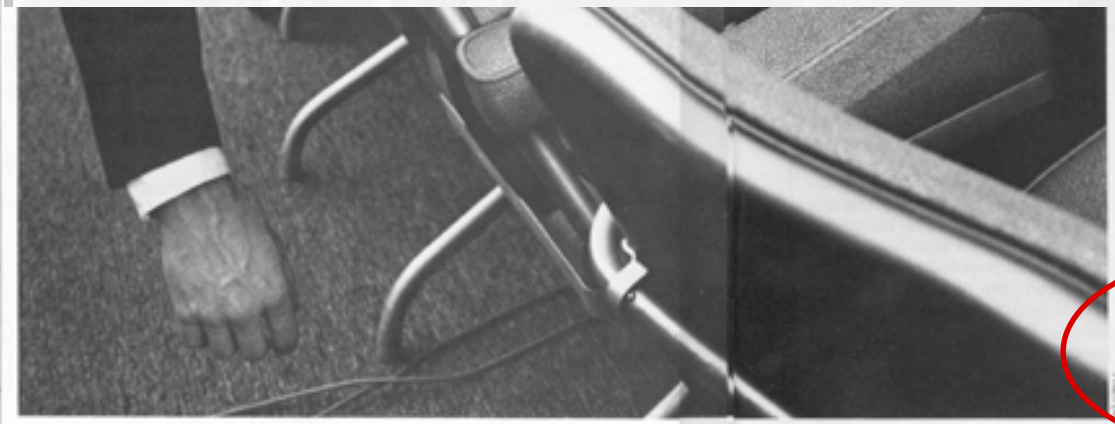
1983

Jim Curran is making one last phone call. His voice cracks, and he's talking slower than usual. He rubs his eyes and sips coffee when he listens. His white shirt is rumpled. He's been in his office at the Centers for Disease Control since 5:30 this morning.

Curran hangs up and glances at his watch. He shuts the door, sits down, and slouches to a comfortable position. He leans his head on his hand and checks his watch again. And he begins to talk about the epidemic.

Jim Curran, Centers for Disease Control

"Very depressing," one CDC doctor said of a January 4 meeting in Atlanta on how to prevent AIDS. "We spent most of the time trying to convince the blood banks it's transmissible. We think there's no doubt, but the blood bank people say give us more proof. We intend to do just that."

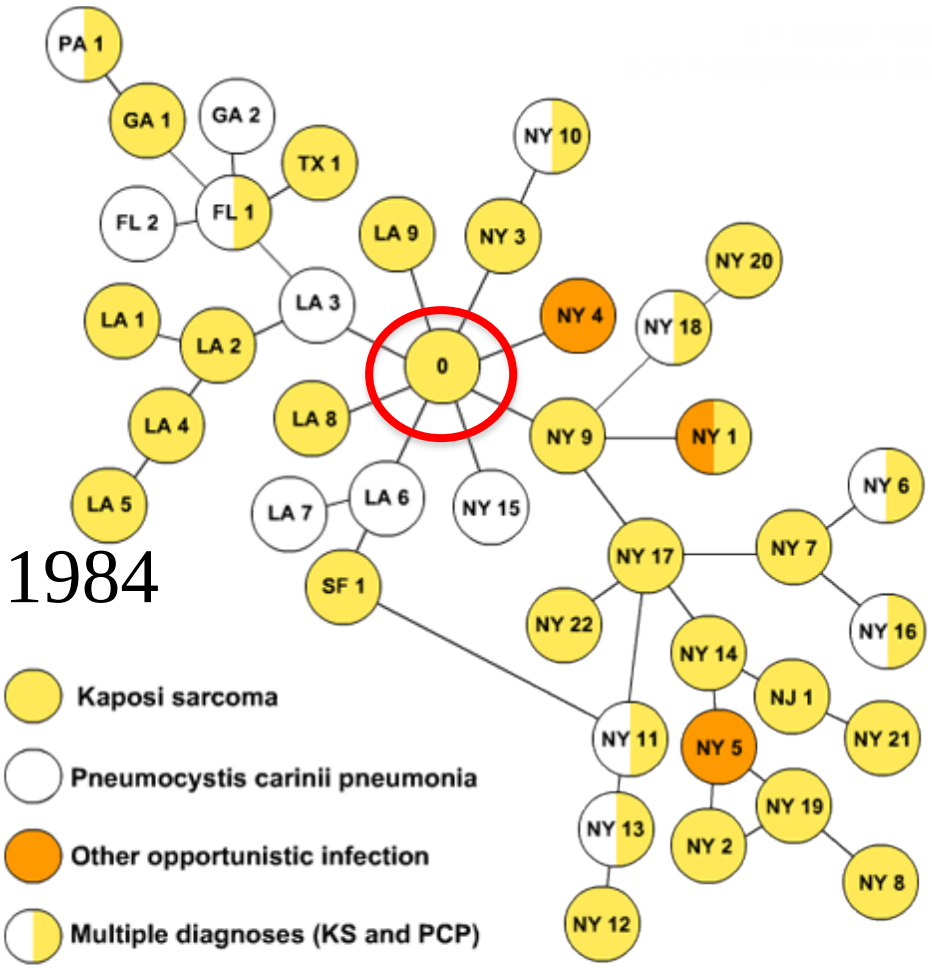


Louis Aledort, National Hemophilia Foundation

Roger Enlow, National Gay Task Force

Donald Francis, Centers for Disease Control

"Very depressing," one CDC doctor said of a January 4 meeting in Atlanta on how to prevent AIDS. "We spent most of the time trying to convince the blood banks it's transmissible. We think there's no doubt, but the blood bank people say give us more proof. We intend to do just that."



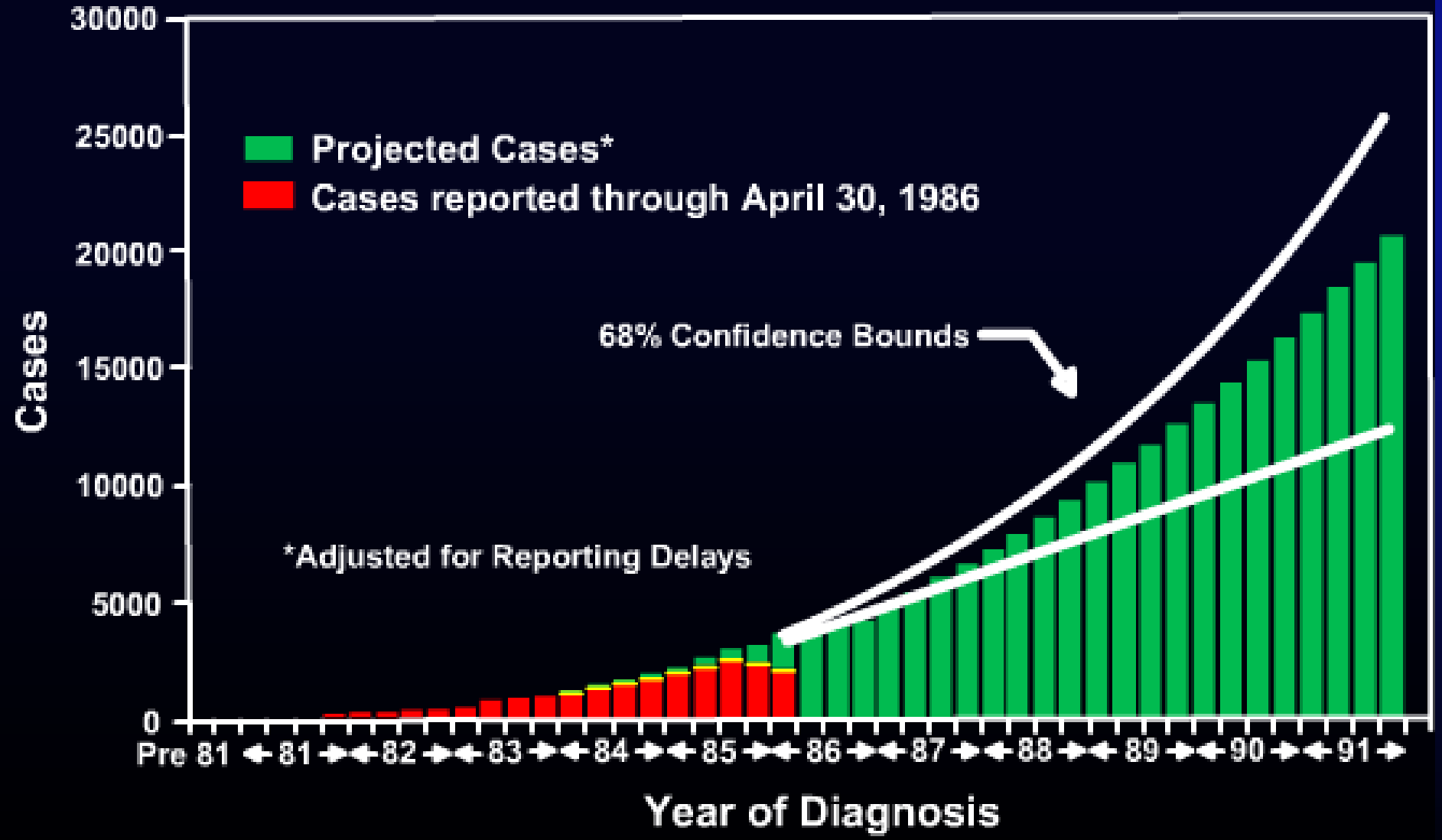
1984

City: LA- Los Angeles, NY - New York, SF - San Francisco

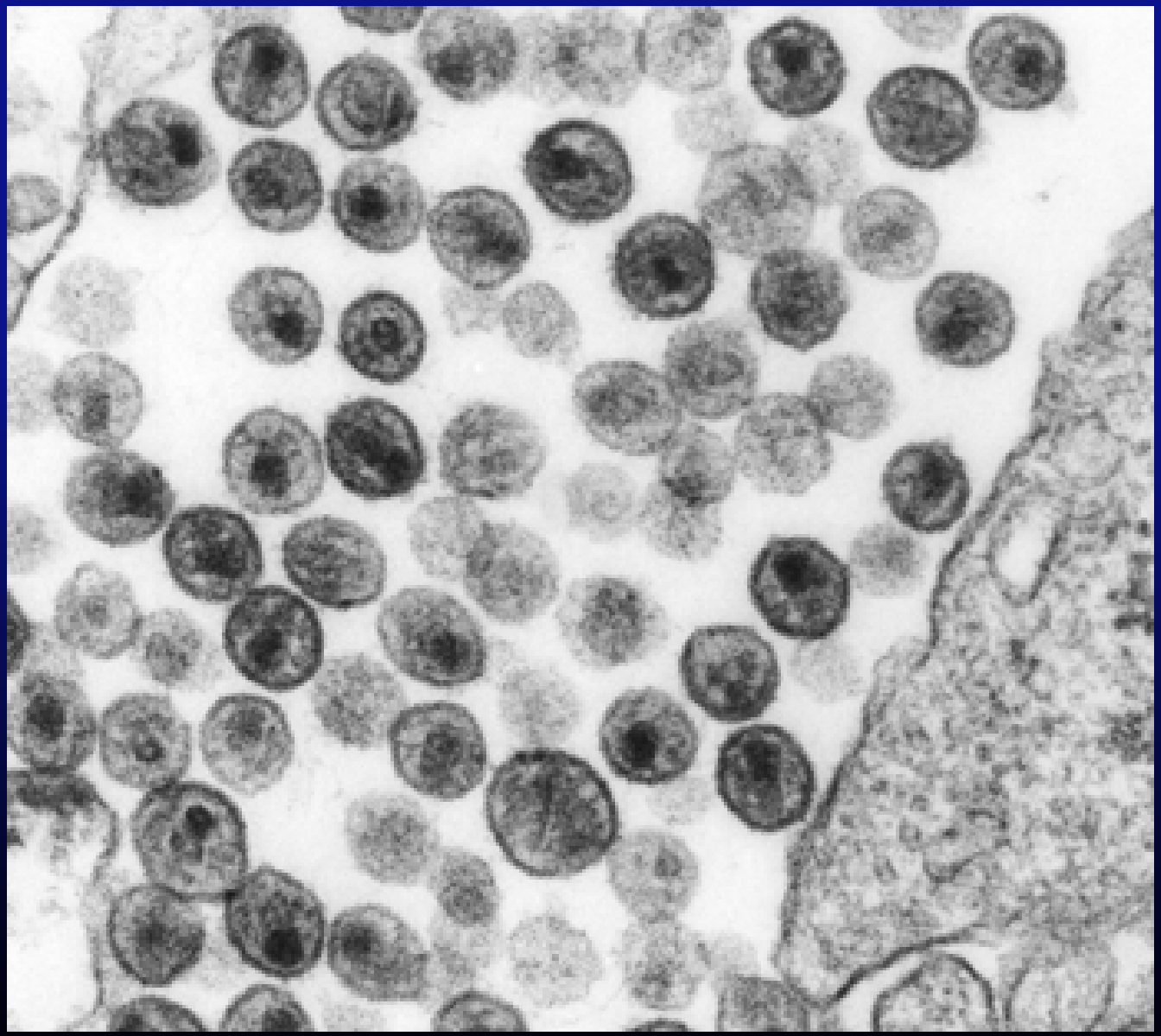
State: FL - Florida, GA - Georgia, NJ - New Jersey, PA - Pennsylvania, TX - Texas

Figure 1. *Sexual contacts among homosexual men with AIDS. Each* ***circle*** *represents an AIDS patient.* ***Lines*** *connecting the circles represent sexual exposures. Indicated city or state is place of residence of a patient at the time of diagnosis. "0" indicates Patient 0 (described in text).*

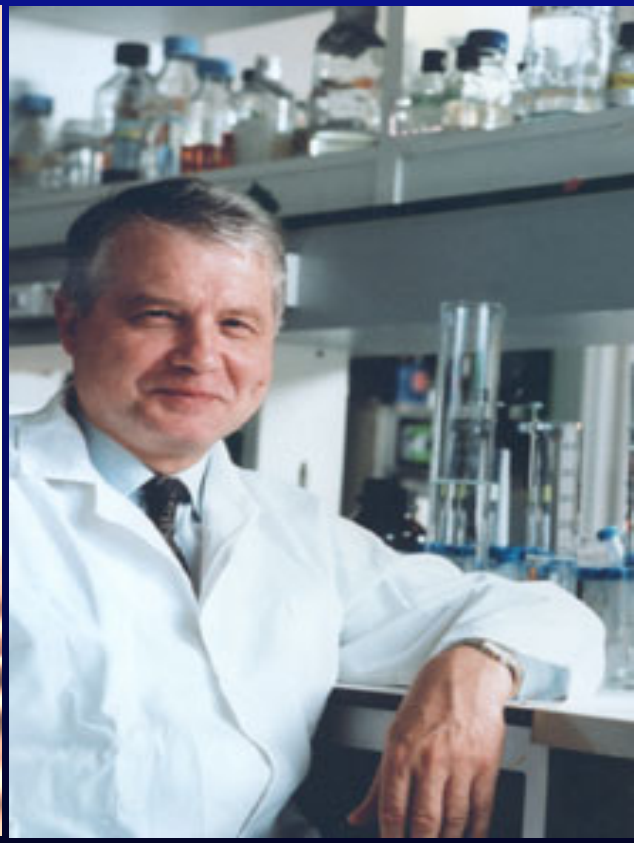
Projected Incidence of AIDS in the U.S.
By Quarter of Diagnosis
Coolfront Planning Conference, May 1986



1983

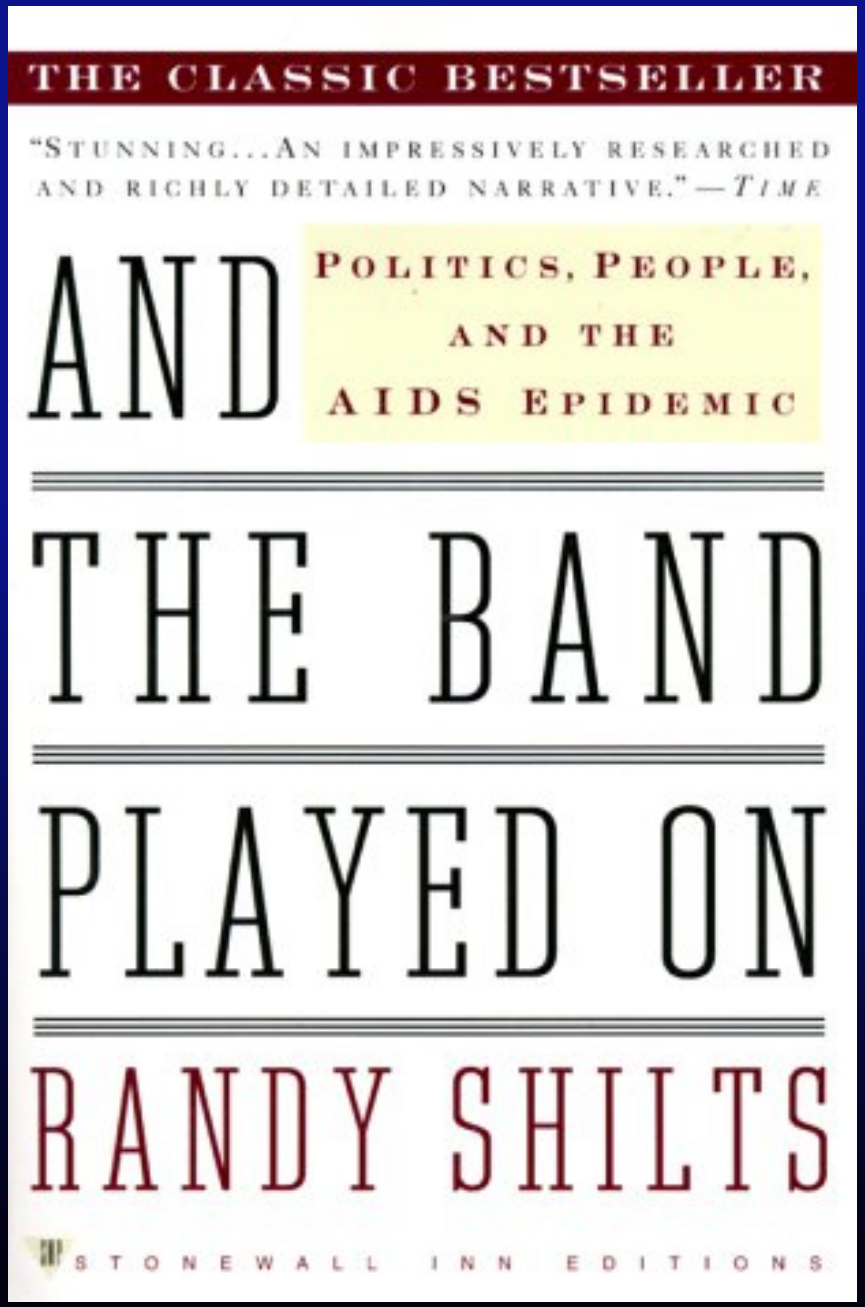


Bob Gallo, Francoise Barre-Sinoussi, and Luc Montagnier

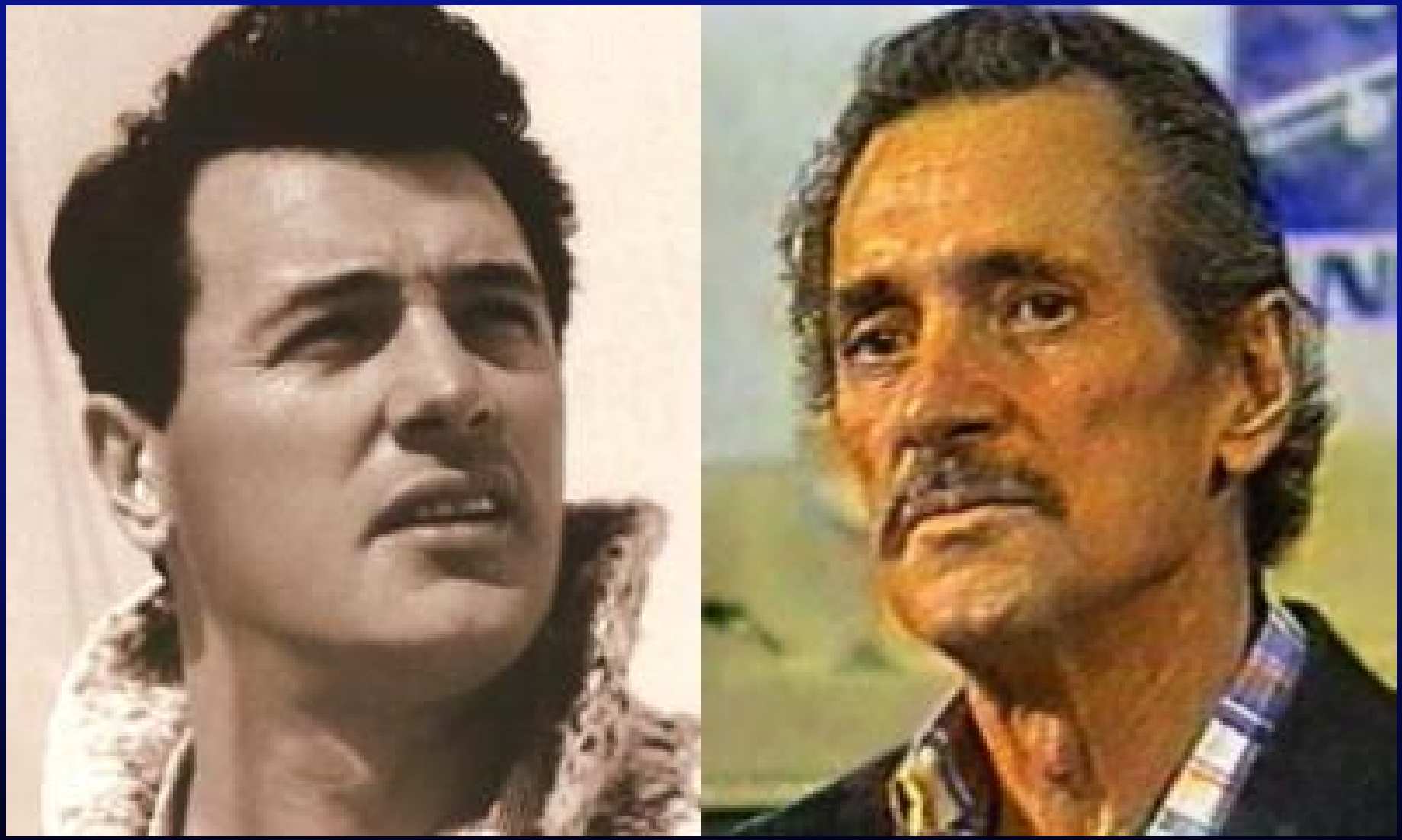


1983-84

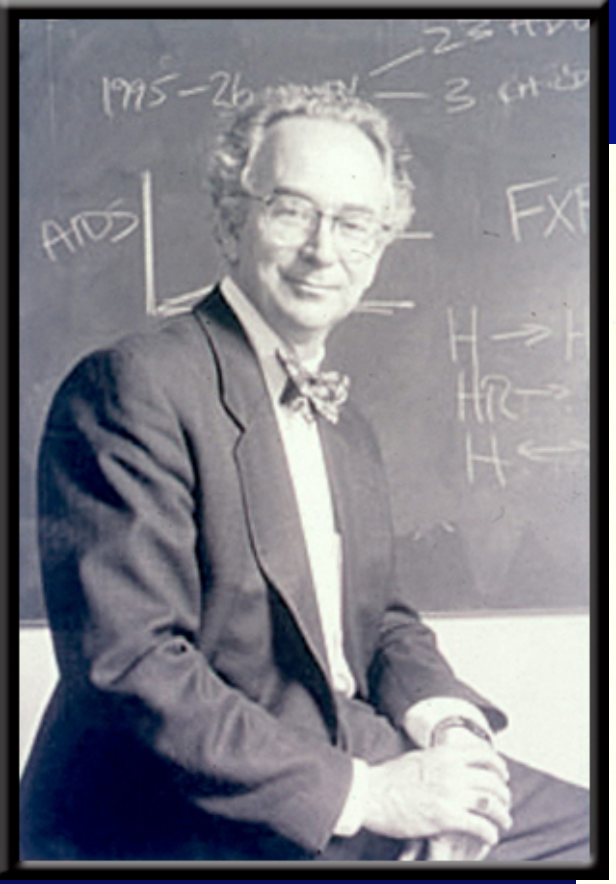
1987


THE CLASSIC BESTSELLER
"STUNNING...AN IMPRESSIVELY RESEARCHED AND RICHLY DETAILED NARRATIVE." —TIME
AND THE BAND PLAYED ON
POLITICS, PEOPLE, AND THE AIDS EPIDEMIC
RANDY SHILTS
STONEWALL INN EDITIONS

1985



Project SIDA Leadership 1984 - 1990



Reprinted from the JAMA® Journal of the American Medical Association
June 20, 1986, Volume 255

Original Contributions

JAMA®
THE JOURNAL of the American Medical Association
June 20, 1986 Vol 255, No. 23

Surveillance for AIDS in a Central African City

Kinshasa, Zaire

Jonathan M. Mann, MD, MPH; Henry Francis, MD; Thomas Quinn, MD; Pangu Kaza Asila, MD, MPH; Ngaly Bosenge, MD; Nzila Nzilambi, MD; Kapita Bila, MD; Muyembe Tamfum, MD; Kalisa Ruti, MD; Peter Piot, MD; Joseph McCormick, MD; James W. Curran, MD, MPH

• **Surveillance for acquired immunodeficiency syndrome (AIDS) in Kinshasa, Zaire, was initiated in July 1984, using a modified version of the case definition developed by the Centers for Disease Control. During the first eight months, 332 patients met all clinical and laboratory criteria; surveillance information was available for 295 (89%) of these patients. Of the sera tested from these patients, 99% had antibodies to human T-cell lymphotropic virus type III/lymphadenopathy-associated virus by both enzyme-linked immunosorbent assay and Western blot procedures. The male-female case ratio was 1:1.1; the mean age of patients was 33.6 years (median, 32 years; range, 1.5 to 64 years); and men were significantly older than women (mean, 37.4 vs 30.0 years). The estimated incidence rate for adults in Kinshasa is 380 cases per 1 million people per year. Peak age-specific incidence rates for men and women occurred among the 30- to 39-year age group, although the rate for men in this age group was 24% higher than the rate for women (786 vs 601 per 1 million). A reasonable estimate of the current annual incidence of AIDS is 550 to 1,000 cases per 1 million people. Surveillance of AIDS in Zaire provides important information on transmission patterns and rates in Africa.**

(*JAMA* 1986;255:3255-3259)

AIDS research project in the capital city of Kinshasa. Researchers involved in this project described epidemiologic and clinical differences between AIDS in Zaire and in the United States and Europe.[2] In response, the Zairian Department of Public Health established a long-term project to study AIDS.

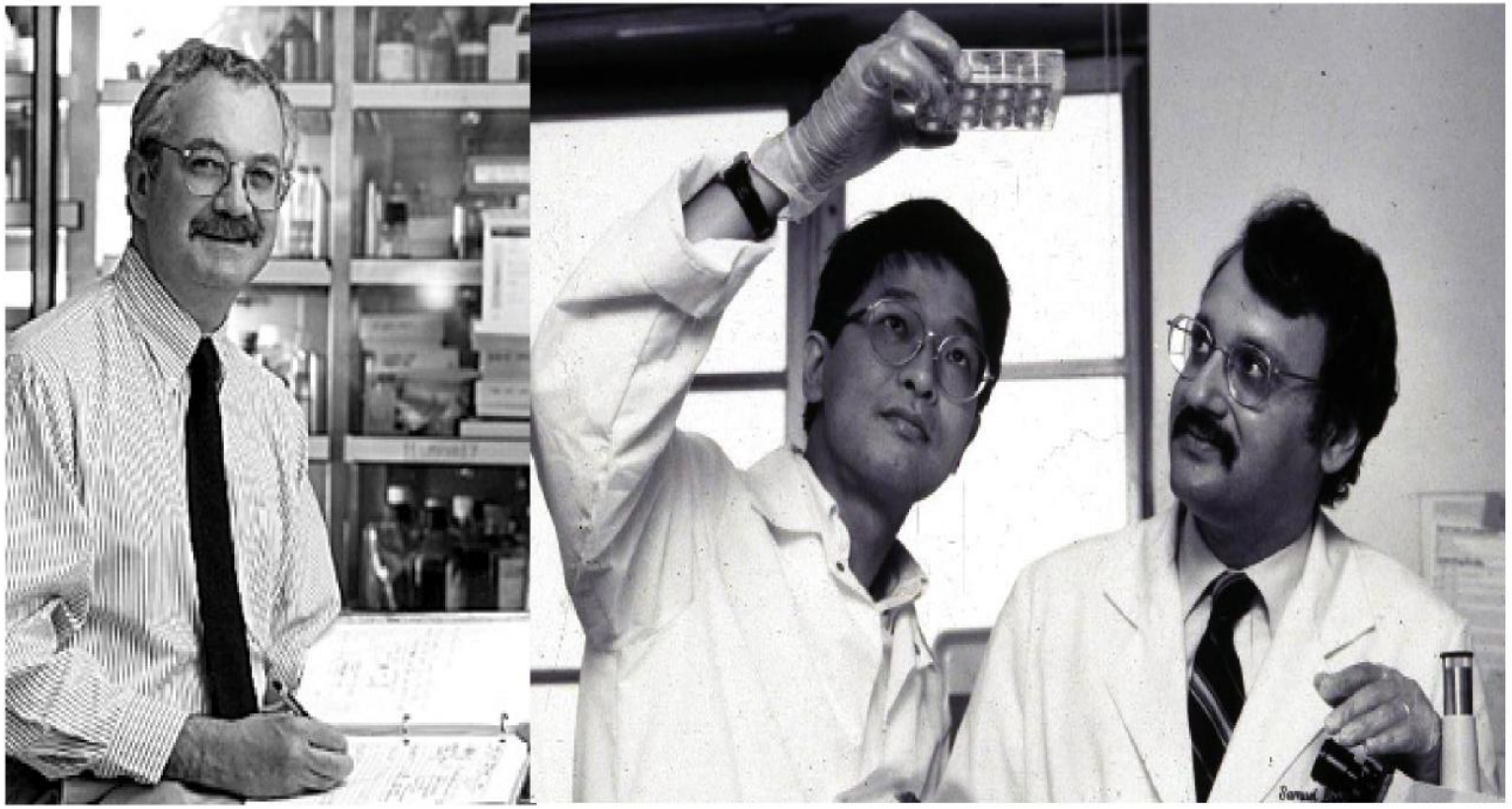
The Project SIDA is a collaborative research program involving the Zairian Department of Public Health, the US Department of Health and Human Services, and the Institute of Tropical Medicine, Antwerp, Belgium. In June 1984, Project SIDA established an AIDS surveillance system in Kinshasa. This report summarizes surveillance data for Kinshasa from July 1984 to February 1985.

Testimony Before the House Appropriations Subcommittee for the NIAID Budget March, 1987

1987

Developing AZT and Other First-Generation Nucleoside Reverse Transcriptase Inhibitors

1986



Drs. Robert Yarchoan, Hiroaki Mitsuya, and Samuel Broder

1985

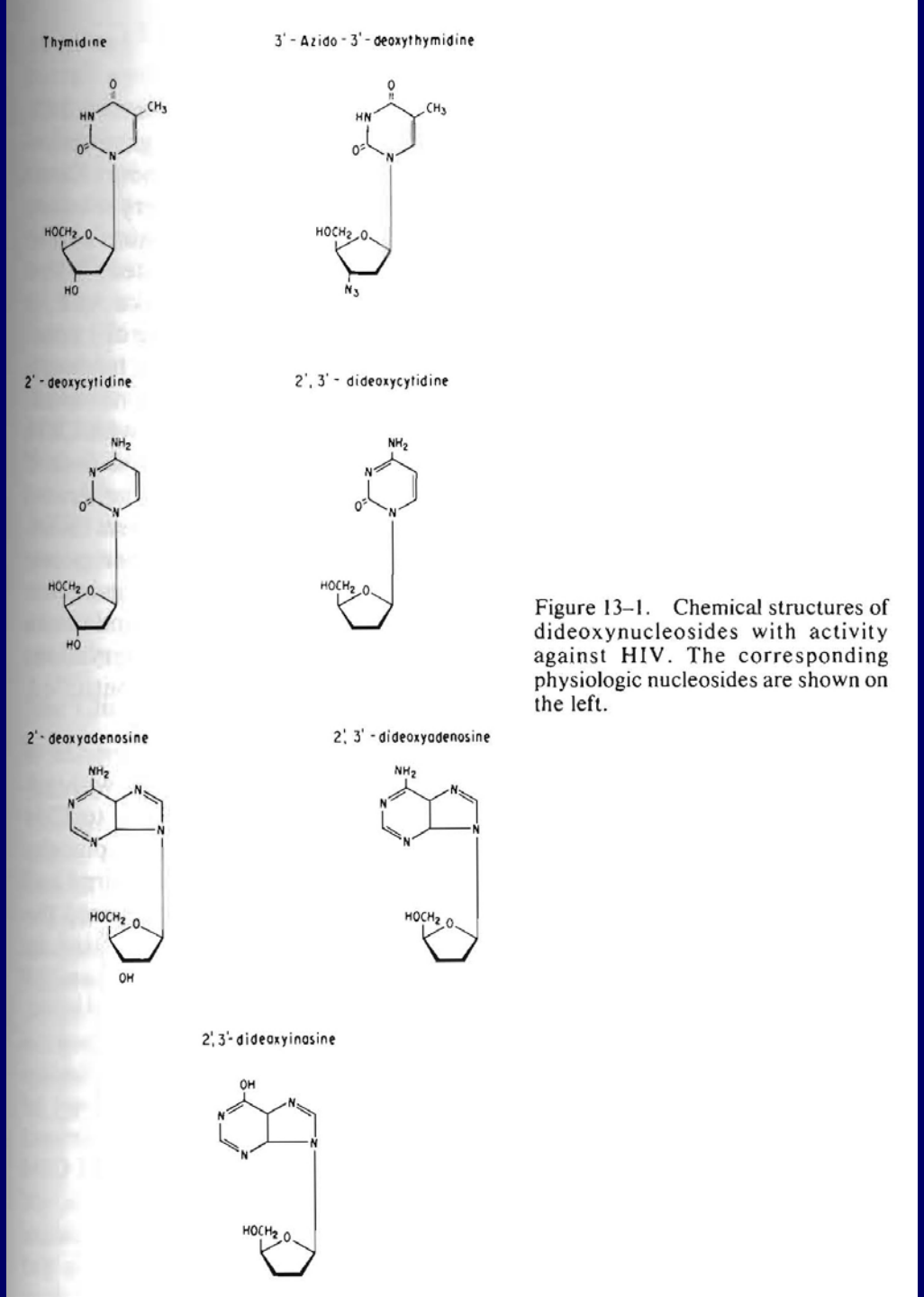


Figure 13–1. Chemical structures of dideoxynucleosides with activity against HIV. The corresponding physiologic nucleosides are shown on the left.

The New England Journal of Medicine

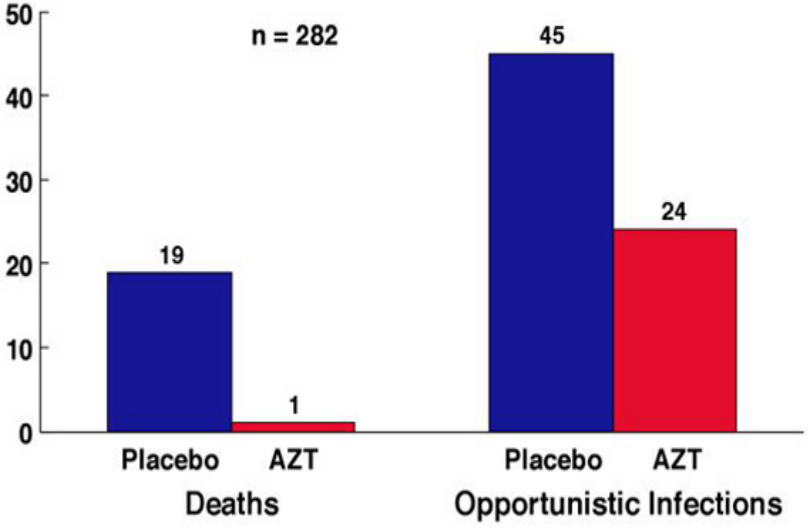
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 317 July 23, 1987 NUMBER 4

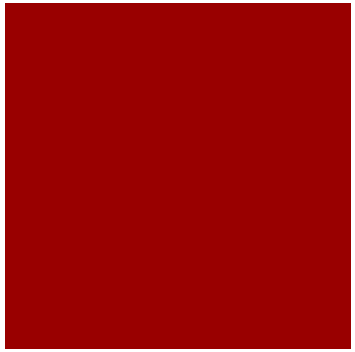
The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex: A Double-Blind, Placebo-Controlled Trial

Margaret A. Fischl, et al.

BW 002: 24-Week Study of AZT vs. Placebo in Patients with AIDS or ARC



1988 -1996



1988

1988

Community Activism

1988

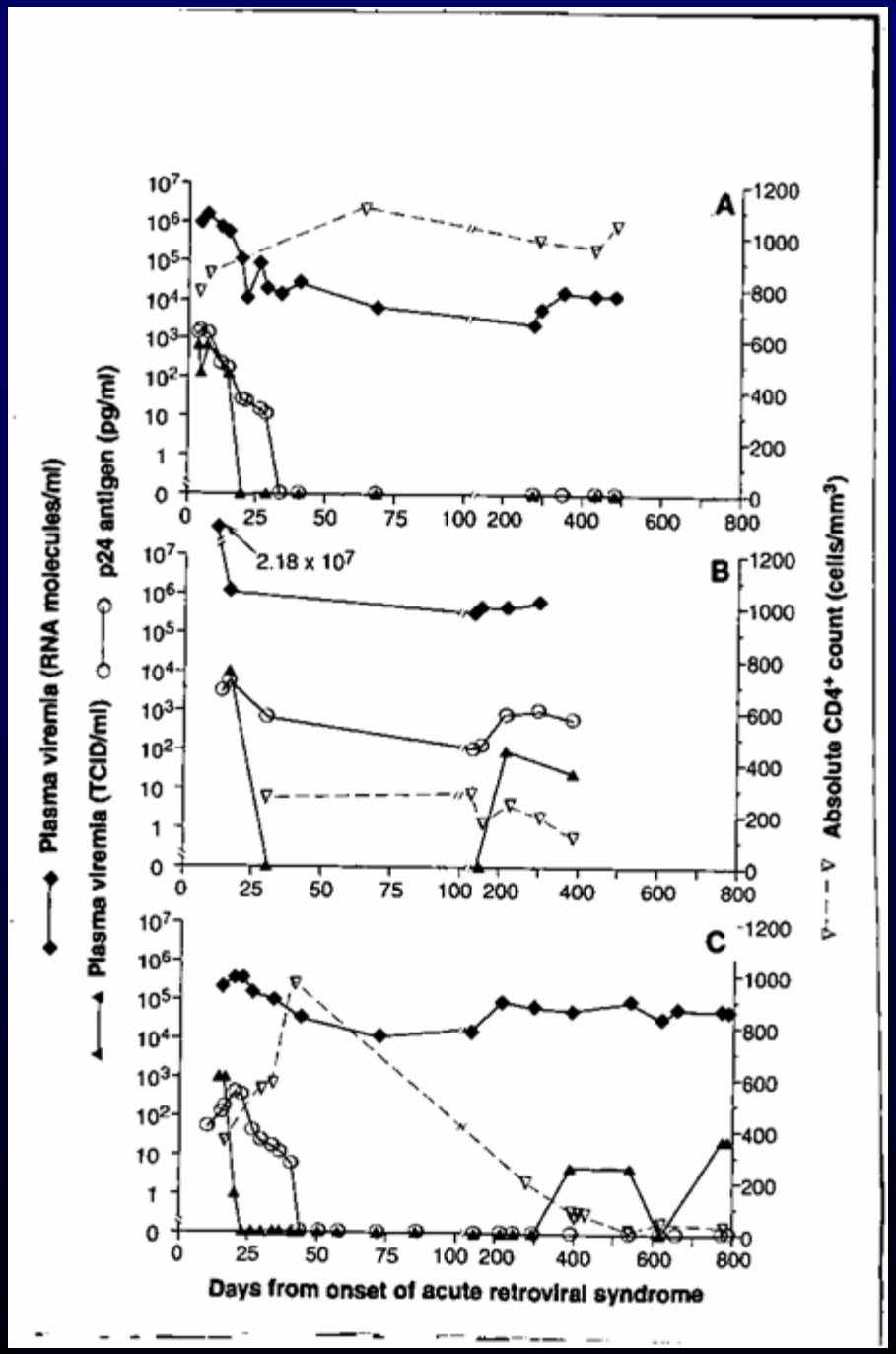
1991

SCIENCE

High Levels of HIV-1 in Plasma During All Stages of Infection Determined by Competitive PCR

M. Piatak, Jr., M. S. Saag, L. C. Yang, S. J. Clark, J. C. Kappes, K.-C. Luk, B. H. Hahn, G. M. Shaw, and J. D. Lifson*

1992



Piatak, et al, Science, 1993

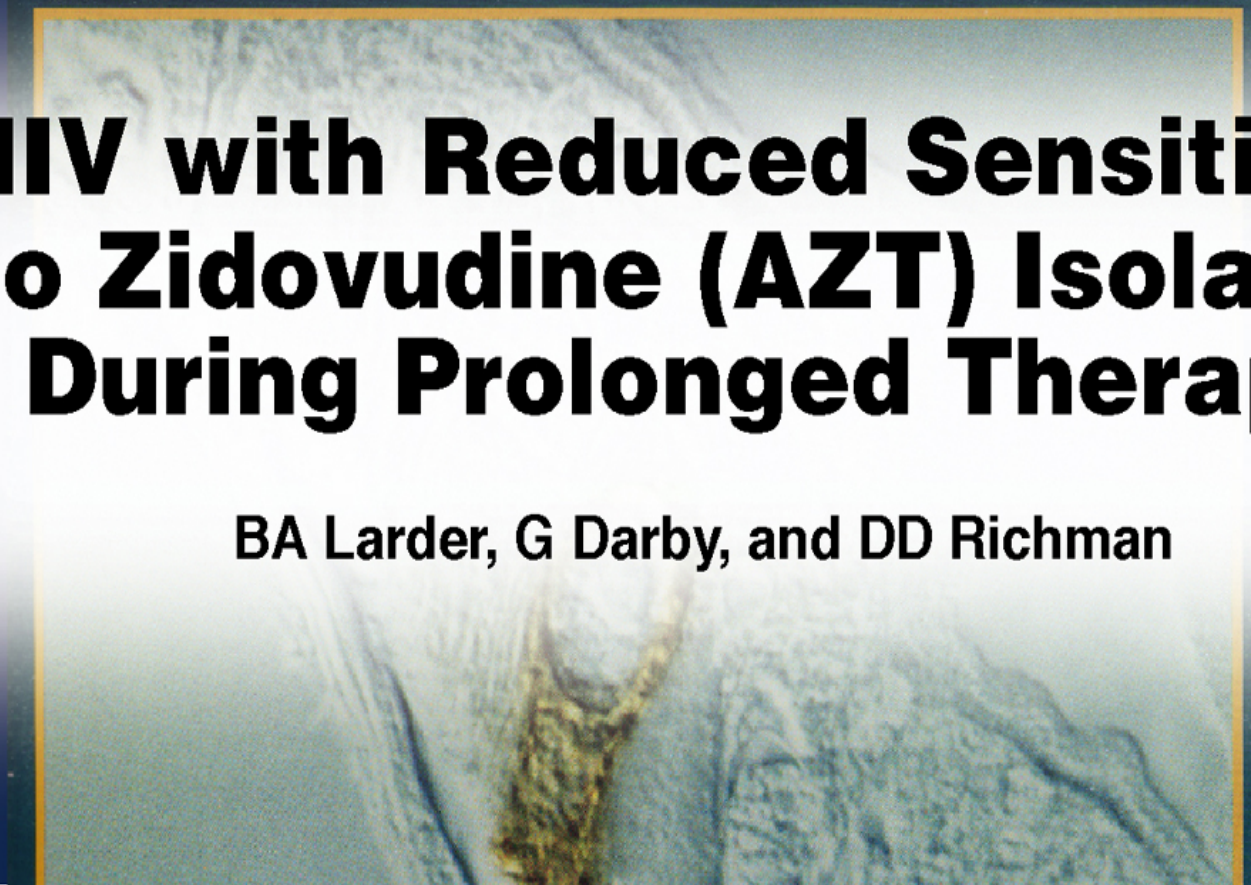
American Association for the Advancement of Science

SCIENCE

31 March 1989 $3.50
Vol. 243 ■ Pages 1641–1760

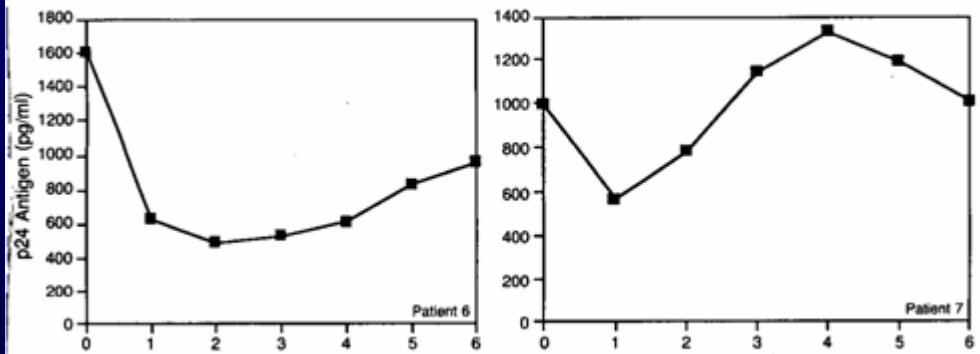
HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy

BA Larder, G Darby, and DD Richman



A SHORT-TERM CLINICAL EVALUATION OF L-697,661, A NON-NUCLEOSIDE INHIBITOR OF HIV-1 REVERSE TRANSCRIPTASE

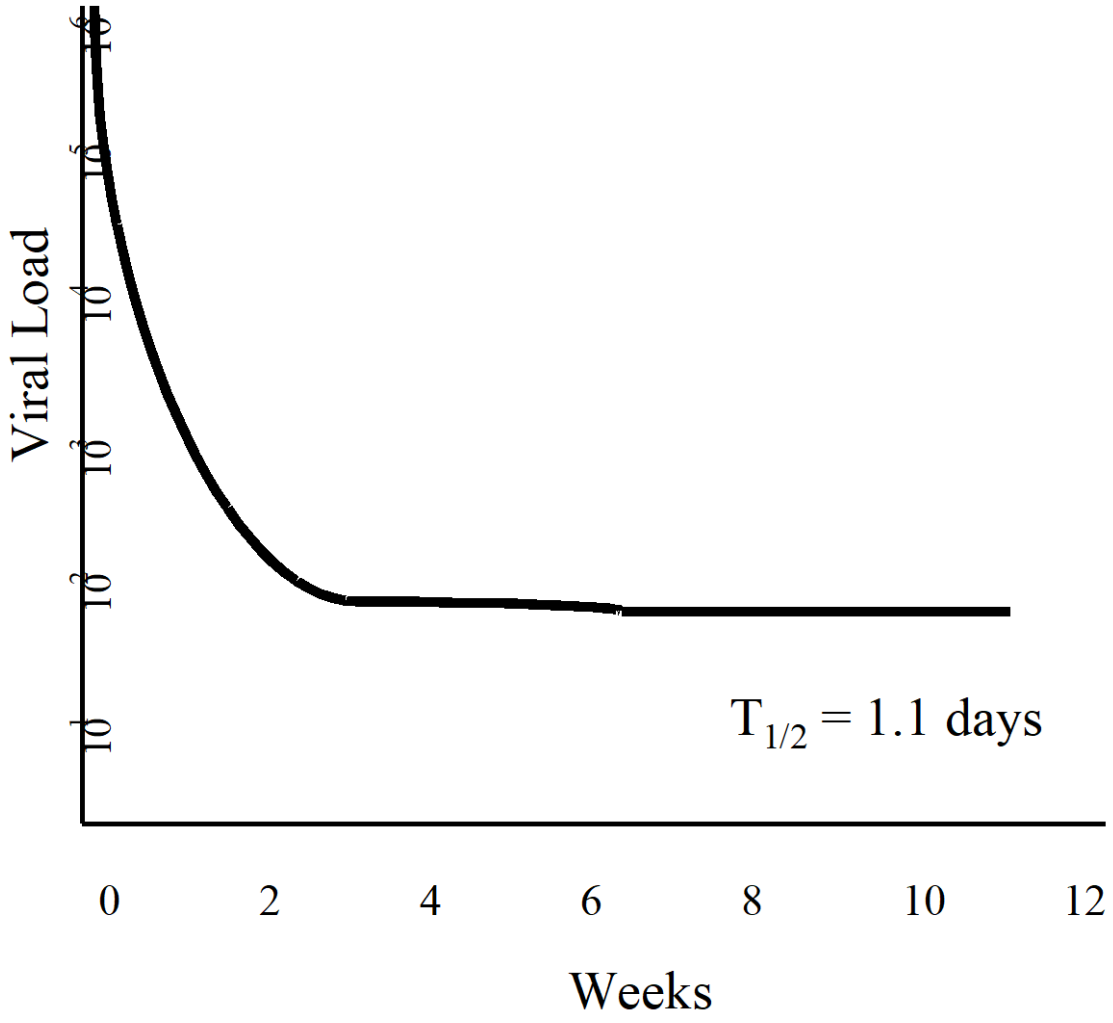
MICHAEL S. SAAG, M.D., EMILIO A. EMINI, PH.D., OSCAR L. LASKIN, M.D., JEFFREY DOUGLAS, M.D., WILLIAM I. LAPIDUS, M.D., WILLIAM A. SCHLEIF, M.SC., RICHARD J. WHITLEY, M.D., CAROL HILDEBRAND, B.S., VERA W. BYRNES, PH.D., JOHN C. KAPPES, PH.D., KEVIN W. ANDERSON, PH.D., FERDINAND E. MASSARI, M.D., GEORGE M. SHAW, M.D., PH.D., AND THE L-697,661 WORKING GROUP*



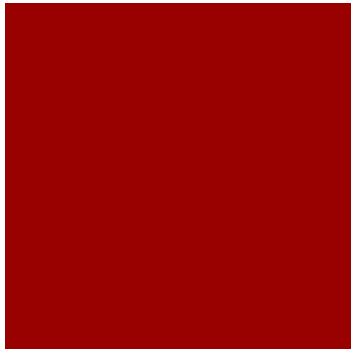
	IC_{90} (nmol/liter)			IC_{90} (nmol/liter)		
	L-697,661	Zidovudine		L-697,661	Zidovudine
Before	100	50	Before	400	100
After	≥12,000	25	After	≥12,000	50

	IC_{90} (nmol/liter)			IC_{90} (nmol/liter)	
	L-697,661	Zidovudine		L-697,661	Zidovudine
Before	50	100	Before	100	25
After	≥6000	50	After	800	25

NEJM, 1993


Viral Load
10^6
10^5
10^4
10^3
10^2
10^1
$T_{1/2}$ = 1.1 days
0
2
4
6
8
10
12
Weeks

1996



Approved Antiretroviral Agents in 1996

Nucleoside RTIs

- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)

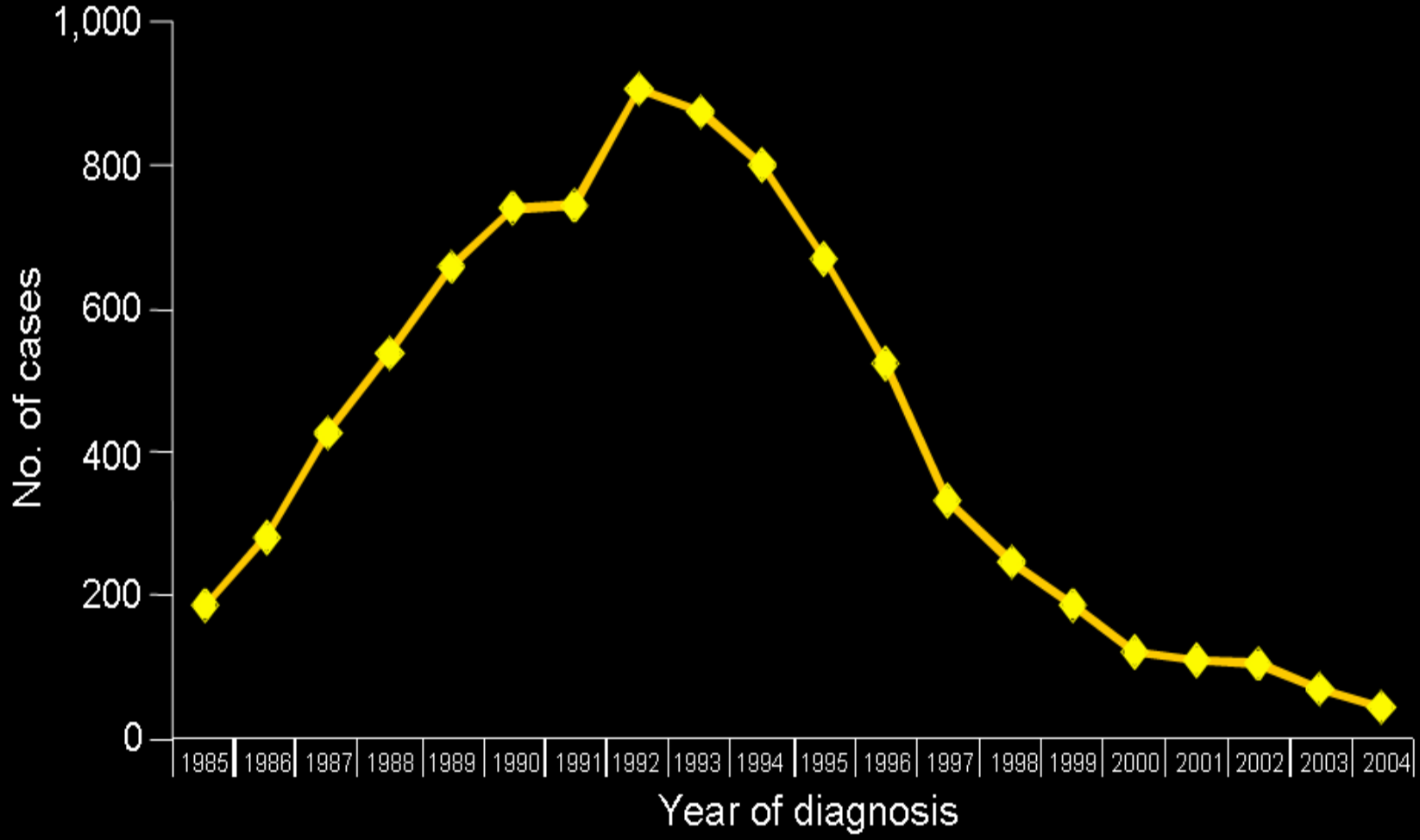
Nonnucleoside RTI

- Nevirapine (NVP)
- Delavirdine (DLV)

Protease Inhibitors

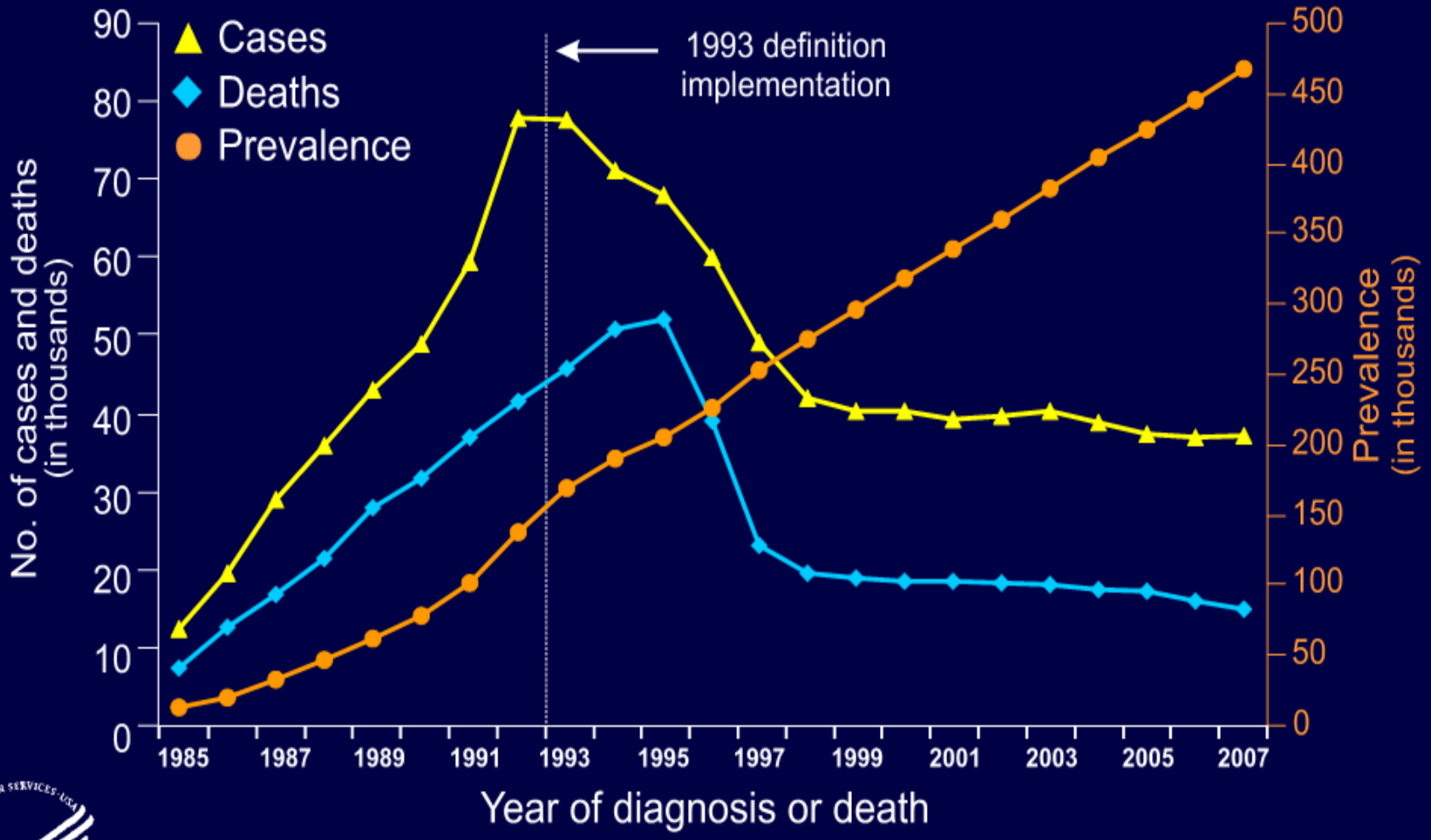
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)

Perinatally Acquired AIDS Cases, 1985-2004, United States

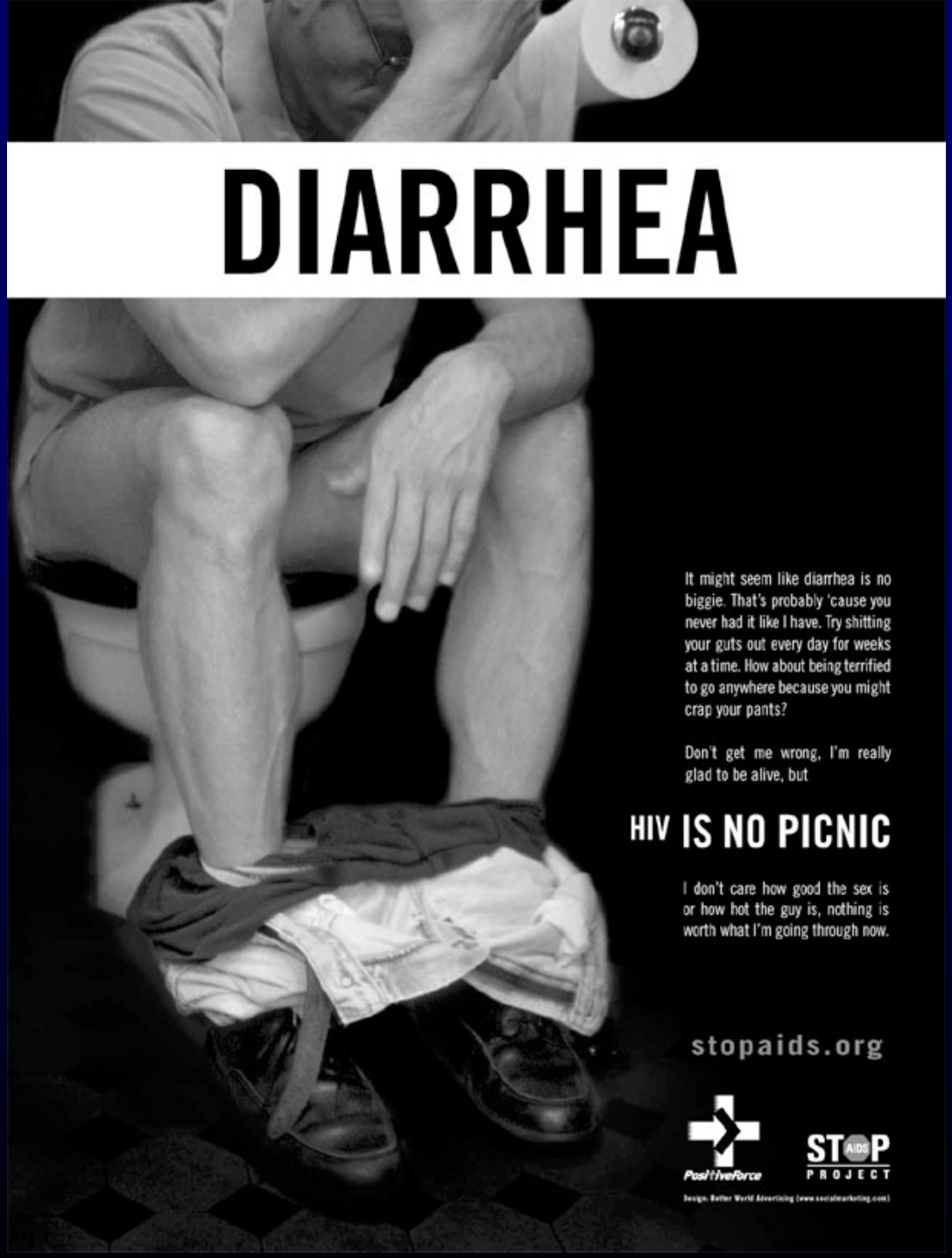


Note. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.

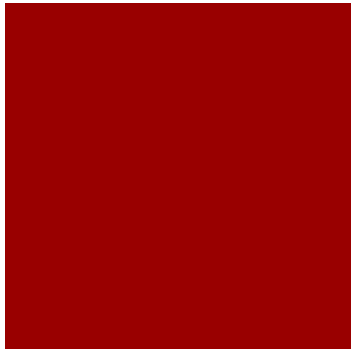
Estimated Numbers of AIDS Cases, Deaths, and Persons Living with AIDS, 1985–2007—United States and Dependent Areas



Note. Data have been adjusted for reporting delays.


DIARRHEA
It might seem like diarrhea is no biggie. That's probably 'cause you never had it like I have. Try shitting your guts out every day for weeks at a time. How about being terrified to go anywhere because you might crap your pants?
Don't get me wrong, I'm really glad to be alive, but
HIV IS NO PICNIC
I don't care how good the sex is or how hot the guy is, nothing is worth what I'm going through now.
stopaids.org
PositiveForce
STOP AIDS PROJECT
Design: Better World Advertising (www.socialmarketing.com)

1997 - 2004



Approved Antiretroviral Agents in 2004

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

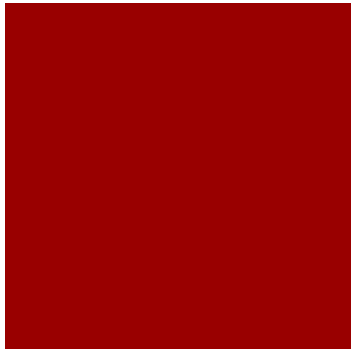
Nucleotide RTI
- Tenofovir DF (TDF)

Nonnucleoside RTI
- Nevirapine (NVP)
- ~~Delavirdine~~ (DLV)
- Efavirenz (EFZ)

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

Fusion Inhibitor
- Enfuvirtide (T-20)

2005 - 2011



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)

Nonnucleoside RTI
- Nevirapine (NVP)
- ~~Delavirdine (DLV)~~
- Efavirenz (EFZ)
- Etravirine (ETV)
- Rilpivirene

Integrase Inhibitor
- Raltegravir (RAL)

N.B.: Seven FDC are approved:
ZDV + 3TC; ZDV + 3TC + ABC; ABC + 3TC;
FTC + TDF; LPV + RTV; TDF + FTC + EFV
RLP + TDF + FTC

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)

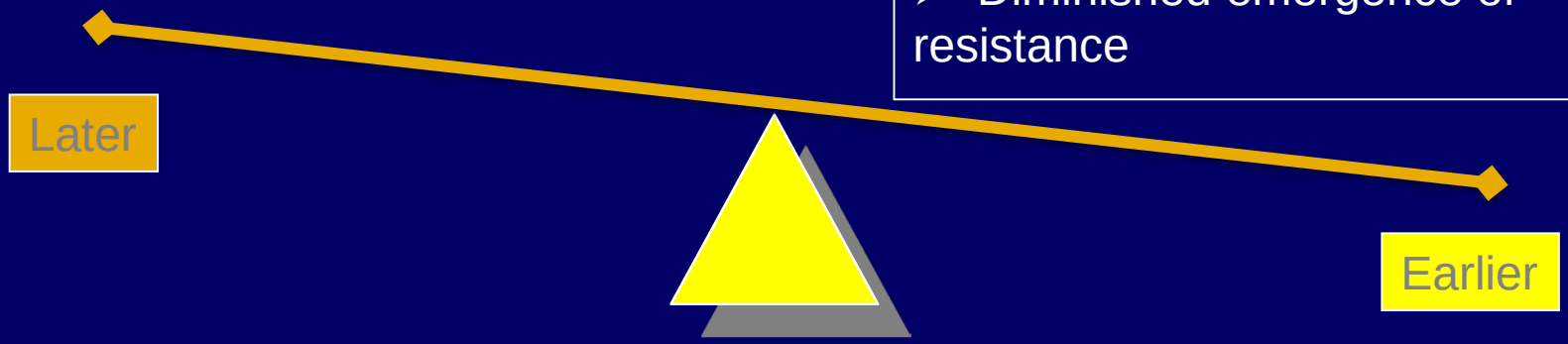
ART 2009

Easier, less toxic, and more potent therapy

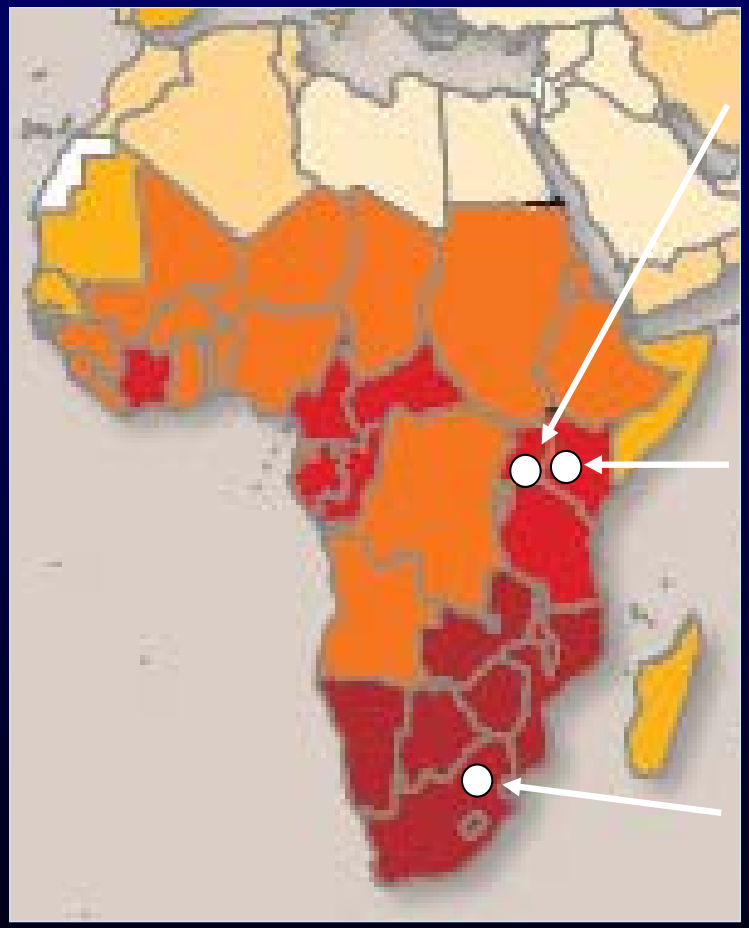
When to Start Therapy: Balance Has Tipped Further in Favor of Earlier Initiation

- Harmful effects of uncontrolled viremia at all CD4 levels
- More treatment options: improved potency, tolerability, durability, simplicity
- Increased ability to suppress virus with multidrug resistance
- Diminished emergence of resistance

- Drug toxicity
- Preservation of treatment options
- Cost



Randomised controlled trials of male circumcision to reduce HIV infection



Rakai, Uganda

Gray *et. al.* (2007) *Lancet*;
51% reduction in transmission

Kisumu, Kenya

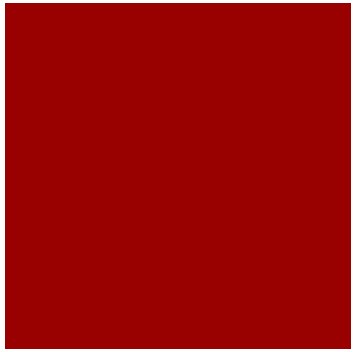
Bailey *et. al.* (2007) *Lancet*;
53% reduction

Orange Farm, South Africa

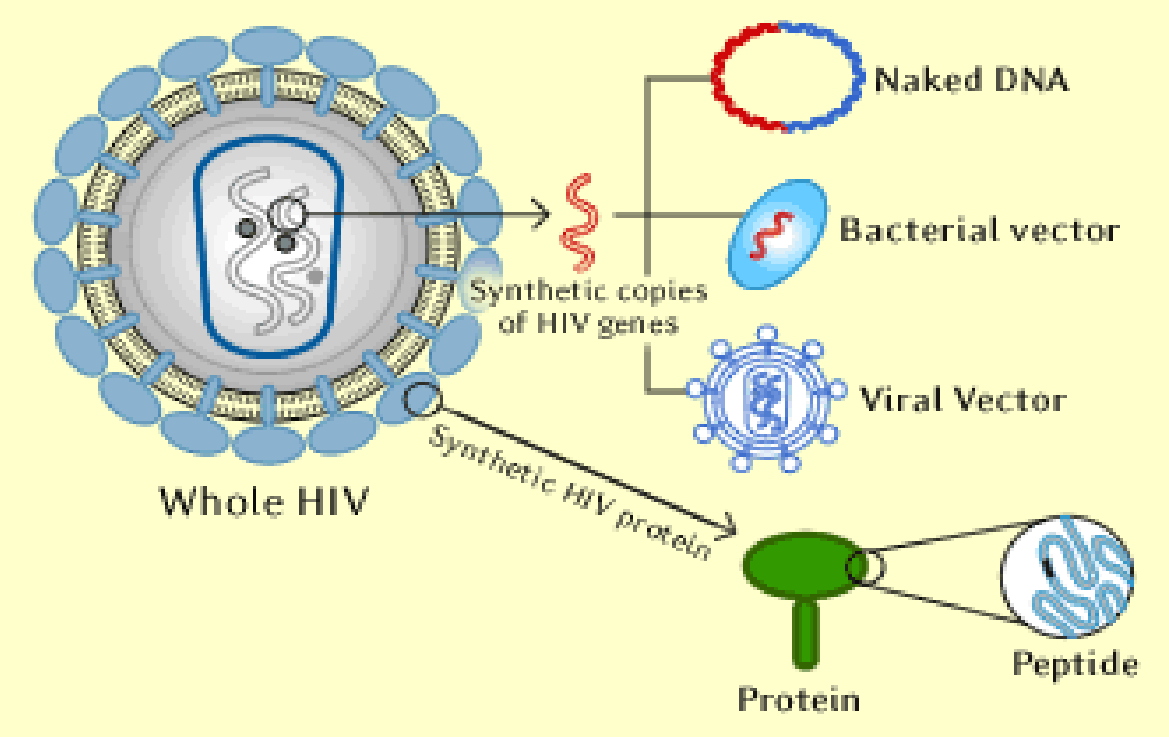
Auvert *et. al.* (2005) *PLoS Med*;
60% reduction


Allisonville
NURSERY
WHERE HOME AND GARDEN MEET
FRESH CUT PENIS
$7.99

Beyond 2011 - 2016



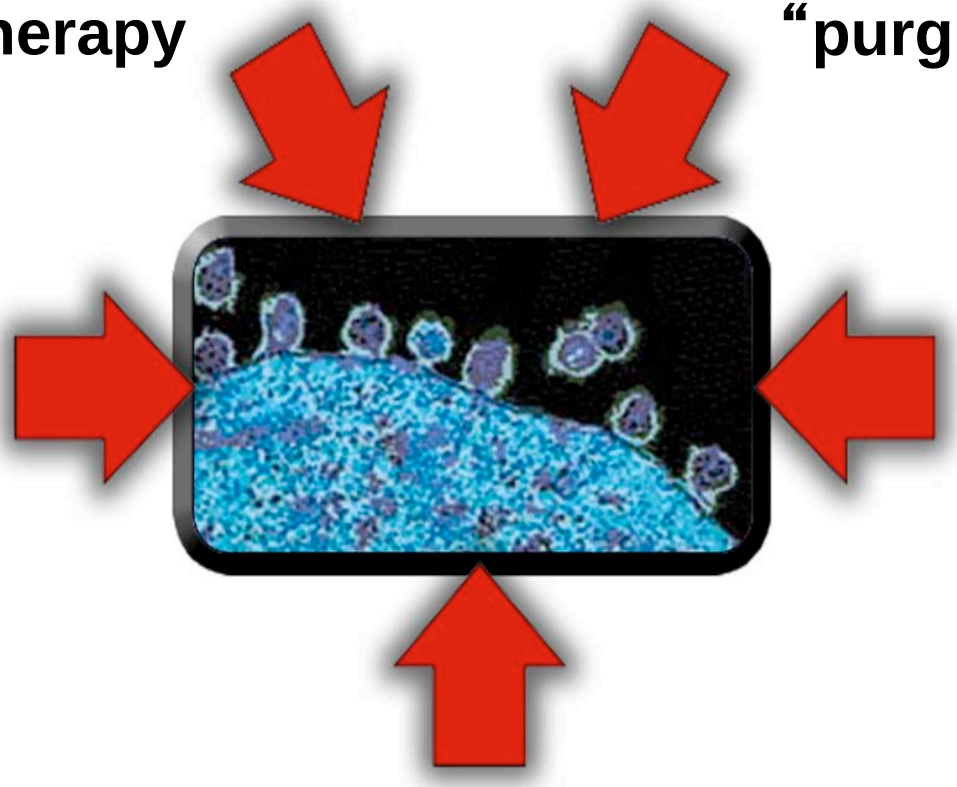
Vaccine Strategies in Current Trials



Potential Strategies for Eradication of HIV

Early initiation of antiretroviral therapy

Use of virus "purging" agents



Addition of newer classes of drugs

Use of immune-modulating agents

Use of HIV-specific killing agent

iPrEx: Adherence is critical to efficacy

Efficacy by as-treated analysis

(data as of Nov 21, 2010)

High (≥ 90% adherence; 49% of visits)

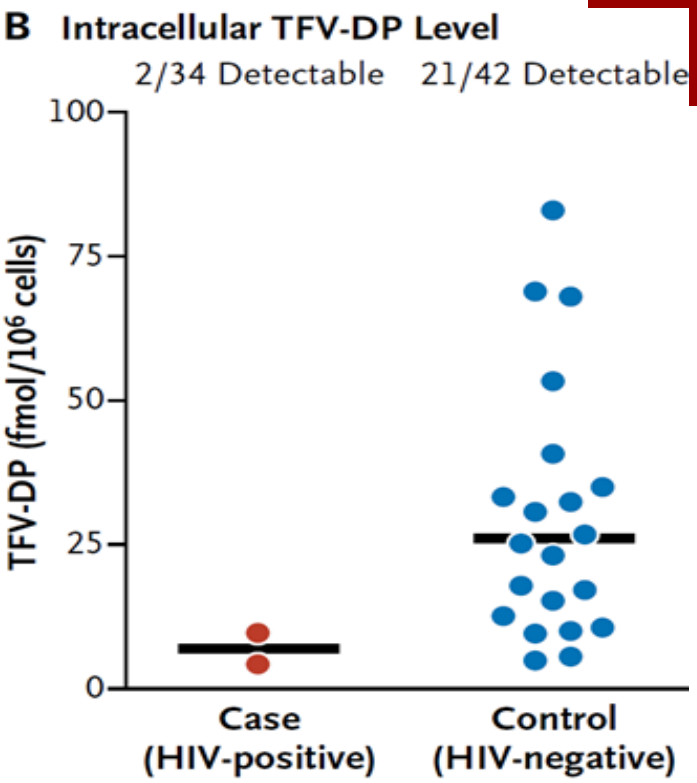
68% efficacy

Intermediate (50-90% adherence; 33% of visits)

34% efficacy

Low (< 50% adherence;18% of visits)

16% efficacy



- 9% of seroconverters had detectable drug at first HIV+ visit
  - vs 51% of nonseroconverters

Grant et al, NEJM 2010

HPTN 052

1763 HIV discordant couples
(HIV+ partner CD4 350-550)

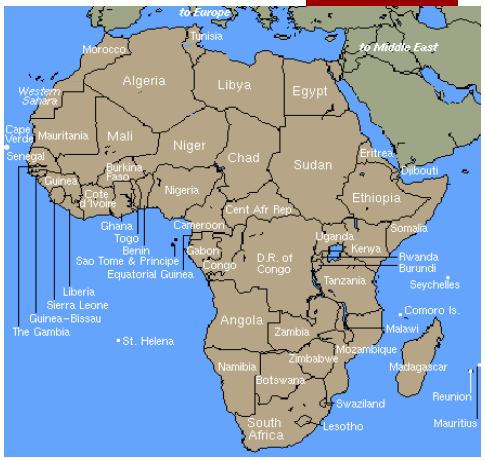
886 immediate HAART

877 delayed HAART (CD4 250)

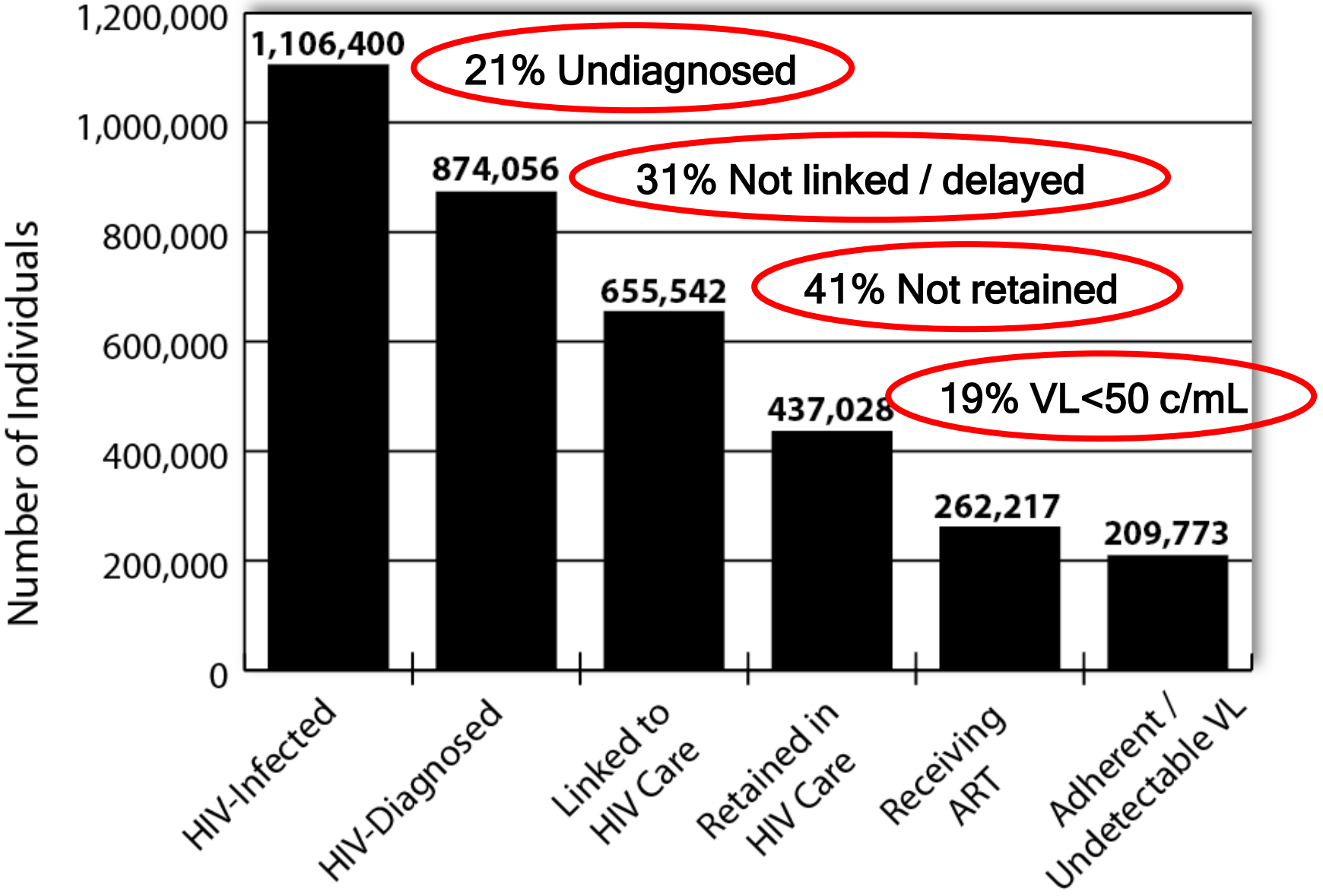
All receiving HIV prevention services

1 transmission*
& 3 cases of extrapulmonary TB

27 transmissions*
& 17 cases of extrapulmonary TB



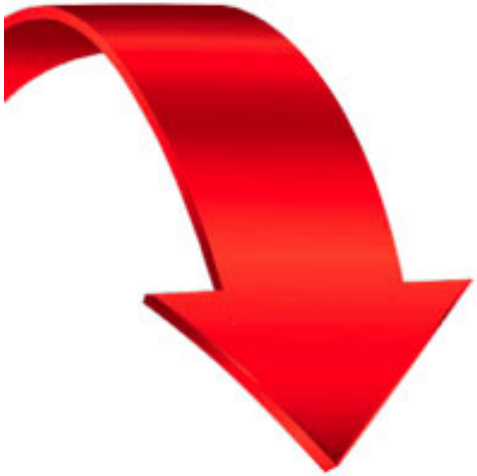
***96% reduction in HIV transmission to HIV-negative partner** median follow-up 2 years



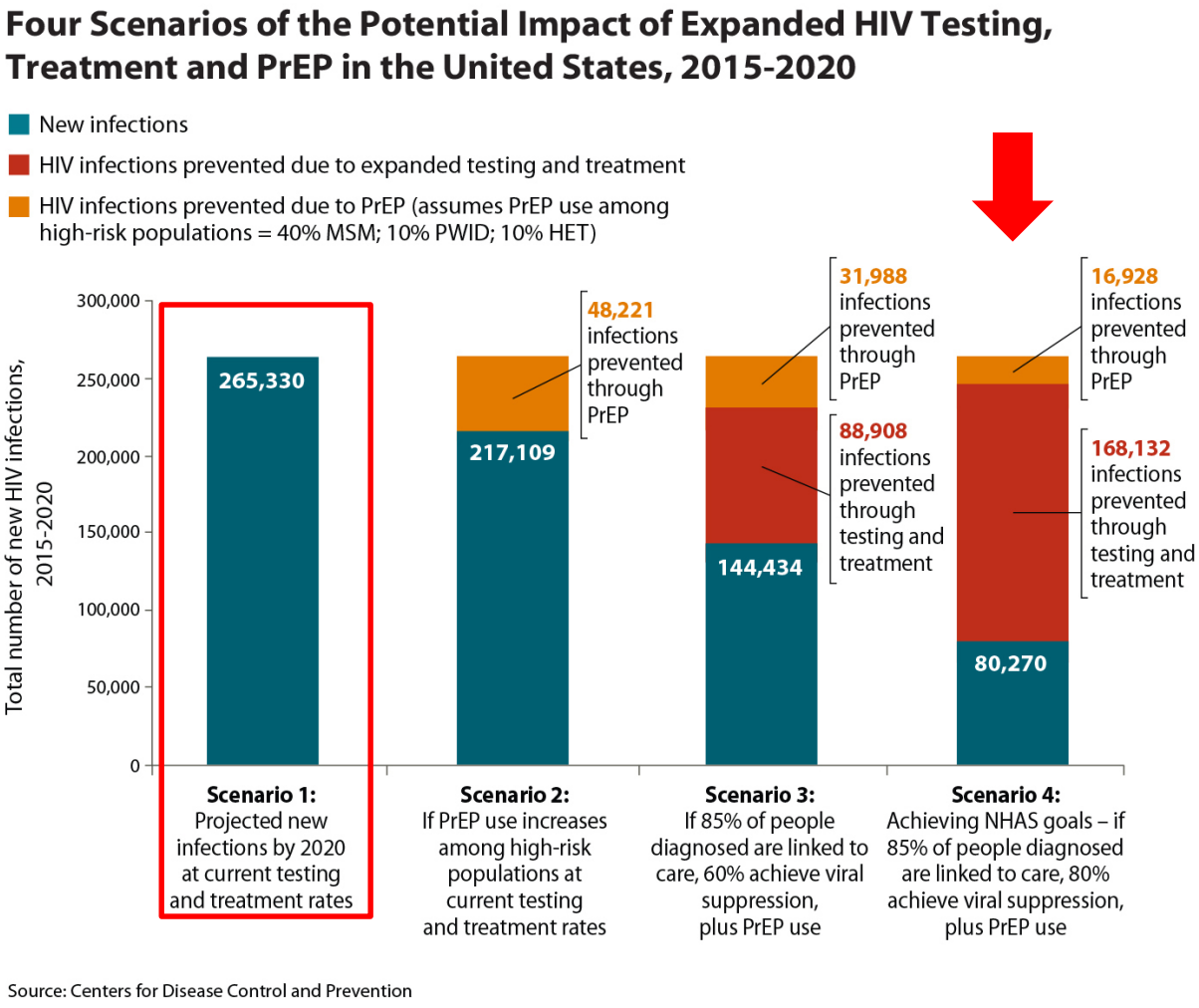
Adapted from: Gardner et al. *Clin Infect Dis* 2011;52:793, Greenberg et al. *Health Affairs* 2009;28:1677, Marks et al. *AIDS* 2010;24:2665

90:90:90
Bending the Epidemic Curve

- Who's at Risk
- Getting to 90:90:90
- Women-controlled prevention



185,000 HIV infections in U.S. in next 5 years could be prevented by expanding testing, treatment, PrEP



http://www.cdc.gov/nchhstp/newsroom/images/2016/croi_four_scenarios_graph.jpg

Beyond 2018...

Antiretroviral Therapy: The Future

??

Long Acting Injectable?

Integrase Era

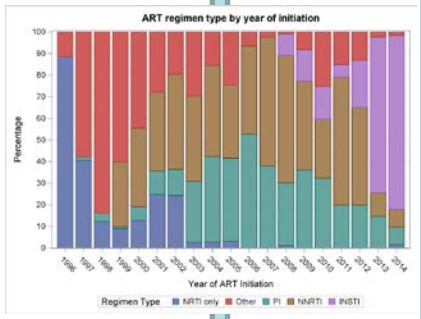
Single Tablet Regimens

Triple Drug Therapy

ZDV/3TC

ZDV monotherapy

HIV-1 discovered



1983 1987 1995 1996 2006 2012-13 2017 2020

Slide courtesy of Joe Eron, MD

The Economist: June 4-10th, 2011

Beyond 2018…

What do you think?