

HIV introduction

Dr. Edmund Wilkins

Head of the HIV Clinical Trials Unit
North Manchester General Hospital





“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the
Medical Assistance & Medical Education
(MAME) Programs



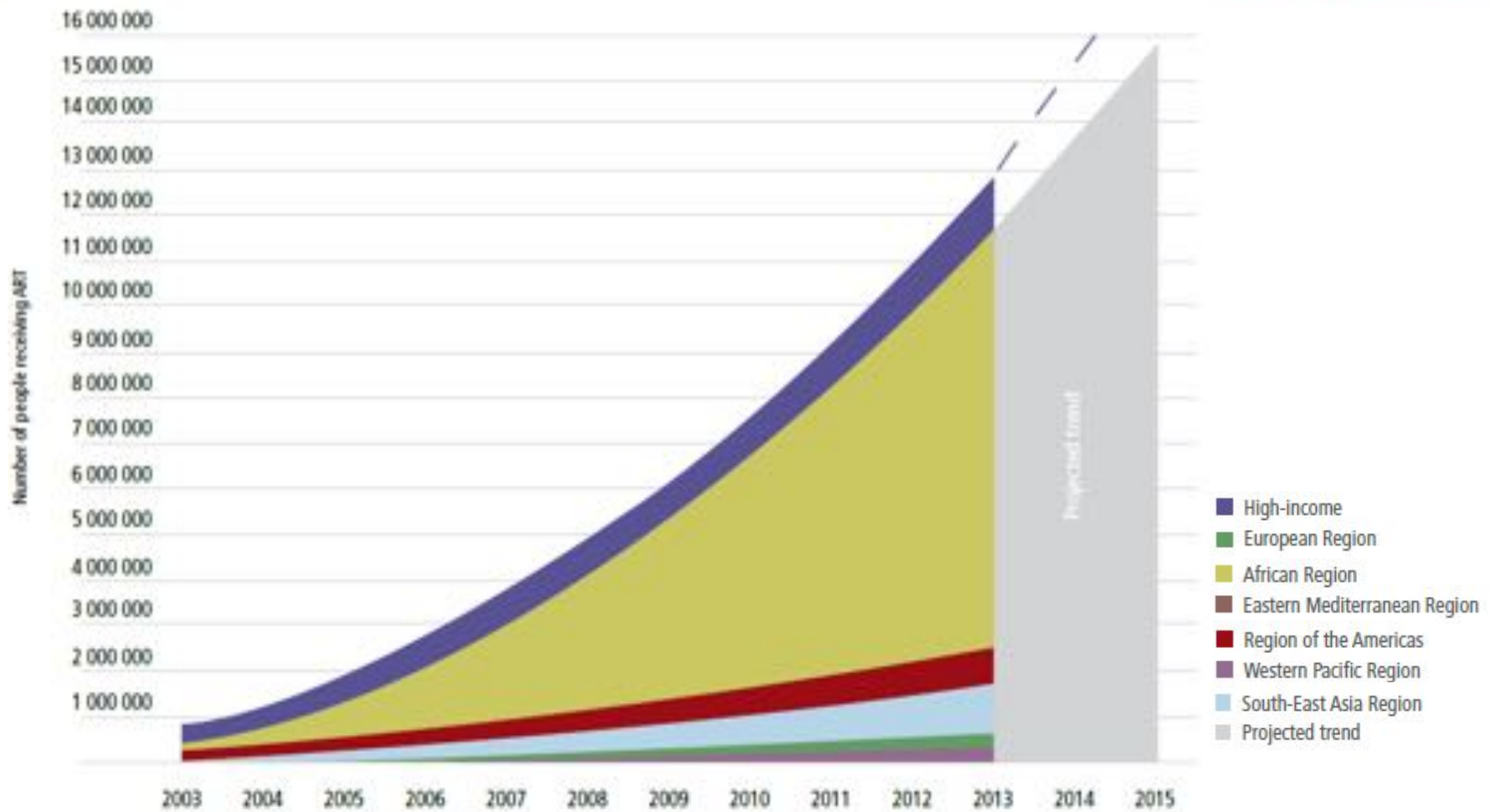
HIV – What do we know so far?

The first 30 years?

Miracles do happen



Why? Because of ARV's...



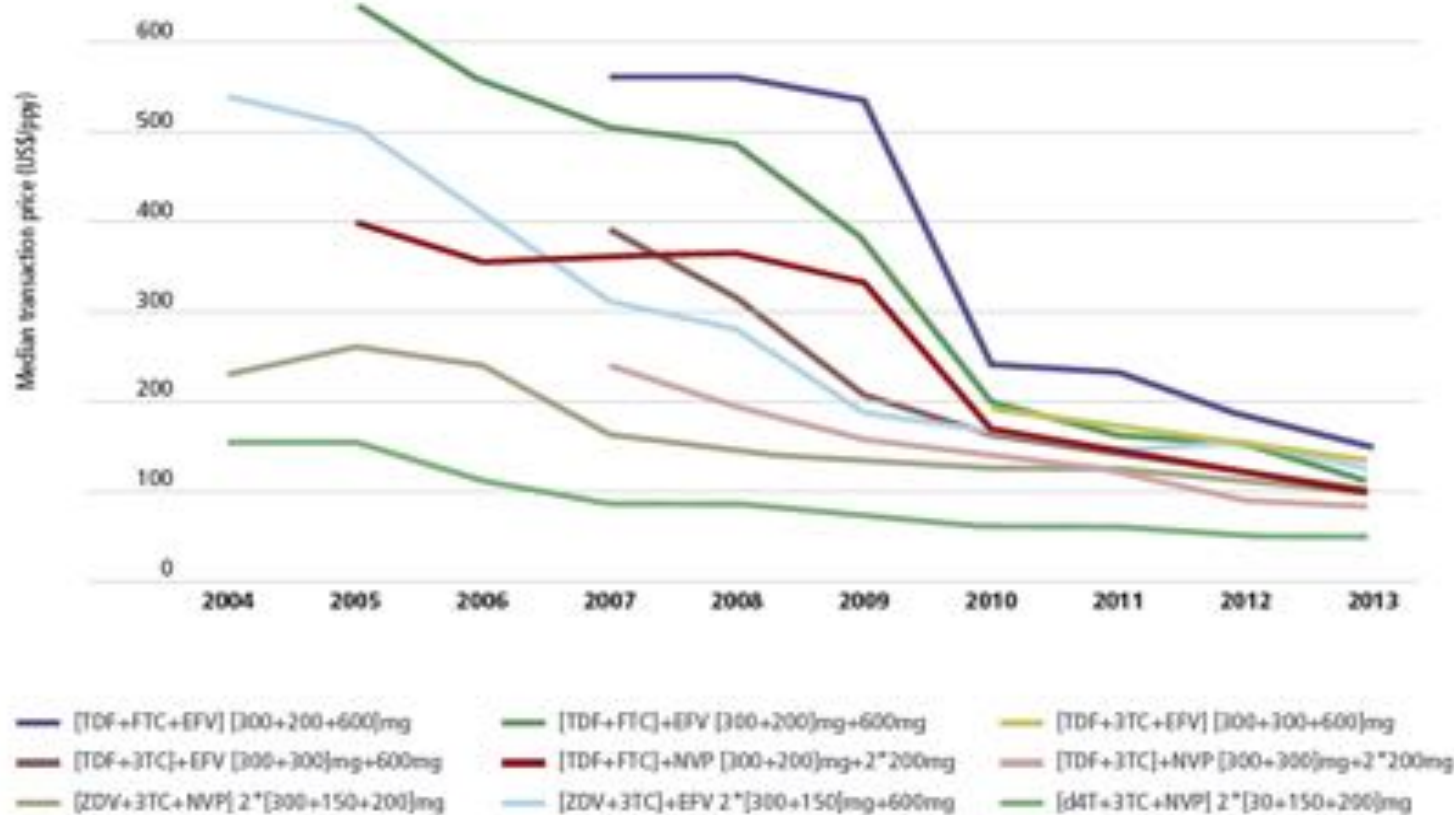
Source: 2014 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS).

How has this happened?



With the price of ART continuing to fall...

Median prices of WHO-preferred first-line regimens per person per year, in US dollars, in low-and middle-income countries, 2004–2013



Gauging recent progress in the global HIV response

2013

2009-2013

1.5 million HIV related deaths

[1.4 – 1.7 million]

320 000 TB-related deaths in PLWHA*

[300 000 – 340 000]

*2012

** 2004-2012

2.1 million HIV infections

[1.9 – 2.5 million]

240 000 HIV infections in children

[210 000 – 280 000]



▼ **25%**



▼ **36%****



▼ **15%**

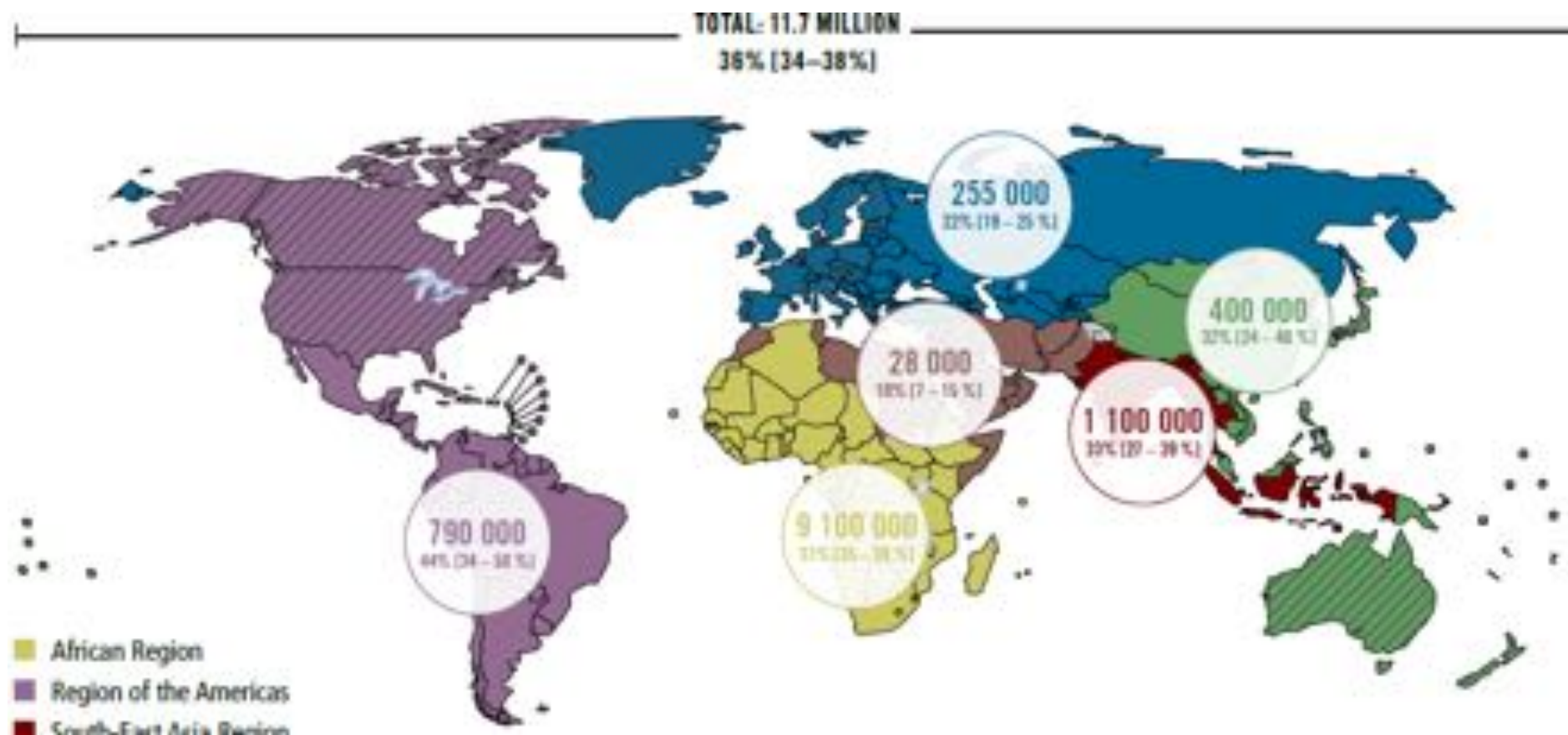


▼ **40%**



World Health
Organization

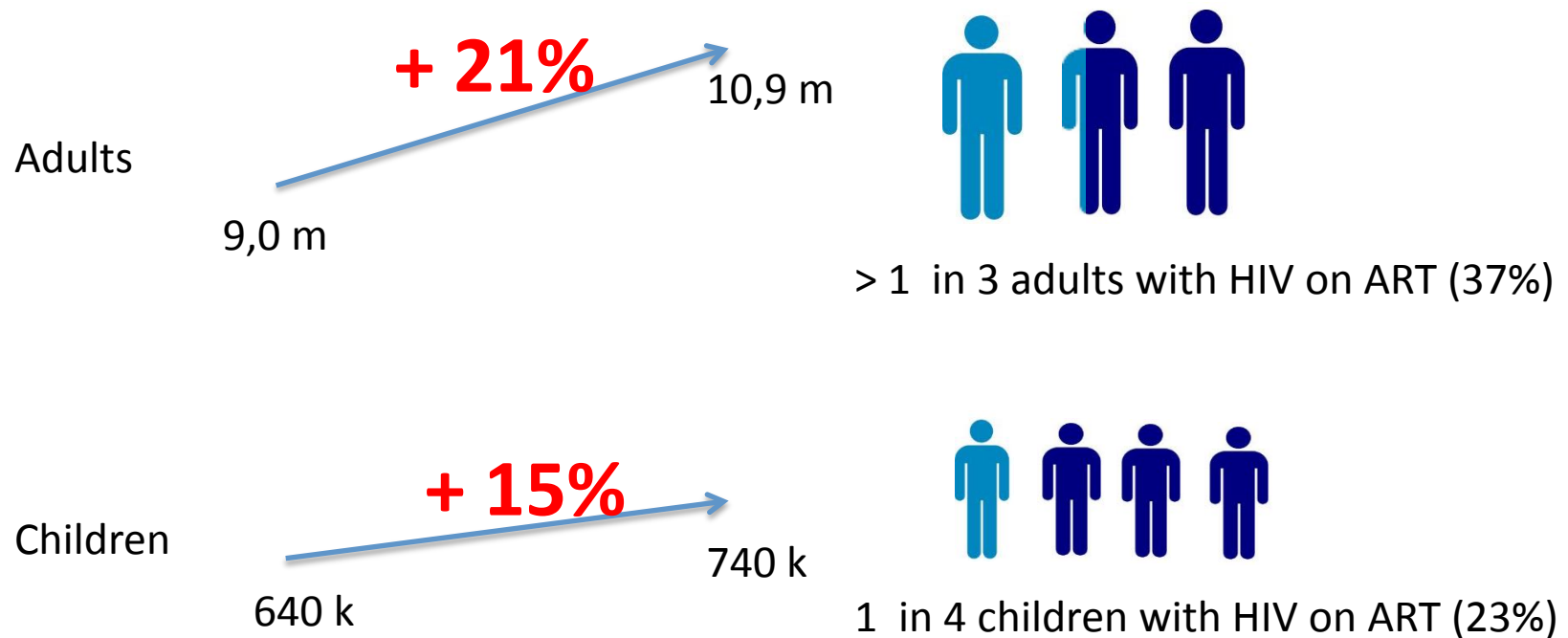
With low ART coverage areas starting to catch Africa up



Source: 2014 Global AIDS Response Progress Monitoring (WHO/UNICEF/UNAIDS) and UNAIDS/WHO/UNICEF estimates



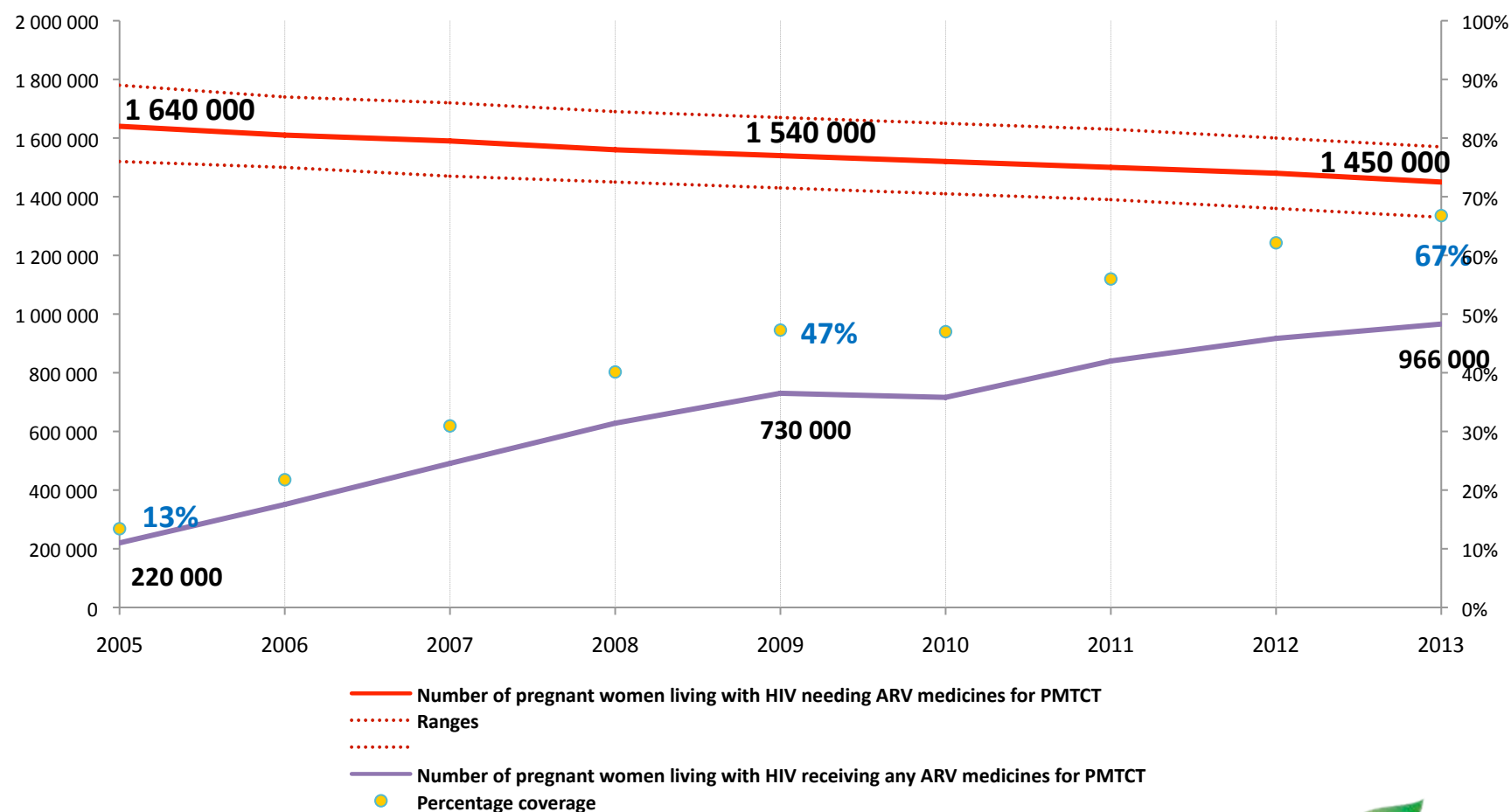
Although the gap between access to ART for children vs. adults continues to widen



Source: 2014 Global AIDS Response Progress Monitoring (WHO/UNICEF/UNAIDS) and UNAIDS/WHO/UNICEF estimates



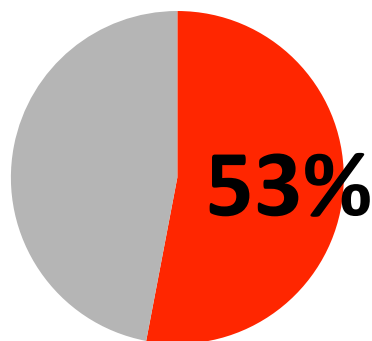
And close to 1 million pregnant women received ARVs, 500,000 still being missed



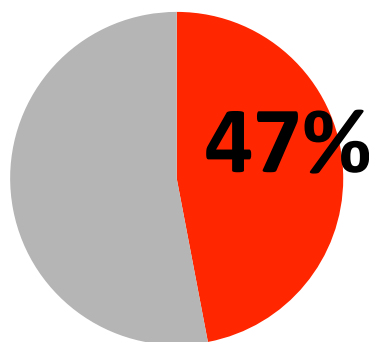
Source: 2014 Global AIDS Response Progress Monitoring (WHO/UNICEF/UNAIDS) and UNAIDS/WHO/UNICEF estimates



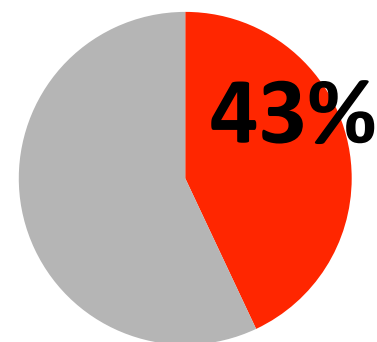
And in multiple countries laws exist that can hinder service provision for key populations



**Sex
workers**



MSM

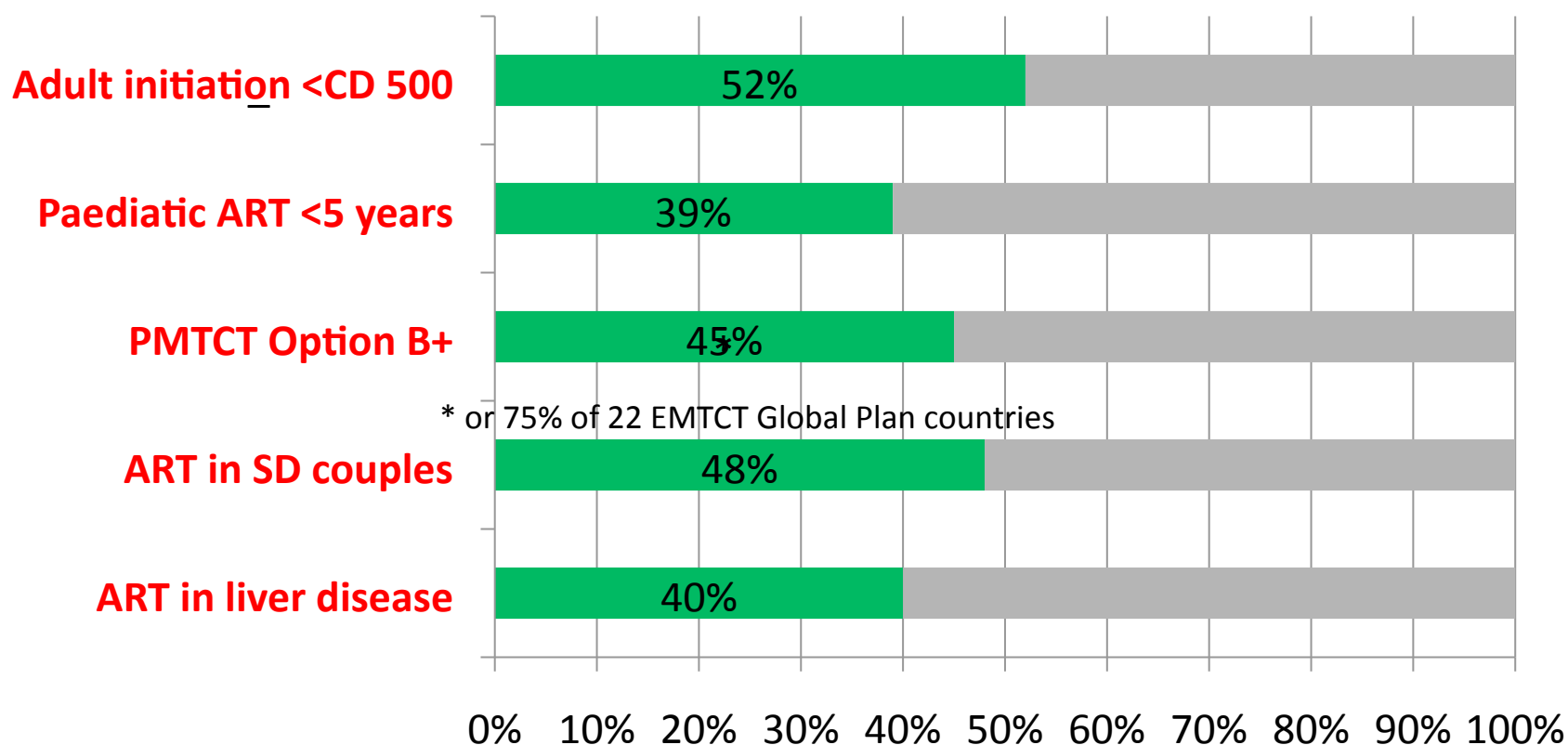


PWID

Source: GARPR 2013 – “Countries reporting existence of laws, regulations or policies that can pose obstacles to effective HIV prevention, treatment, care and support services for key populations”



And global update of 2013 WHO guidelines increasing eligibility for treatment



Percentage of 58 WHO HIV Focal Countries with confirmed adoption of select WHO 2013 ARV recommendations, June 2014

Source: WHO HIV Country Intelligence Database, June 2014

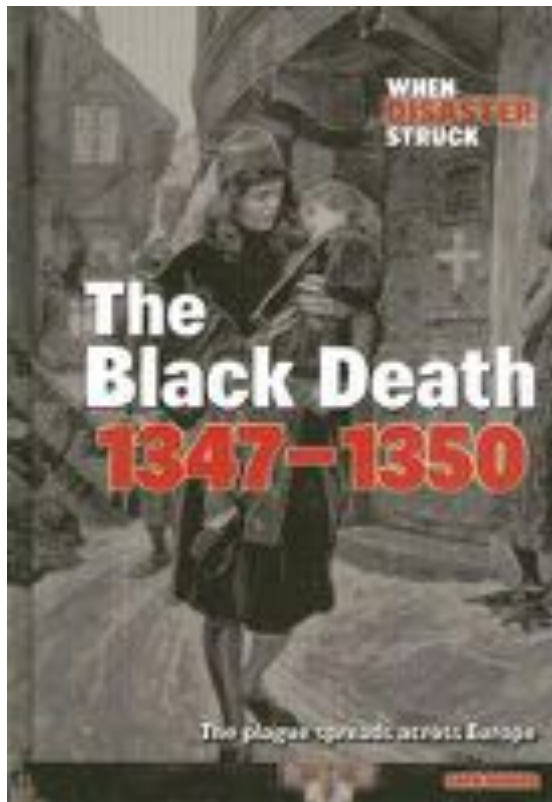




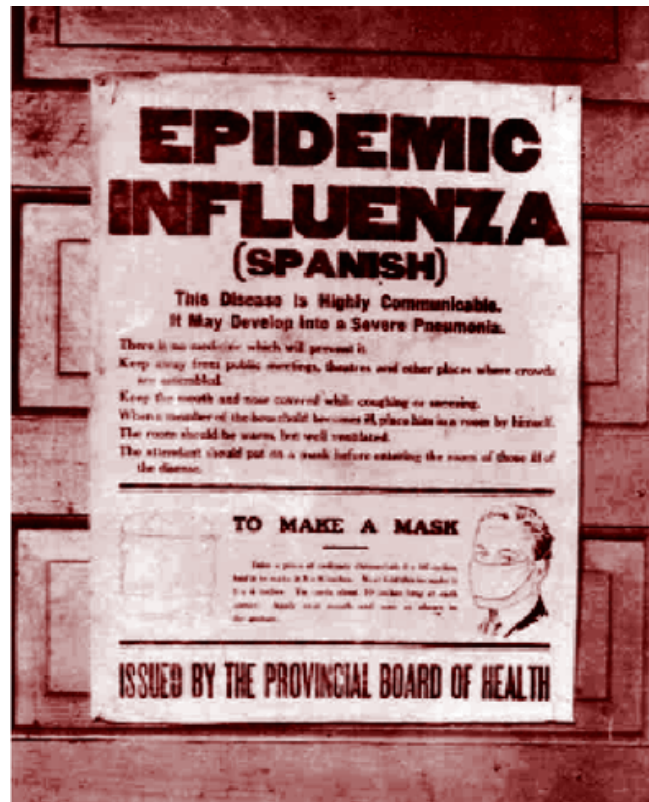
How did the epidemic start?

HIV

New epidemics last millennium



100,000,000



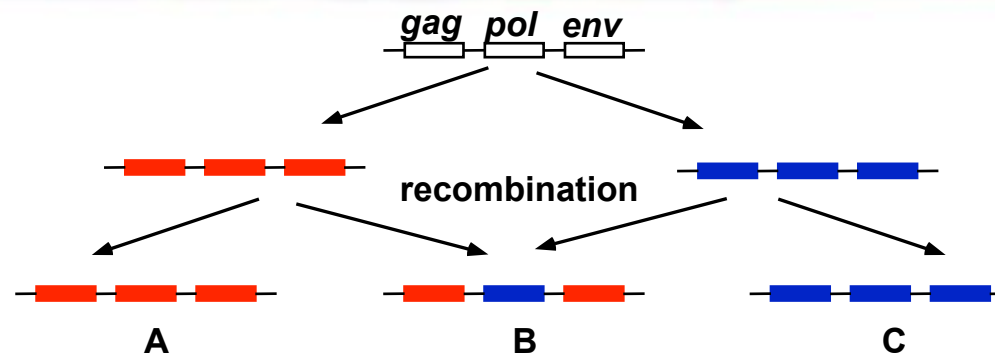
75,000,000



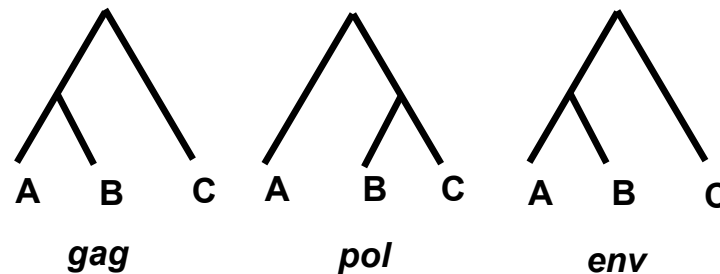
35,000,000



The Origin of HIV: a chimp was bitten twice a million years ago...



Red-capped mangabey



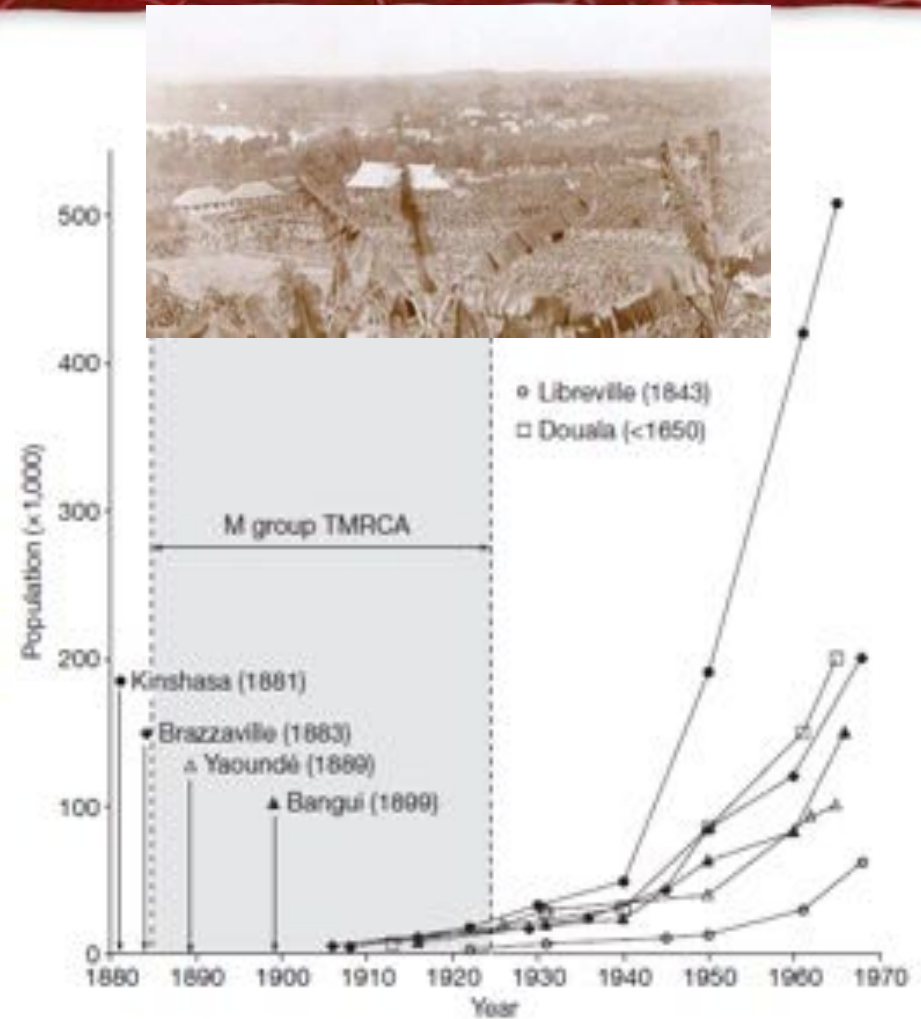
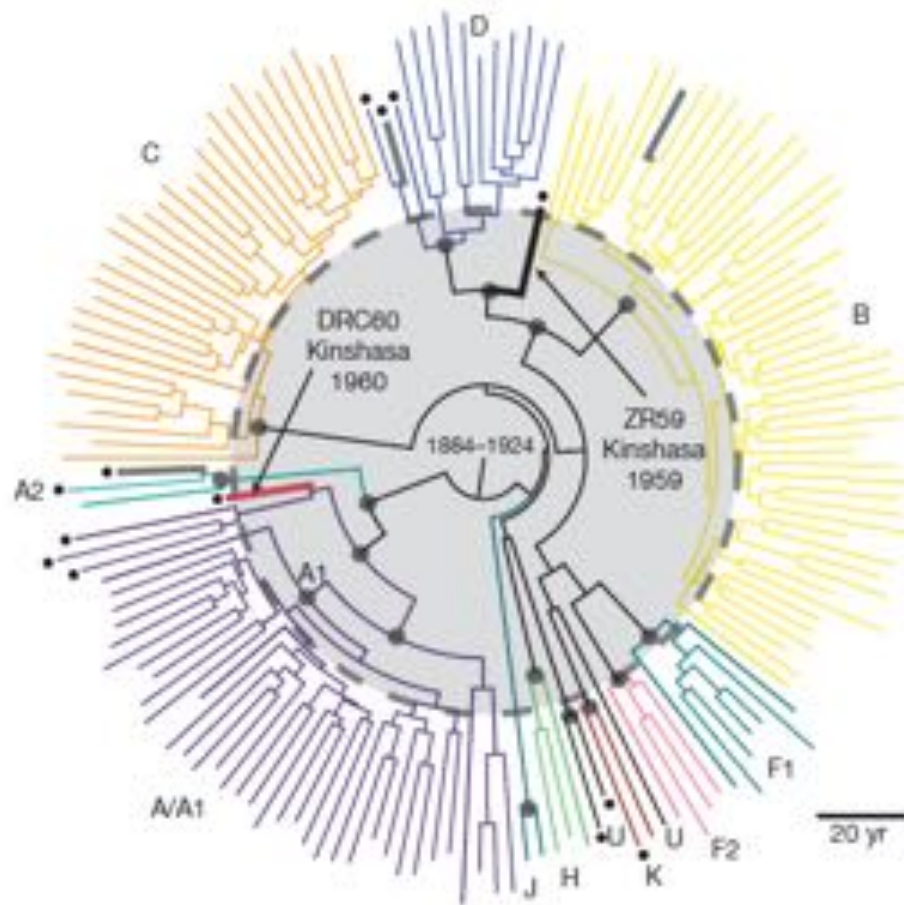
Chimpanzee troglodytes



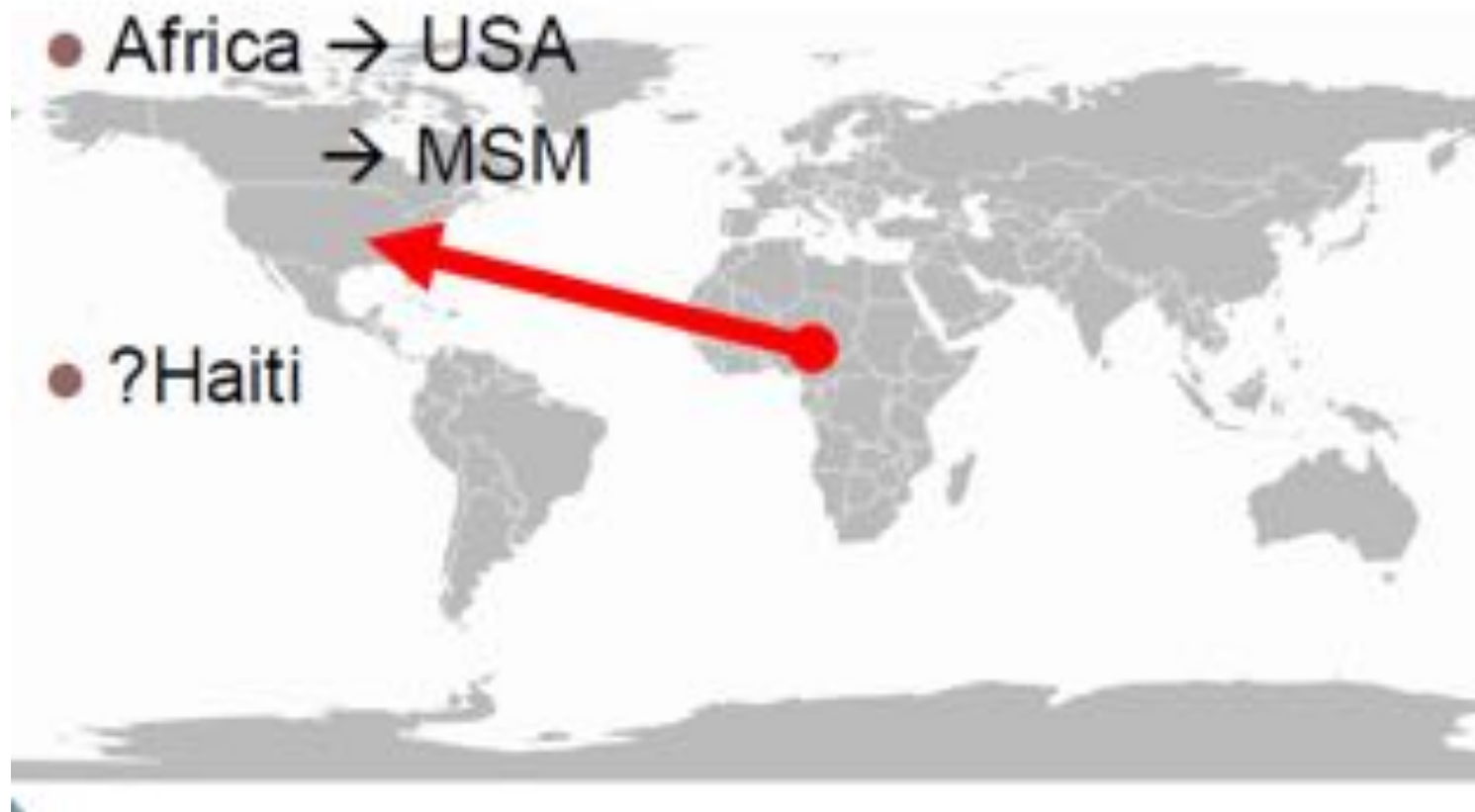
Greater Spot – nosed monkey
(*Cercopithecus nictitans*)



When it began 1900...



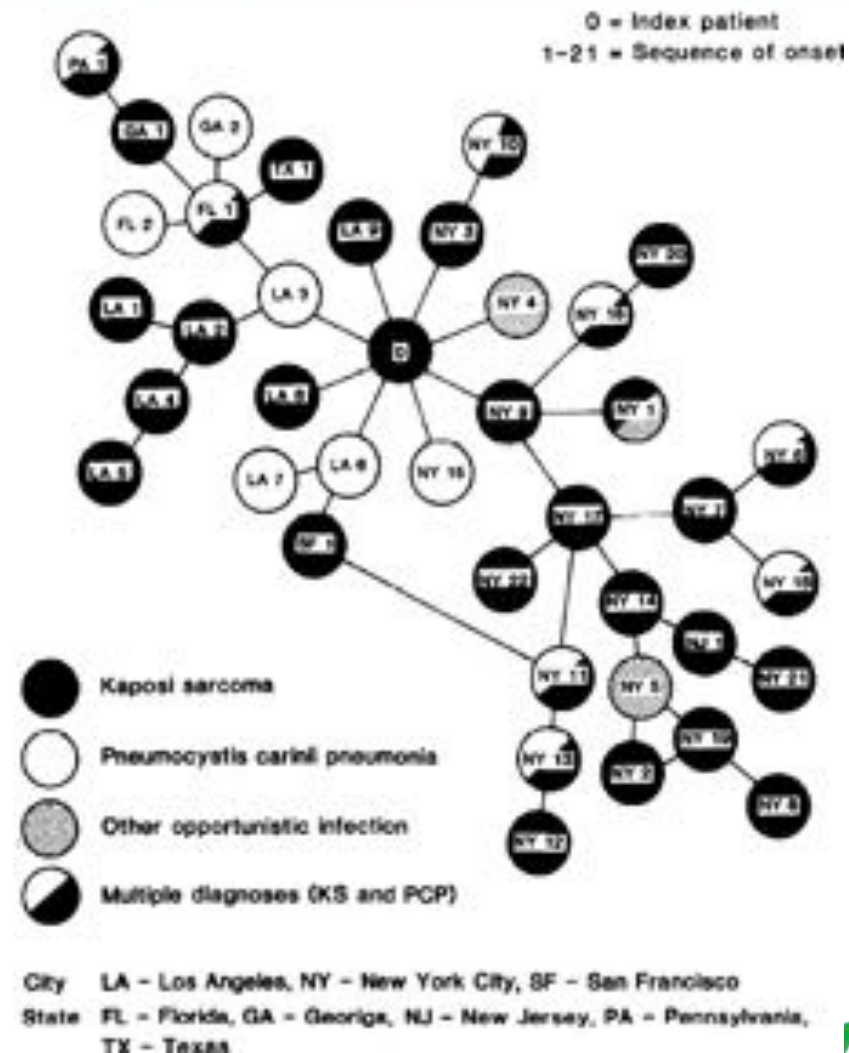
Transmission across continents?



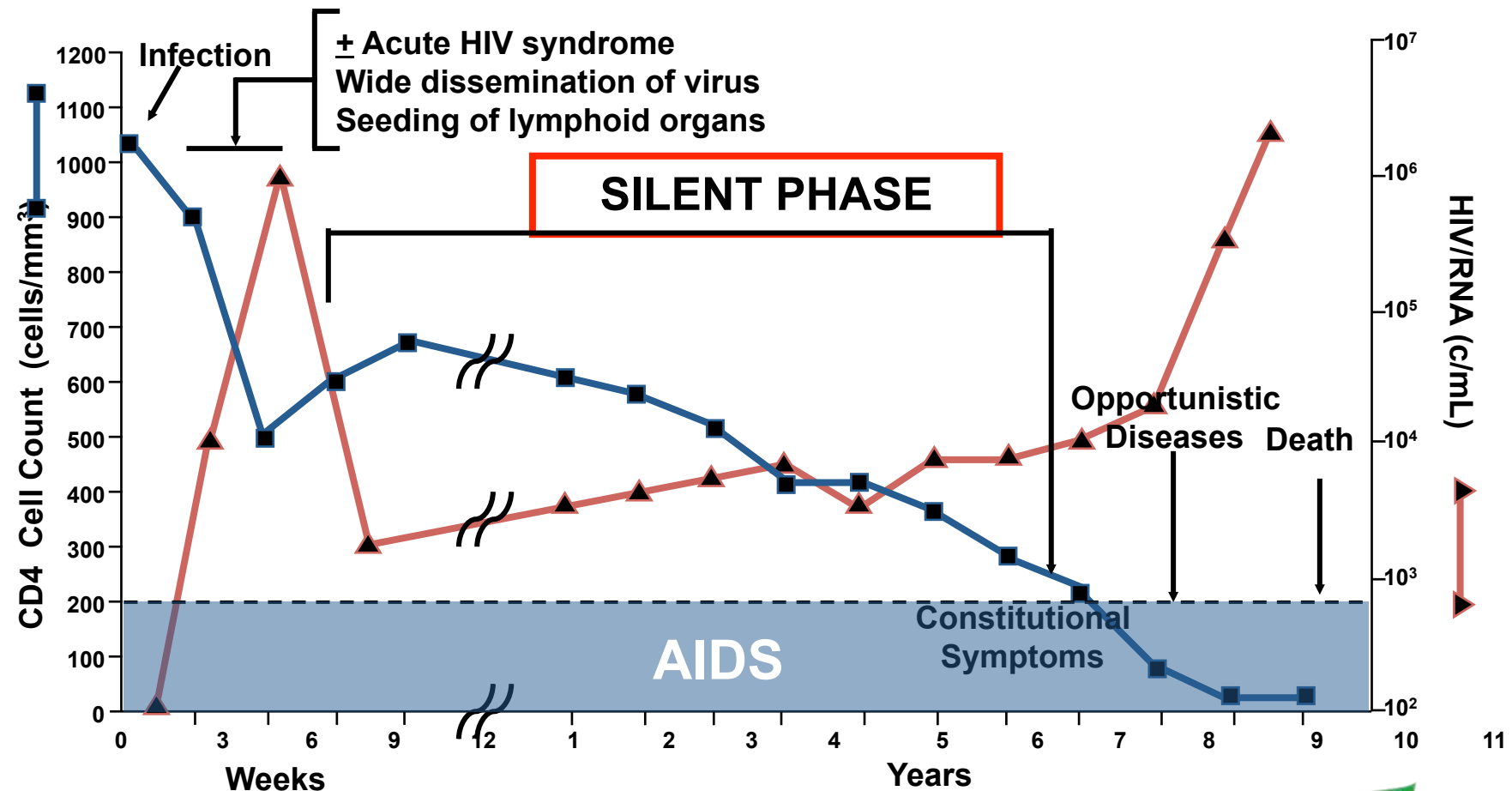
At a time when technology was moving fast



Transmission happened quietly and effectively

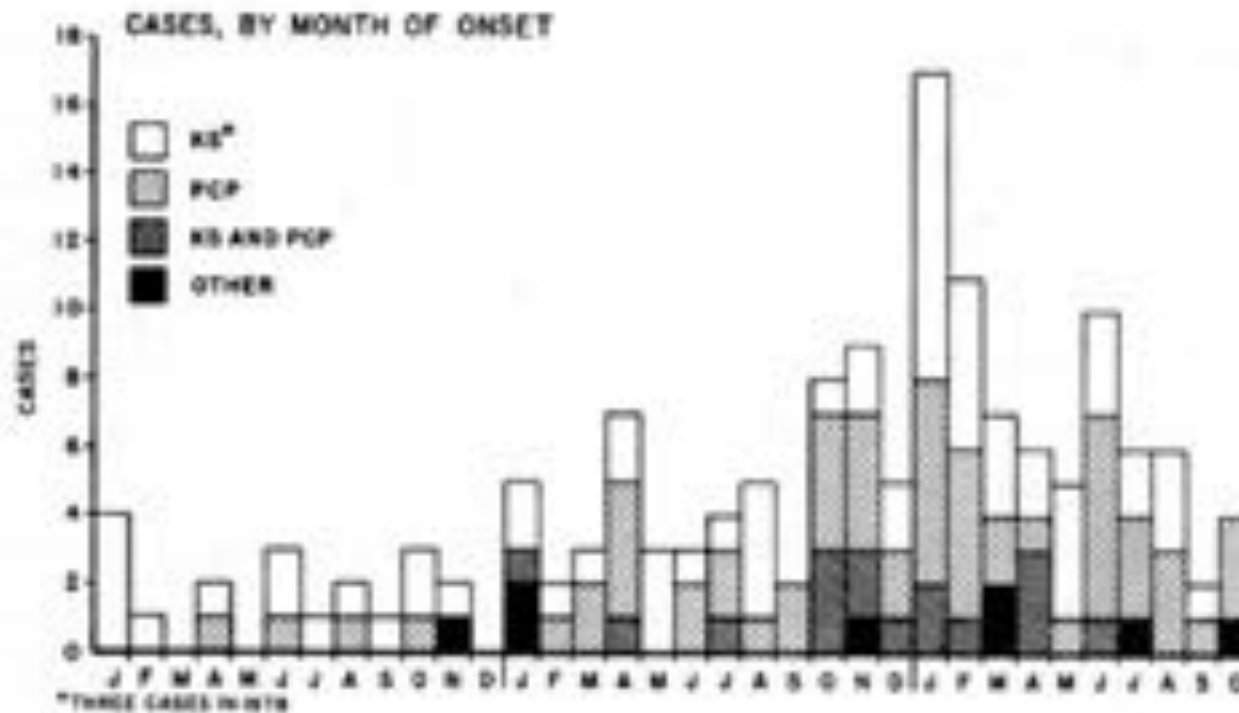


Natural History of Untreated HIV Infection



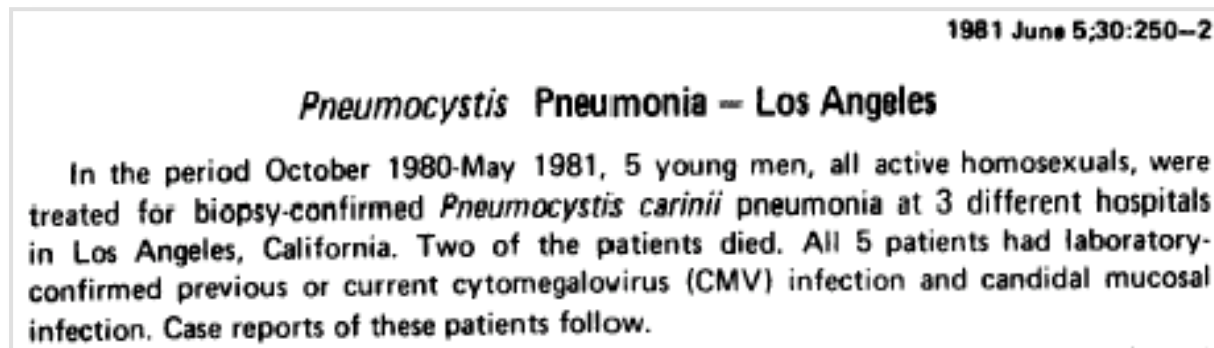
1981: The first Recognition of a new Illness...

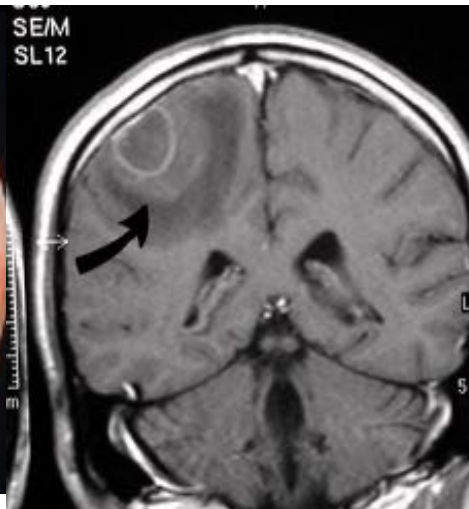
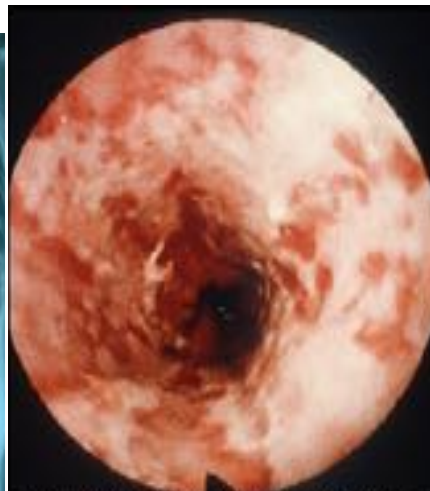
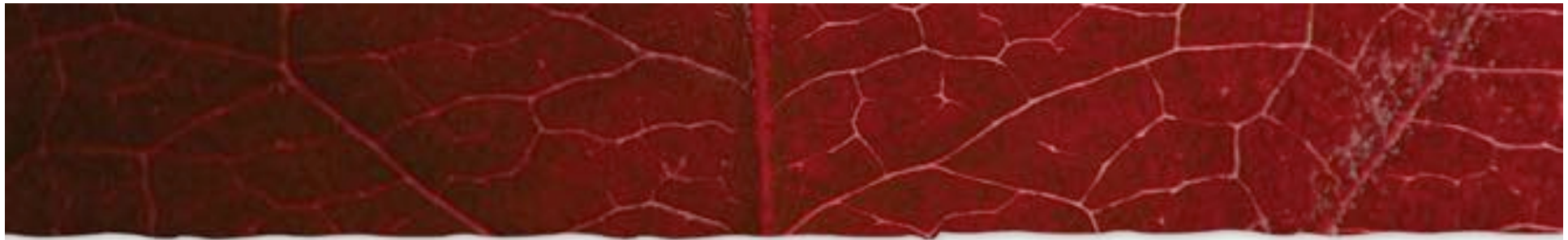
FIGURE 1. Incidence of Kaposi's Sarcoma (KS), *Pneumocystis carinii* Pneumonia (PCP), and other opportunistic infections — United States, 1979–1981



Initial Reports

- June 5, 1981: 5 cases of PCP in gay men from UCLA (MMWR)¹
- July 3, 1981: 26 additional cases²
- Dec 10, 1981: 3 NEJM papers describe cases³







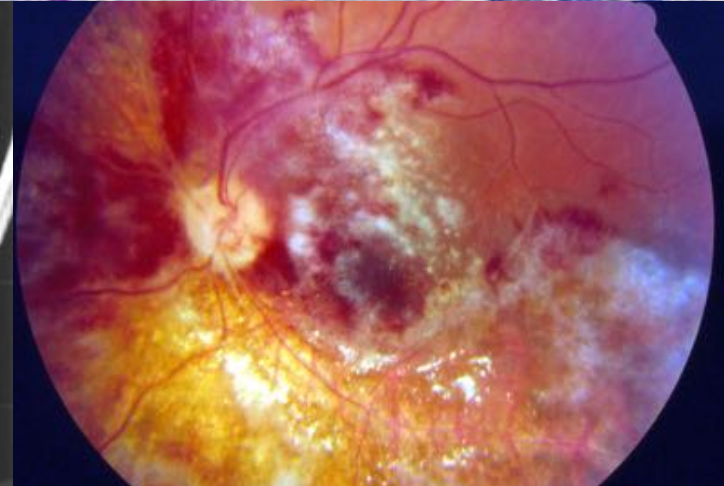
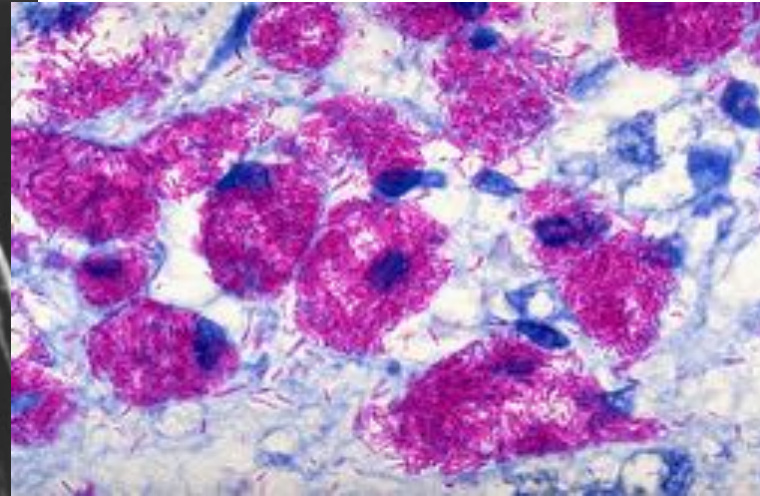
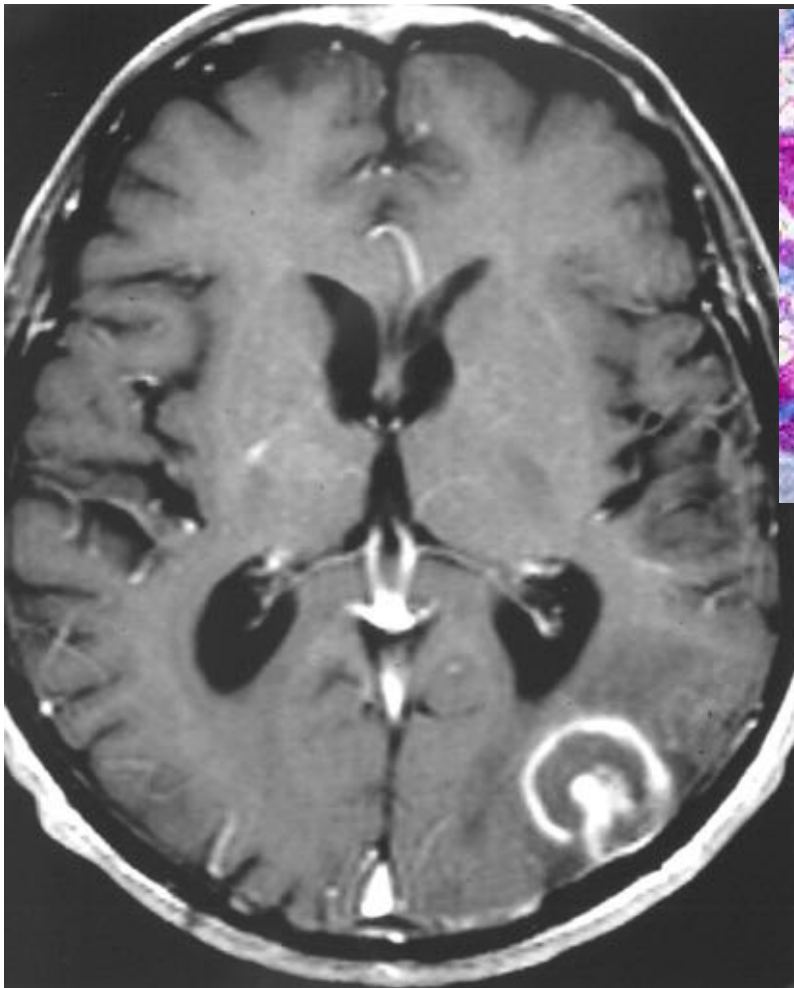
Aids – Case definition

2008 CDC Case Definition for HIV Infection: AIDS-Defining Clinical Conditions

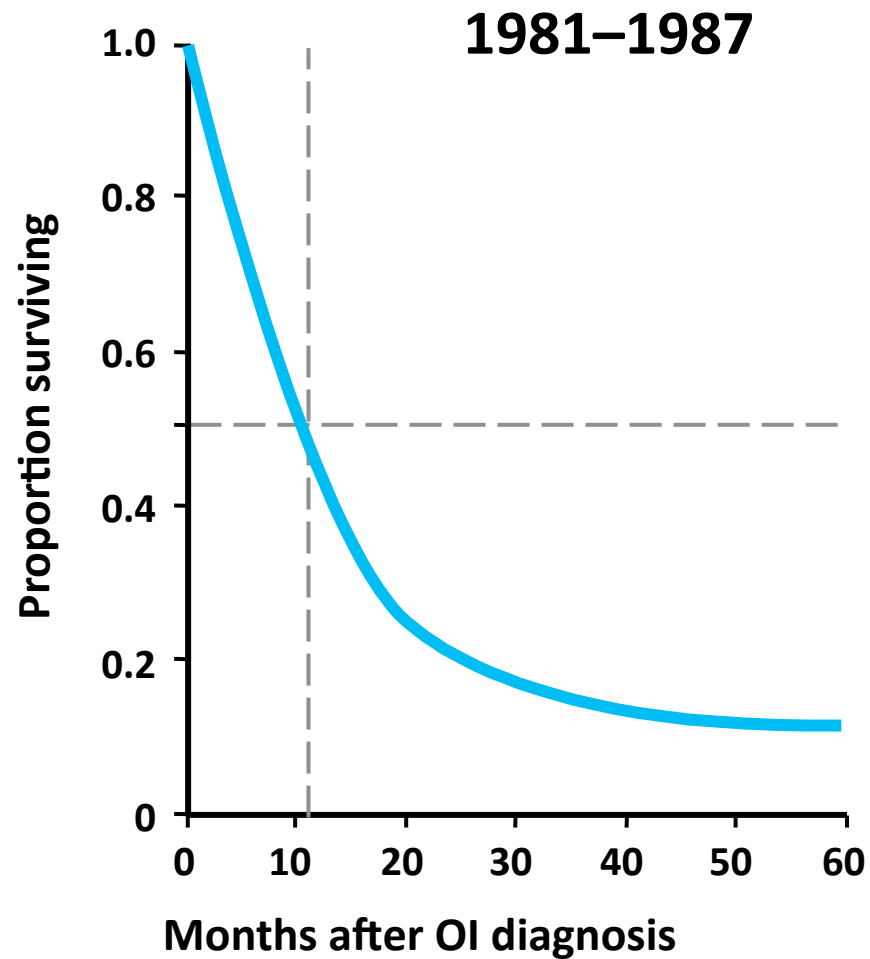
- Candidiasis (trachea, bronchia, or lung)
- Candidiasis (esophageal)
- Cervical cancer (invasive)
- Coccidioidomycosis (disseminated or extrapulmonary)
- Cryptococcosis (extrapulmonary)
- Cryptosporidiosis (intestinal, for longer than 1 month)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy (HIV-related)
- Herpes simplex: chronic ulcers (present for longer than 1 month)
- Herpes simplex: bronchitis, pneumonitis, or esophagitis
- Histoplasmosis (disseminated or extrapulmonary)
- Isosporiasis (intestinal, for longer than 1 month)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary of brain
- *Mycobacterium avium* complex, disseminated or extrapulmonary
- *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Recurrent pneumonia (≥ 2 episodes in 1-year period)
- Progressive multifocal leukoencephalopathy
- *Salmonella* (recurrent septicemia)
- Toxoplasmosis (brain)
- Wasting syndrome due to HIV: $>10\%$ involuntary weight loss plus either chronic diarrhea (≥ 2 stools per day for at least 30 days) or chronic weakness and documented fever (for at least 30 days) in the absence of a concurrent illness or condition other than HIV that could explain this finding.



Physicians getting used to multiple infections...



Inevitably fatal in most...



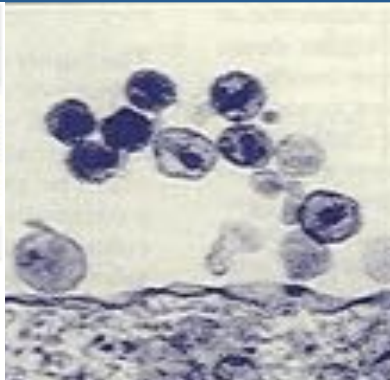
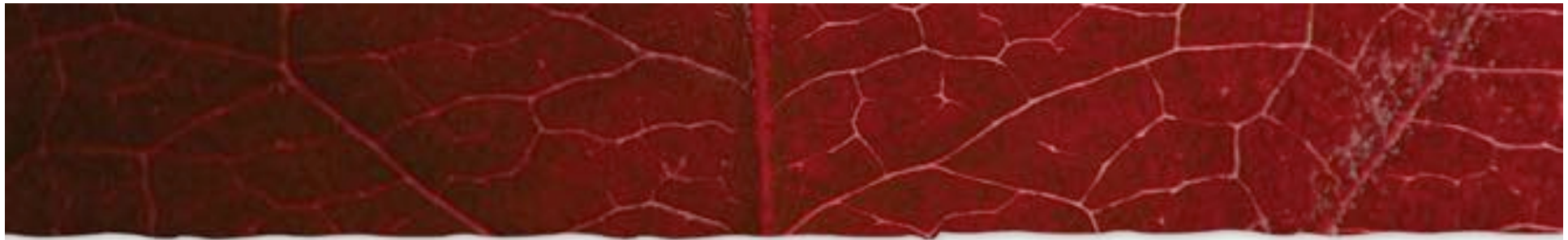
Source: National AIDS case surveillance data, CDC



Early Mistakes – CDC statement 1981

- **CDC – “no apparent danger to non-homosexuals from contagion”.**
- **“The best evidence against contagion is that no cases have been reported to date outside the homosexual community or in women”**

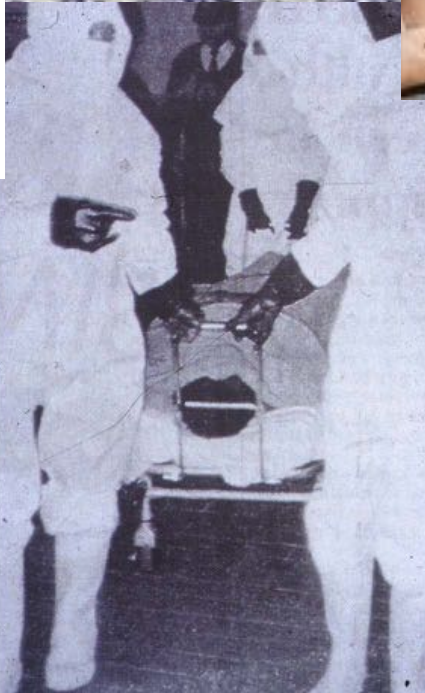




**This is not a
setting for AIDS.**

THE FEAR OF AIDS

Ignorance and Uncertainty Fuel
Growing Public Concern







1983: The cause is discovered

Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)

F. BARRÉ-SINOSSI, J. C. CHERMANN
F. REY, M. T. NUGEYRE
S. CHAMARET, J. GRUEST
C. DAUGUET, C. AXLER-BLIN
Institut Pasteur, Département de

Science
18 November 2011 | 510

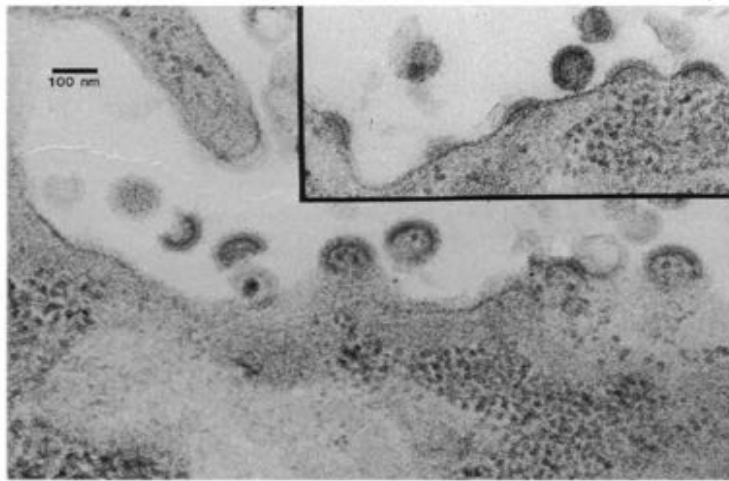


Fig. 2. Electron microscopy of thin sections of virus-producing cord lymphocytes. The inset shows various stages of particle budding at the cell surface.

‘We tentatively conclude that this virus [...] belong[s] to a **family of T-lymphotropic retroviruses** that are **horizontally transmitted in humans** and may be **involved in several pathological syndromes, including AIDS.**’

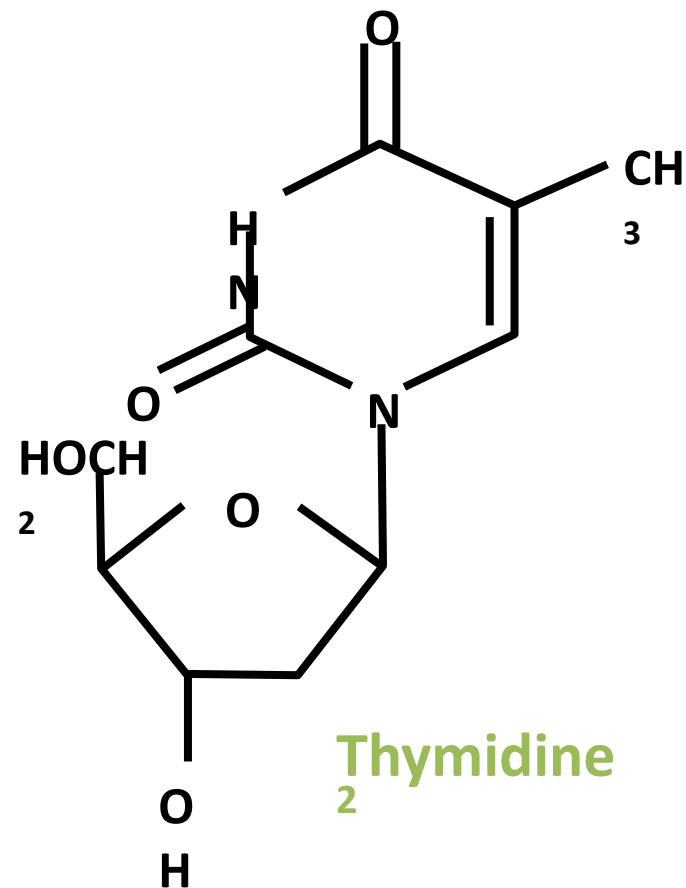
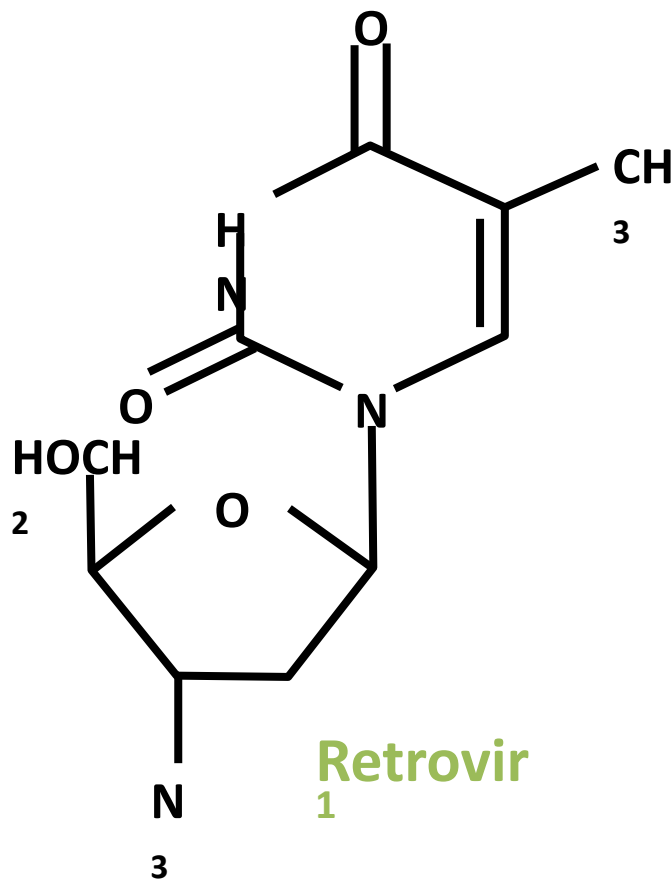


Treatment for survival....

- 1980's: finding drugs with *any* antiviral efficacy



The first active drug is found...



US Retrovir Prescribing Information. Revised Nov 2009
Levene PA and Tipson RS. *Science* 1935;81(2091):623-630

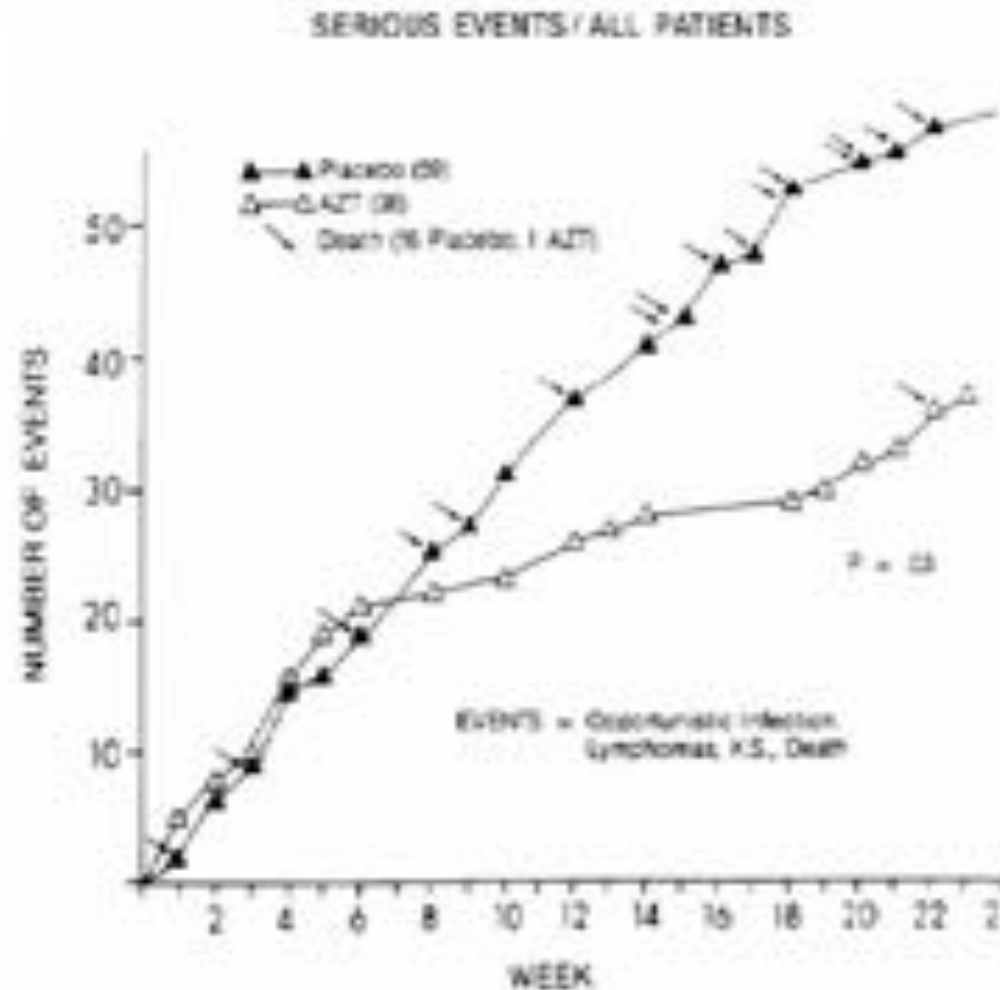


The first active drug is found...



The NEW ENGLAND
JOURNAL of MEDICINE

'AZT administration was associated with a **four-to-six-fold reduction in the mortality rates** in the study population at nine months



Scientific Expectation

“We hope to have a vaccine against AIDS ready for testing in two years”

“Yet another terrible disease is about to yield to patience, persistence and outright genius”



Not a moment too late...

Trends in Annual Rates of Death from Leading Causes of Death
Among Persons 25-44 Years Old, USA, 1982-1988

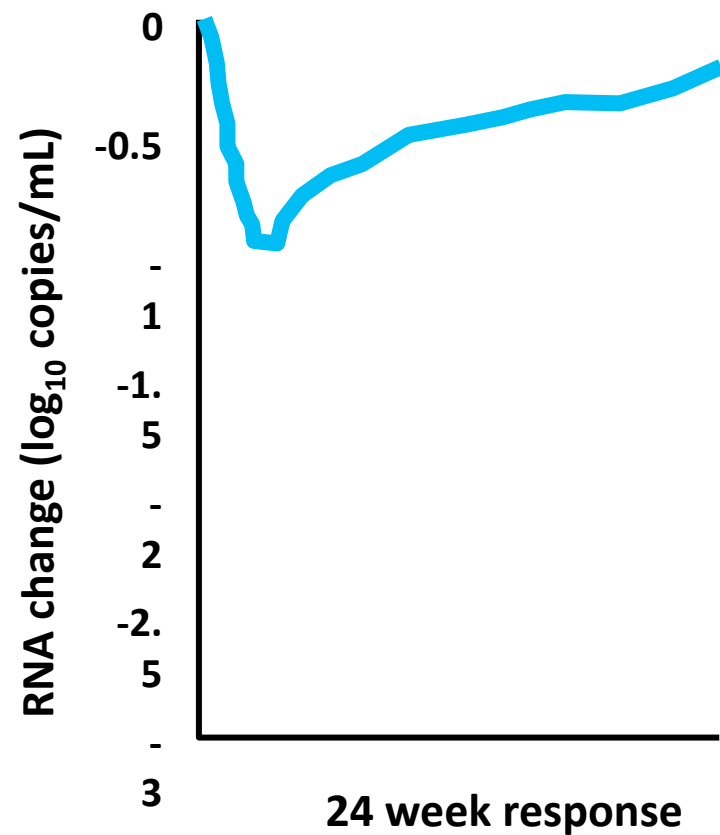


National Center for Health Statistics
National Vital Statistics System

*Preliminary 1998 data

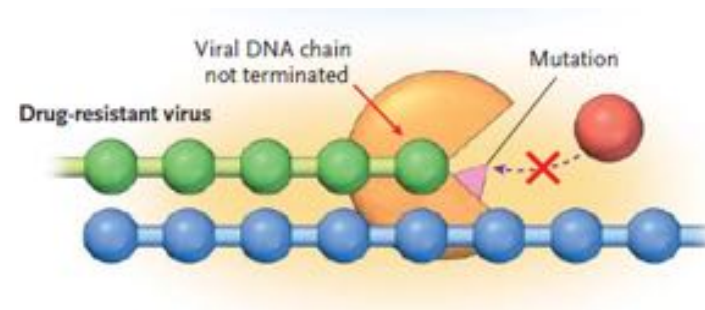
Expectations dashed

1987 AZT Monotherapy

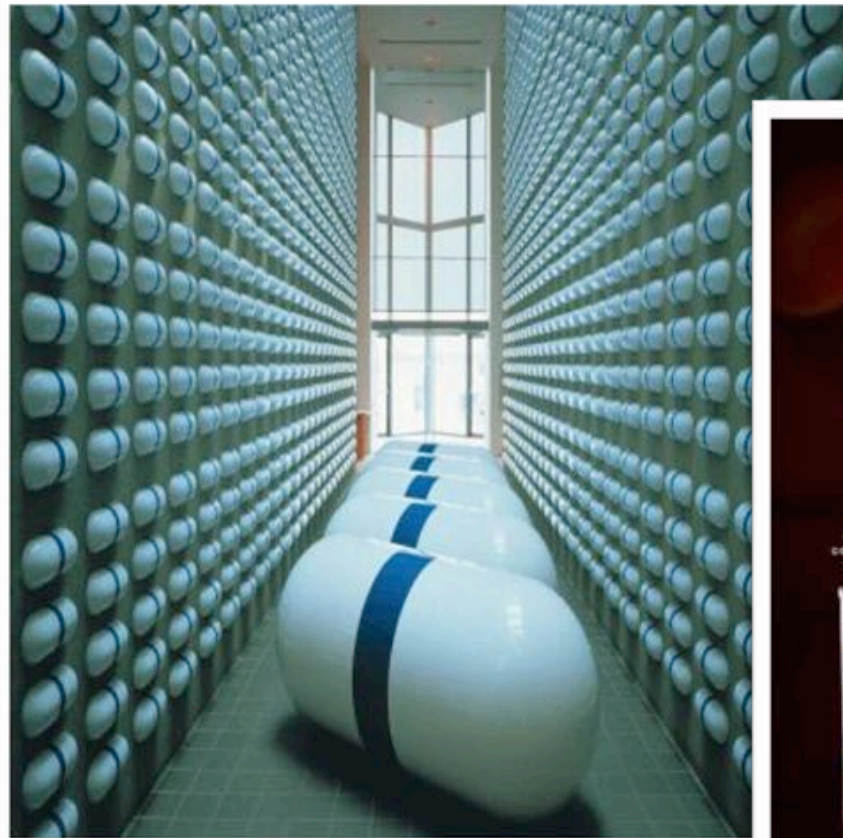


Drug-Resistant Strains of AIDS Virus Found

The emergence of AZT-resistant strains of the AIDS virus in patients treated with the drug has serious implications for treating AIDS and preventing its spread

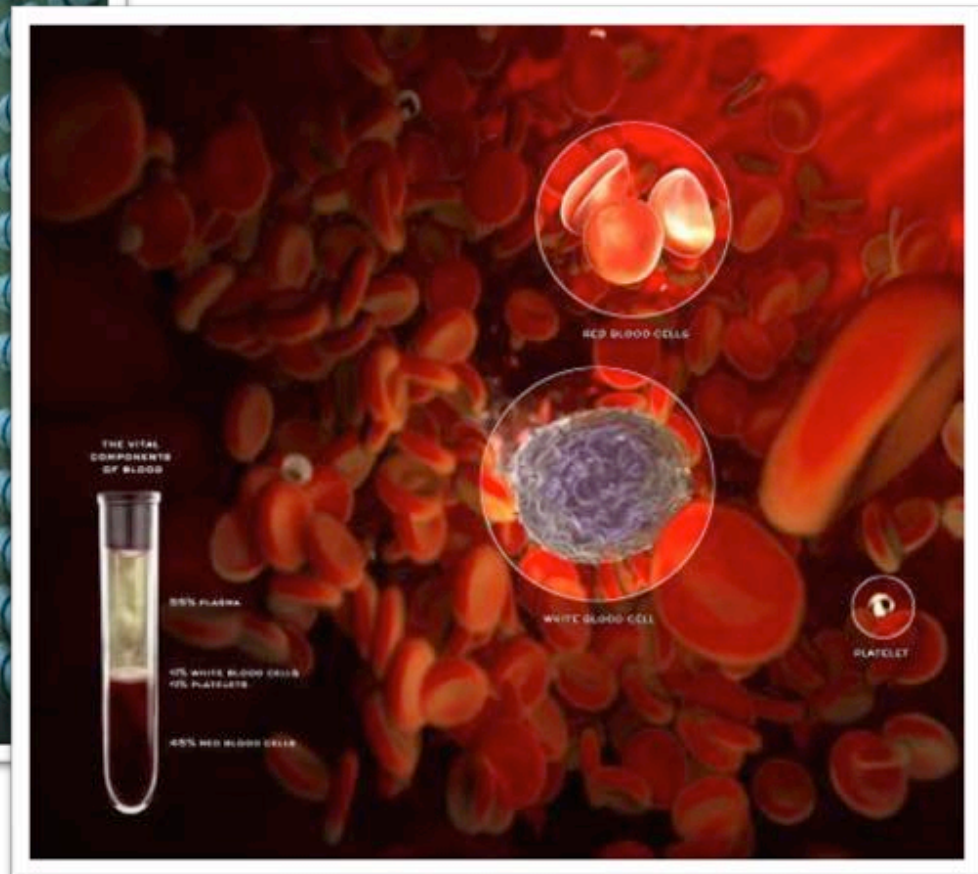


Issues with early Antiretroviral Therapy

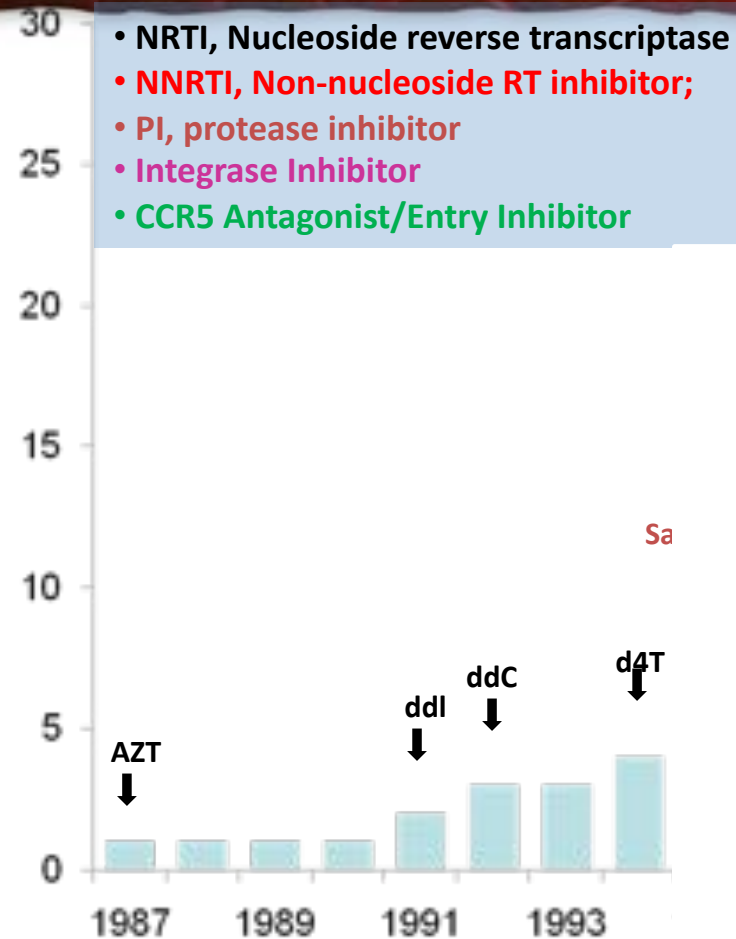


Adherence

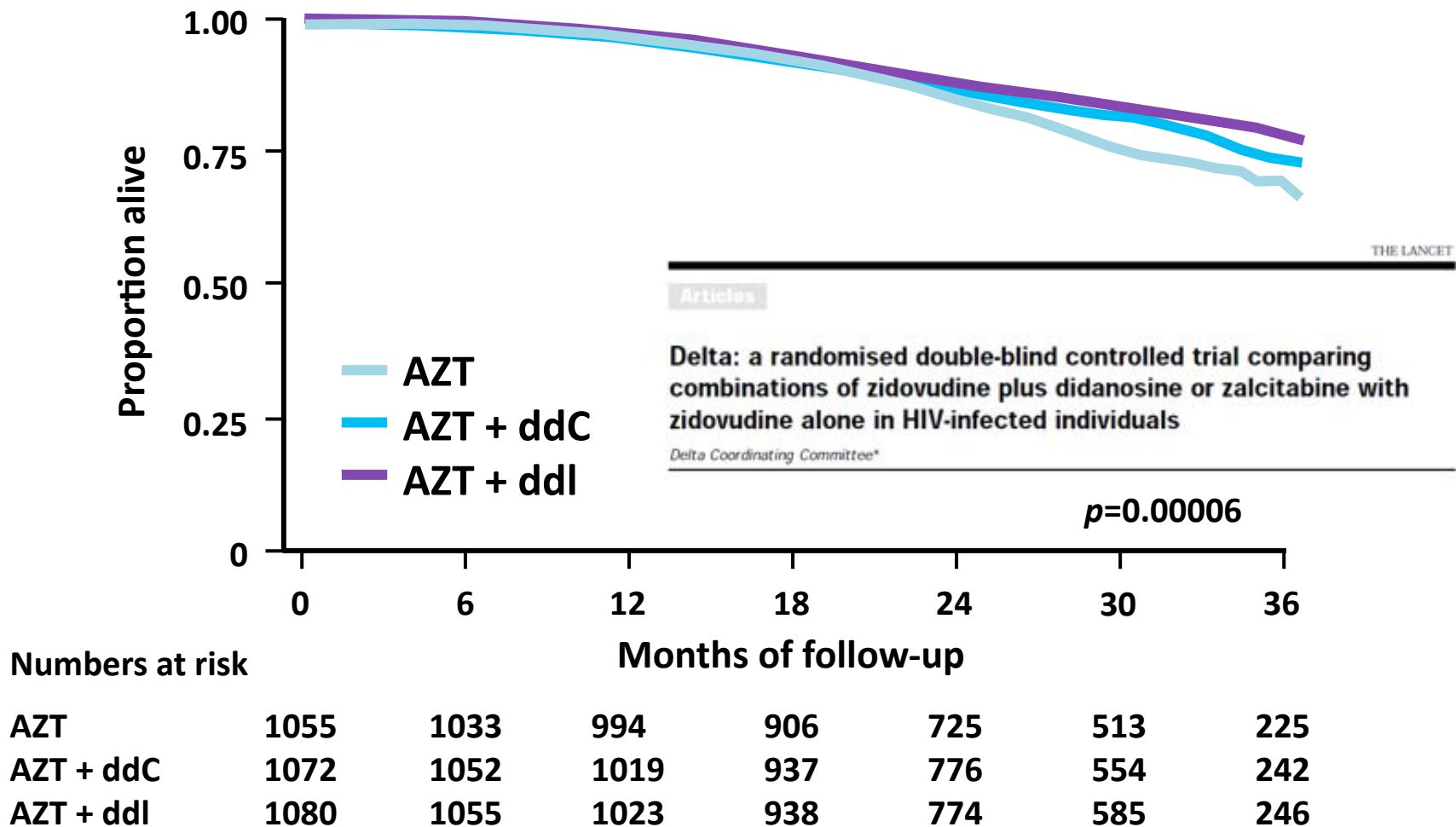
Toxicity



Additional NRTI's became available

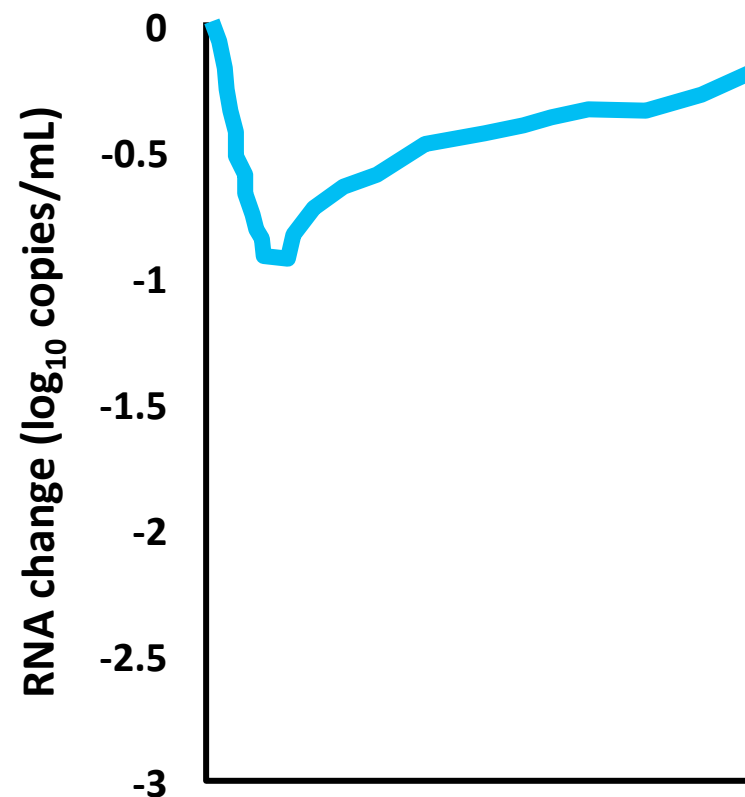


All-cause mortality: DELTA 1 and 2

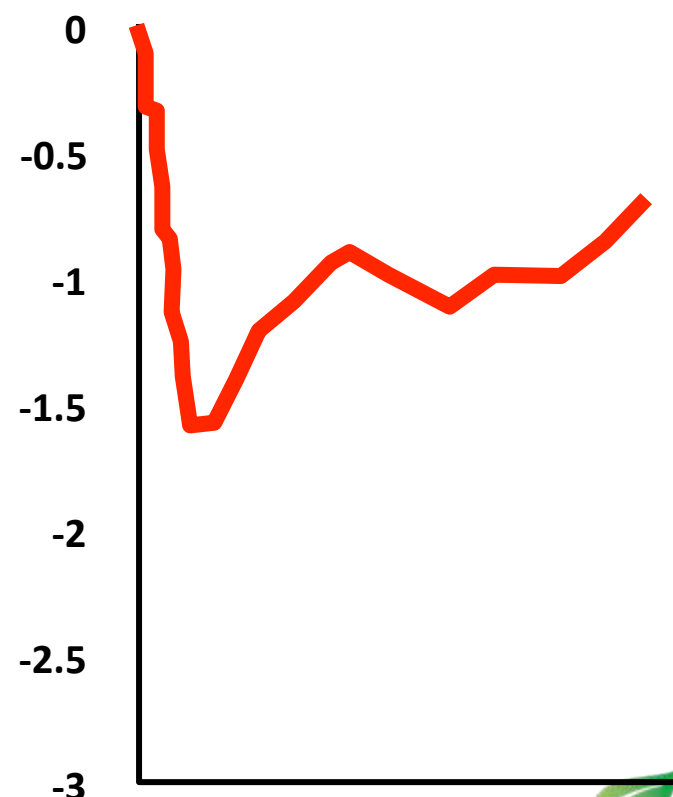


Again, expectations dashed

1987 AZT
Monotherapy



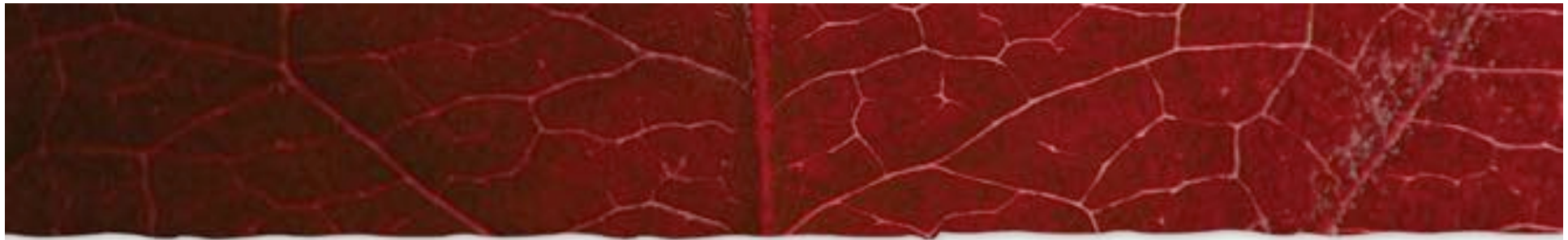
1994
Two drug therapy



Adapted from Fischl MA *et al.* *NEJM* 1987;317:185–91c

24 week response





No halt in epidemic

Trends in Annual Rates of Death from Leading Causes of Death
Among Persons 25-44 Years Old, USA, 1982-1988



National Center for Health Statistics
National Vital Statistics System

*Preliminary 1998 data



However, there were successes

Concepts in Emergency and Critical Care

Roger C. Bone, MD, Section Editor

Acquired immunodeficiency syndrome and critical care

Journal of Intensive Care Medicine

<http://jic.sagepub.com/>

Outcomes
in Patients
Immunocompromised

AIDS has created economic, social, emotional and medical issues, some of which are reviewed by Layon and D'Amico (1). We would like to discuss some of the ethical issues that AIDS has caused for practitioners of critical care. Questions have been raised concerning the ethical and economic appropriateness of using expensive life-sustaining treatments that do not alter a patient's underlying disease process or eventual outcome during a period of scarce critical care and medical resources. Accurate medical knowledge is required to answer these questions and to make difficult decisions in a sound ethical manner.

in the virulence of the organism or attributes of the host (9), it may also be related to medical selection of a subgroup of AIDS patients with a better prognosis. For instance, over the last few years, I (C.L.S.) have observed less AIDS patients admitted to the ICU with respiratory failure, especially if they had already received treatment for PCP for >5 days. Even with this improved ICU survival, the overall 1-yr survival rate of AIDS patients with severe PCP remains <10% and

Vol. 11
No. 11
Nov. 1990

Journal of Intensive Care Medicine

Questions have been raised concerning the ethical and economic appropriateness of using expensive life-sustaining treatments that do not alter a patient's underlying disease process or eventual outcome...

AIDS patients with severe PCP (8), newer data (6), a change in the ethical selection of patients for prognosis. I (C.L.S.) have observed less AIDS patients admitted to the ICU with respiratory failure, especially if they had already received treatment for PCP for >5 days. Even with this improved ICU survival, the overall 1-yr survival rate of AIDS patients with severe PCP remains <10% and long-term survival remains unaltered (9). Therefore,

The prognosis for patients with AIDS is poor. In a recent study, 35 (4%) had a median survival of 35 days. In patients with AIDS and respiratory failure, the overall 1-yr survival rate of AIDS patients with severe PCP remains <10% and long-term survival remains unaltered (9). Therefore,

survivors, only 2 patients remain alive. However, early intervention in patients with AIDS and respiratory failure is associated with a poor outcome and probably does not alter the ultimate course in most cases.

an overall mortality of approximately 30% to 40% (1,2). Other opportunistic pulmonary infections that occur in patients with AIDS include *Mycobacterium avium-intracellulare*, *Cytomegalovirus*, *Cryptococcus neoformans*, *Aspergillus fumigatus*,

medical resources. Accurate medical knowledge is required to answer these questions and to make difficult decisions in a sound ethical manner.

Only recently have we become aware of the extent of

received treatment for PCP for >5 days. Even with this improved ICU survival, the overall 1-yr survival rate of AIDS patients with severe PCP remains <10% and long-term survival remains unaltered (9). Therefore,

Response rates for PCP



Acute respiratory failure secondary to *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A potential role for systemic corticosteroids.



Improved survival in patients with AIDS, *Pneumocystis carinii* pneumonia, and severe respiratory failure.

Y Friedman, C Franklin, E C Rackow and M H Weil

Chest 1989;96:862-866
DOI 10.1378/chest.96.4.862

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.chestpubs.org/content/96/4/862>



CORTICOSTEROIDS AS ADJUNCTIVE THERAPY FOR SEVERE *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

A Double-Blind, Placebo-Controlled Trial

SUZANNE GAGNON, M.D., AHMAD M. BOOTA, M.D., MARGARET A. FISCHL, M.D., HORST BAIER, M.D., OTIS W. KIRKSEY, PHARM.D., AND LAWRENCE LA VOIE, PH.D.



PCP Survival improved

PATIENT SAMPLE REPORT 24 MAY 2005 20:01
SYSTEM 865-00022 Analysis Date 24 MAY 2005
Sequence no 1732 Analysis Time 20:01
Connection no Draw Date
Source Draw Time
Operator ID
Patient ID Sex
Birthdate Physician ID
Age Location

on air

SYRINGE SAMPLE
ACID/BASE 37°C

	Units	Reference Range
pH	7.388	(7.350 - 7.450)
pCO2	3.75	kPa (4.67 - 6.00)
pO2	11.26	kPa (10.00 - 13.33)
HCO3-alk	18.2	mmol/L
H(18)	-7.8	mmol/L

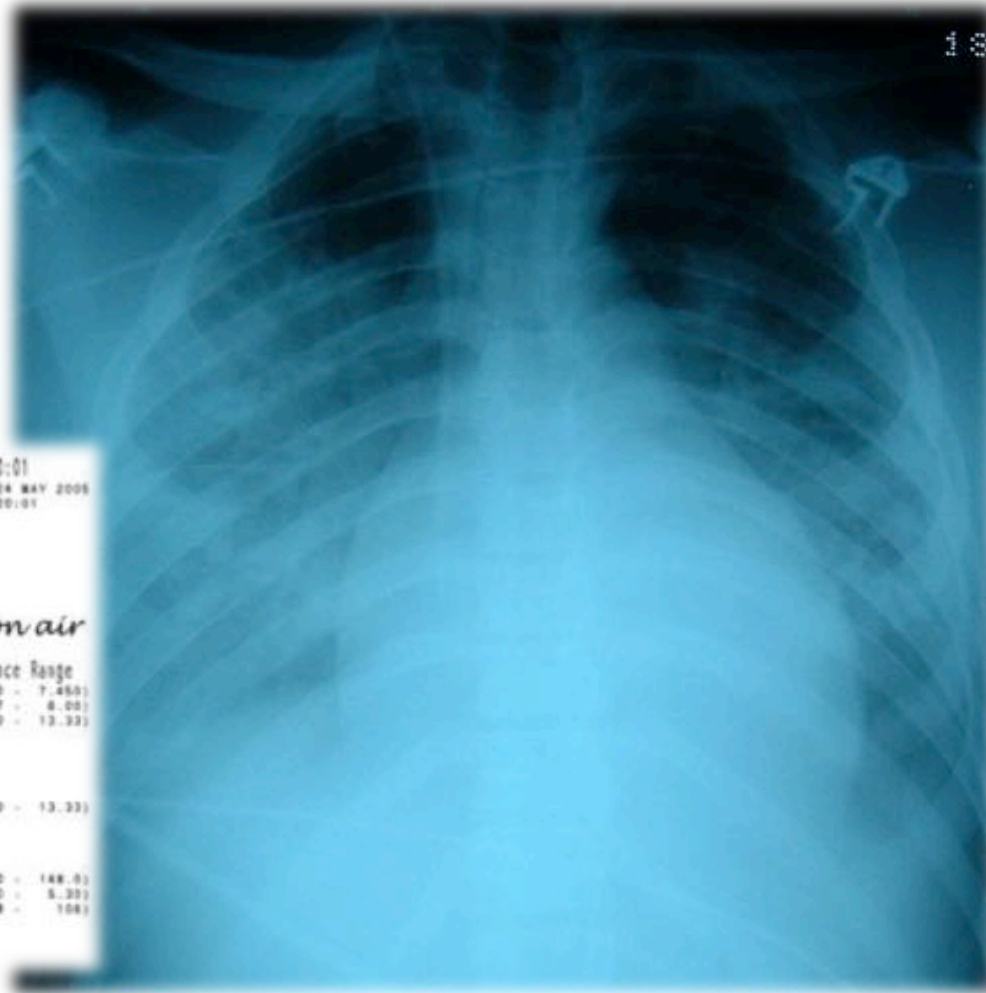
OXYGEN STATUS 37°C

pO2	11.26	kPa (10.00 - 13.33)
OSAT	88.2	%

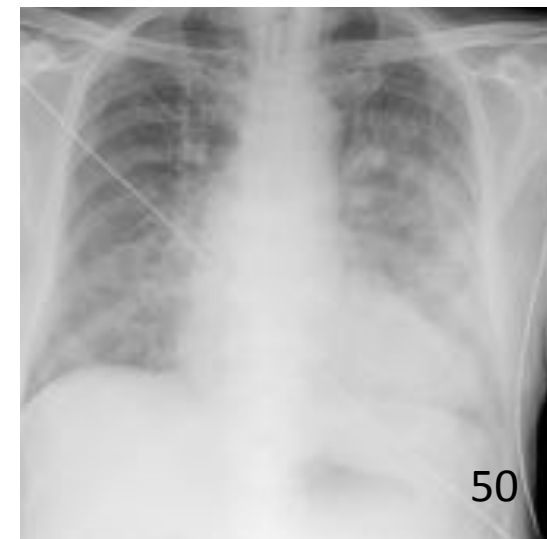
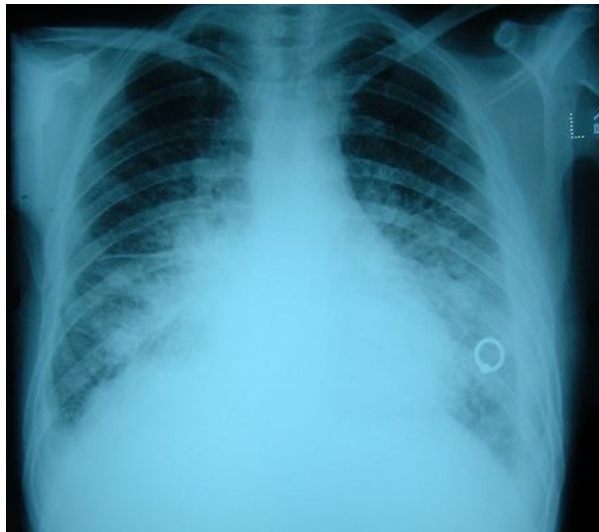
ELECTROLYTES

Na+	143.7	mmol/L (135.0 - 148.0)
K+	5.37	mmol/L (3.50 - 5.30)
Cl-	110.1	mmol/L (98 - 108)

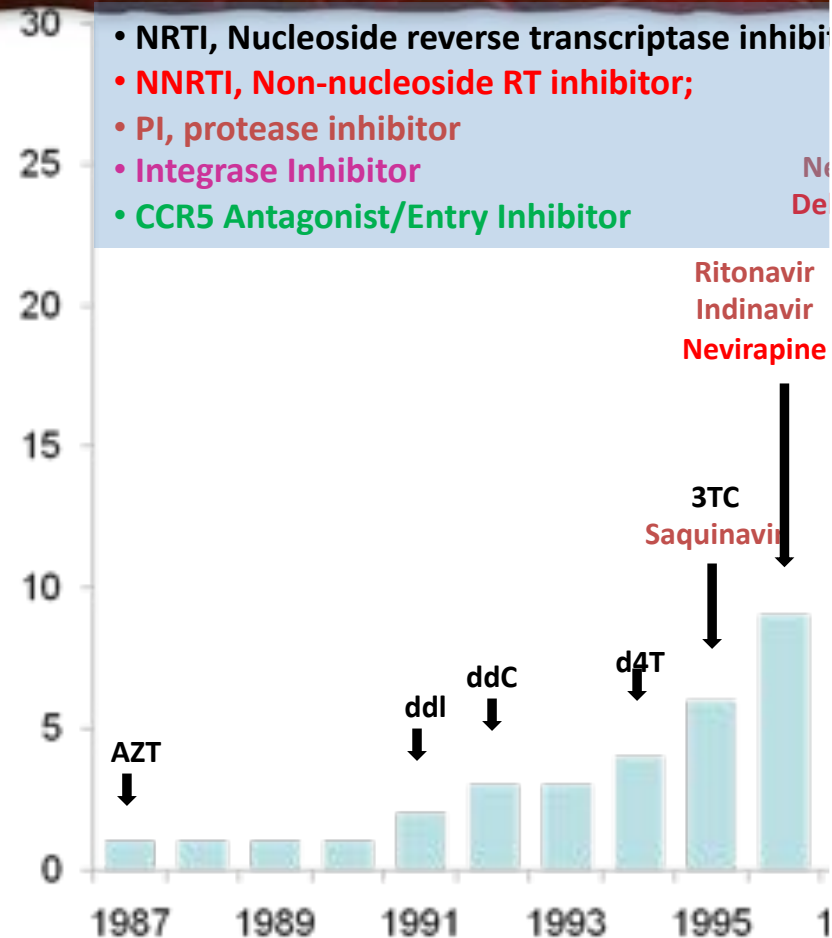
↑ or ↓ = exceeds reference range



And there was more testing...



Triple therapy investigated...



Viral load assays also become available as a surrogate marker 1996

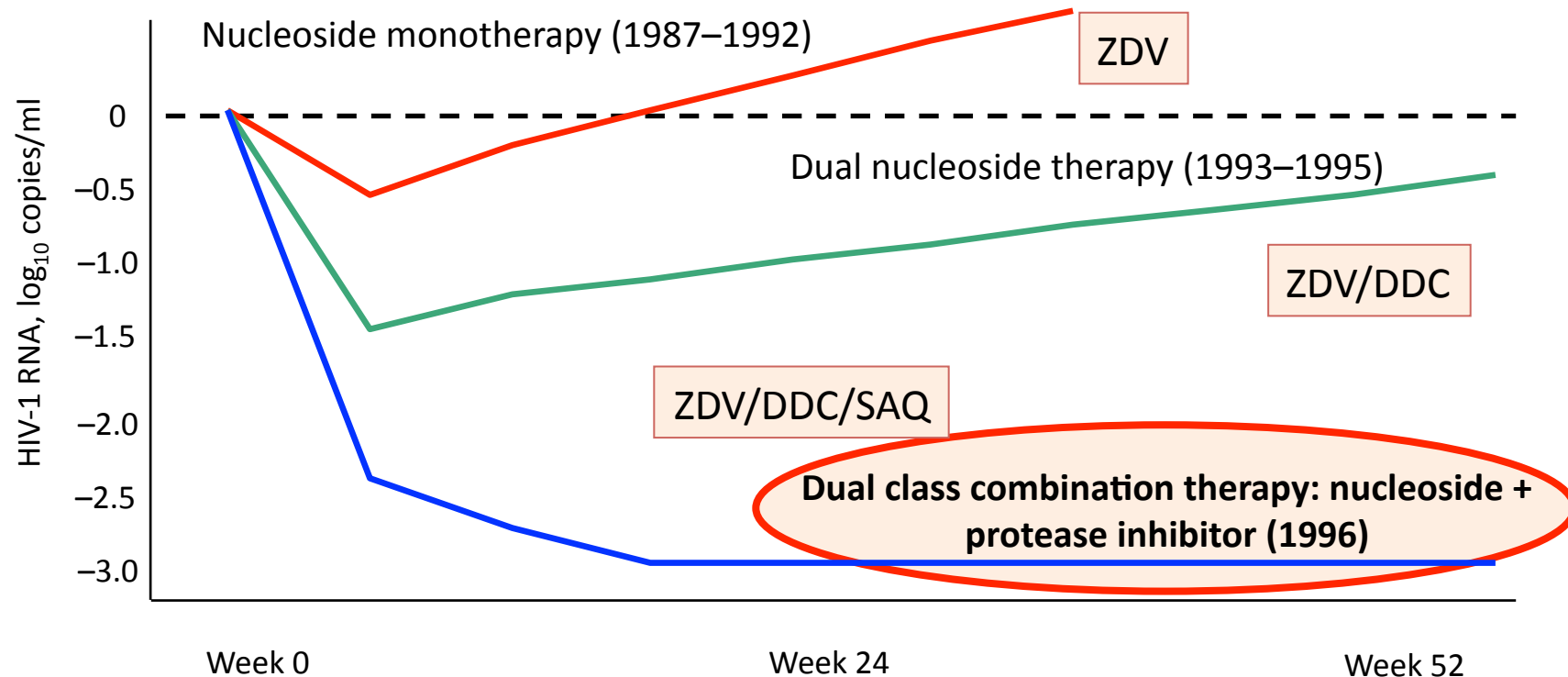


Viral load assays

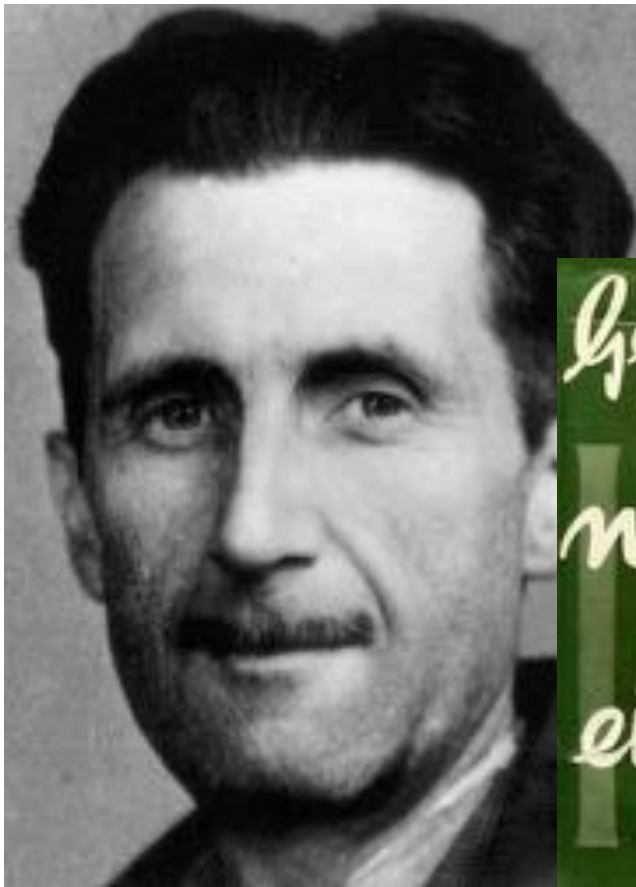


Combination therapy succeeded where 2NRTI failed – no more clinical endpoint trials

Relative viral load suppression with mono- and combination therapies



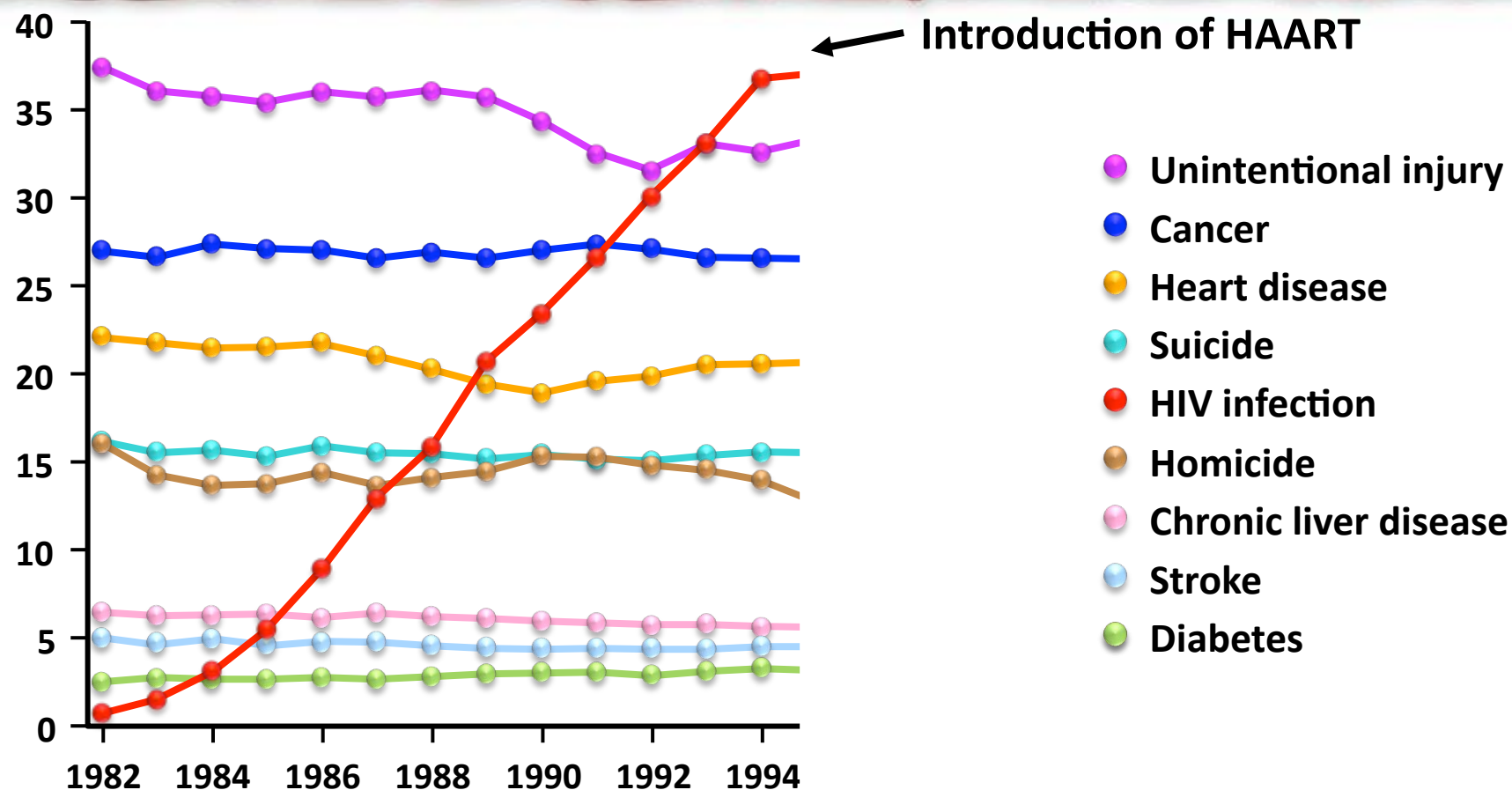
One drug is not enough in chronic infections



George Orwell
nineteen
eighty-four
a novel



Mortality among persons 25-44 years old, USA 1982-1998 falls...

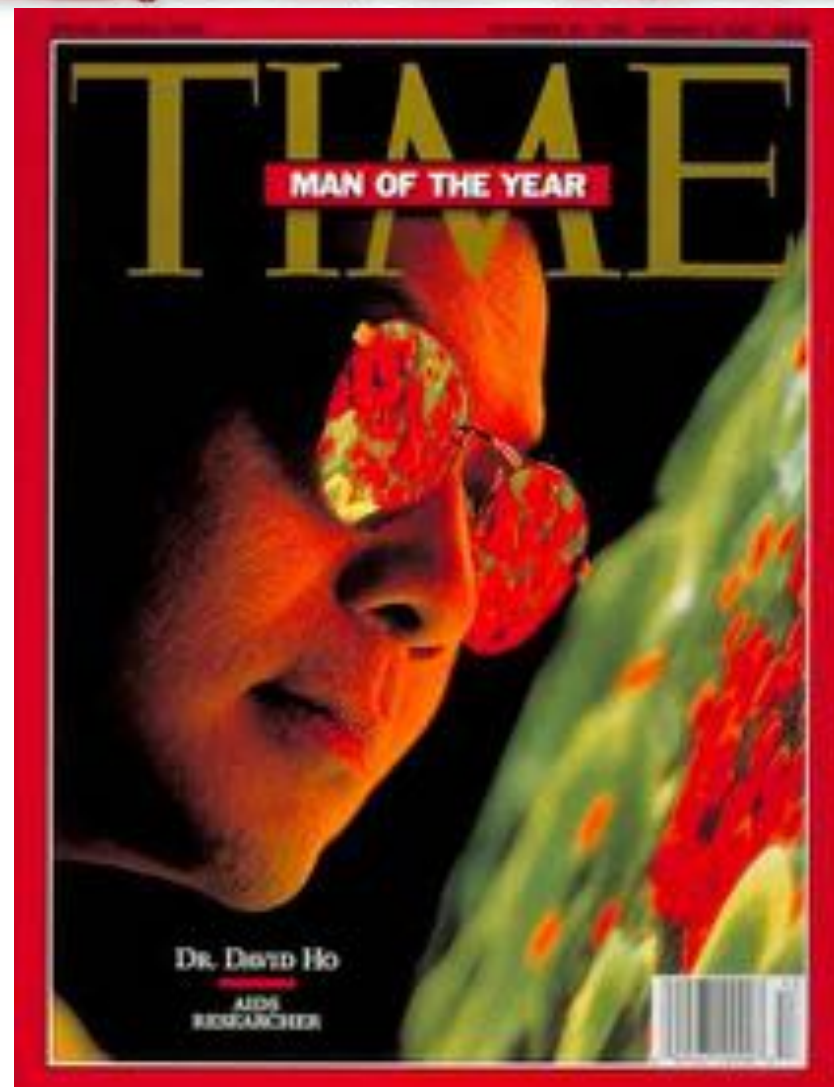


* Preliminary 1998 data

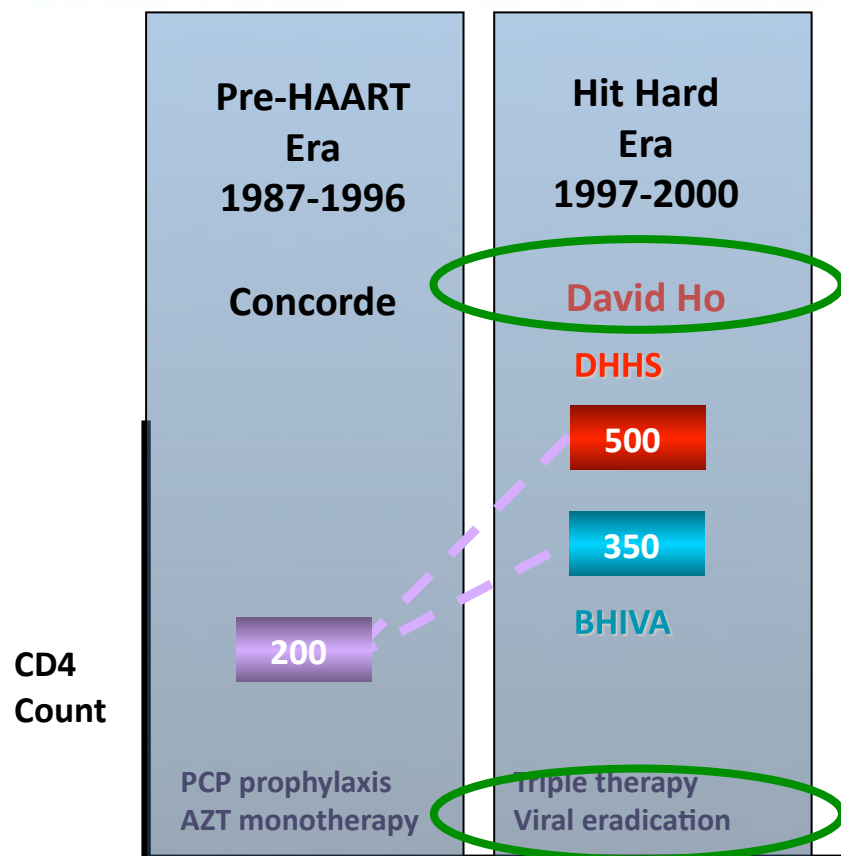
Centers for Disease Control HIV Mortality (through 2005). Available at:
<http://www.cdc.gov/hiv/topics/surveillance/resources/slides/mortality/index.htm>.
Accessed June 10, 2009



Hopes...



Combination therapy succeeded where 2NRTI failed



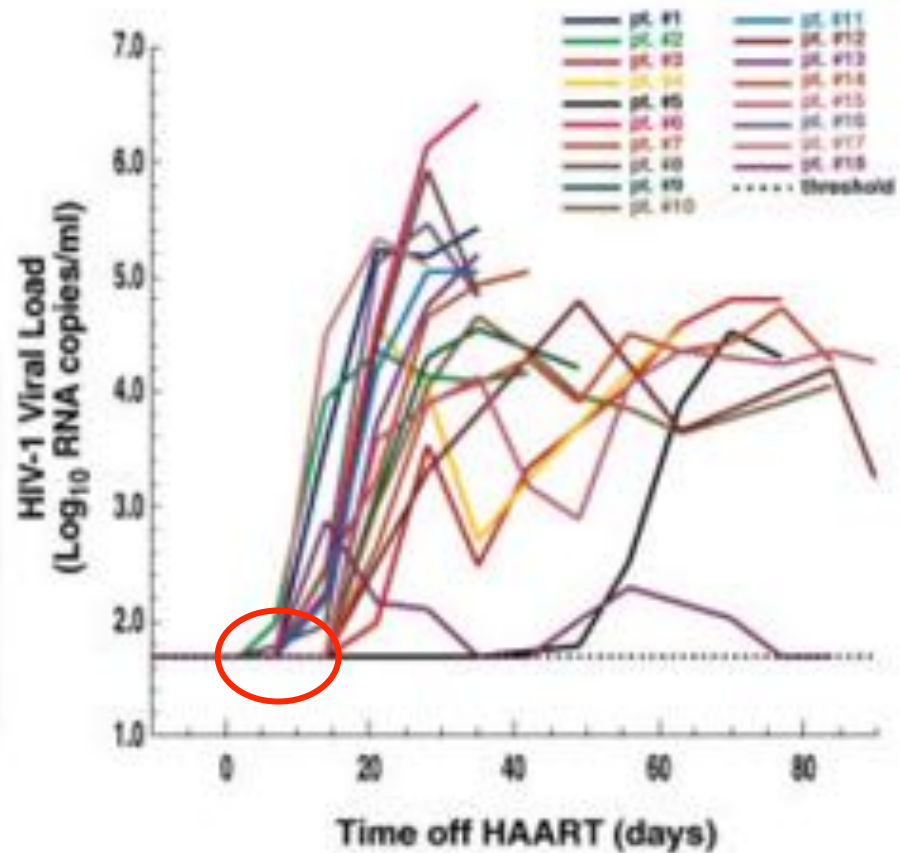
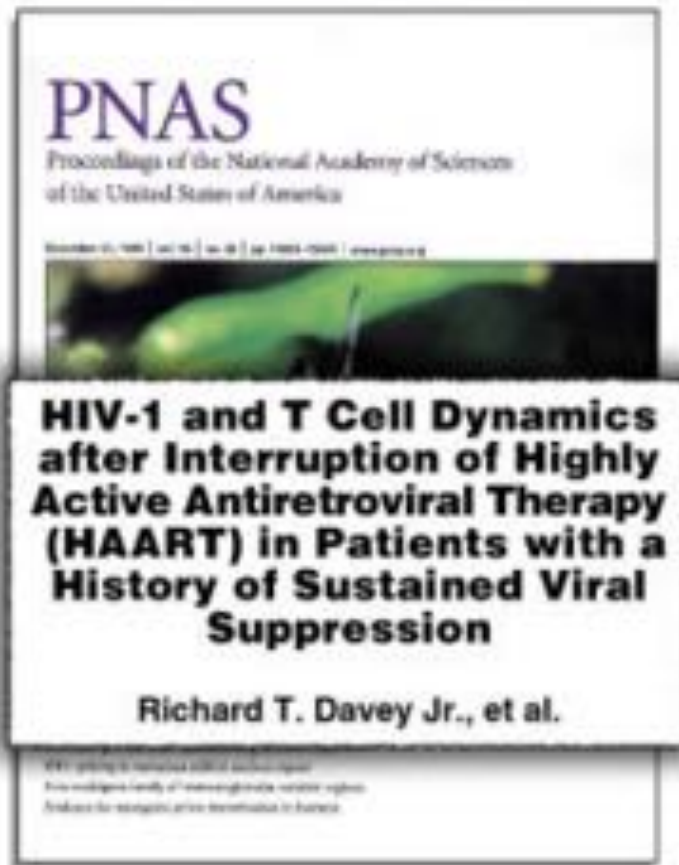
D Ho NEJM 1995; 333:450-451

Treatment for success...

- 1980's: finding drugs with *any* antiviral efficacy
- 1990's: attempting to get ***durable*** antiviral efficacy

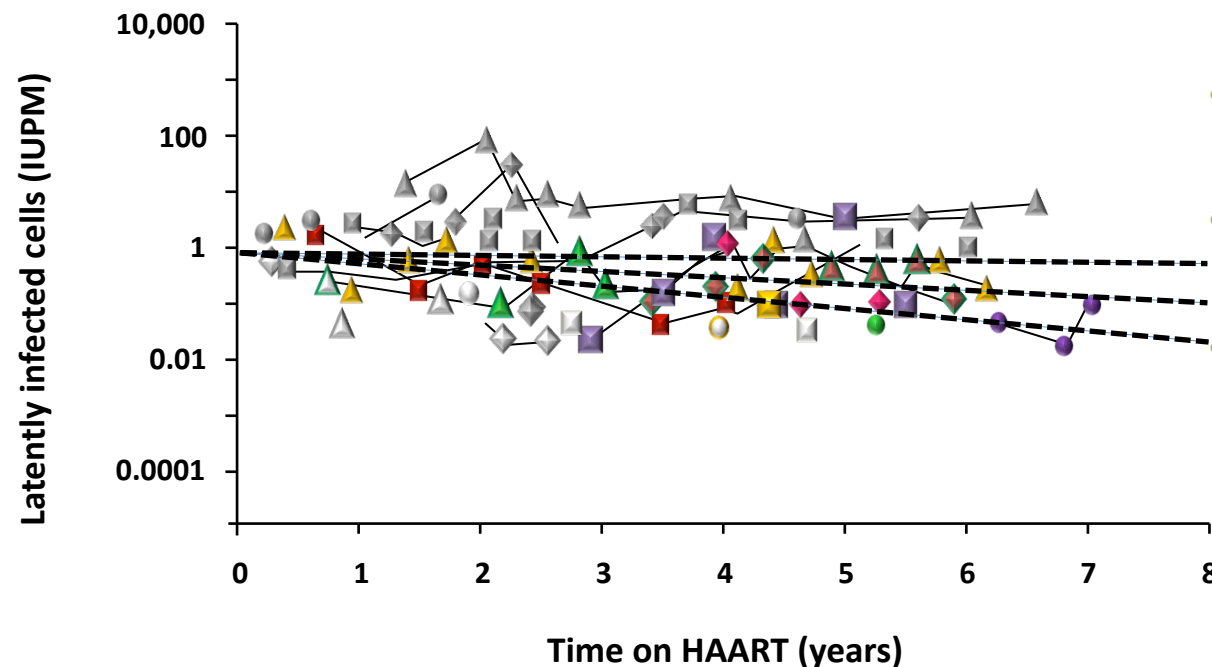


Eradicating impossible



With standard HAART – The Reservoir of latently infected Cells decays slowly

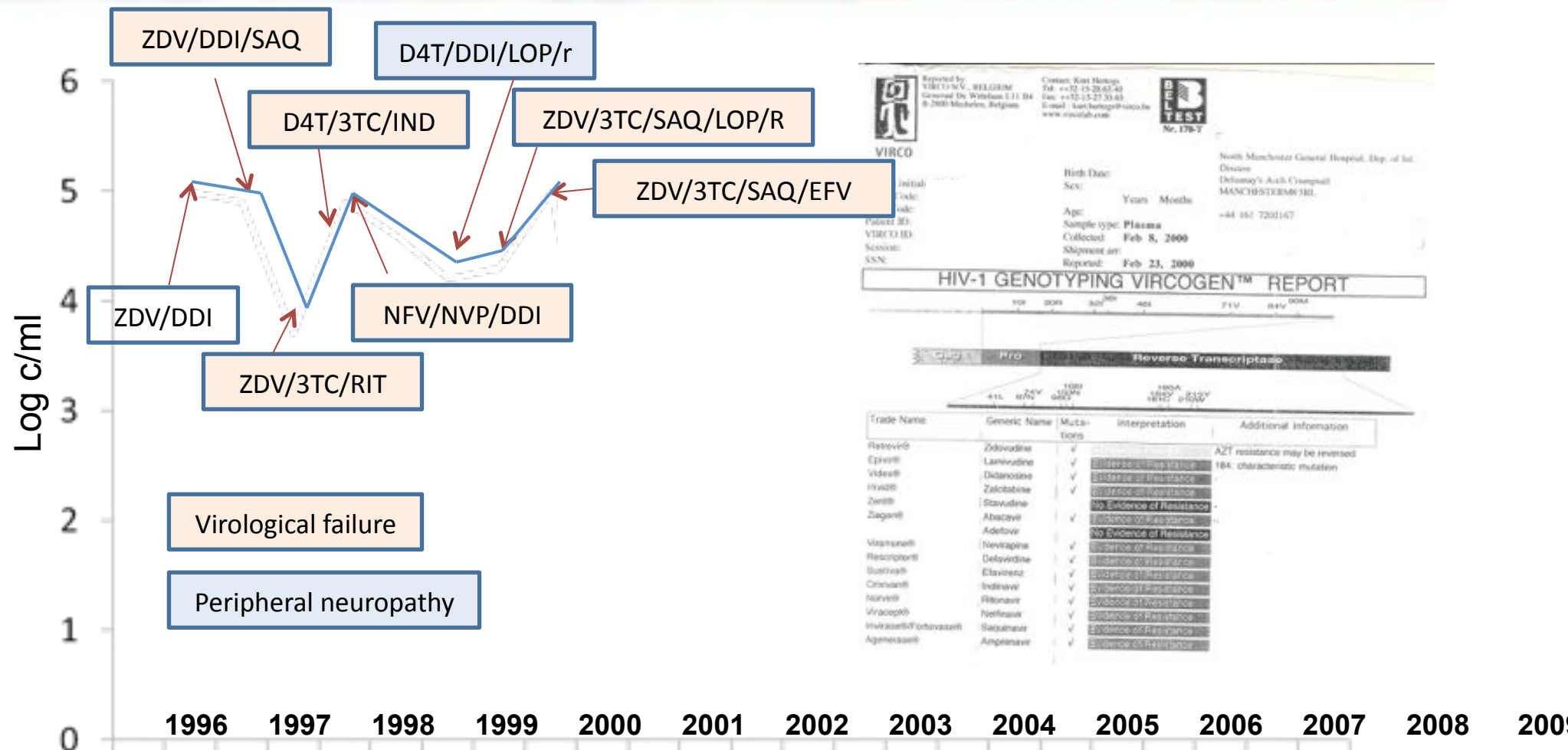
Decay of Latent Reservoir in Patients with full HAART suppression for 3-7 years



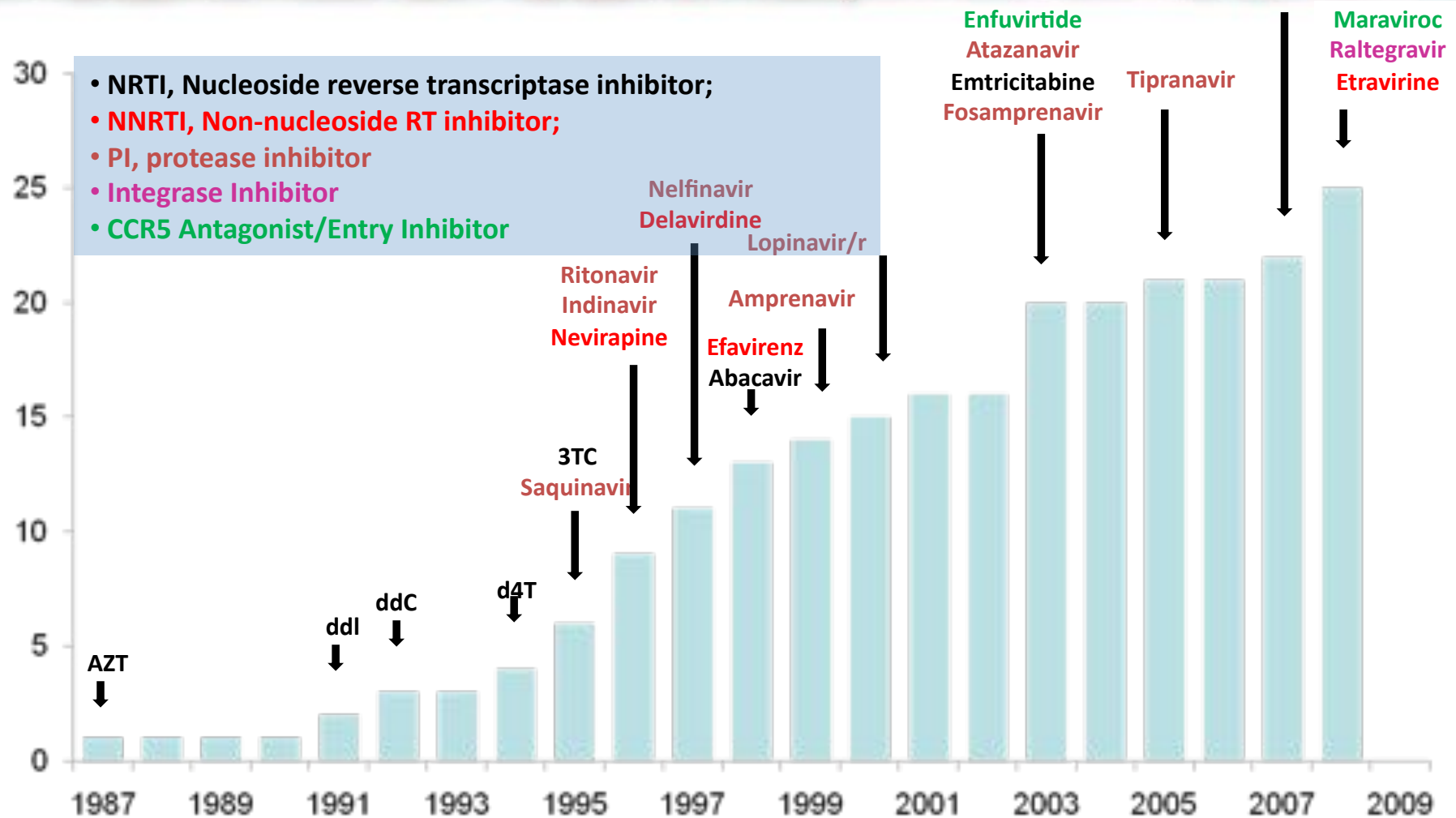
- HIV Integrates into cells with extremely long biological half-life
- Integrated HIV persists in patients on HAART
- Latent reservoir makes HIV infection incurable
- Potential for clonal expansion of latently infected cells and proliferation

≈ 70y before cure

Resistance test became widely used – Mistakes made...



Further drugs lead to the advent of ART



Where are we now with treatment?

- 1980's: finding drugs with *any* antiviral efficacy
- 1990's: getting *durable* antiviral efficacy
- **2000's: making treatments easier and less toxic**
- **2010's: aiming for normal life expectancy**

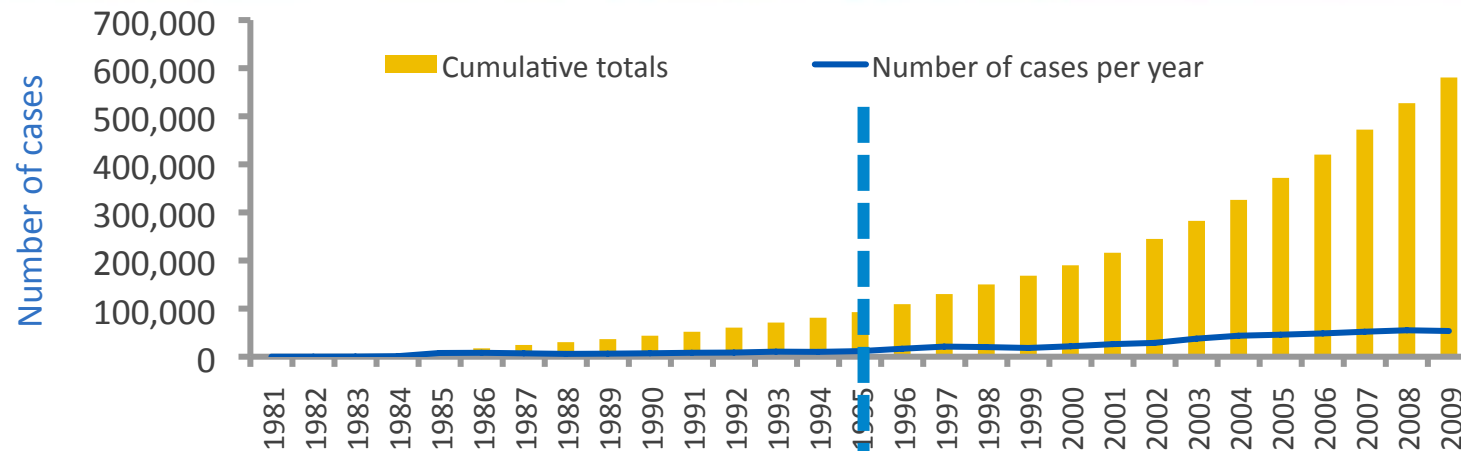


We live in the resourced nations where...

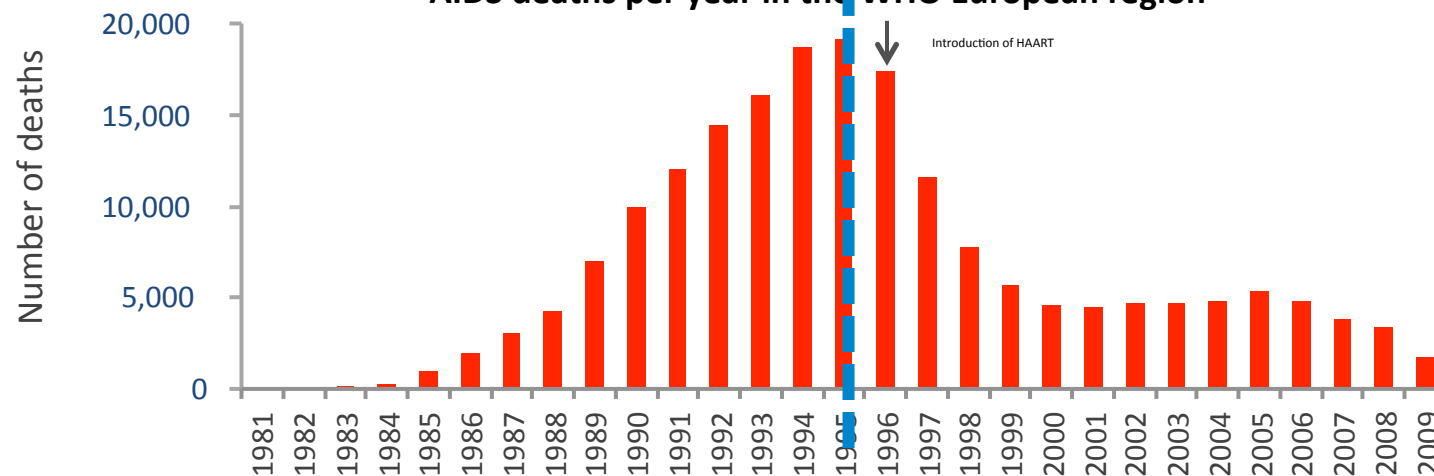


Prevalence of HIV-infected individuals is increasing, but mortality rate is decreasing

Diagnosed HIV infected individuals in the WHO European region¹



AIDS deaths per year in the WHO European region^{2,3}



* Numbers may rise, for recent years, as further reports are received.

1. Adapted from HIV/AIDS Surveillance Europe. 2009 presentation http://ecdc.europa.eu/en/healthtopics/spotlight/spotlight_aids/Pages/index.aspx (accessed June 2011). 2. HIV/AIDS in Europe. Moving from death sentence to chronic disease management (WHO). http://www.euro.who.int/_data/assets/pdf_file/0010/78562/E87777.pdf (accessed June 2011); 3. HIV/AIDS surveillance in Europe 2009 report (WHO) http://ecdc.europa.eu/en/healthtopics/spotlight/spotlight_aids/Pages/index.aspx (accessed June 2011).

Treatment is easy...

HIV

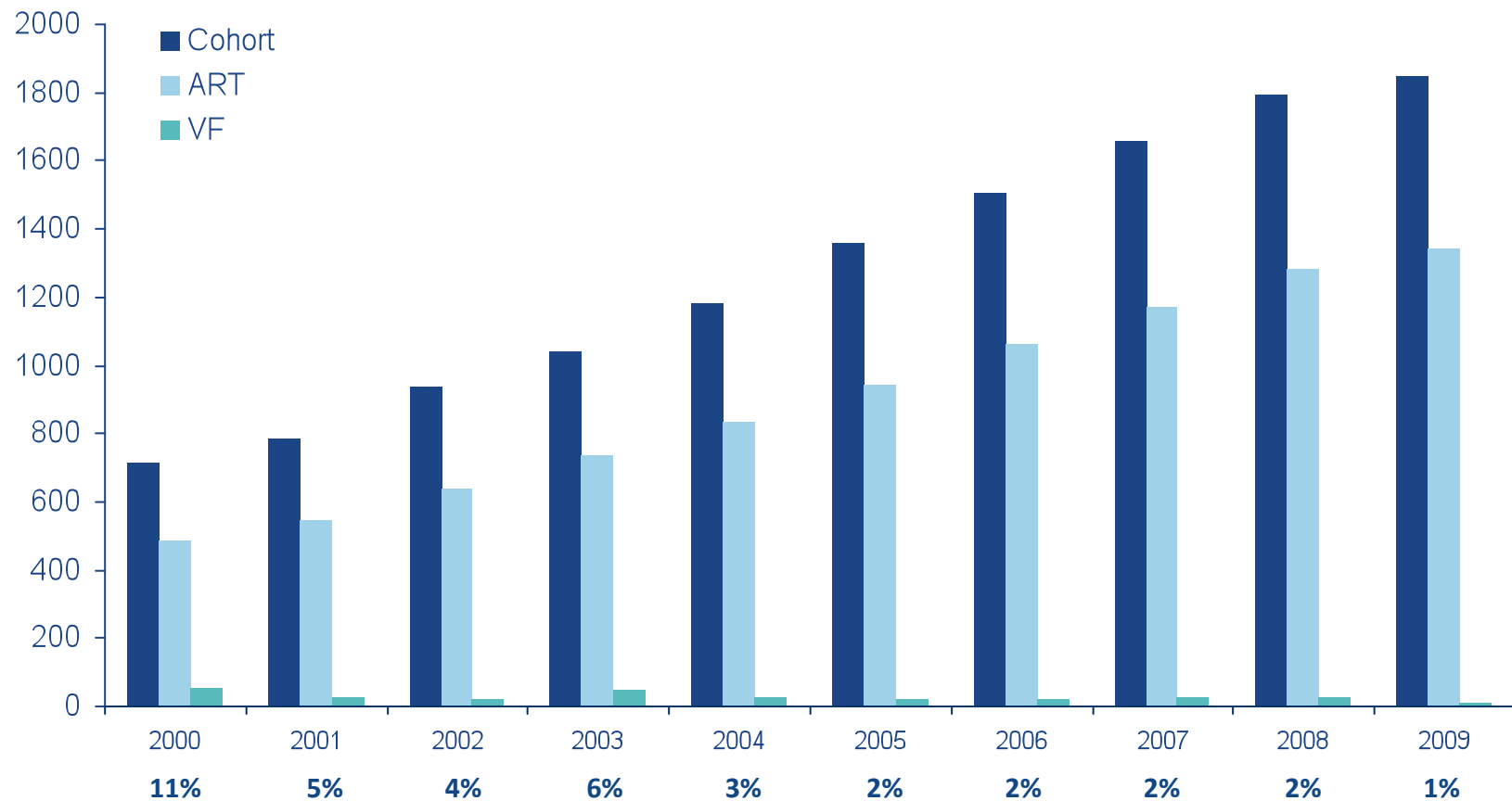


Type 1 Diabetes



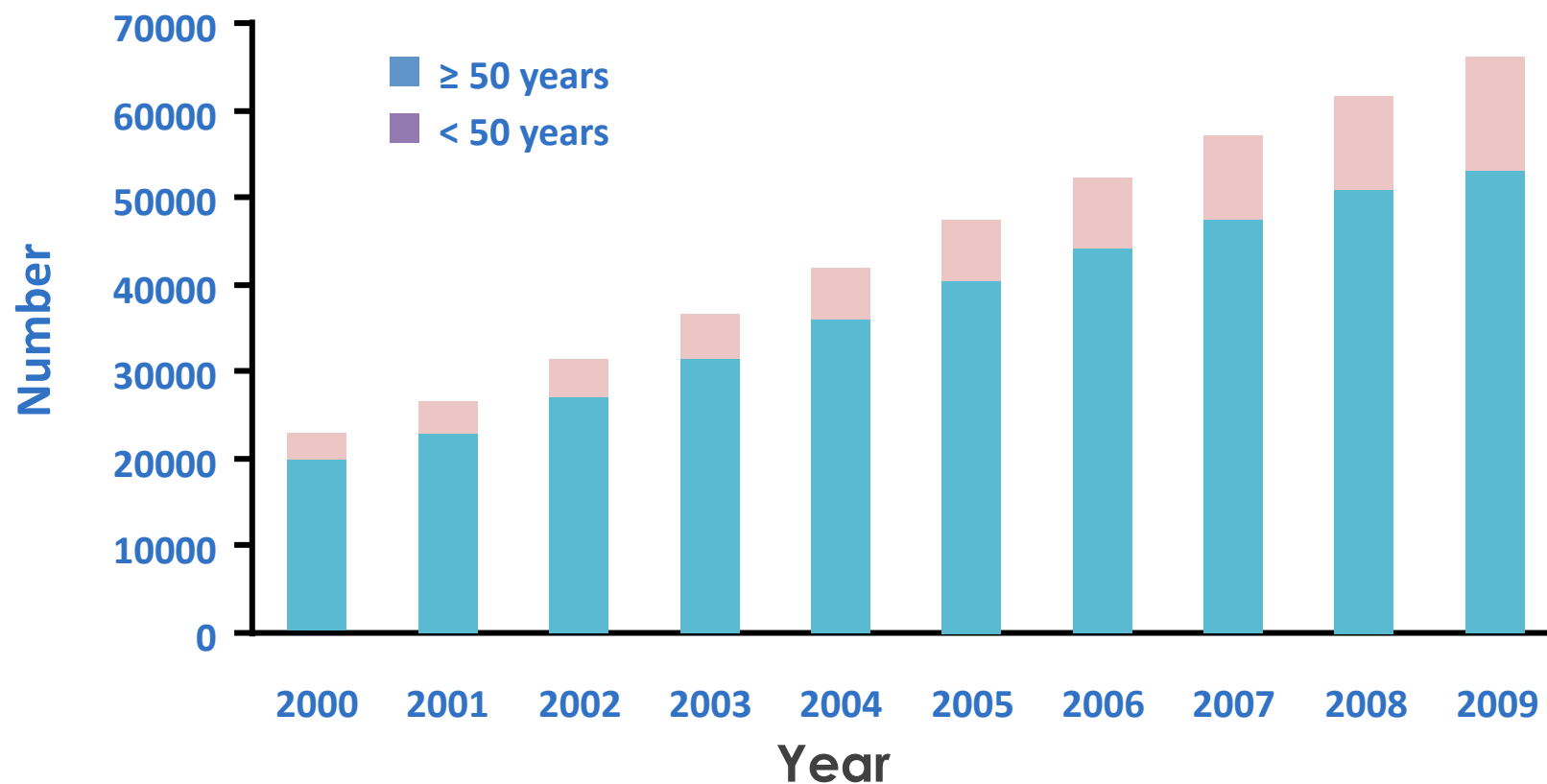
If patients take their tablets they don't fail

UK cohort, ART uptake, and virological failure



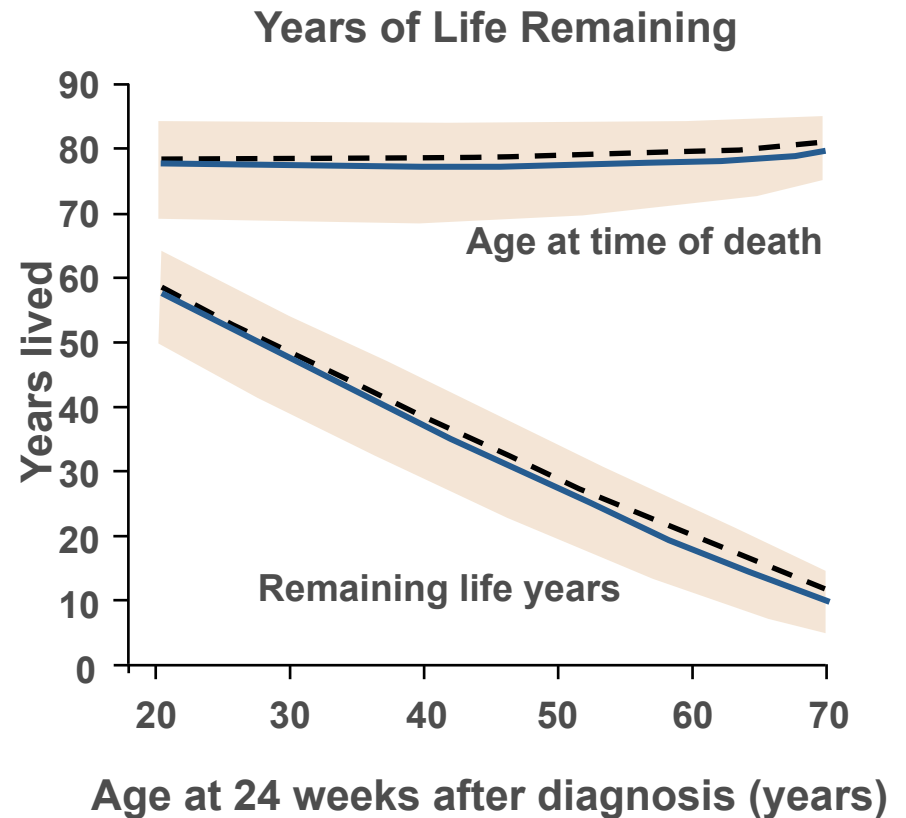
A growing number of people with HIV are reaching older age

Number of people living with diagnosed HIV infection and accessing HIV-related care, by age group, UK: 2000-2009



Life-expectancy approached that of HIV- individuals

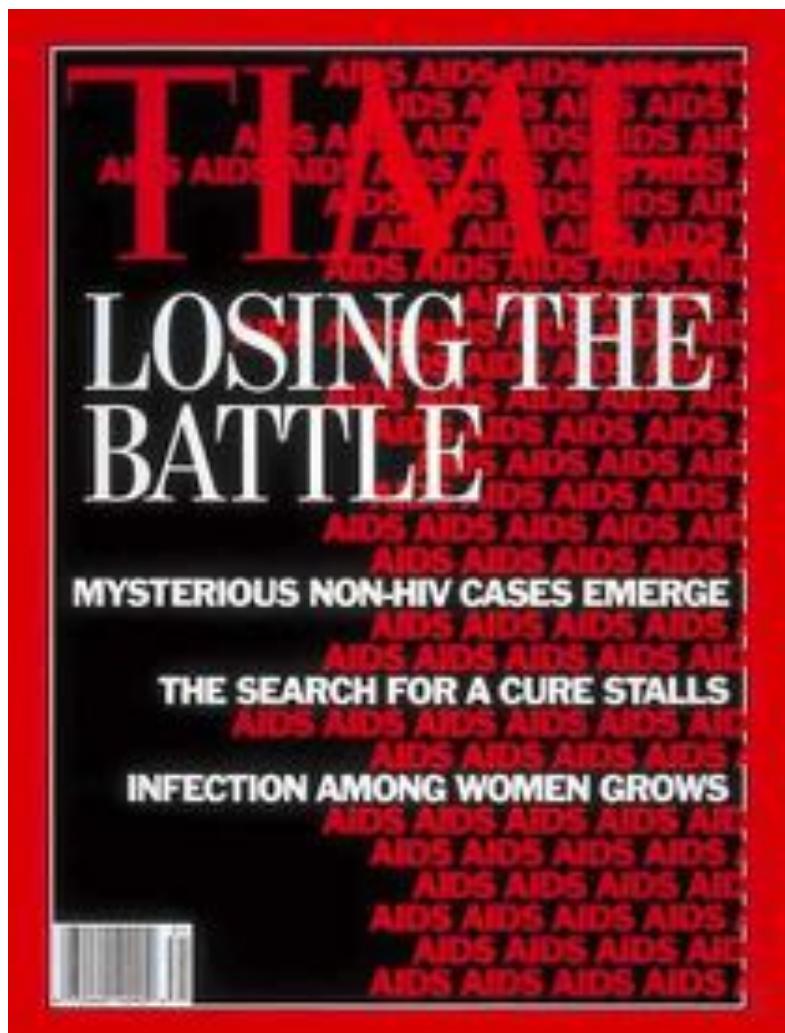
HIV cohort
Prediction life expectancy
From age 24y
Taking HAART



Shaded areas represent the interquartile range and dashed lines represent the general population.

Van Sighem A et al. AIDS 2010; 24(10) 1527–1535.





The only one?

From bloodjournal.hematologylibrary.org at University of Liverpool Library on April 7, 2015. For personal use only.

blood

2011 117: 2791-2799
doi:10.1182/blood-2010-09-309591

Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation

Kristina Allers, Gero Hütter, Jörg Hofmann, Christoph Lüddecke, Kathrin Rieger, Eckhard Thiel and Thomas Schneider

Updated information and services can be found at:
<http://bloodjournal.hematologylibrary.org/content/117/10/2791.full.html>

Articles on similar topics can be found in the following Blood collections

Immunobiology (4405 articles)

Transplantation (1519 articles)

Free Research Articles (1110 articles)

Clinical Trials and Observations (1155 articles)



Attacking the reservoir...

- Intensification?
- New drugs in current classes?
- Purging the reservoir?
- Novel agents?

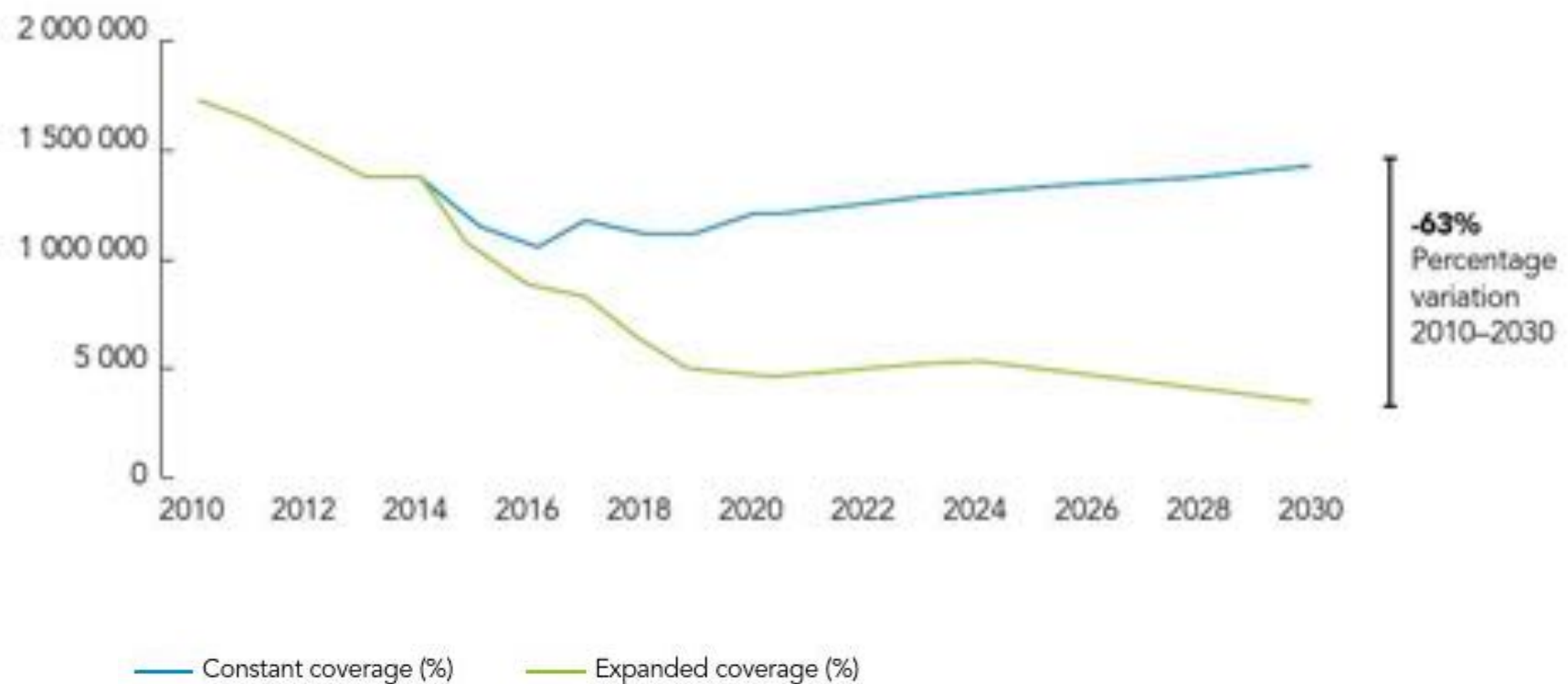
Until then - Prevention



96%



Ending the AIDS epidemic by 2030



Source: UNAIDS estimates (2014), Gap report



Thank you

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