

HIV/AIDS at 30: Back to the Future
BHIVA / Wellcome Trust Multidisciplinary Event to mark World AIDS Day 2011

British HIV Association **BHIVA** Supported by **wellcome**trust

**HIV/AIDS at 30:
Back to the Future**
*Multidisciplinary Event
to mark World AIDS Day*

1500–2045
Thursday 1 December 2011
Wellcome Collection Conference Centre
London

In support of World AIDS Day

In partnership with CHIRP, HIV, DHIVA

British HIV Association (BHIVA) 2011


HIV/AIDS at 30: Back to the Future
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Professor Brian Gazzard
Chelsea and Westminster Hospital
London

Thursday 1 December 2011, Wellcome Collection Conference Centre, London




The logo for aighd, featuring a stylized network of red dots connected by lines, with the text "aighd" below it.

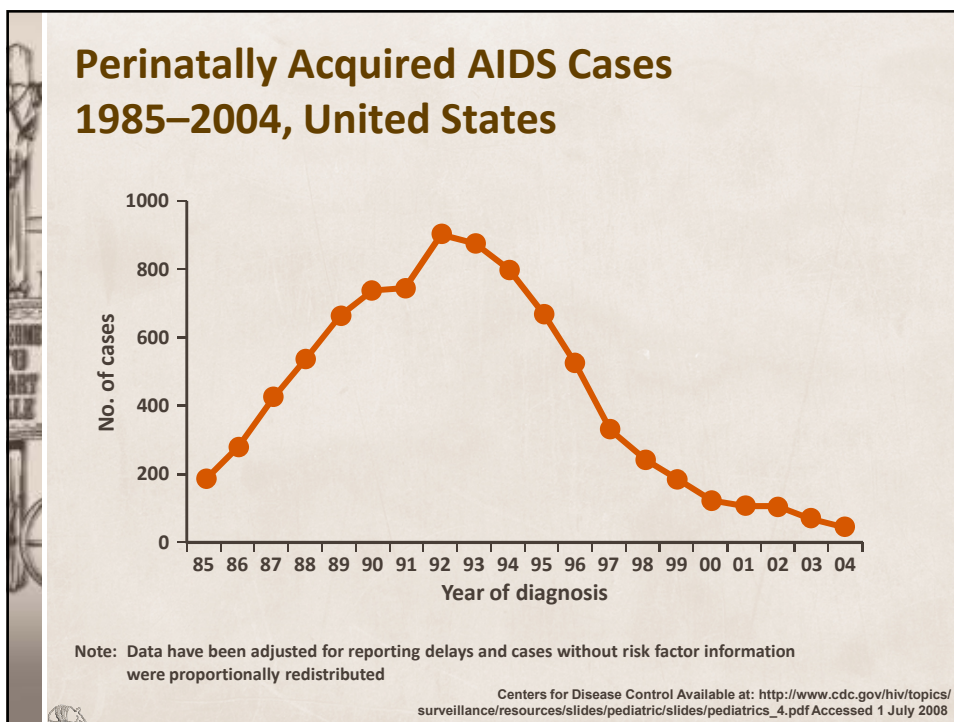
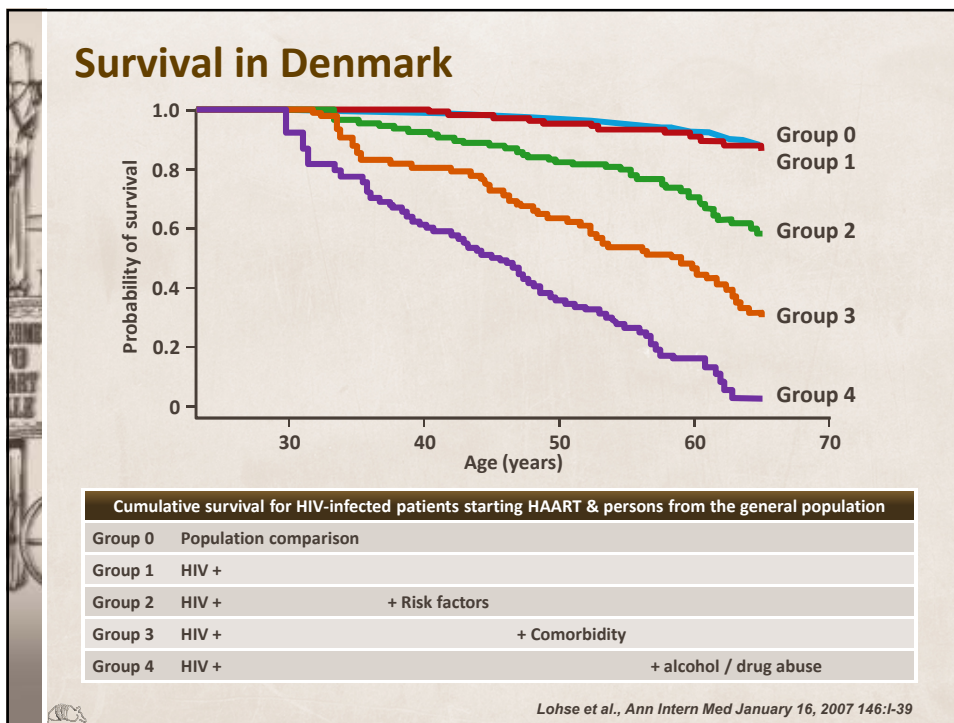
Before ...

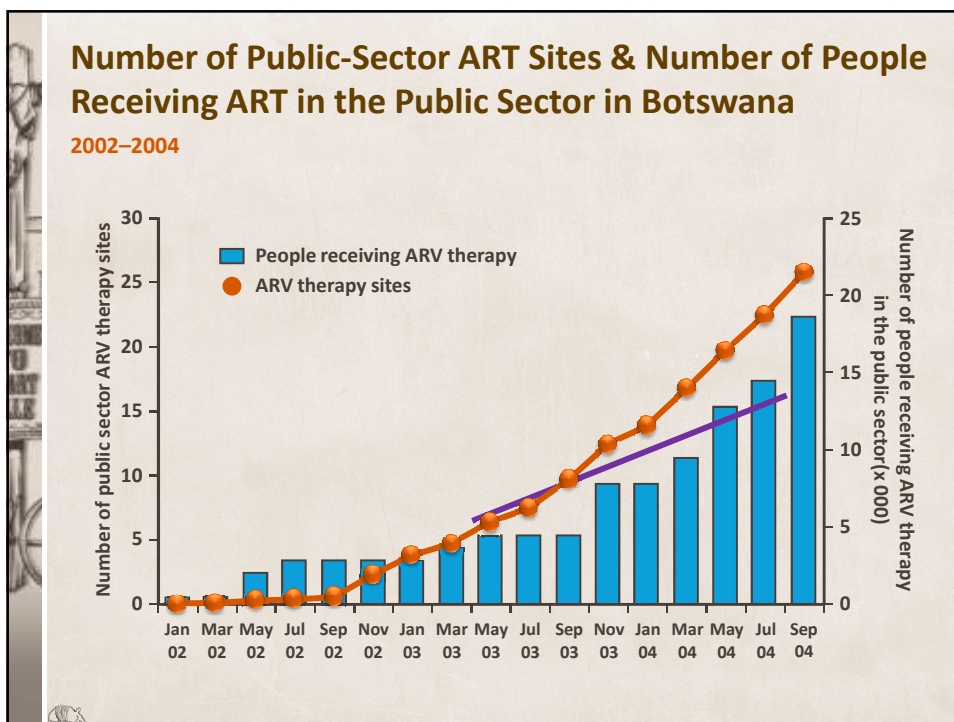
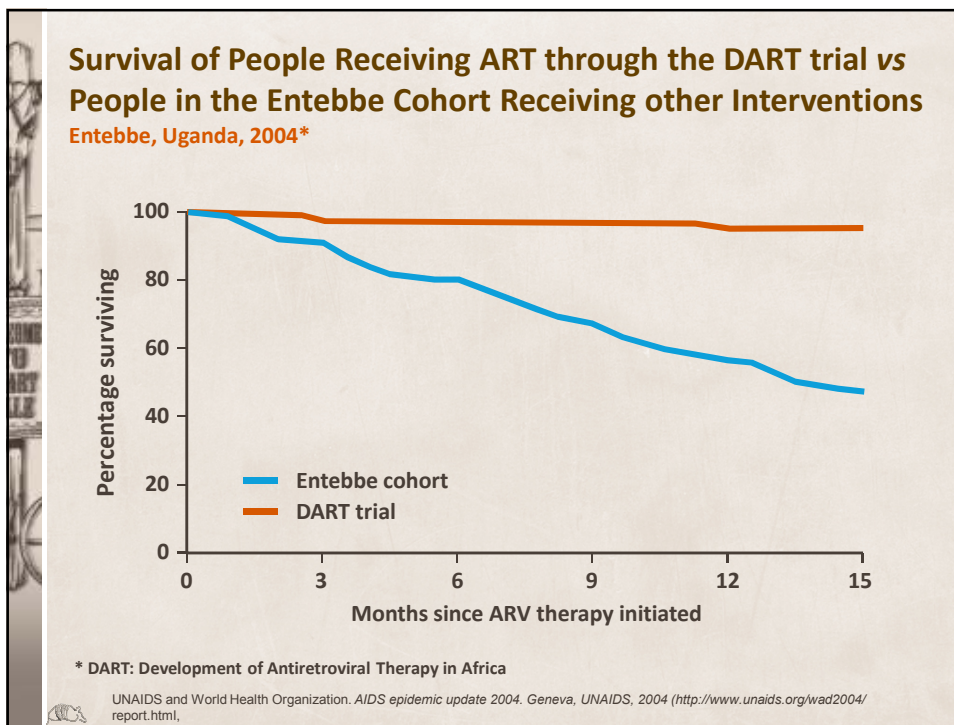


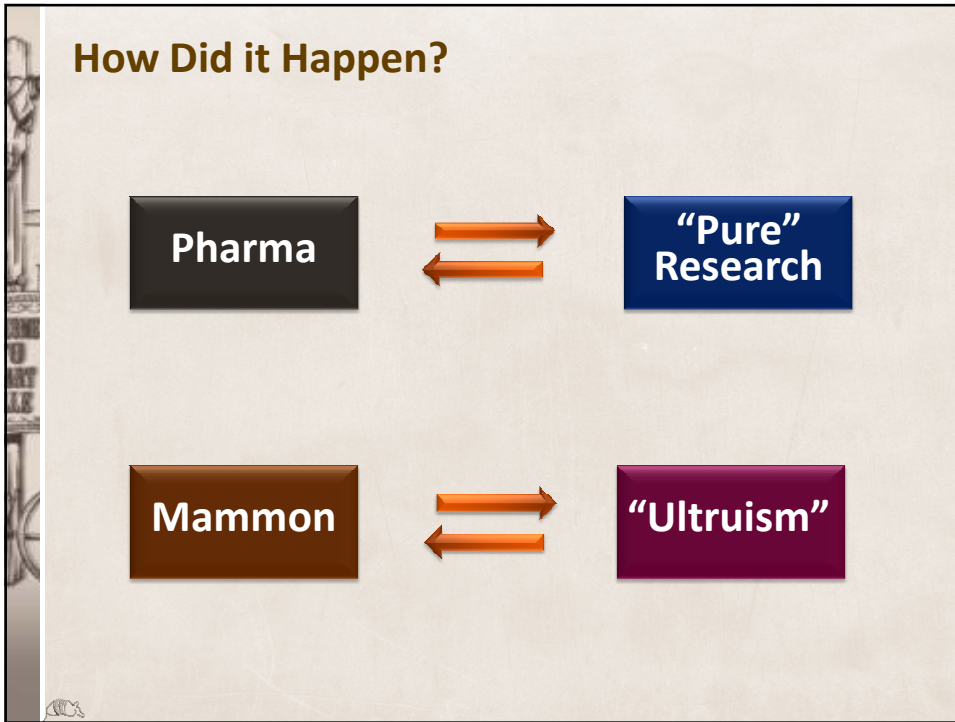
After ...

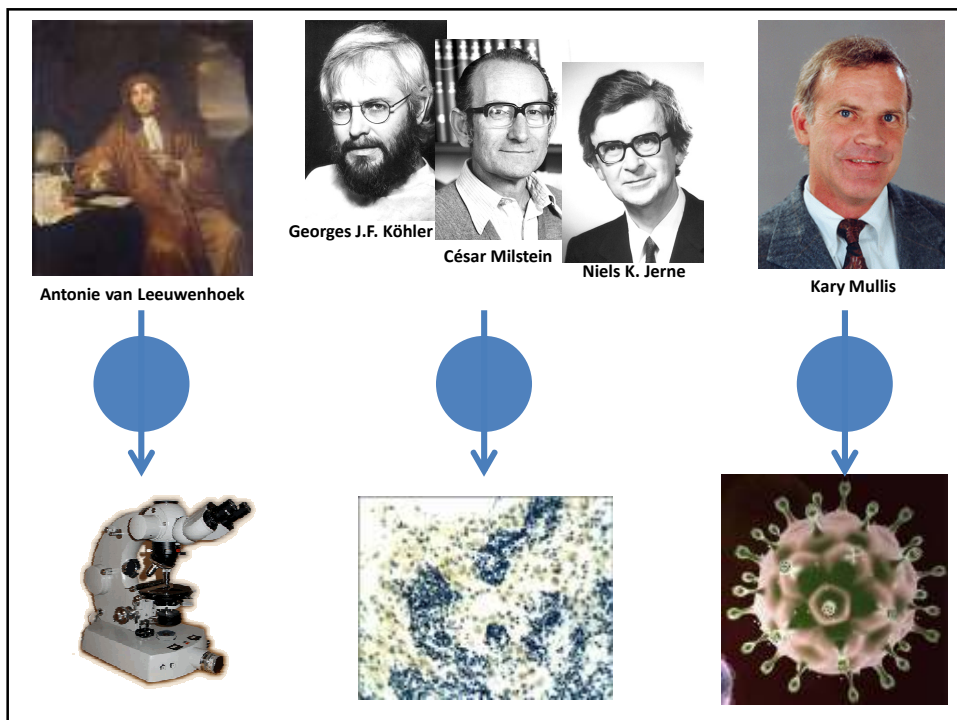
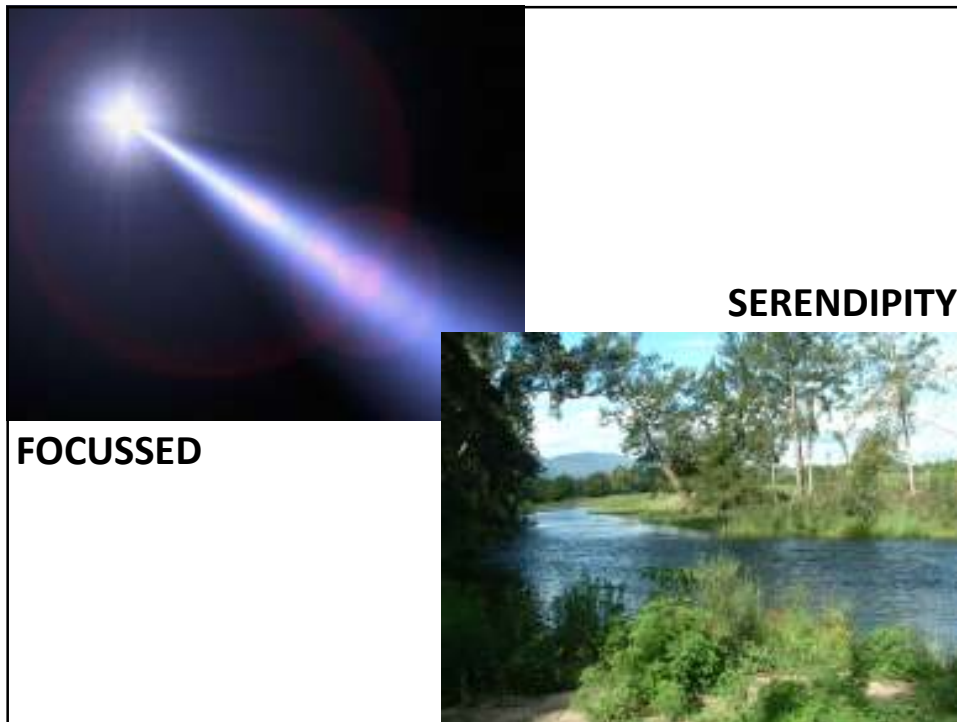


4









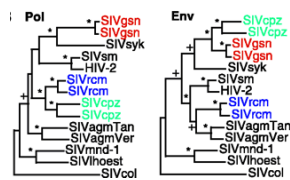
1 million years ago...

- 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 (*Cercocebus torquatus*)

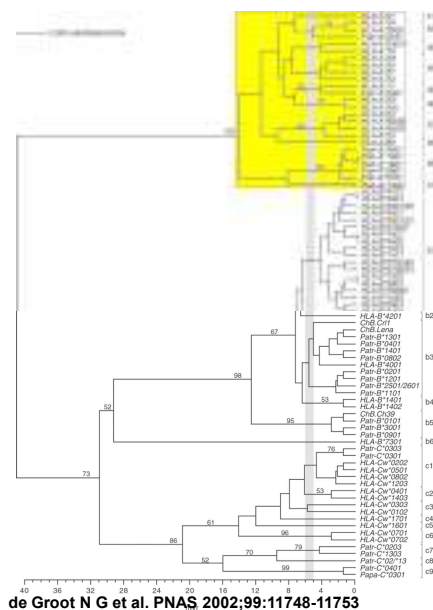
Gsn=greater spot-nosed monkeys (*Cercopithecus nictitans*)



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.



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

**Fang Gao¹, Elizabeth Bailes¹, David L. Robertson¹,
Yalu Chen¹, Cynthia M. Rodenburg¹, Scott F. Michael²,
Larry B. Cummins¹, Larry O. Arthur¹, Martine Peeters³,
George M. Shaw⁴, Paul M. Sharp⁵ & Beatrice H. Hahn⁶**

¹ *Departments of Medicine and Microbiology, University of Alabama at Birmingham, 701 S. 19th Street, LEBB 613, Birmingham, Alabama 35294, USA*
² *Institute of Genetics, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK*
³ *Laboratory of Structural and Genetic Information, CNRS, Marseille 13402, France*
⁴ *Southwest Foundation for Biomedical Research, San Antonio, Texas 78245, USA*
⁵ *AIDS Vaccine Program, National Cancer Institute-Frederick Cancer Research and Development Center, SAIC/Frederick, Frederick, Maryland 21702, USA*
⁶ *Laboratoire Retrovirus, ORSTOM, BP 5045, Newquay 29032, France*
⁶ *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*)^{5,6}, the origin of HIV-1 remains uncertain. Viruses related to HIV-1 have been isolated from the common chimpanzee (*Pan troglodytes*)^{7,8}, but only three such SIVcpz infections have been documented^{1,9,10}, one of which involved a virus so divergent¹¹ that it might represent a different primate lentiviral lineage. In a search for the HIV-1 reservoir, we have now sequenced the genome of a new SIVcpz

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

Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BH. *Nature* 1999; 397: 436-441.

A brief history of HIV

1 Million Years ago (Africa) **1899 (Kinshasa)** **1979 (Haiti)** **1981 (PCP)** **2011**

A horizontal timeline with five circular markers. The first four markers are connected by a solid line, and the fifth is connected by a dashed line. Below the markers are labels for key events: '1 Million Years ago (Africa)', '1899 (Kinshasa)', '1979 (Haiti)', '1981 (PCP)', and '2011'. Below the first marker is a citation: 'Gao F, et al. Nature'. Below the fourth marker is a citation: 'N Engl J Med 1981; 305:1425-31'. Below the timeline is a small thumbnail of the 'Origin of HIV-1 in the chimpanzee' paper cover.

Gao F, et al. *Nature* N Engl J Med 1981; 305:1425-31

Origin of HIV-1 in the chimpanzee
Pan troglodytes troglodytes

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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



1981

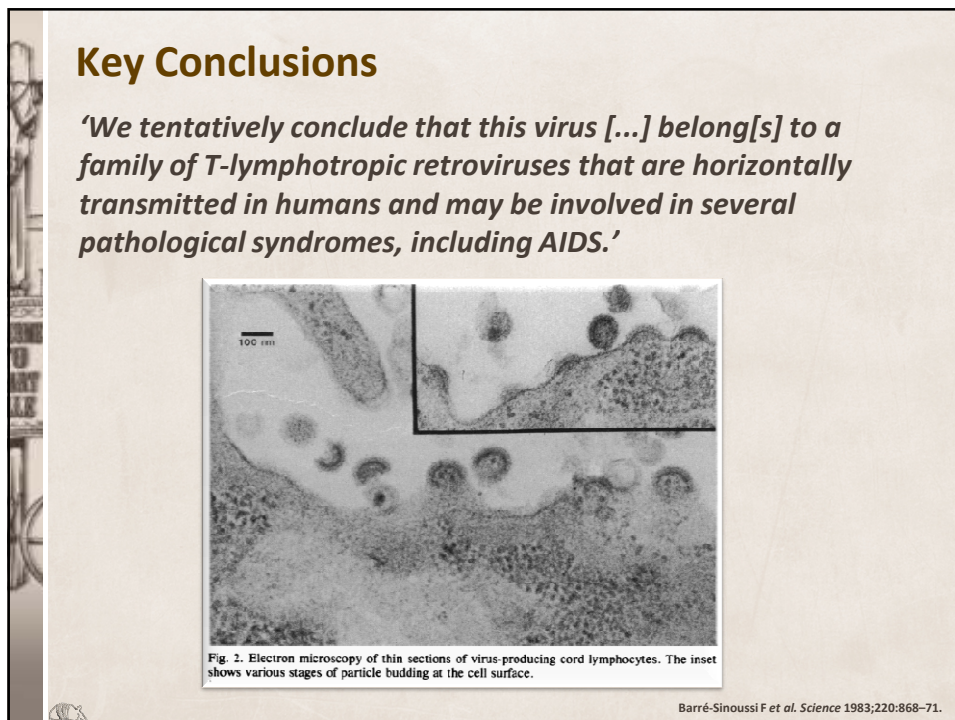
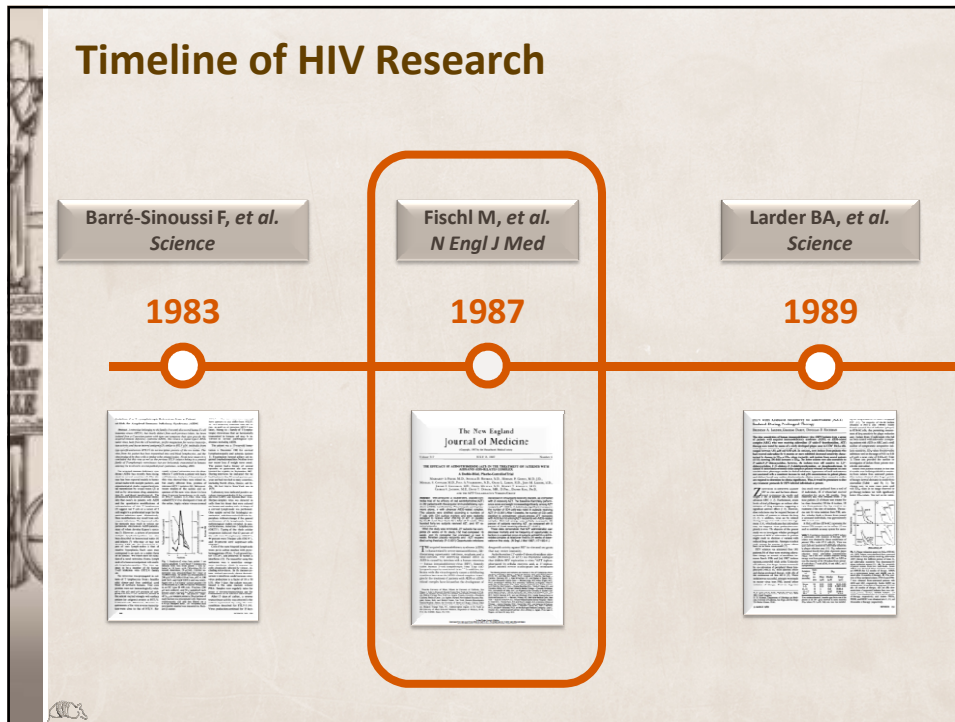
- Gay lifestyle, “Poppers”

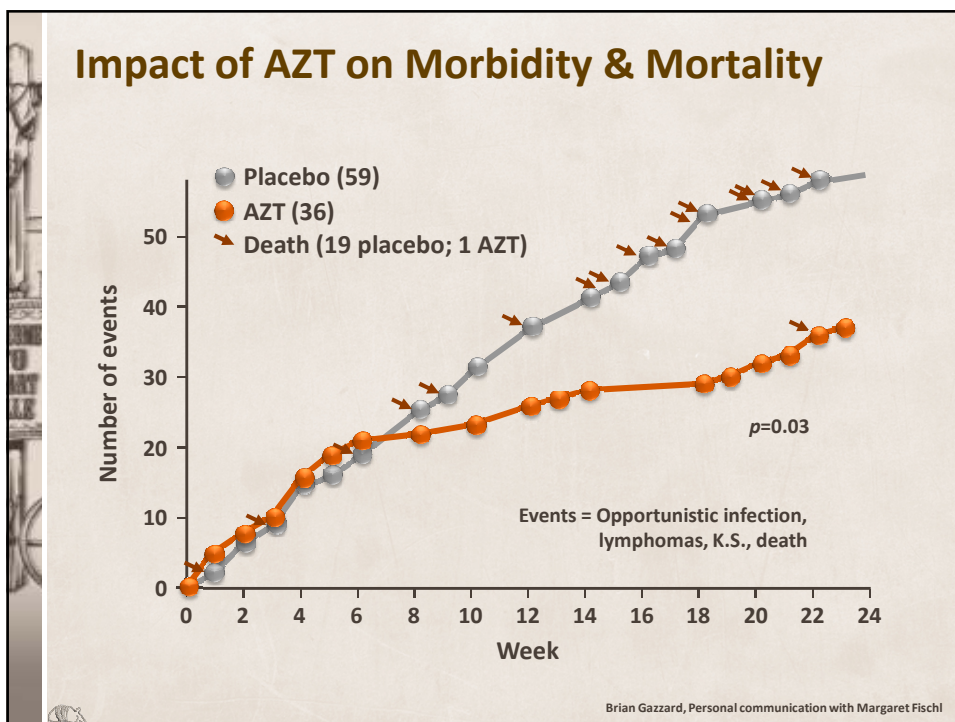
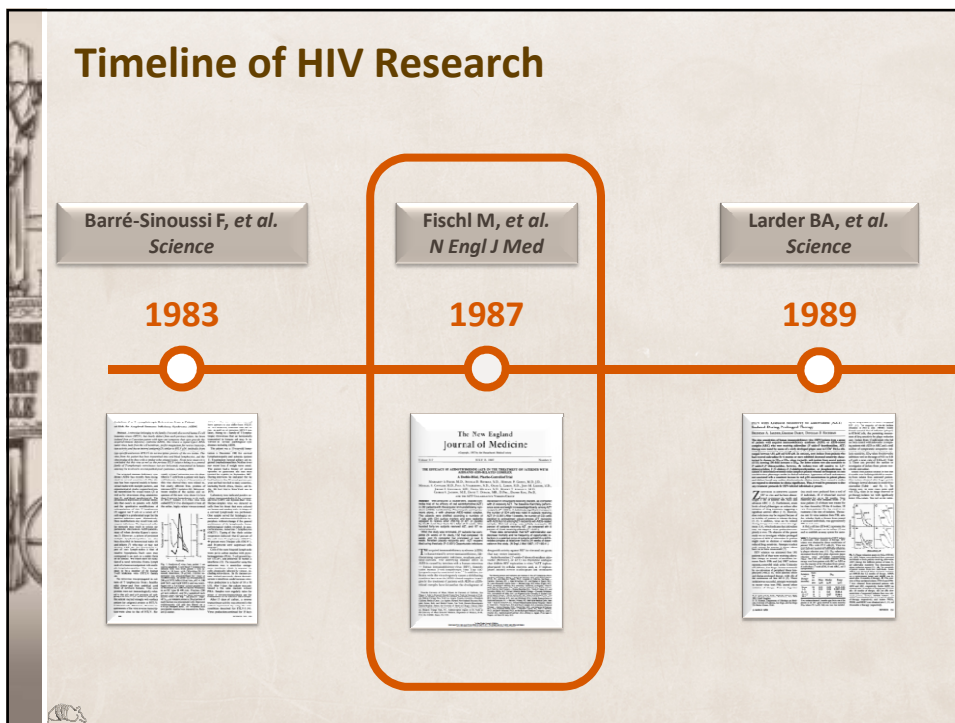
1982

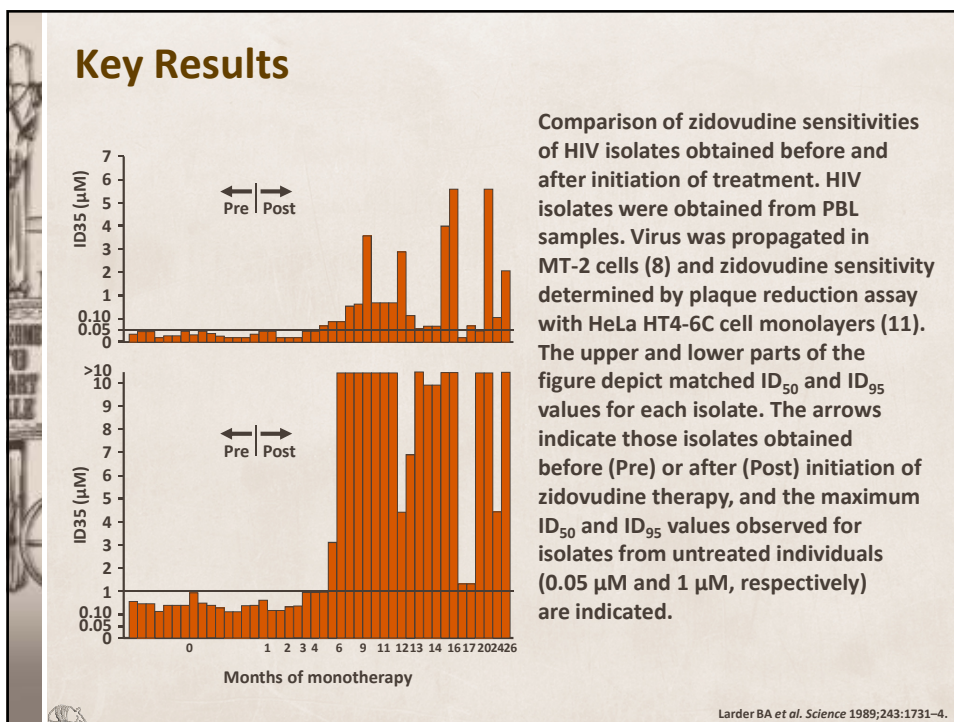
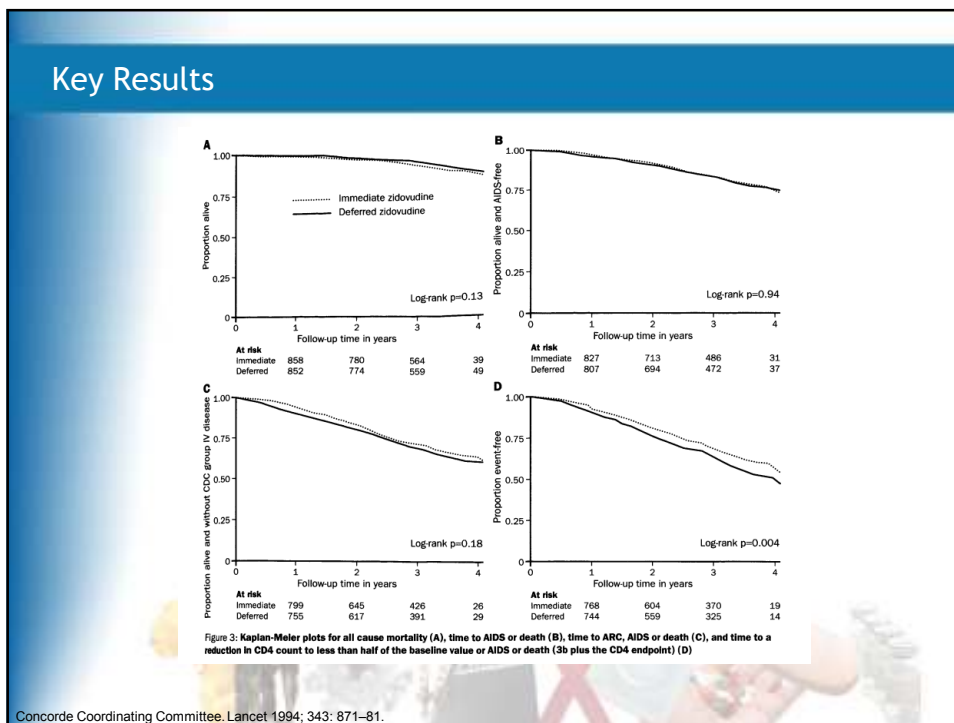
- IVDU
 - Blood
 - Factor VIII
- } Low risks groups

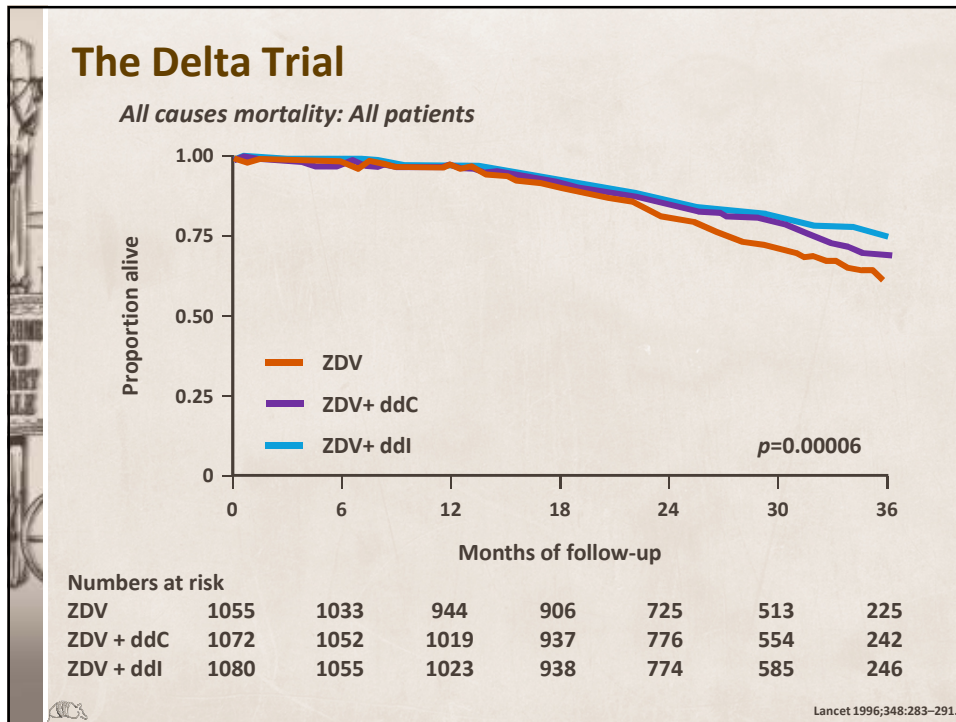
HIV Origins

1. An infection – blood
2. T4 cells  – retrovirus










XI International AIDS Conference, Vancouver 1996


Data were presented that show the improved benefits of triple therapy

Triple care became the standard of care – something which remains the case to this day

Viral Replication

 10^2 Replication/day

 10^{-3} Codons

 10^{-5} Mistakes



The New England Journal of Medicine

A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less

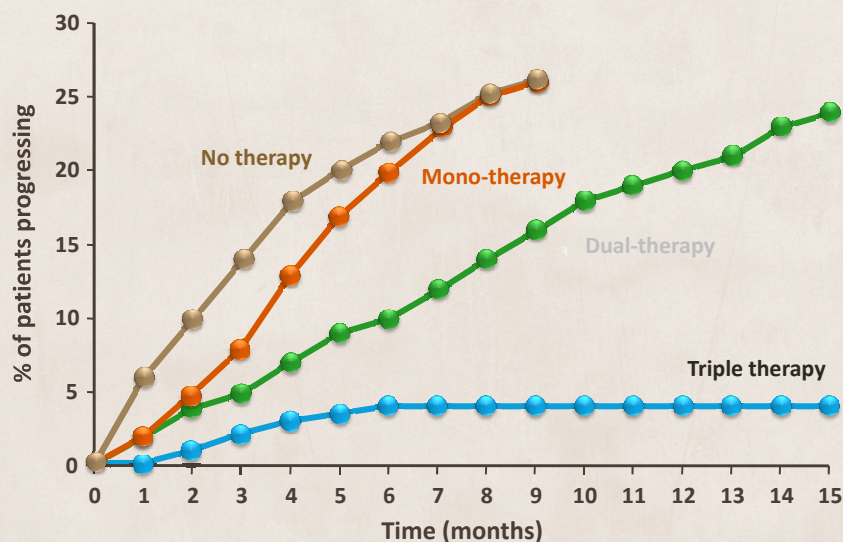
Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, Eron JJ Jr, Feinberg JE, Balfour HH, Deyton LR, Chodakewitz JA, Fischl MA, for the AIDS Clinical Trials Group 320 Study Team. *N Engl J Med* 1997; 337: 725-33.

Key Conclusions

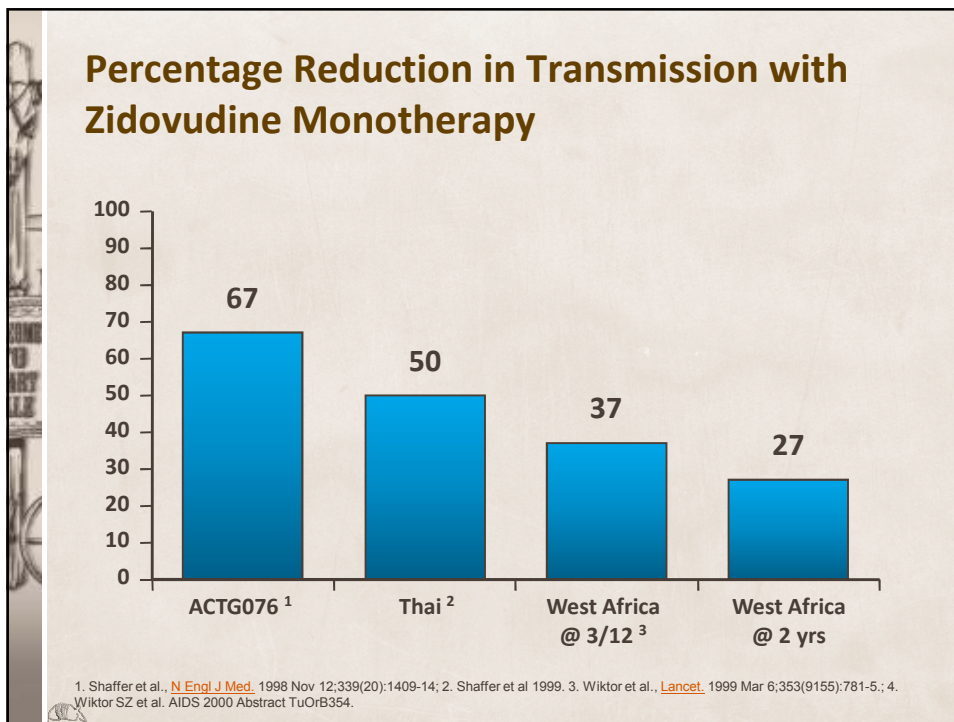
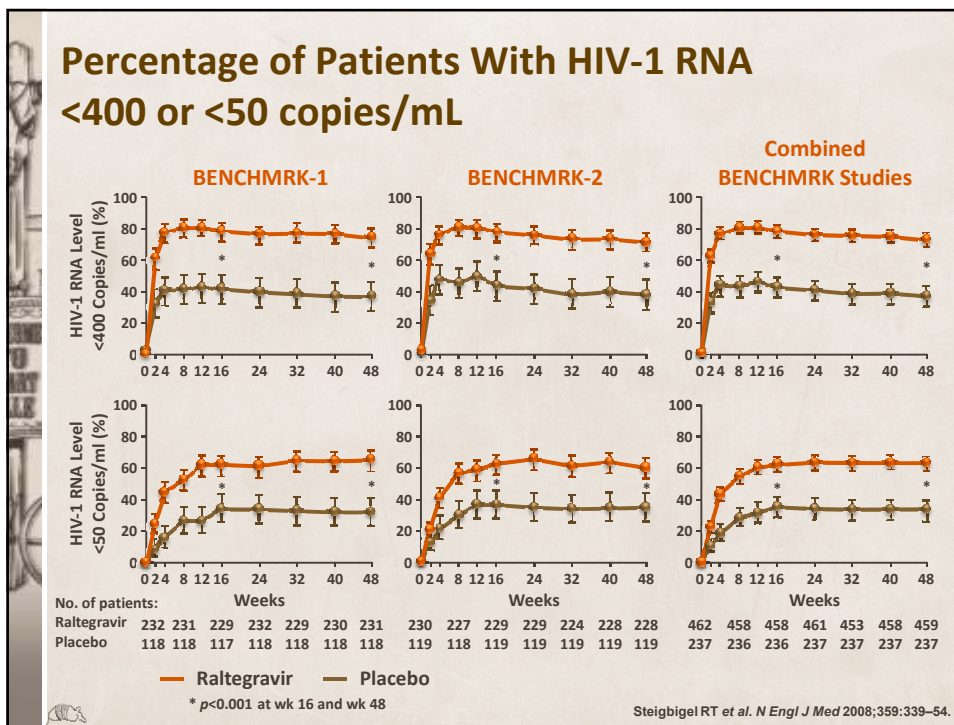
- ✦ 'This study showed the **clinical superiority of the three-drug regimen** containing indinavir over the two-nucleoside combination in patients previously treated with zidovudine who had CD4 cell counts of 200 per cubic millimeter or less.'
- ✦ 'The proportion of patients whose **disease progressed to AIDS or death** was reduced from 11 percent to 6 percent by the **three-drug combination**, a **50 percent reduction ($p=0.001$)**'
- ✦ '**Mortality**, low in both groups, was **reduced** from 3.1 percent to 1.4 percent with the **three-drug regimen ($p=0.04$)**.'
- ✦ 'This study supports the view that employing **well-tolerated regimens of increasing potency** will translate into **greater clinical benefits** for patients with HIV-1 infection.'

Hammer SM et al. *N Engl J Med* 1997;337:725-33.

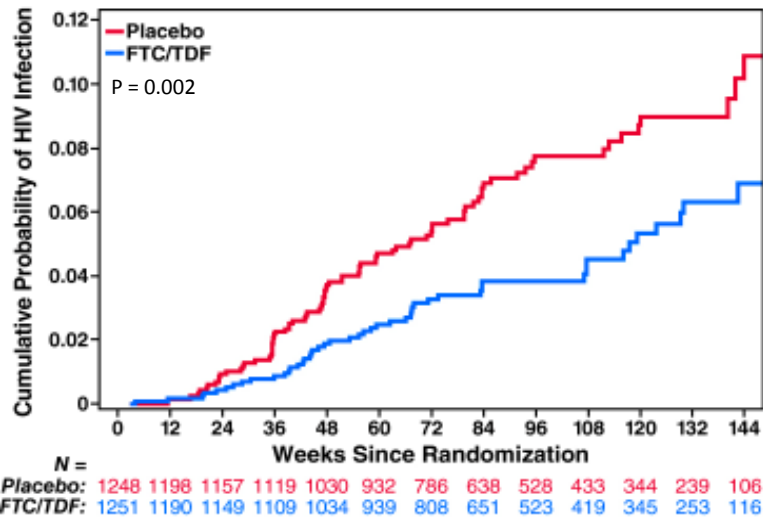
Progression to AIDS/Death



Adapted from: Hogg R et al. *JAMA* 1998;279(6):450-454;
Hogg R et al. *CMAJ* 1999;160(5):659-655.

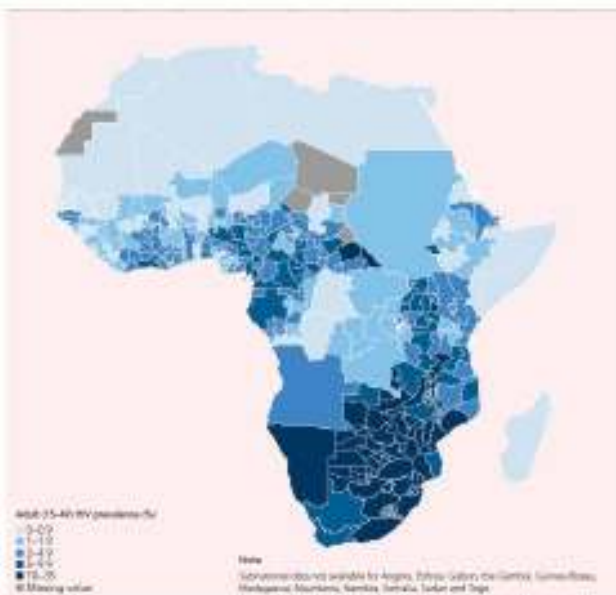


Efficacy (MITT) 44% (15-63%) Through May 1, 2010
 Durable Through 144 Weeks in the Final Analysis



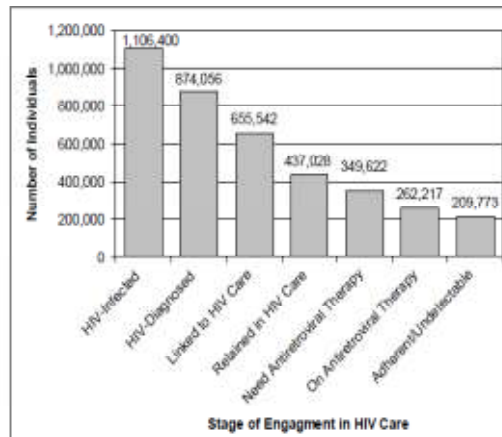
Grant et al, CROI 2011

Five year epidemic: subnational estimates of HIV prevalence in sub-Saharan Africa, 2001-2010

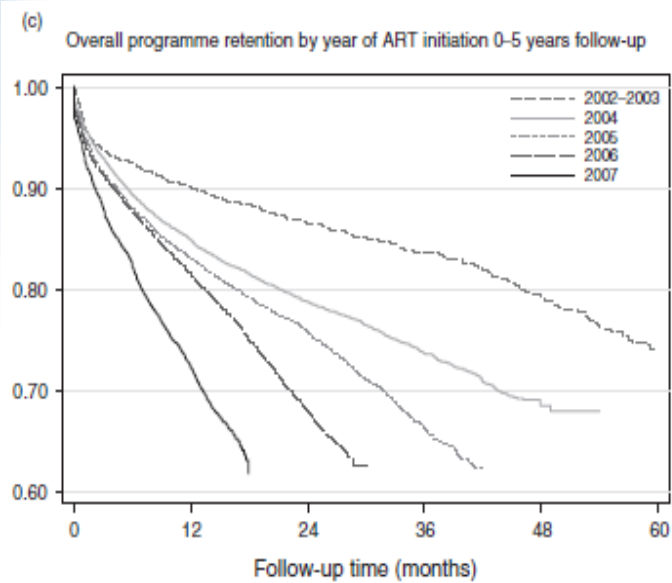


Gardner EM et al.
 relevance to "Test and Treat" strategies for prevention of HIV infection.
 Clin Infect Dis 2011;52:793-800.

Figure 2. The spectrum of engagement in HIV care in the United States spanning from HIV acquisition to being fully engaged in care, receiving antiretroviral therapy and achieving complete viral suppression. We estimate that only 19% of HIV infected individuals in the United States have an undetectable HIV viral load.

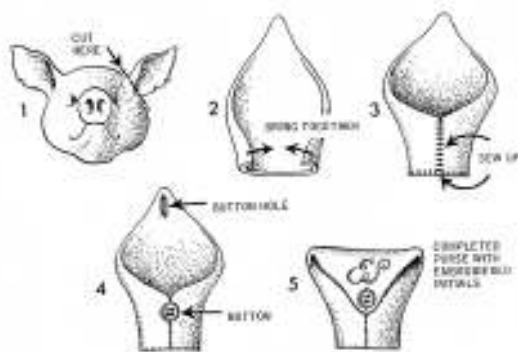


Cornell J et al.
 programme outcomes among adult patients initiating antiretroviral therapy across South Africa. AIDS 2010;24:2263-70.



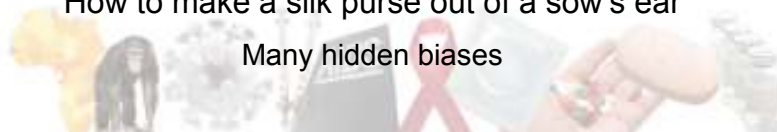
CAUSATION
≠
ASSOCIATION

Cohort Studies



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

Many hidden biases

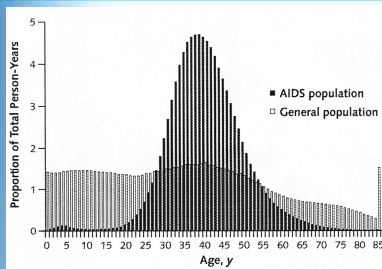


Cohort studies

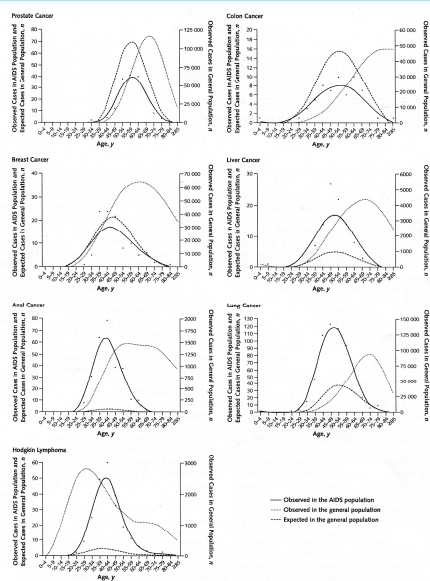
1. Channelling biases
2. Missing events
3. Lead / lag time



Cancer in the AIDS population



Follow-up time at risk for cancer in both the AIDS and general populations, by age, for regions covered by the HIV/AIDS Cancer Match Study (1996 to 2007).



Points represent cases of cancer observed among persons with AIDS.



Problem of controls - inflammation

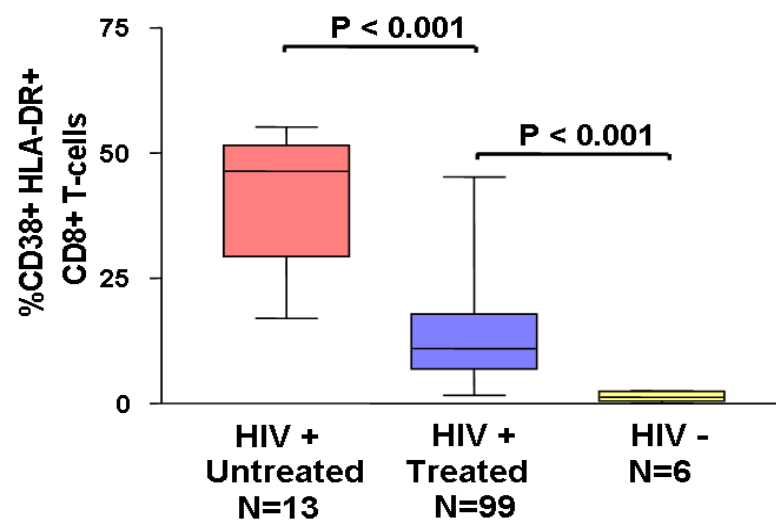
HIV is a marker for **many** infections

(?) much of CV risk is driven by CMV



Immune Activation, HIV Infection and




ART



Hunt PW, et al. *J Infect Dis.* 2003;187:1534-1543.

Other Shibboleths

HIV associated with:

1. Life expectancy 
2. Ageing 
3. Losing memory
4. Inflammation 

Causation

? of correlation

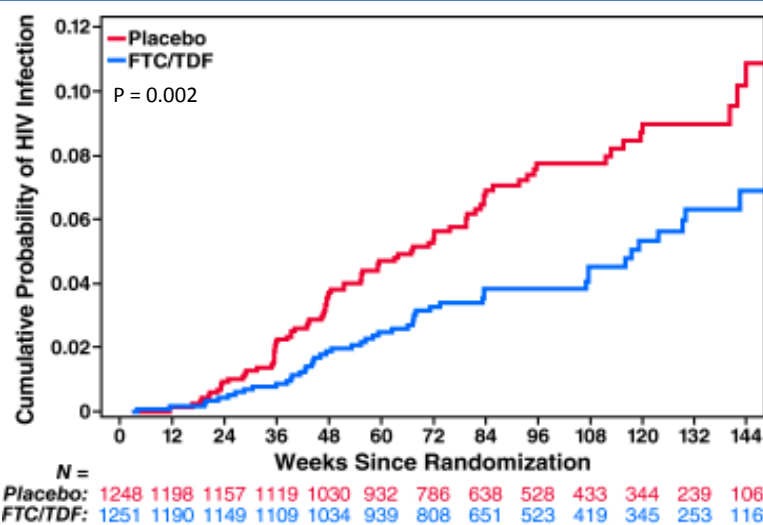
? effects of eradication

Biological Plausibility

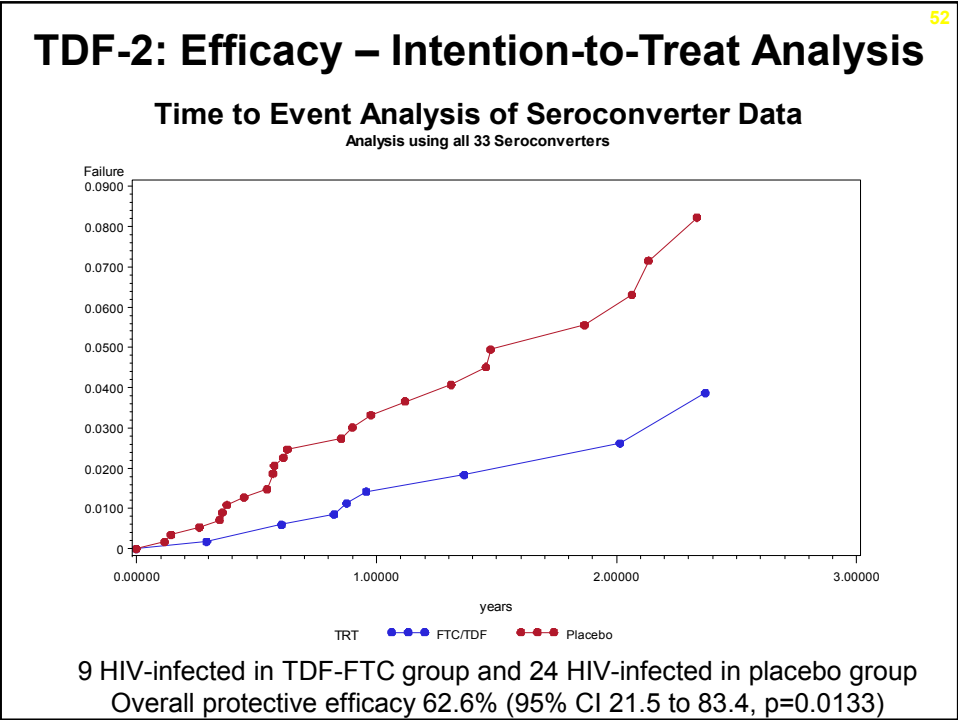
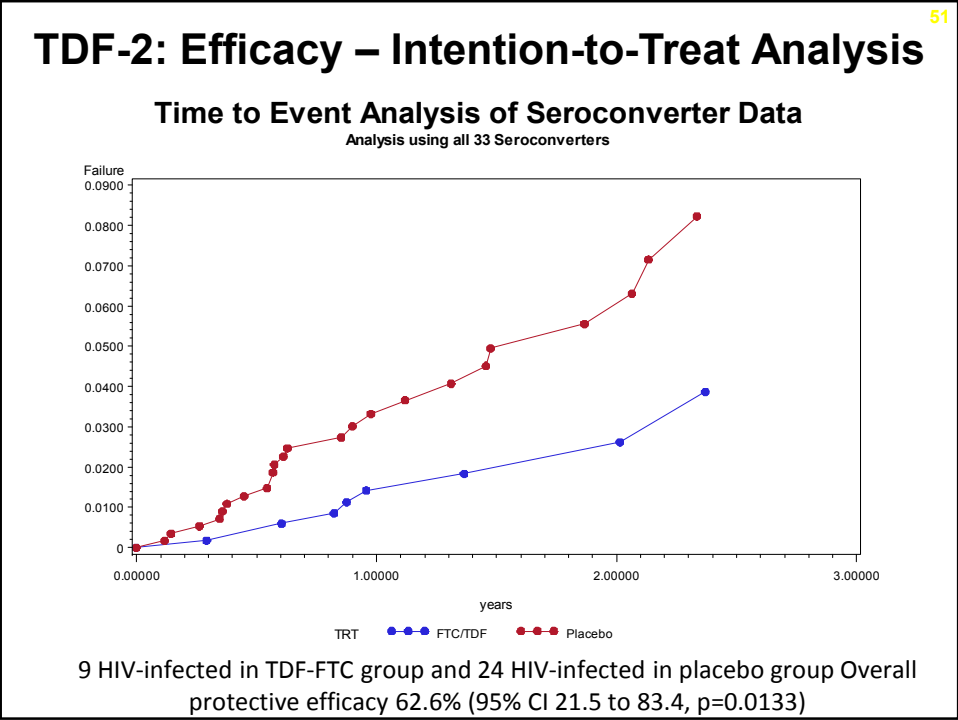
Koch's Postulates

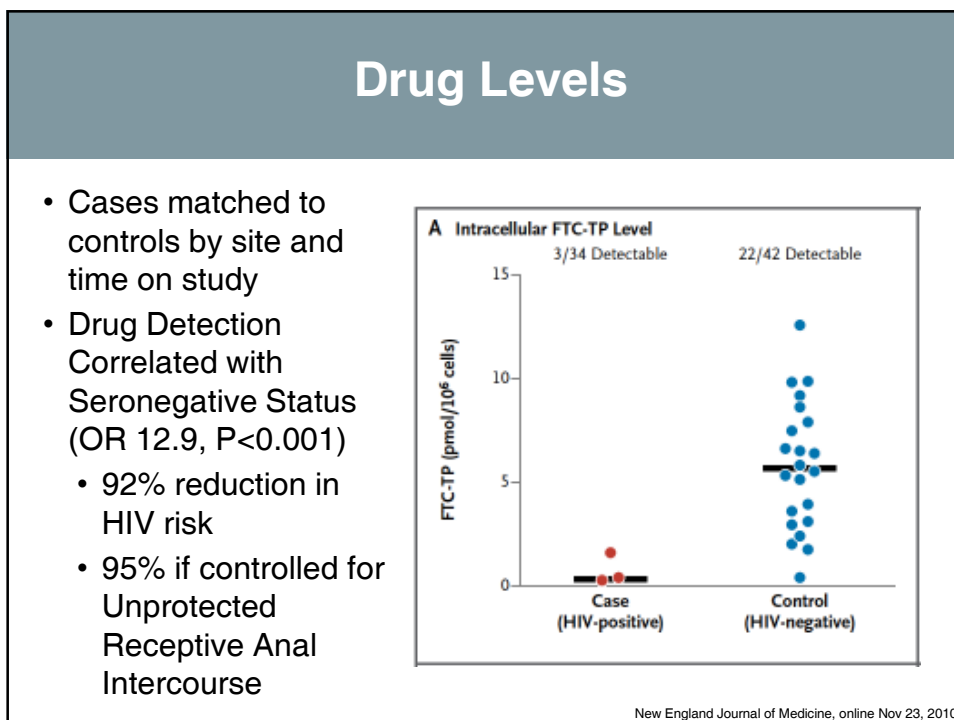
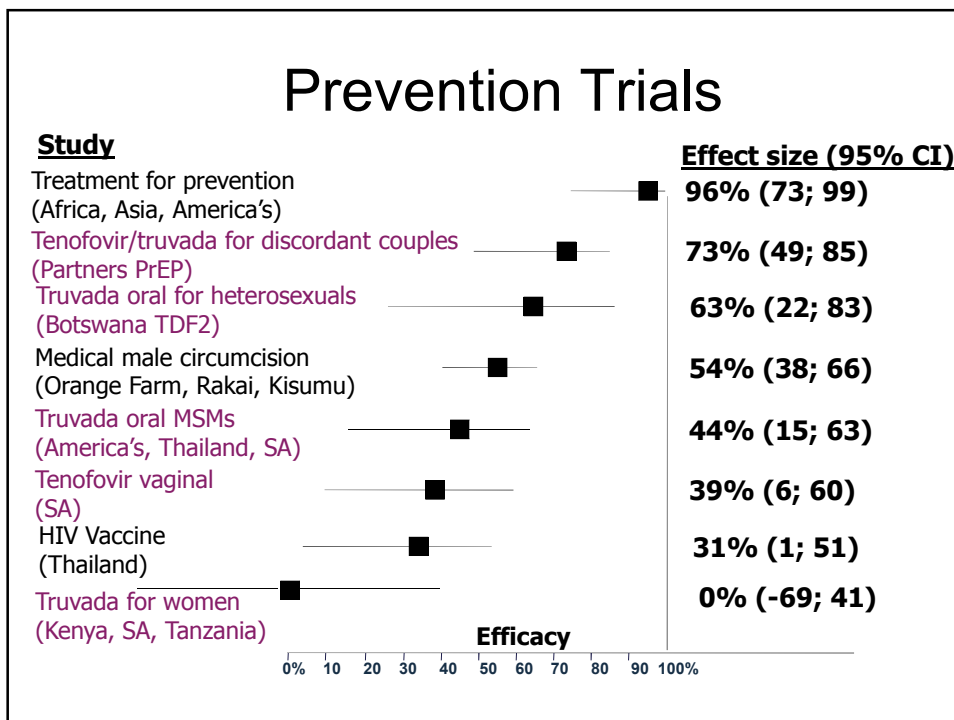
- (1) *H. pylori* → Acute Gastritis
(no disease in animals)
- (2) ERADICATION

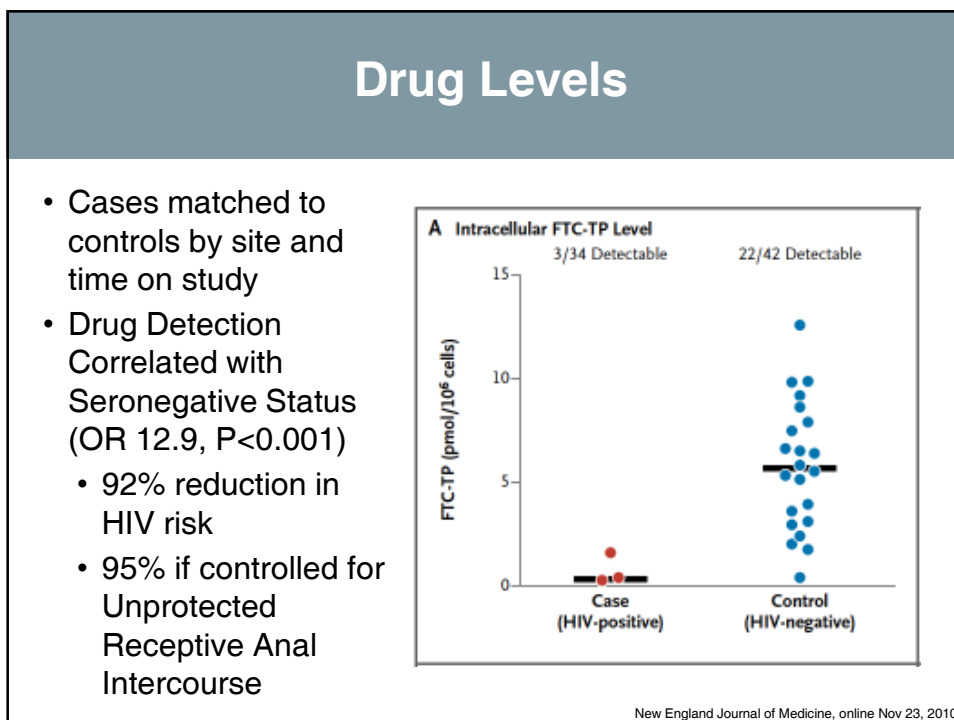
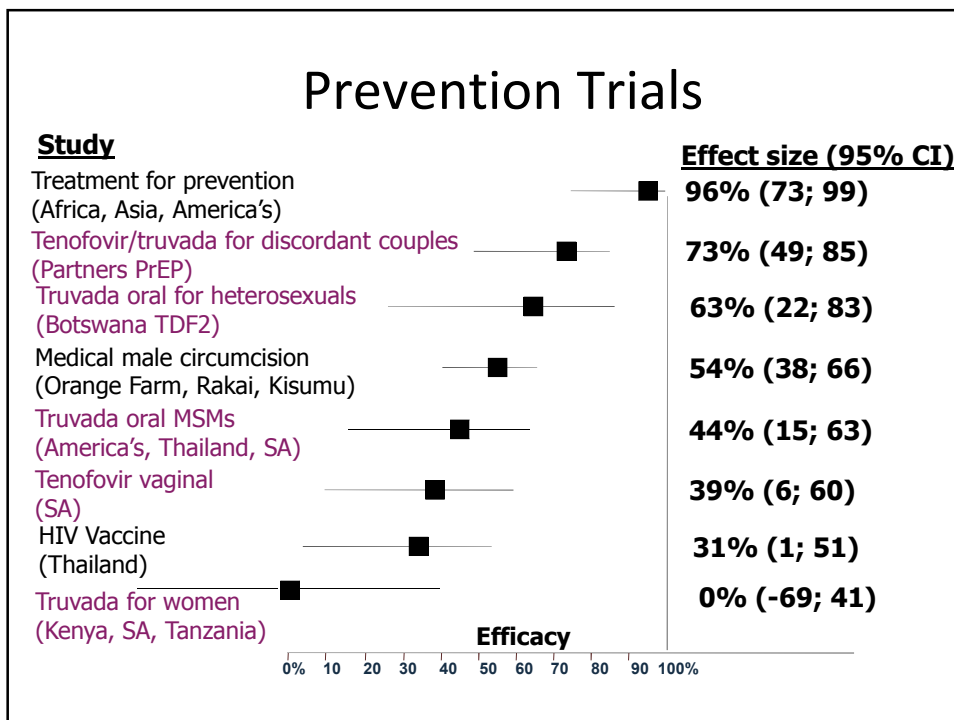
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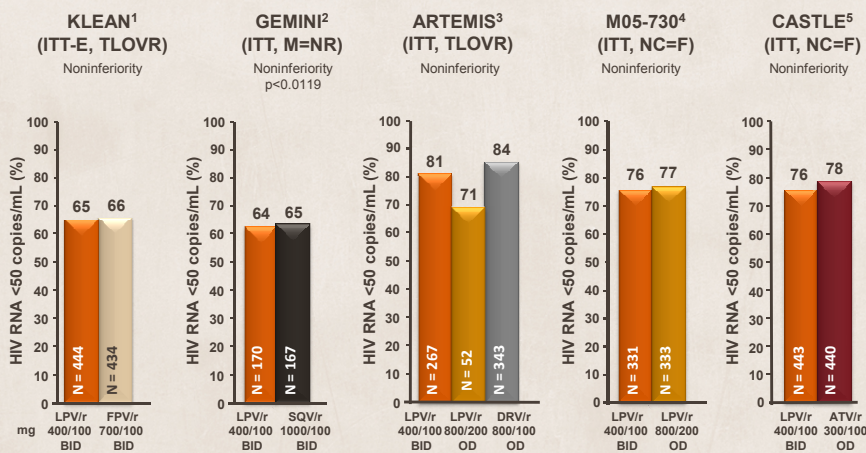




Rubbish

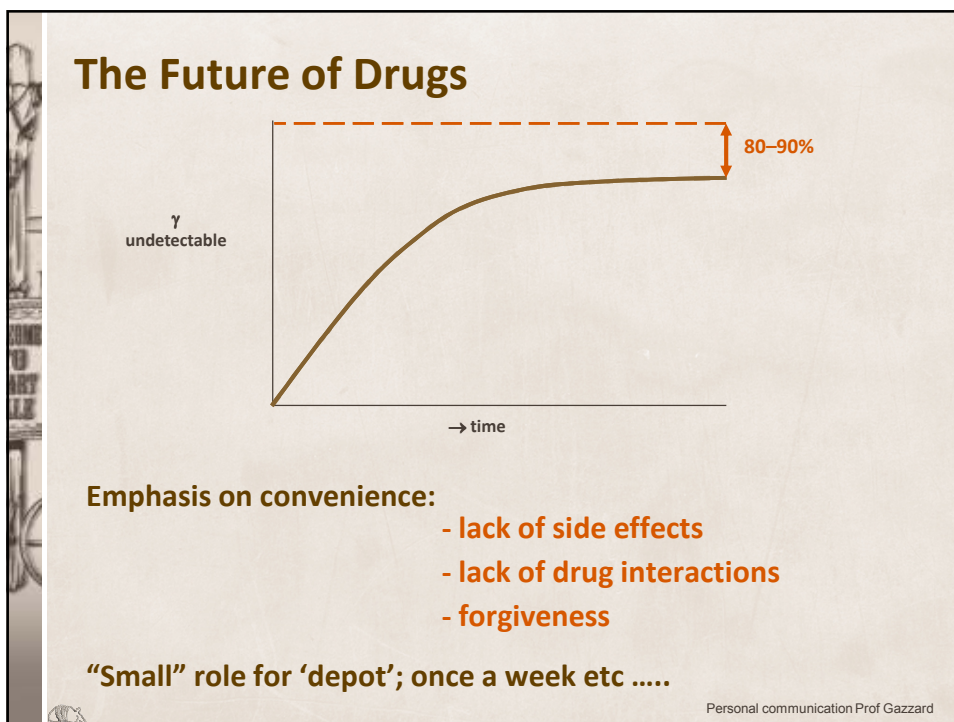
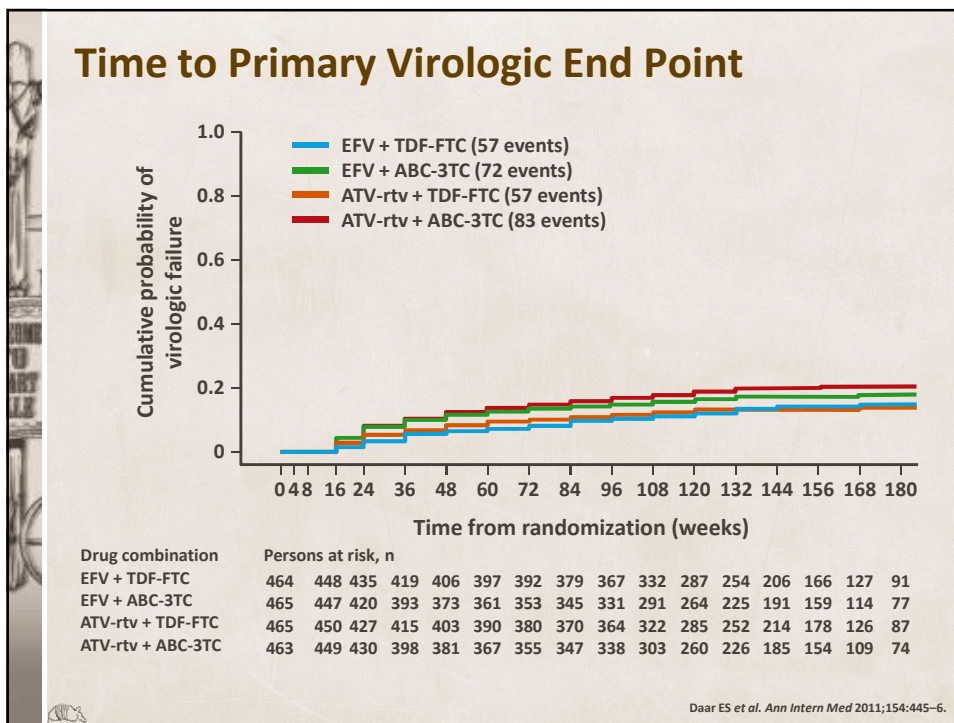
1. AZT monotherapy works
2. d4T / ddI, best thing since sliced bread
3. Drug holidays good
4. Maxi therapy life saving
5. CRiX belly does not exist

Boosted PIs: Efficacy Across the Board

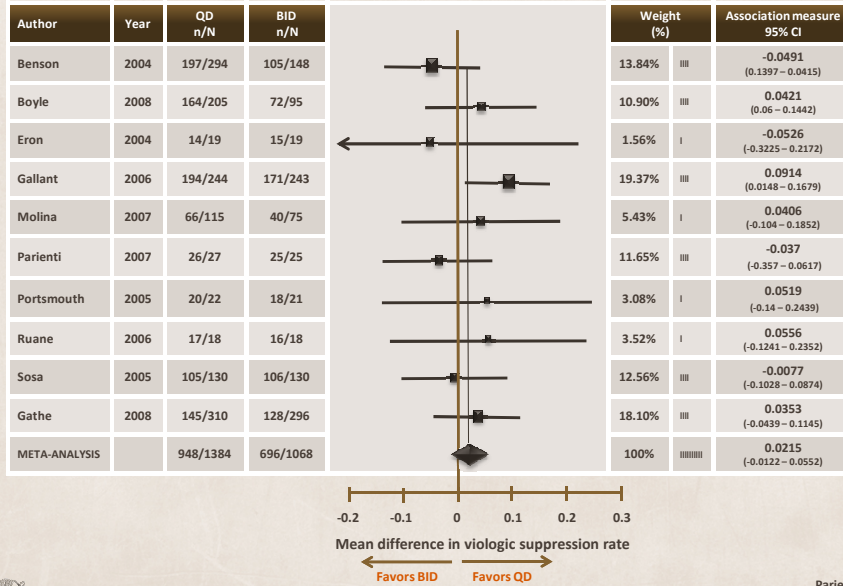


Neither FPV/r nor LPV/r OD are licensed in the EU. The EU licensed dose of DRV/r is 600/100 mg BID
 Data in figures are from different studies and cannot be compared directly. Cross-study comparisons are not valid
 ITT-E, intent-to-treat exposed.

Adapted from: 1. Eron J *et al. Lancet* 2006;368:476-482; 2. Walmsley S *et al. EACS* 2007, Abstract PS1/4; 3. De Jesus E *et al. ICAAC* 2007, Abstract LBA H-718b; 4. Gathe J *et al. CROI* 2008, Abstract 775; 5. Molina J *et al. CROI* 2008, Presentation 37



Meta-Analysis of Cohort Based Studies

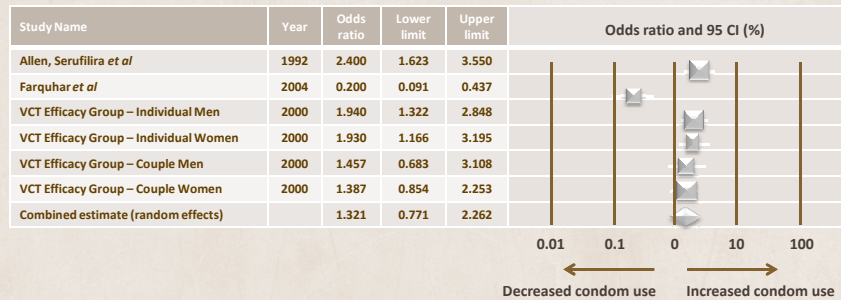


Future Perspectives

- ✦ Vaccines
- ✦ Behaviour
- ✦ Treatment as prevention & PrEP

Behavioural Interventions for HIV + Prevention in Developing Countries: A Systematic Review & Meta-Analysis

Meta-analysis of condom use among HIV- individuals following a behavioural intervention



Kennedy C E *et al.* Bull World Health Organ 2010;88:615–623.

So where are we now in terms of drugs? Backbones

Truvada vs. Kivexa

- ASSERT
 - Similar efficacy, differences in biomarkers¹
- 5202
 - High viral load- more virologic failure on Kivexa²
 - Low viral load- similar efficacy³
 - Over all- differences in safety?³

1. Post *et al.* JAIDS. 2010;55(1):49-57
 2. Sax *et al.* NEJM. 2009; 361: 2230-2240
 3. Daar ES, *et al.* Ann Intern Med 2011;154:445–6.

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In partnership with   HIV 

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