

17TH ANNUAL CONFERENCE OF THE
BRITISH HIV ASSOCIATION (BHIVA)



Professor Brian Gazzard

Chelsea and Westminster Hospital, London

6-8 April 2011, Bournemouth International Centre

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COMPETING INTEREST OF FINANCIAL VALUE $\geq$ £1,000:	
Speaker Name	Statement
Professor Brian Gazzard:	Professor Gazzard has given consultancy advice for Gilead Sciences, Bristol-Myers Squibb and ViV Healthcare.
Date	1 April 2011

6-8 April 2011, Bournemouth International Centre

History of HIV and AIDS

Professor Brian Gazzard





"What can I say? The medicines are eloquent enough. What they have done for me is amazing. Everyone was shocked when I went home for Christmas. I was so sick before I started treatment. I was skinny, and the medicines made me big again. I was so weak I could not walk, and now look at me."

Lessons learnt

Miracles do happen!

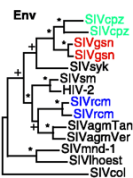
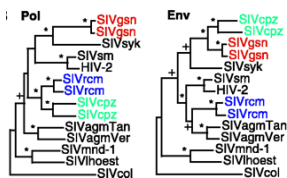
1 million years ago...

- A chimp was bitten by 2 monkeys:

- Red-capped mangabey



- Greater Spot-nosed (Cercopithecus nictitans)



A part of SIVcpz (the pol gene) is closer to SIVrcm,
and another part (env) is closer to SIVgsn



rcm = red-capped mangabeys (*Cercopithecus torquatus*)

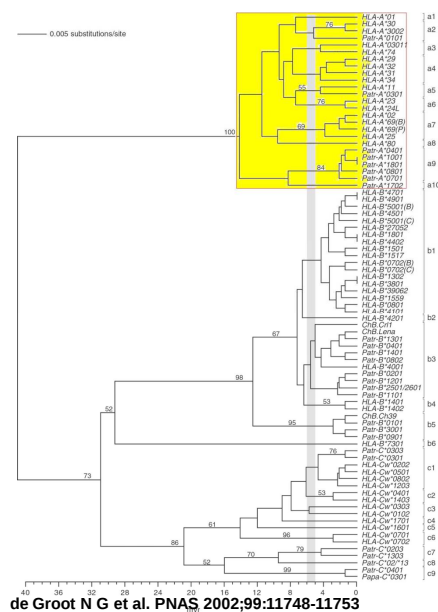
Gsn=greater spot-nosed monkeys (*Cercopithecus nictitans*)



Next 100,000 years...

- 95% of chimp population eradicated
- Restricted MHC repertoire

UPGMA phylogenetic tree of human and chimpanzee MHC class I intron 2 sequences.



1999. Nature

Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*

Feng Gao*, Elizabeth Bailes†, David L. Robertson‡, Yalu Chen*, Cynthia M. Rodenburg*, Scott F. Michael*§, Larry B. Cummins||, Larry O. Arthur*, Martine Peeters#, George M. Shaw*¶, Paul M. Sharp† & Beatrice H. Hahn*

* Departments of Medicine and Microbiology, University of Alabama at Birmingham, 701 S. 19th Street, LHRB 613, Birmingham, Alabama 35294, USA

† Institute of Genetics, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK

‡ Laboratory of Structural and Genetic Information, CNRS, Marseilles 13402, France

§ Southwest Foundation for Biomedical Research, San Antonio, Texas 78245, USA

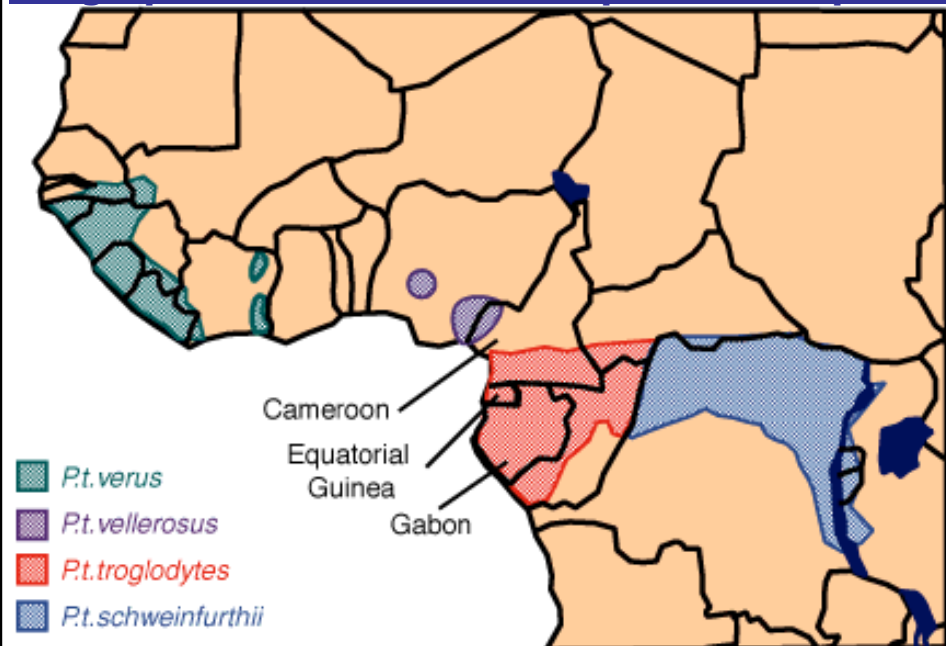
¶ AIDS Vaccine Program, National Cancer Institute-Frederick Cancer Research and Development Center, SAIC Frederick, Frederick, Maryland 21702, USA

Laboratoire Retrovirus, ORSTOM, BP 5045, Montpellier 34032, France

¶ Howard Hughes Medical Institute, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA

The human AIDS viruses human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) represent cross-species (zoonotic) infections¹⁻⁴. Although the primate reservoir of HIV-2 has been clearly identified as the sooty mangabey (*Cercocebus atys*)^{2,4-7}, the origin of HIV-1 remains uncertain. Viruses related to HIV-1 have been isolated from the common chimpanzee (*Pan troglodytes*)^{8,9}.

Geographic distribution of chimpanzee subspecies



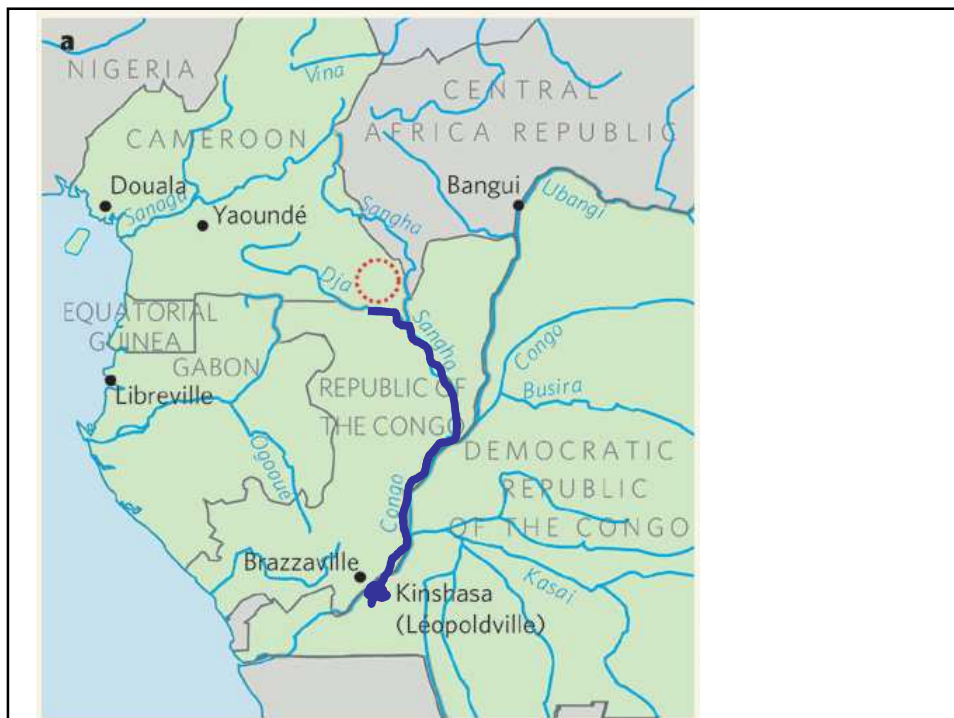
Kinshasa

1950's

Histopathology Department – unexplained death

HIV DNA extracted

Molecular clock → 1899



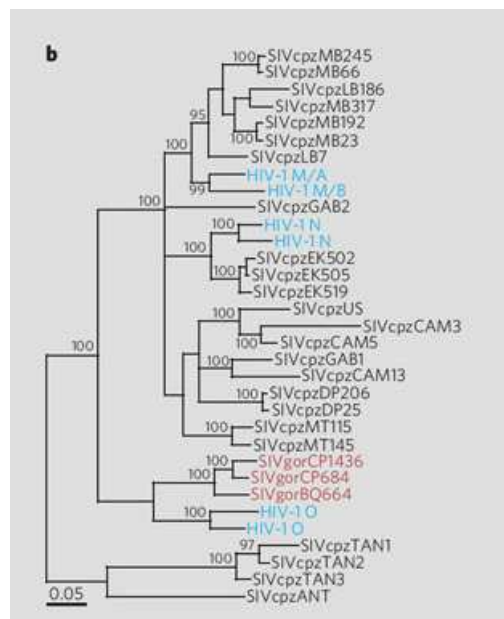
Why 1900s?

Simply because only around that time, major cities, including Kinshasa emerged.

Kinshasa 1896



Kinshasa 1955



Bayesian
analysis



HIV-1 O is a sister
clade of SIV from
Gorilla!

Transmission

- Africa → USA
→ MSM

- ?Haiti



Transmission

- Gay steward
- Several hundred partners:

- New York
- San Francisco



AH 1979

- Temperature
- Lymphadenopathy
- Weight loss
- VDRL +
- Penicillin

AH – no better in 1980

- Weight loss
- Acquired ichthyosis
- Pigmented
- Laparotomy – Whipples



Initial report

N Engl J Med. 1981 Dec 10;305(24):1425-31.

Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency.

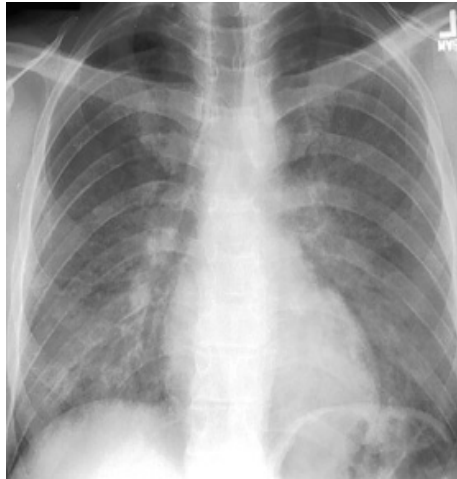
Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A.

<http://www.ncbi.nlm.nih.gov/pubmed/6272109>

AH 1981

- All teeth fell out
- Died in 1984
- Multiple Cerebral Lymphoma

Chest X ray: PCP with bilateral, diffuse granular opacities



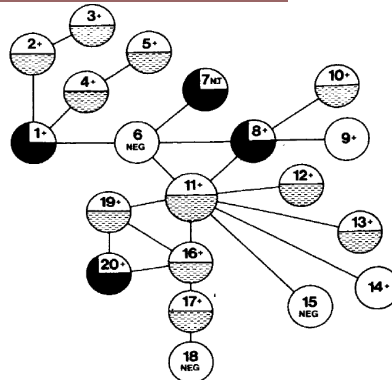
Sexual network

Lancet, 1984 Sep 1;2(8401):480-3.

Clinical findings and serological evidence of HTLV-III infection in homosexual contacts of patients with AIDS and persistent generalised lymphadenopathy in London.

Gazzard BG, Shanson DC, Farthing C, Lawrence AG, Tedder RS, Cheingsong-Popov R, Dalgleish A, Weiss RA.

<http://www.ncbi.nlm.nih.gov/pubmed/6147547>



Microsporidial diarrhoea



Lessons learnt

Sexual history not always reliable!

Careful study of 1 patient can produce
lots of papers



HIV origins

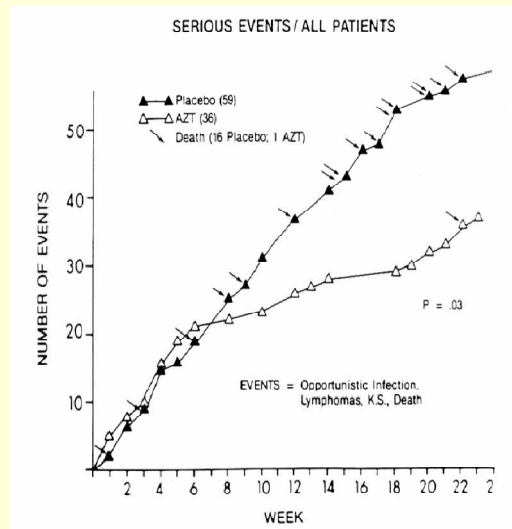
1. An infection - blood
2. T4 cells ↓ - retrovirus



Lessons learnt

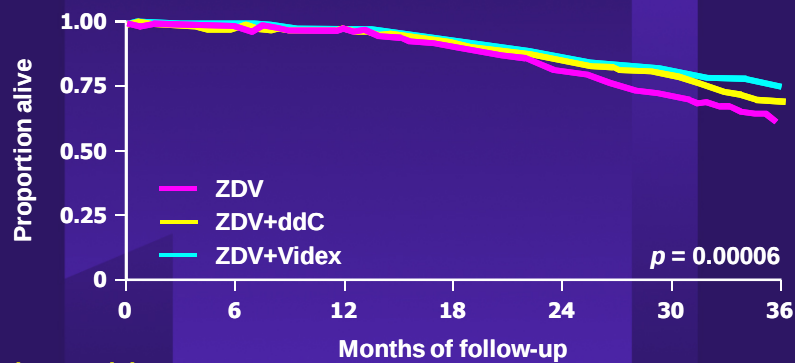
Pressures to be first are overwhelming
Science and politics provide complex motivations
Humbleness never goes amiss

Fischl new england j med 1987



The Delta Trial

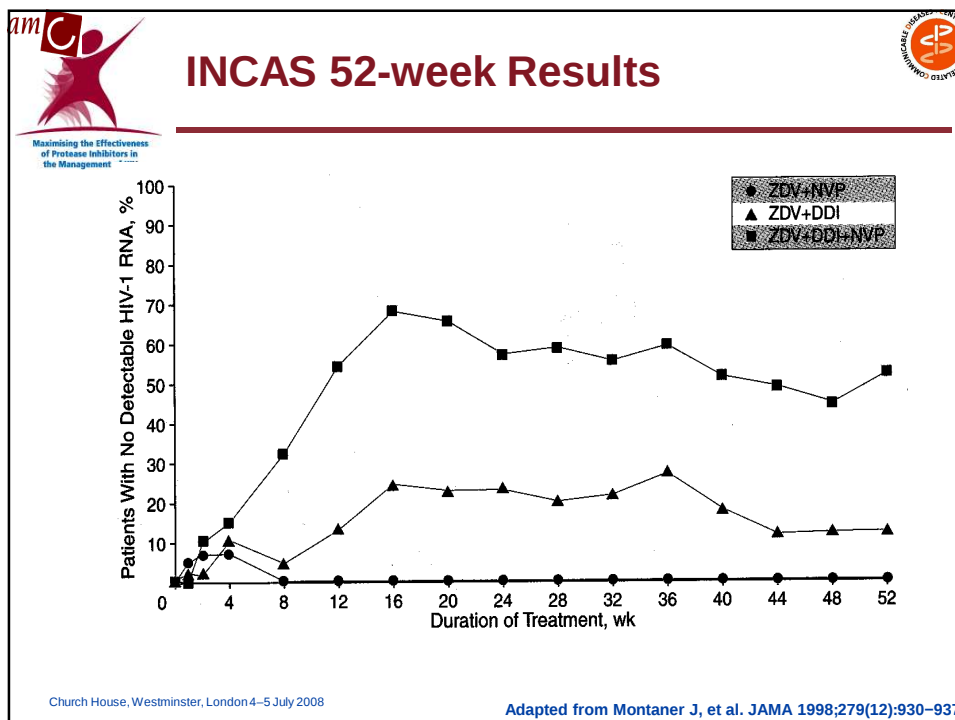
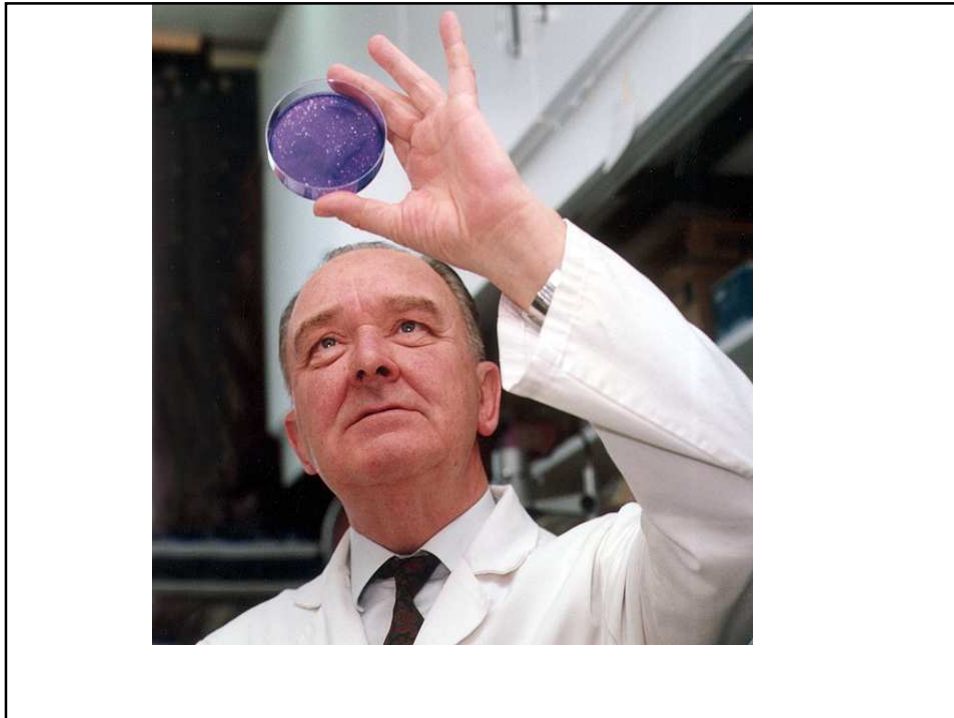
All causes mortality: All patients



Numbers at risk

ZDV	1055	1033	944	906	725	513	225
ZDV+ddC	1072	1052	1019	937	776	554	242
ZDV+Videx	1080	1055	1023	938	774	585	246

Lancet 1996; 348: 283-291.



Lessons learnt

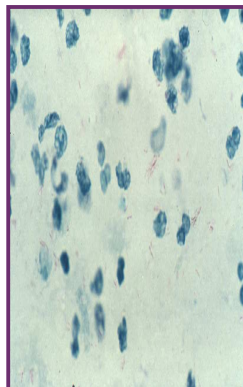
RCT's are important

long

?big

Church House, Westminster, London 4-5 July 2008

George Orwell



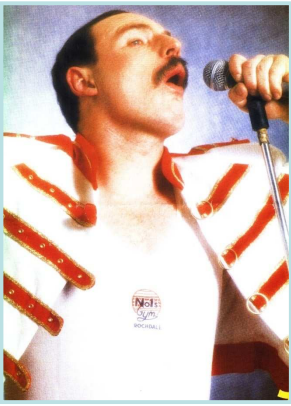
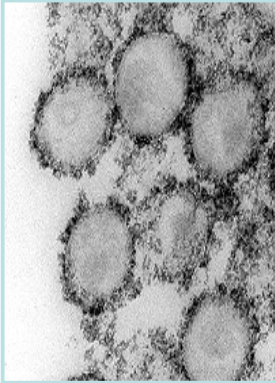
Church House, Westminster, London 4-5 July 2008



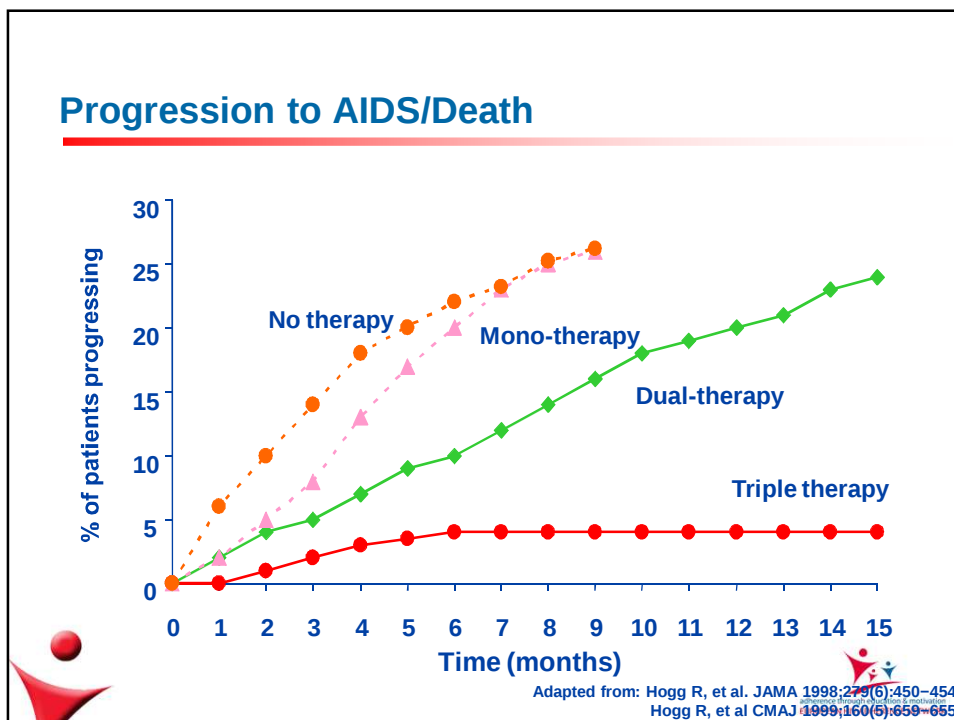
Maximising the Effectiveness
of Protease Inhibitors in
the Management of HIV

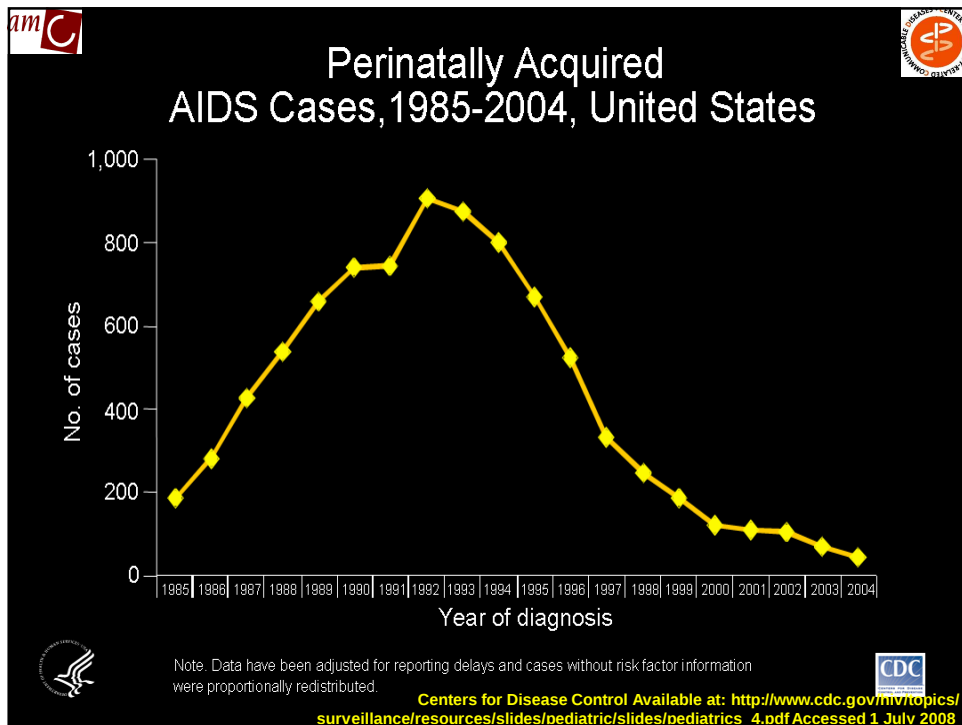
Freddie Mercury




Church House, Westminster, London 4-5 July 2008





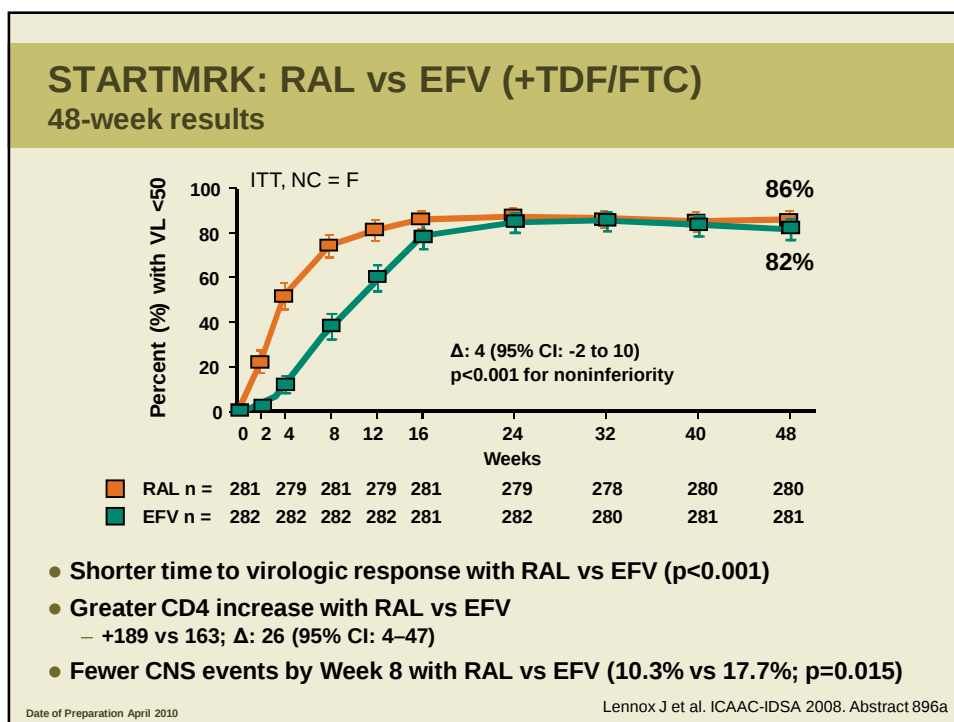
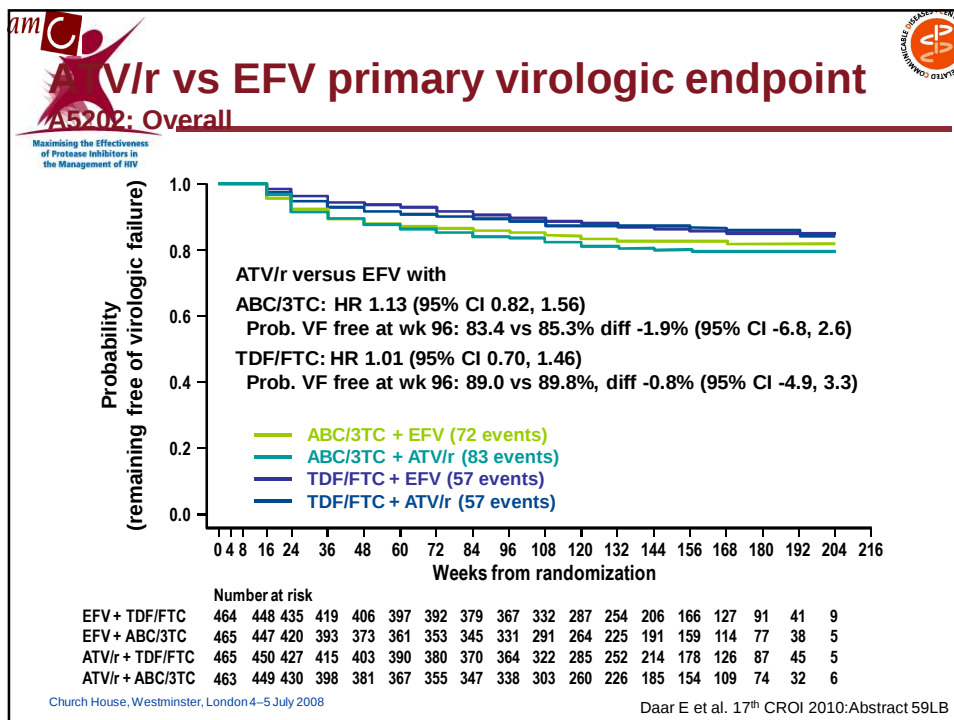
Now a 'generic' market

- Most combinations are of equal potency

Decisions for prescribing based upon:

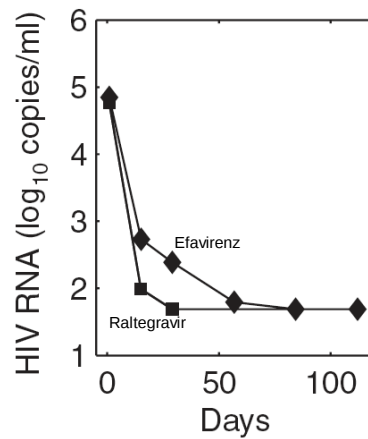
- convenience
- toxicity
- price

Church House, Westminster, London 4-5 July 2008

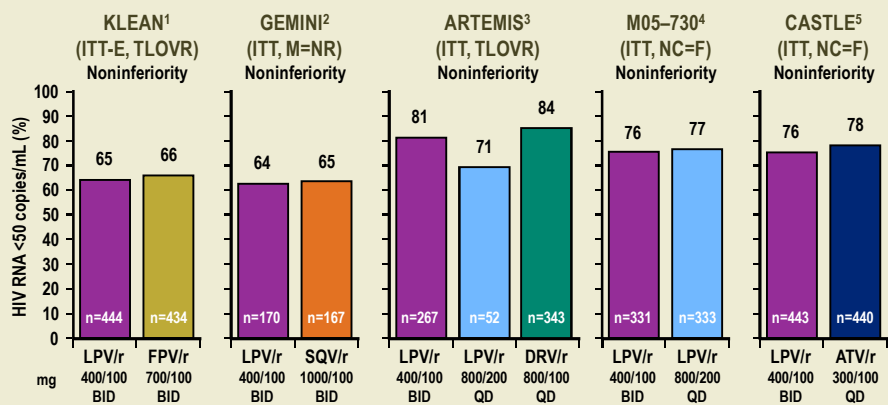


Antiretroviral therapy with the integrase inhibitor Raltegravir alters the kinetics of HIV, significantly reducing the second phase.

J. Murray et al., AIDS 2007, 21: 2315-2321



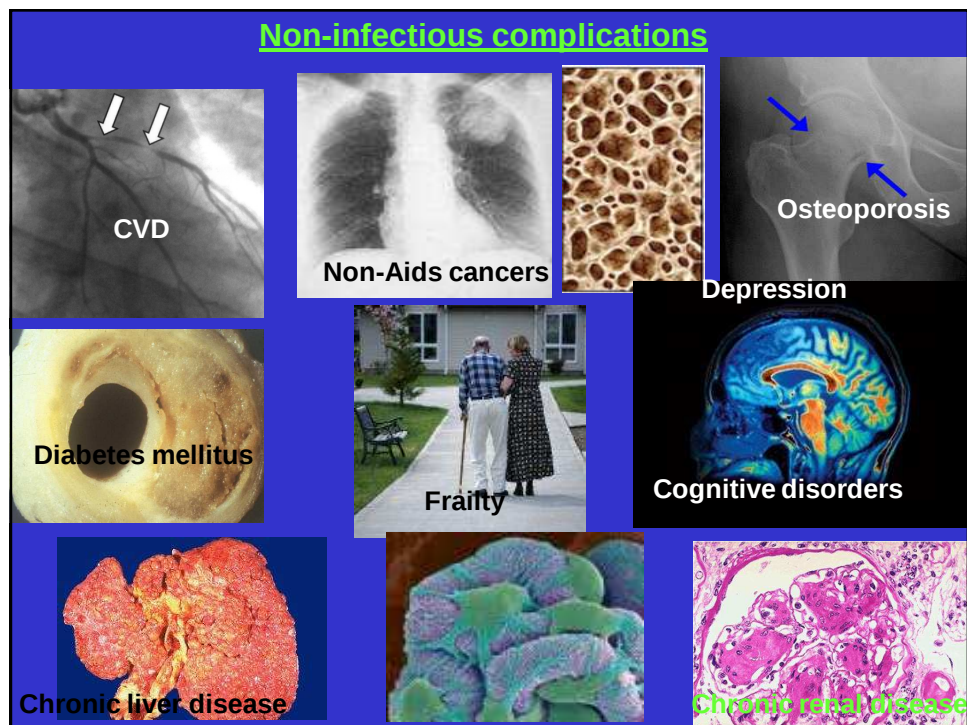
Boosted PIs in ARV naïve patients Virological suppression at 48 weeks



Data in figures are from different studies and cannot be compared directly.
ITT-E, intent-to-treat exposed

Adapted from: 1. Eron J et al. Lancet 2006;368:476-4822; 2. Walmsley S et al. EACS 2007; 3. De Jesus E et al. ICAAC 2007. Abstract LBA H-718b; 4. Gathe J et al. CROI 2008. Abstract 775; 5. Molina J-M et al. Lancet 2008;372:646-655

Date of Preparation April 2010

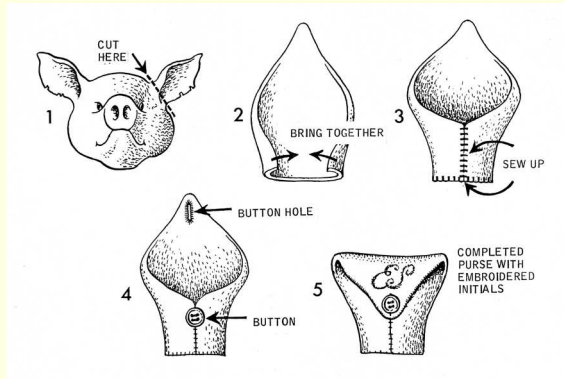


Now – major issues

- 1) Are there major diseases which are not corrected by ART?

Lesson: don't jump on every bandwagon!

Cohort Studies

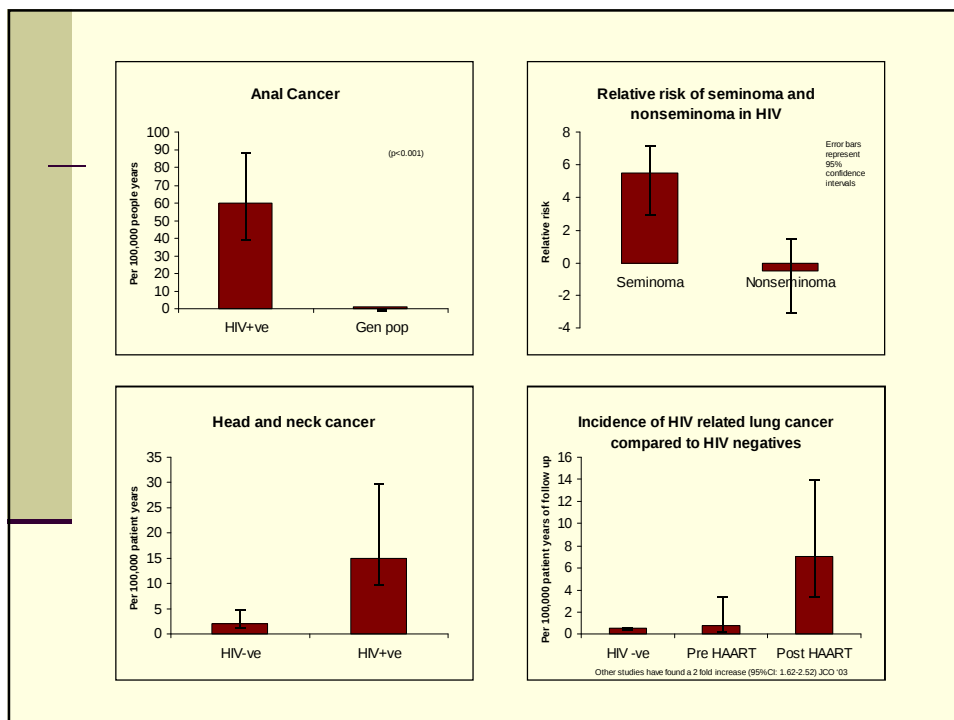


How to make a silk purse out of a sow's ear

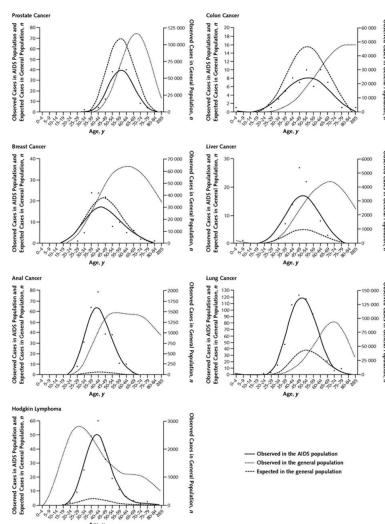
Many hidden biases

Cohort studies

1. Channelling biases
2. Missing events
3. Lead / lag time



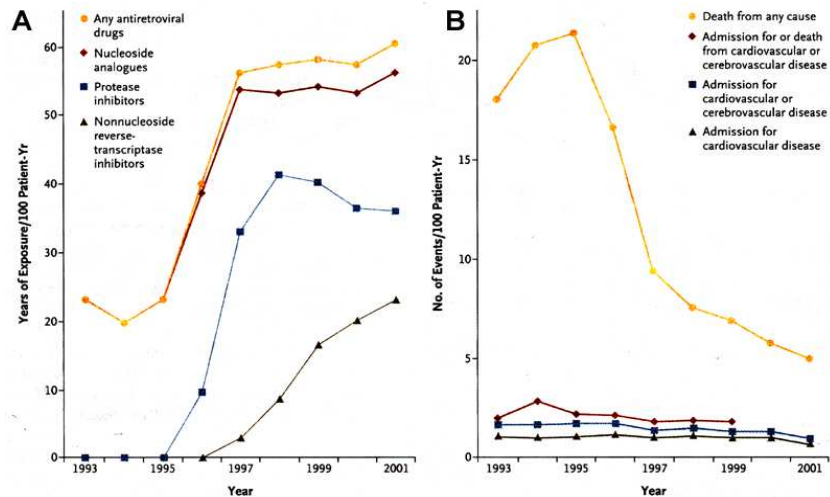
Age at cancer diagnosis among persons with AIDS and the general population in the United States, 1996–2007. Points represent cases of cancer observed among persons with AIDS.



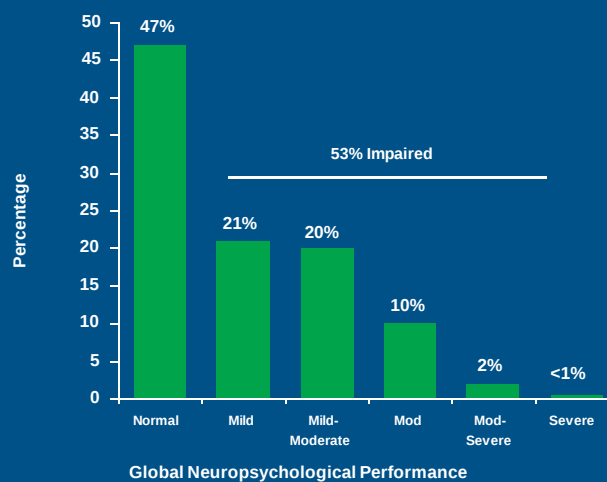
Shiels M S et al. Ann Intern Med 2010;153:452-460

Annals of Internal Medicine

Changing Rates of Use of Antiretroviral Drugs (Panel A) and Vascular Events and Death (Panel B)



CHARTER study: high prevalence of neurocognitive impairment



CHARTER Study data: 2003–2007

Heaton et al, CROI 2009

Charter Study

- 1) Not all patients undetectable
- 2) Nadir <50: structural brain damage

What about:

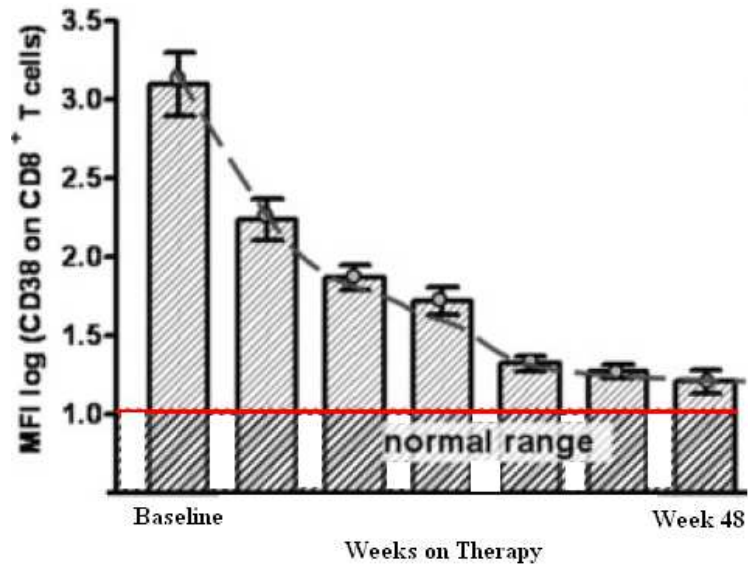
- heroin?
- Hep C?
- crystal meth?
- etc

Pathogenesis

Continuing activation – all the rage

Is it true?

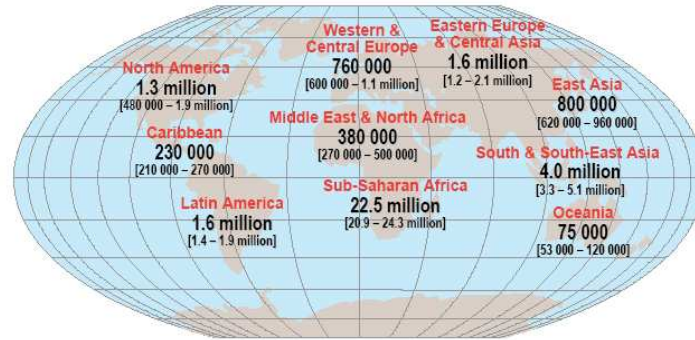
Alteration in immune activation after ART



Prevention

- 1) Vaccines
- 2) Behaviour
- 3) DRUGS**

Adults and children estimated to be living with HIV, 2007

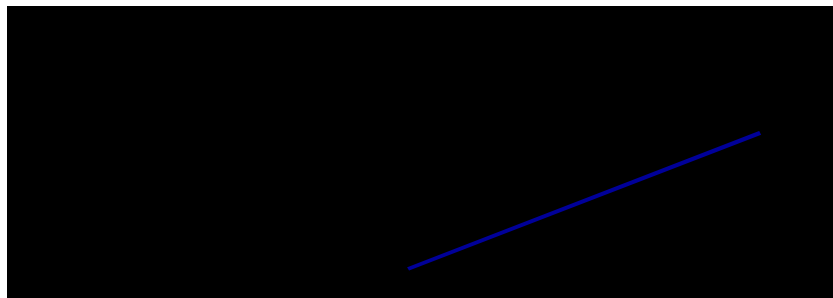


Total: 33.2 (30.6 – 36.1) million

December 2007 e

4

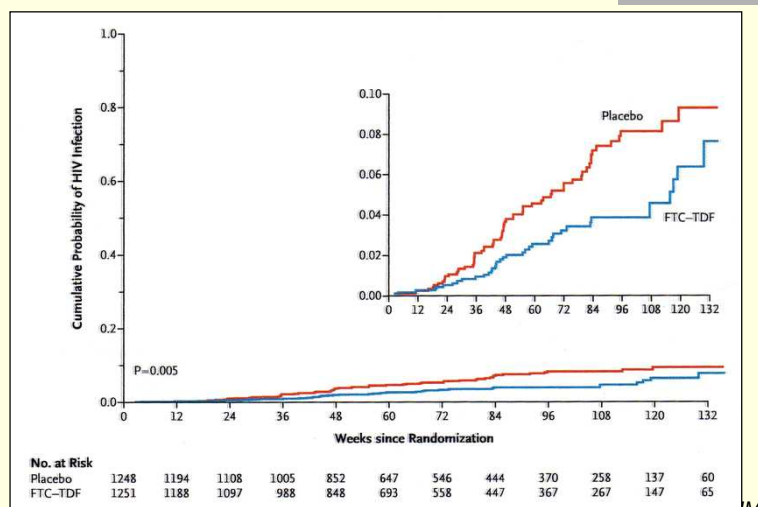
Number of public-sector ARV therapy sites and number of people receiving ARV therapy in the public sector in Botswana, 2002–2004



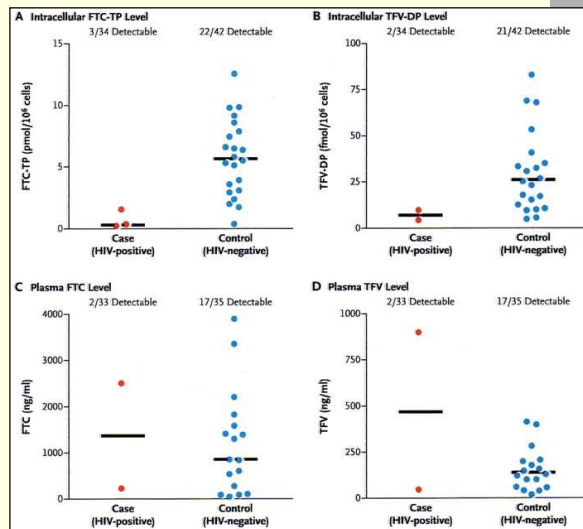
Prevention

- 1) Swiss HIV Commission statement
- 2) Multiple studies confirming
- 3) Find and treat policy
- 4) Cost to stop epidemic: £100 billion
(cost to rescue the banks)

Prep Results

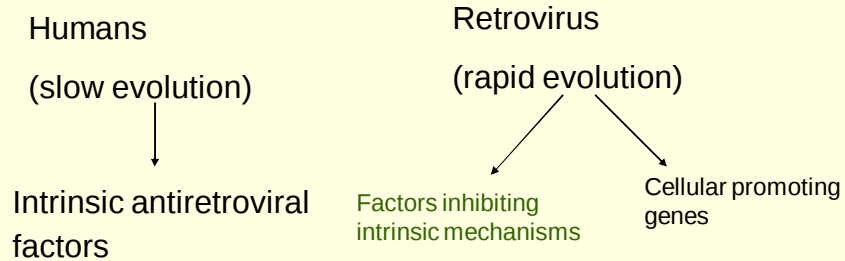


Drug levels and Prep results

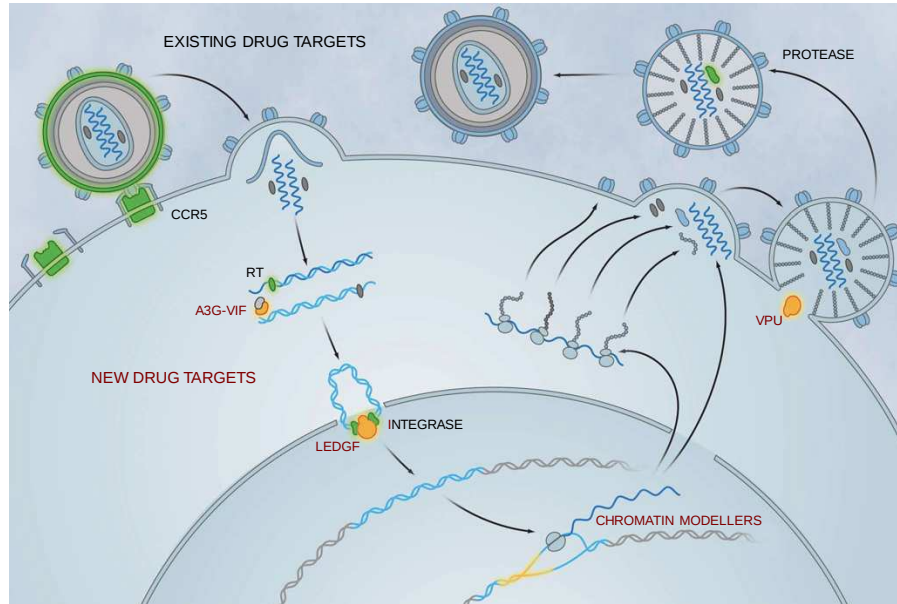


NEJM

The Arms Race



New therapeutic targets in HIV-1 replication



Summary

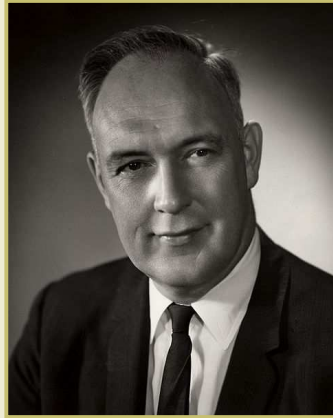
Life is wonderful

Doctors can still do what they were trained to do

Do not give too many hostages to fortune

William Stewart, MD

Surgeon General, United States 1965–69



*"The time has come to close the book on infectious diseases.
We have basically wiped out infection in the United States"*

Date of Preparation April 2010

