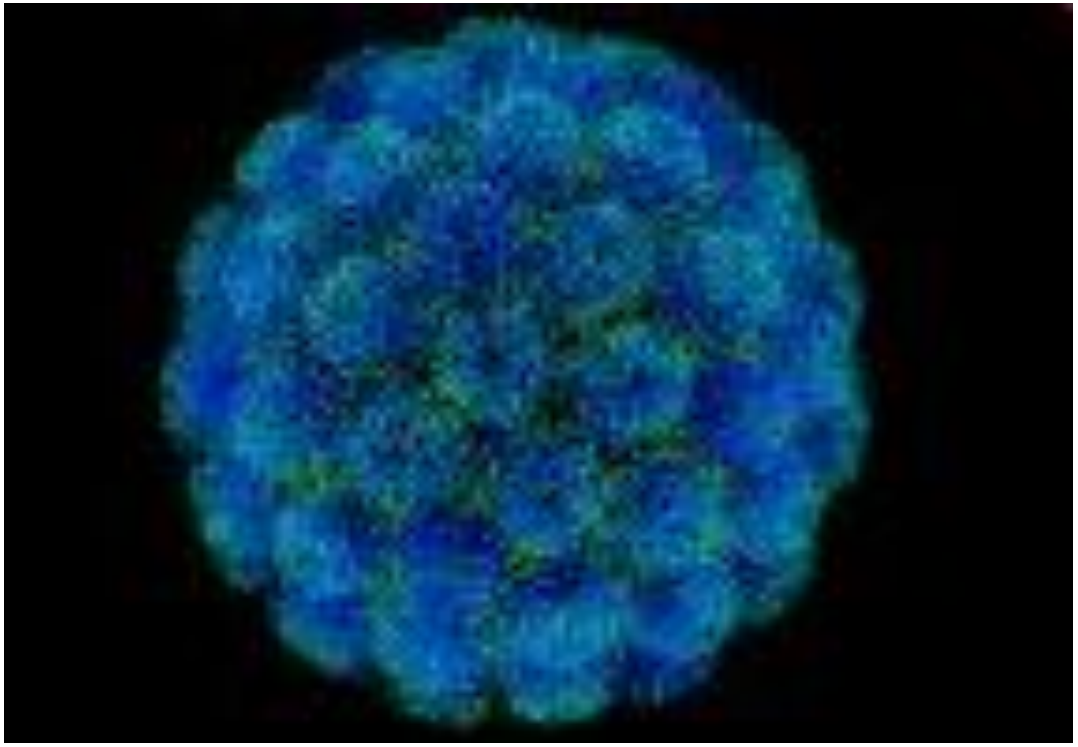
ART to prevent HIV transmission in Africa

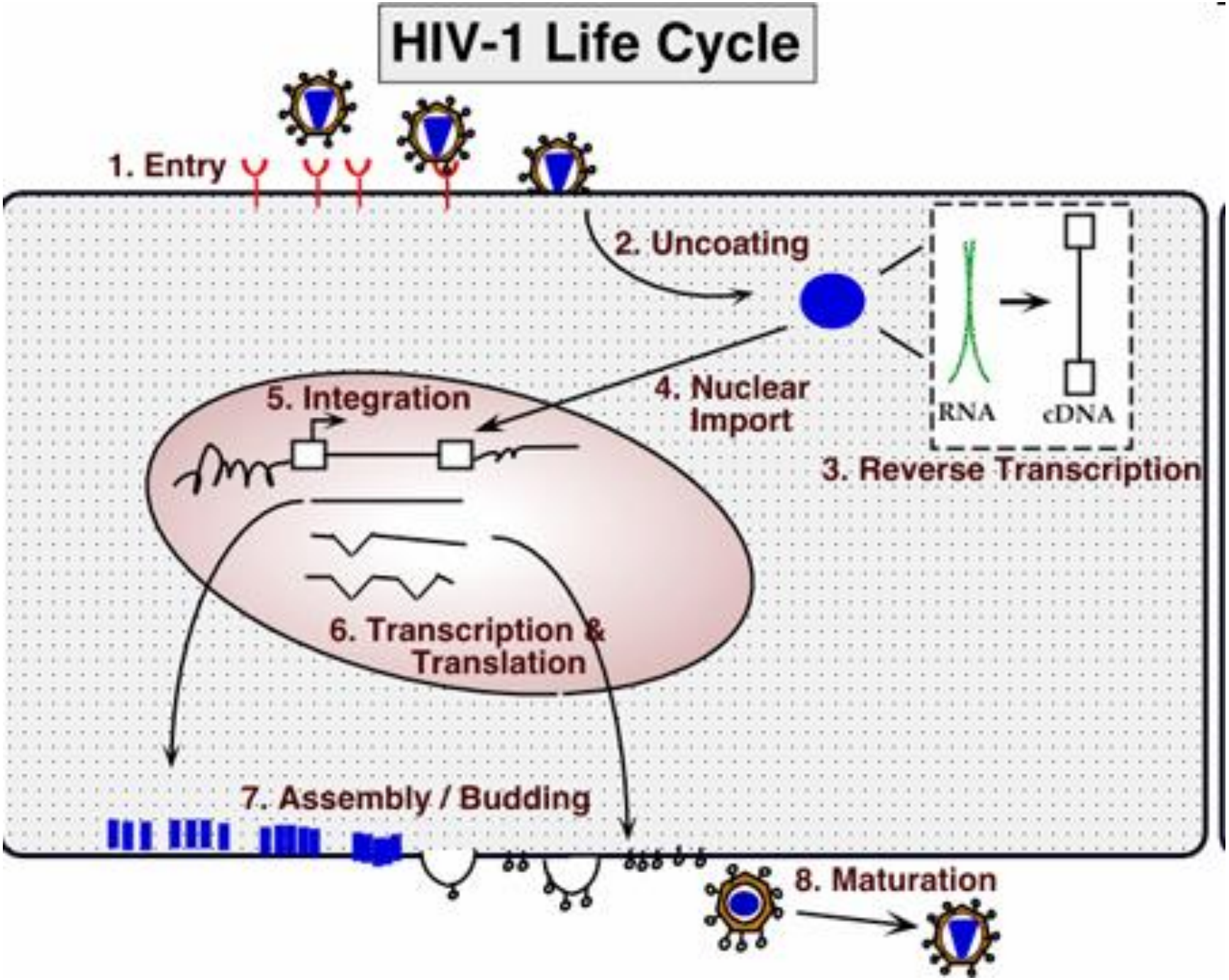
Could we should we and HOW?

Goals of this lecture

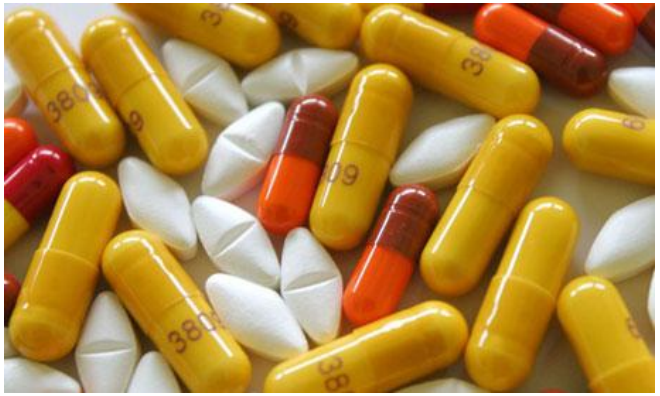
- Reminder of the biology of HIV infection
- Summary of HIV transmission
- The global HIV epidemic
- The universal test and treat concept
- Evidence to support the idea
- Could it work- data from ecological studies
- How to test the hypothesis- PopART
- Should we try it? The ethics

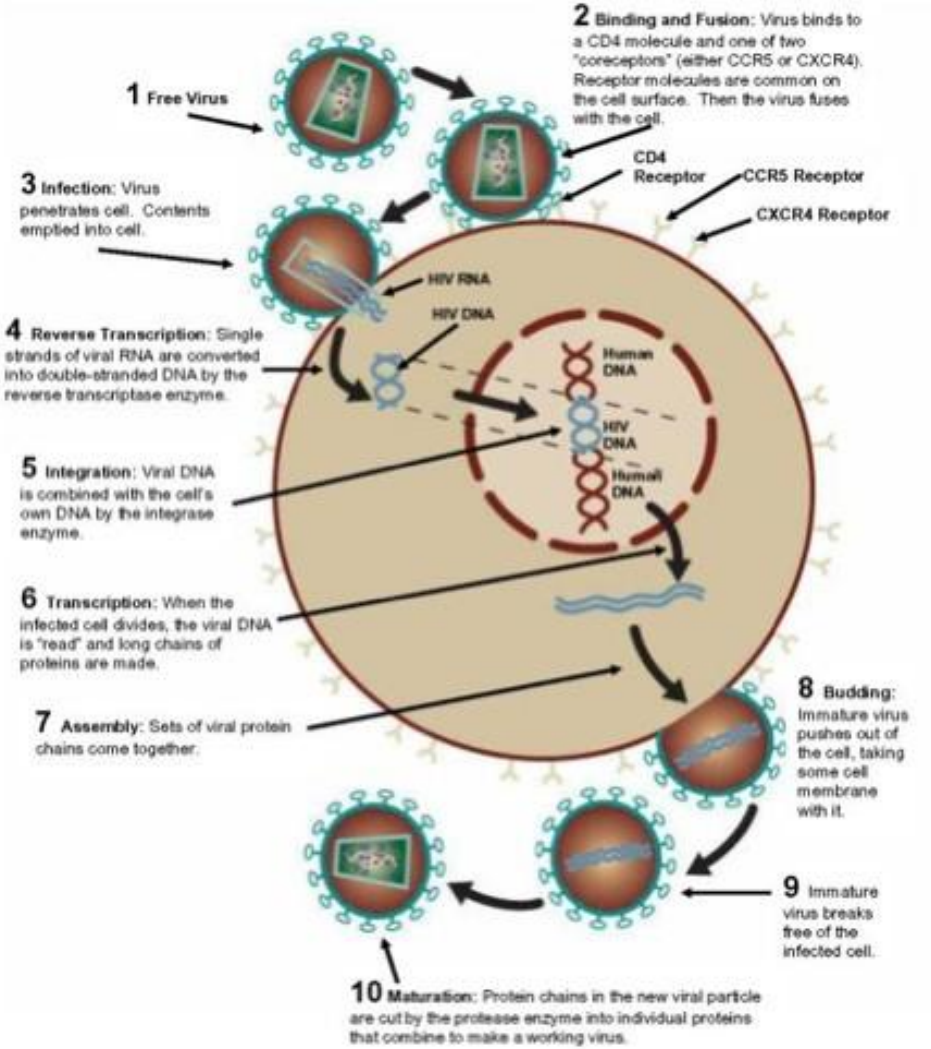
HIV Biology




HIV-1 Life Cycle
1. Entry
2. Uncoating
RNA
cDNA
3. Reverse Transcription
4. Nuclear Import
5. Integration
6. Transcription & Translation
7. Assembly / Budding
8. Maturation

How the drugs work





Drugs: Block viral replication

CCR5 antagonists

Fusion inhibitors

NRTI

NNRTI

Integrase inhibitors

Protease inhibitors

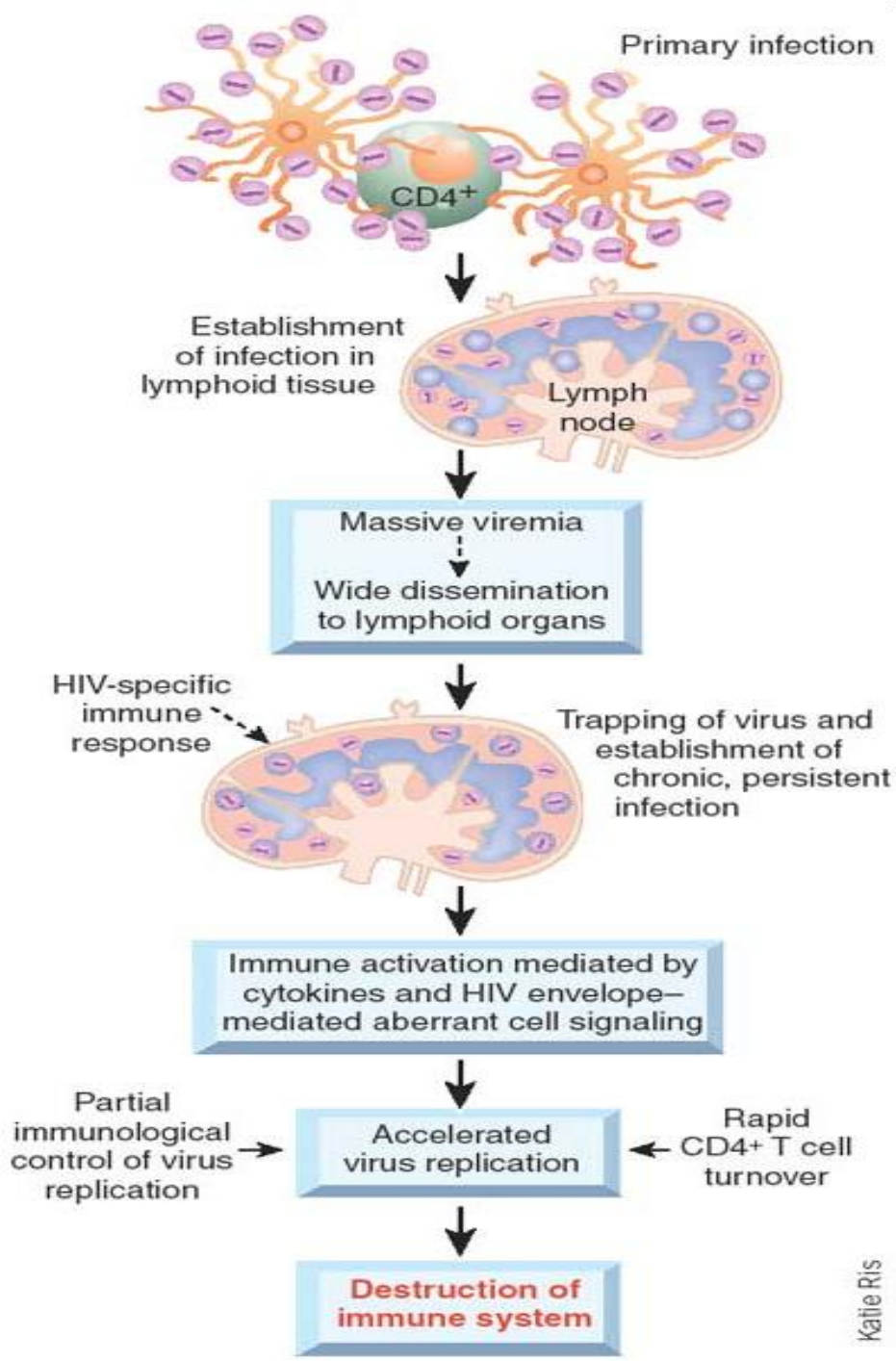
HIV transmission

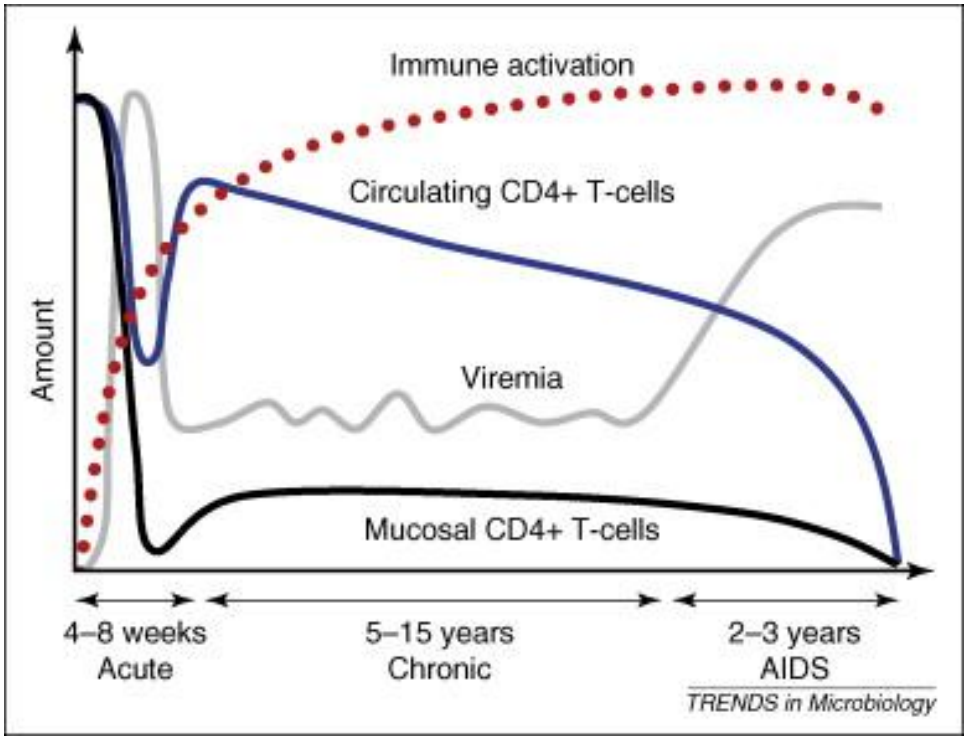
Commonest route global HIV is sexual transmission

- Multiple virions (usually clonal) are passed from an HIV+ individual through sexual, blood products, maternal-foetal routes, shared needles
- Breach of mucosal membranes facilitates transmission,
- Establishment of infection following transmission is rapid- within 1-3 days track to local LN, days to systemic dissemination by 10-25 days
- An inaccessible viral ‘reservoir’ is rapidly established where virus rests in memory CD4 cells

Natural history of HIV Disease

- HIV ‘seroconversion’ is usually asymptomatic of non-specific with generalised flu-like symptoms that resolve within 10 days- hyper infectious with very high viral loads
- Immediate CD4 infection and destruction never completely recovers even after ART
- Establishment of HIV viral reservoir early
- Recover and HIV-specific immunity develops controlling viral replication
- Gradual loss of CD4+ T-cells- average 50-75/year infected
- Without ART CD4 cells lost < 200 leads to profound immunosuppression opportunistic infections and death
- Start ART only when CD4 < 350 (Current WHO treatment guidelines - < 500 in USA)


Primary infection
CD4+
Establishment of infection in lymphoid tissue
Lymph node
Massive viremia
Wide dissemination to lymphoid organs
HIV-specific immune response
Trapping of virus and establishment of chronic, persistent infection
Immune activation mediated by cytokines and HIV envelope–mediated aberrant cell signaling
Partial immunological control of virus replication
Accelerated virus replication
Rapid CD4+ T cell turnover
Destruction of immune system
Katie Ris


Immune activation
Circulating CD4+ T-cells
Amount
Viremia
Mucosal CD4+ T-cells
4–8 weeks
Acute
5–15 years
Chronic
2–3 years
AIDS
TRENDS in Microbiology

WHO staging of HIV

Clinical Stage I

- Asymptomatic
- Persistent generalised lymphadenopathy (PGL)

Performance scale 1: Asymptomatic, normal activity

Clinical Stage II

- Weight loss, < 10% of body weight
- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular chelitis)
- Herpes zoster, within the last five years
- Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)

and/or performance scale 2: symptomatic, normal activity

Clinical Stage III

- Weight loss, >10% of body weight
- Unexplained chronic diarrhoea, > 1 month
- Unexplained prolonged fever (intermittent or constant) > 1 month
- Oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis, within the past year
- Severe bacterial infections

and/or performance scale 3: bedridden, < 50% of the day during the last month

Clinical Stage IV

- HIV wasting syndrome, as defined by CDC a
- Pneumocystic *carinii* pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea, > 1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus (MCV) disease of an organ other than liver, spleen or lymph nodes
- Herpes simplex virus (HSV) infection, mucocutaneous > 1 month, or visceral any duration
- Progressive multifocal leukoencephalopathy (PML)
- Any disseminated endemic mycosis (i.e. histoplasmosis coccidioidomycosis)
- Candidiasis of the oesophagus, trachea bronchi or lungs
- Atypical mycobacteriosis, disseminated
- Non-typhoid Salmonella septicaemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma (KS)
- HIV encephalopathy, as defined by CDC b

and/or performance scale 4: bedridden, < 50% of the day during the last month

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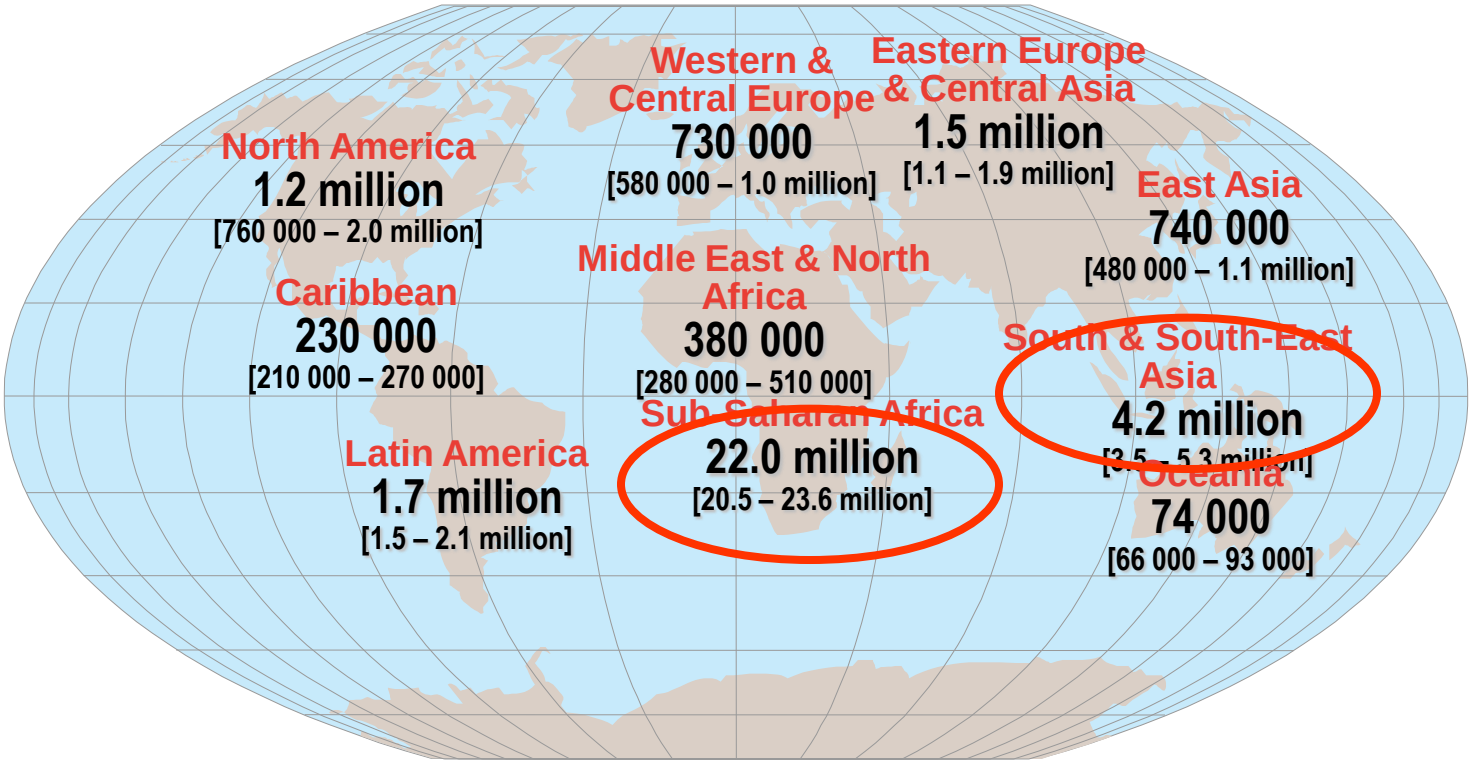
2009 WHO figures HIV AIDS

- **People living with HIV** — **33** million [30 – 36 million]
- **New HIV infections in 2009** — **2.7** million [2.2 – 3.2 million]
- **Deaths due to AIDS in 2009** — **2.0** million [1.8 – 2.3 million]



Total: 33 million (30 – 36 million)

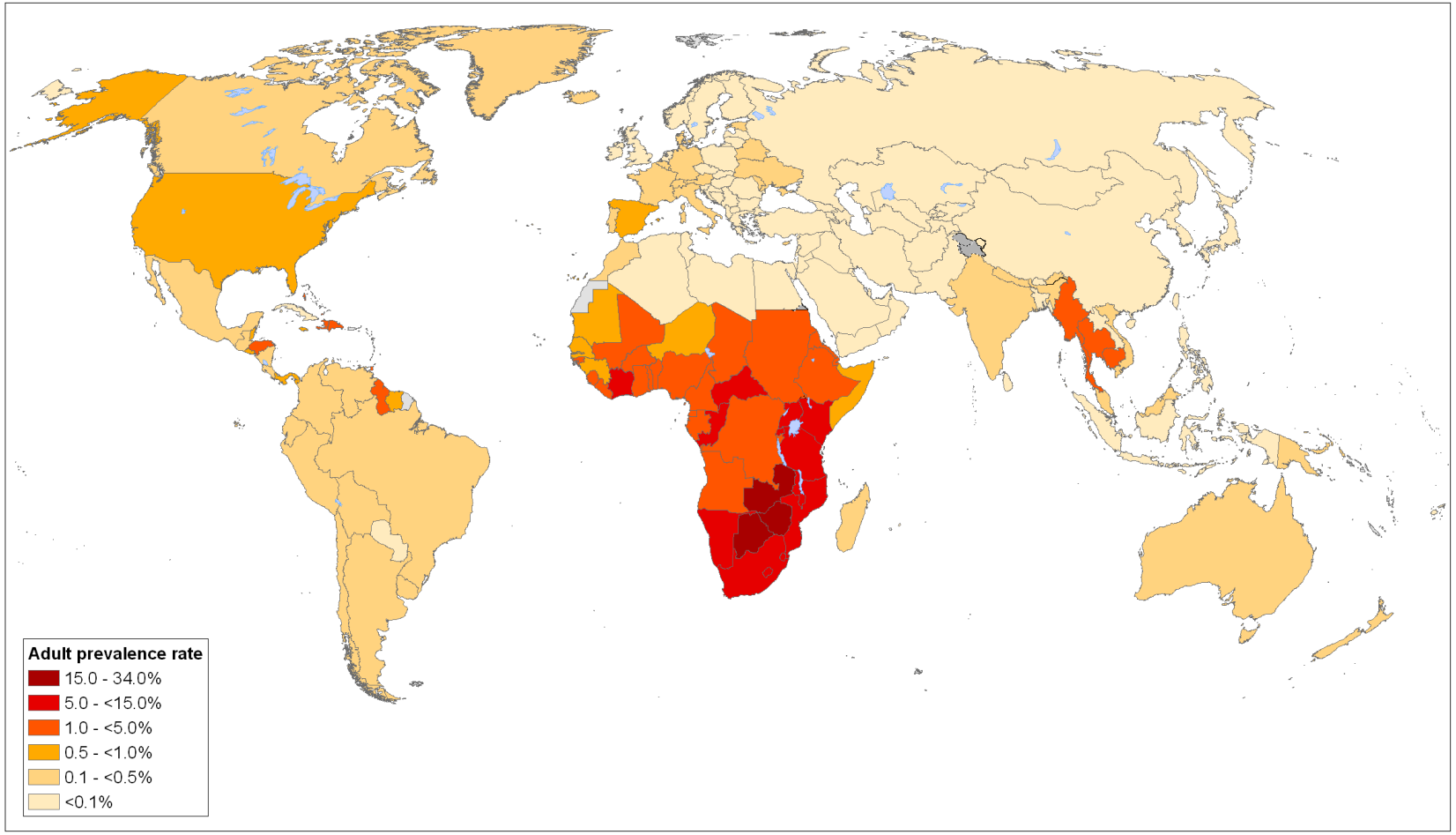
Prevalence

- The frequency of a disease in a population at a point in time

$$= \frac{\text{number of cases in population}}{\text{number of people in population}}$$

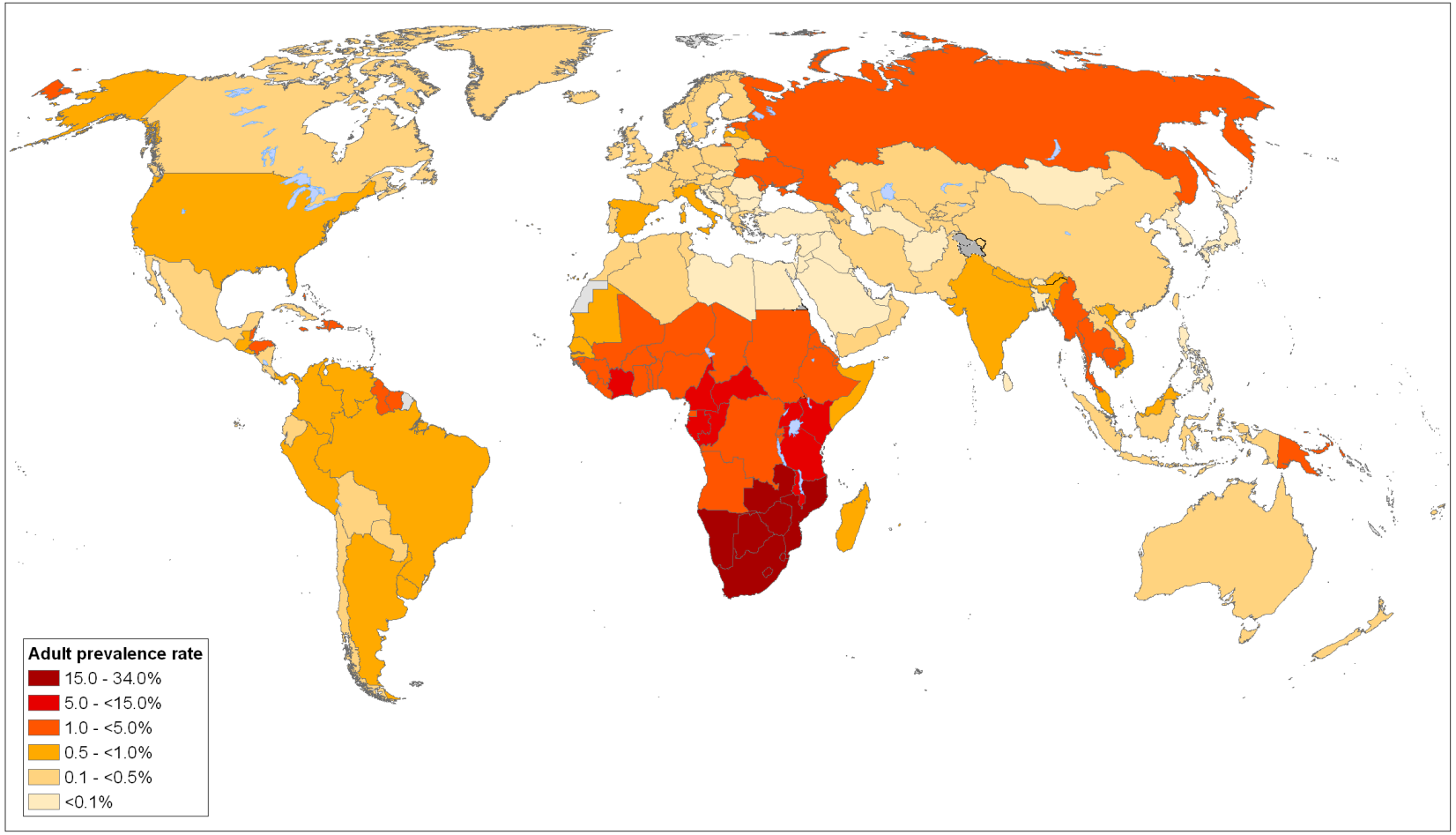
- Prevalence measures burden of disease in a population
- It is useful for planning
- It can be used to compare burden of chronic disease between populations

Global HIV prevalence in adults, 1995



UNAIDS/WHO, 2006

Global HIV prevalence in adults, 2005



UNAIDS/WHO, 2006

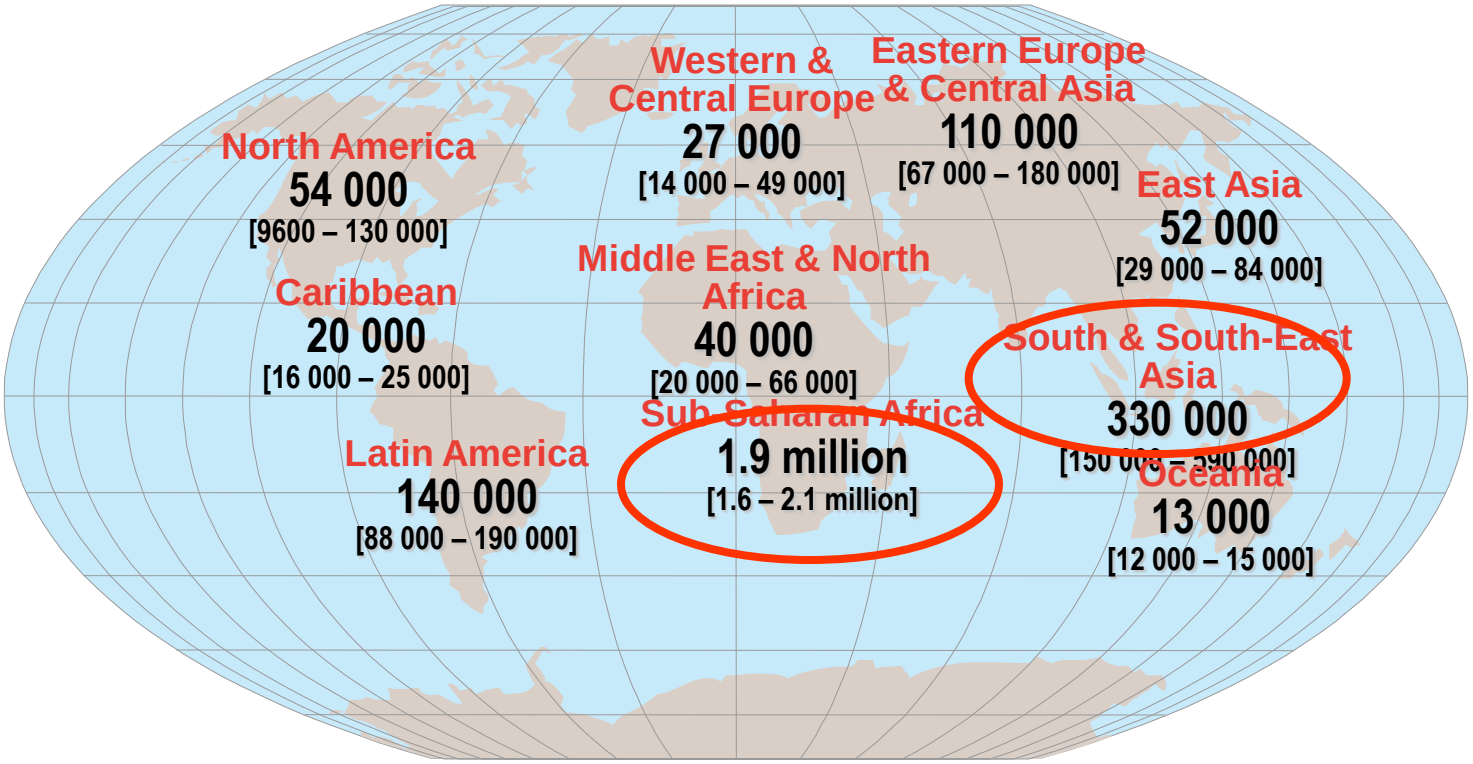
Incidence

The number of new infections within a population over time

Incidence

- Number of new cases of disease in a population over a given time
  - cumulative incidence (risk)

    $$\frac{\text{new cases of disease in a given time period}}{\text{number of disease free people at start of time period}}$$



Total: 2.7 million (2.2 – 3.2 million)

Mortality

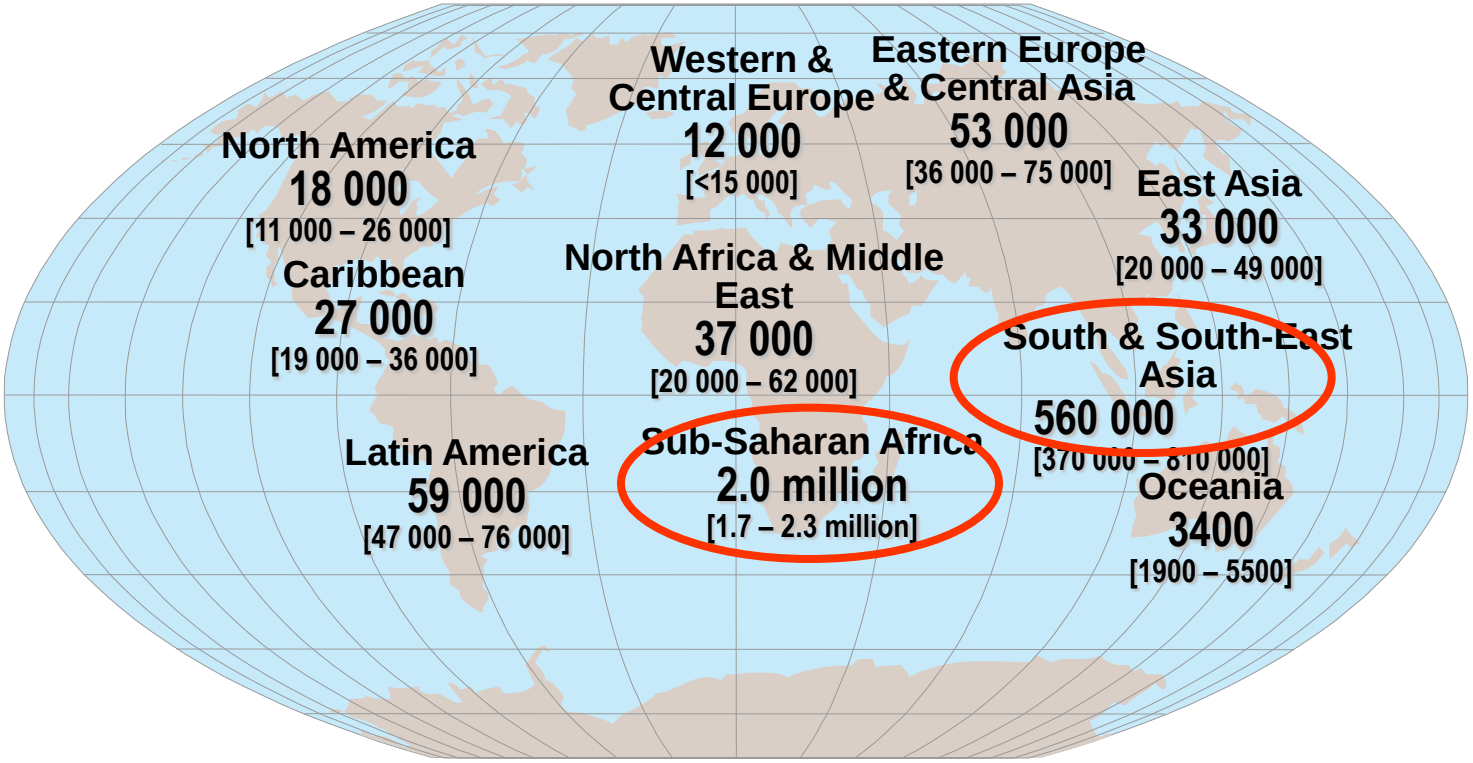
- Number of deaths from a disease in a population over a given time

$$= \frac{\text{Deaths from disease in a given time period}}{\text{population at start of time period}}$$

Deaths due to HIV AIDS 2010

- Since the beginning of the epidemic almost 60 million people have been infected with HIV
- Estimated 25 million people have died from HIV related causes
- 2.7 million new infections/year (40% in ages 15-24 years)
- 2 million deaths/year
- 67% of all HIV cases are in Sun-Saharan Africa, 91% of all new infections in children are in SSA

Estimated adult and child deaths from AIDS, 2005



Total: 2.8 (2.4 – 3.3) million

2006 High Level Meeting on AIDS

2. Note with alarm that we are facing an unprecedented human catastrophe; that a quarter of a century into the pandemic, AIDS has inflicted immense suffering on countries and communities throughout the world; and that more than 65 million people have been infected with HIV, more than 25 million people have died of AIDS, 15 million children have been orphaned by AIDS and millions more made vulnerable, and 40 million people are currently living with HIV, more than 95 per cent of whom live in developing countries;

UN General Assembly, 2 June 2006

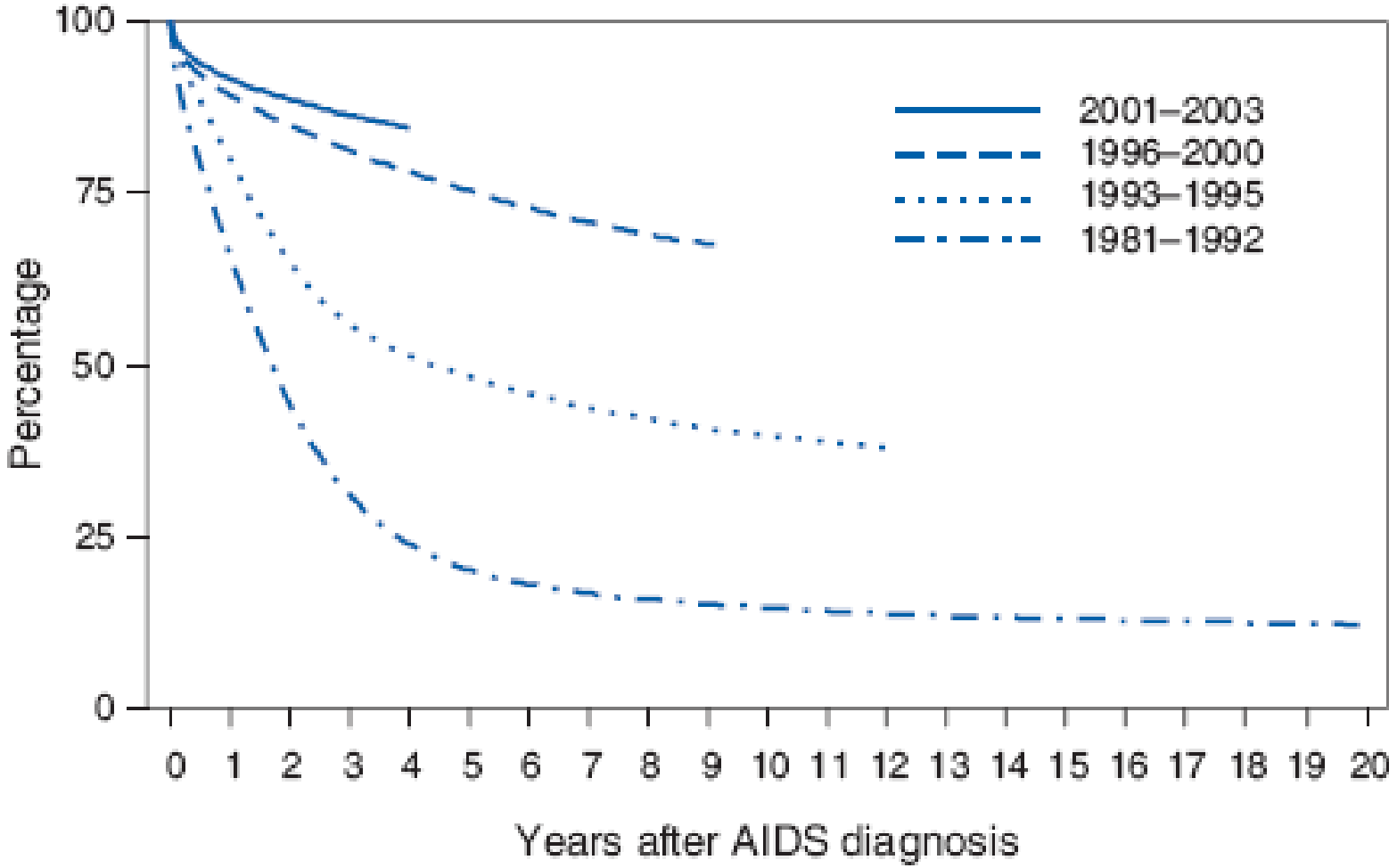
Antiretroviral treatment (ART) works!!

Haitian Patient, before and after Receiving Free Treatment for HIV Infection and Tuberculosis.

The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public–private partnerships.

Its impact on mortality incidence and prevalence

FIGURE 2. Percentage of persons surviving through June 2005, by years after acquired immunodeficiency syndrome (AIDS) diagnosis cohorts during 1981–2003 and by year of diagnosis — United States



Annual incidence 2.7 million
Annual mortality 2.8 million

- If mortality = incidence the epidemic is stable
- BUT
- If we keep more people alive with ART then the mortality reduces and potentially people are alive longer to transmit virus then incidence may go up as mortality goes down and prevalence increases
- BUT if ART eliminates transmission then prevalence over time will reduce

A world apart - 2005

- USA
- 1.3 million with HIV
- 43,000 new cases
- 18,000 deaths

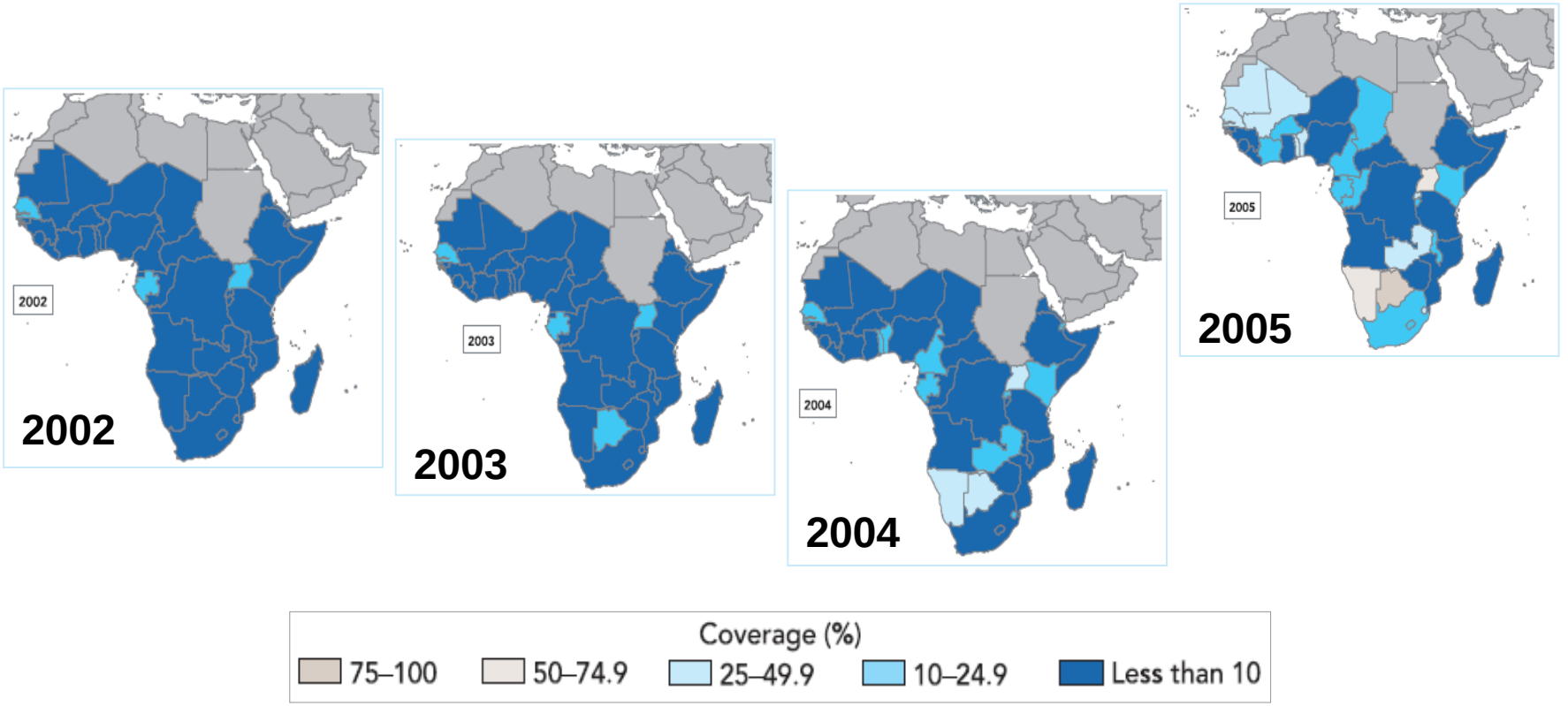
- Mortality in people with HIV = 1.4% per year

- Sub Saharan Africa
- 24.5 million with HIV
- 2.7 million new cases
- 2 million deaths

- Mortality in people with HIV = 8.2% per year

New infections outstrip Treatment by 5:2

People in sub-Saharan Africa on antiretroviral treatment as percentage of those in need, 2002–2005



Source: WHO/UNAIDS (2005). Progress on global access to HIV antiretroviral therapy: An update on “3 by 5.”

What is it like to live in an area of the world with 24% prevalence of HIV

- http://www.youtube.com/watch?v=3r9jFwCyW6k

IAS 2010 Treatment 2.0

- i) Recognize and use HIV treatment as a tool for preventing new infections
- ii) Develop better combination antiretroviral medications and cheaper diagnostics tools
- iii) Find ways to lower other HIV-related costs
- iv) Expand the availability of HIV testing and build stronger links between HIV testing and care
- v) Encourage and support community leadership in expanding and improving local HIV responses.

Funding

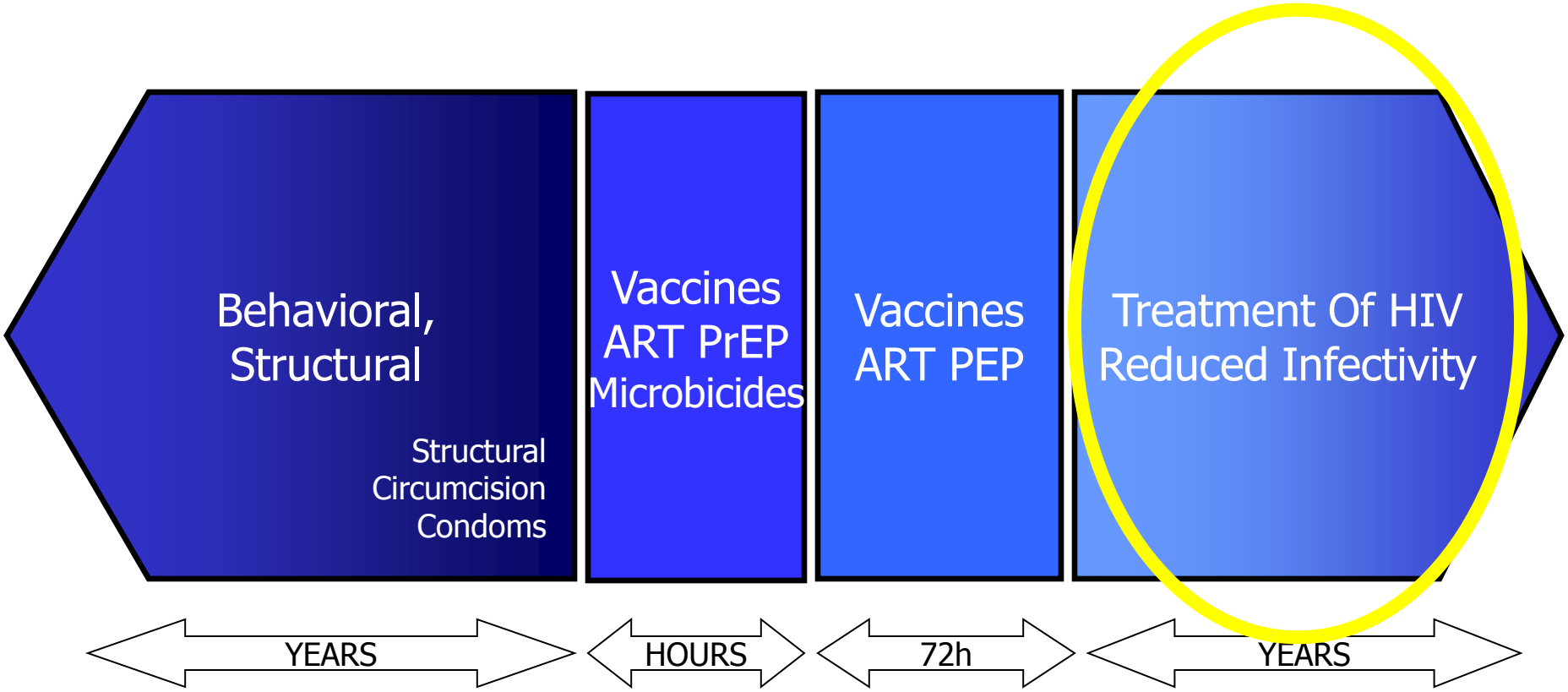
- At the current rate of infection the projected costs of delivering and maintaining “universal ART access” is;
- $42 billion in 2010
- $54 billion by 2015
- Preventing the 3,550 HIV infections that were probably acquired, and subsequently diagnosed in the UK in 2008, would have reduced future HIV-related costs by more than **£1.1 billion.**

What can be done?

- **Prevention**:
- Prophylactic HIV vaccine,
- Vaginal ART microbicide,
- Pre- exposure prophylaxis (PrEP)- use of ART prior to sexual exposure
- Post exposure prevention (PEP), - use of ART after exposure-
- male circumcision, reduces the risk by 50-60%
- or
- Universal HIV test and treat-
  - UTT a utopian model

Four Prevention Opportunities

Cohen et al, JCI, 2008
Cohen IAS 2008



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What is the concept

- The amount of HIV virus present in the secretions of an infected individual directly correlate with the risk of onward viral transmission
- Hypothesis:
- If the viral load of the HIV+ individual remains at the lowest level (< 50 copies HIV RNA/ml) measureable achieved by ART then no transmission can occur

Why Now?

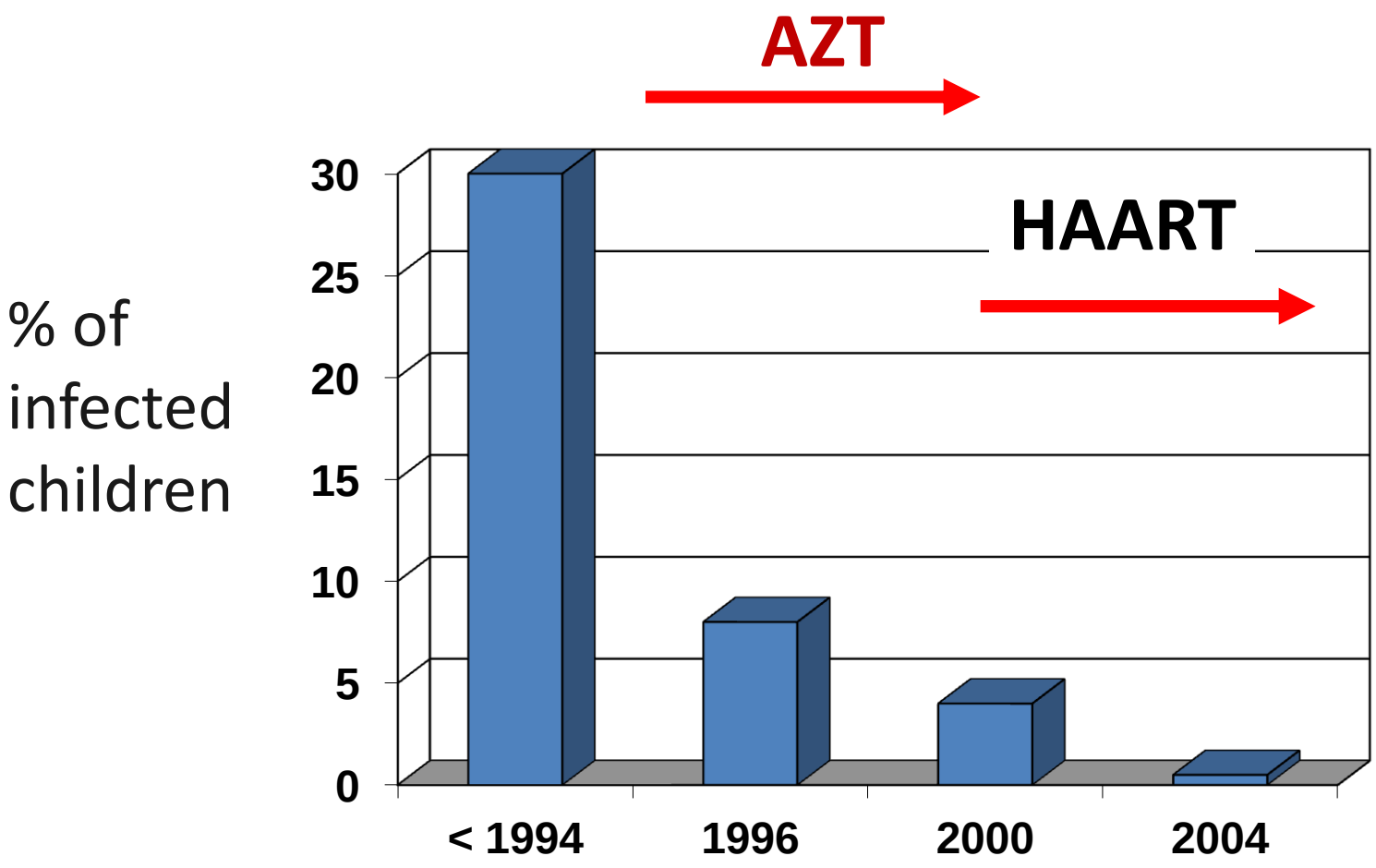
- Treatment for HIV has been available for nearly 15 years but was overpriced, complex, multiple pills multiple doses with many toxicities
- It is now cheaper- thanks to pressure on pharma companies to provide generic drugs and low costs to developing countries (Clinton/ Piot)

Antiviral Treatment as Prevention

- Extensive biological plausibility
  - The concentration of HIV-1 in blood and genital tract correlates with sexual transmission
  - Antiretroviral agents that concentrate in the genital tract reduce HIV-1 VL

- Most observational reports indicate ART reduces transmission of HIV-1 in couples

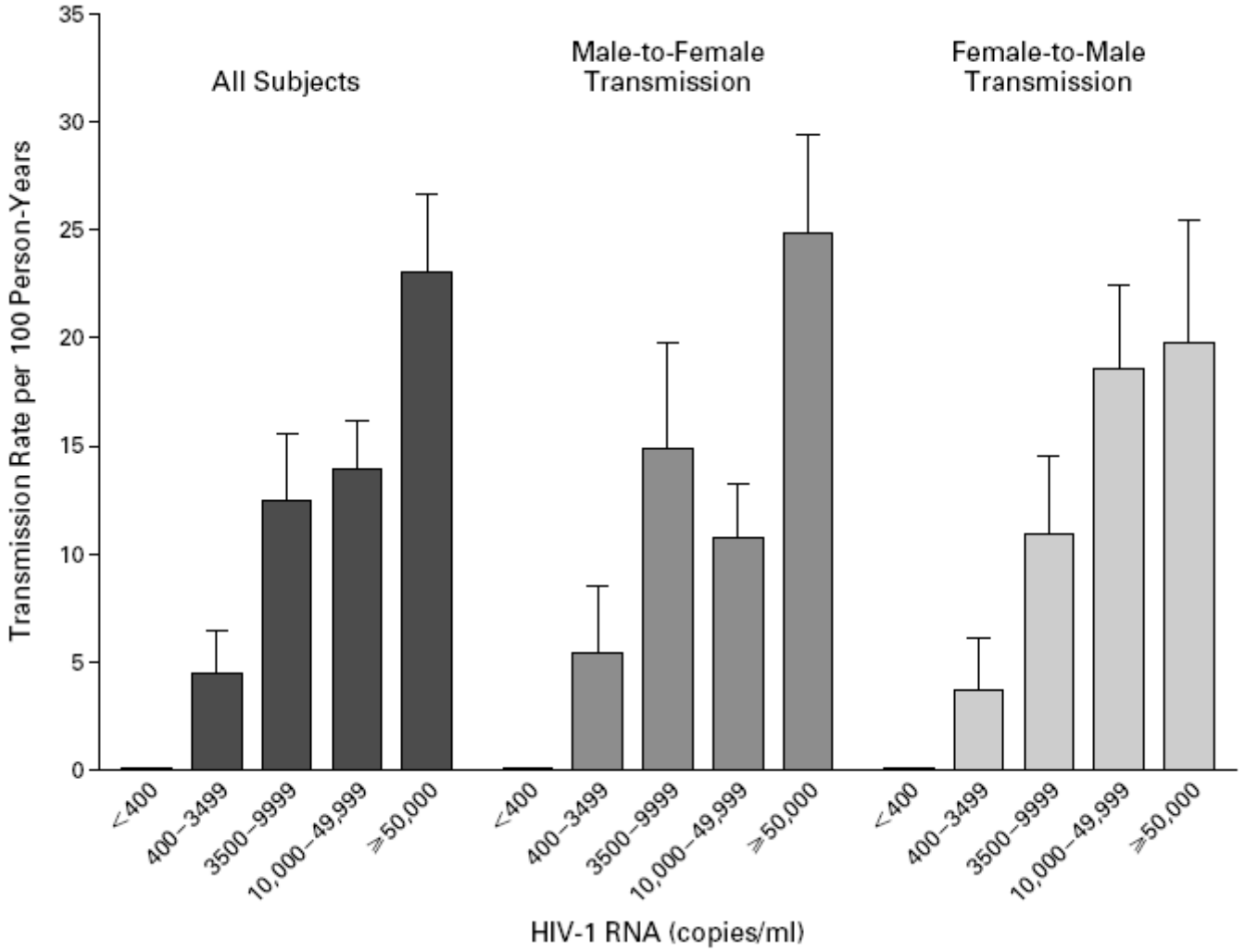
Mother to Child Transmission



Adapted from Coovadia and Lallemant, NEJM 2004

Rakai Study: Transmission risk = viral load

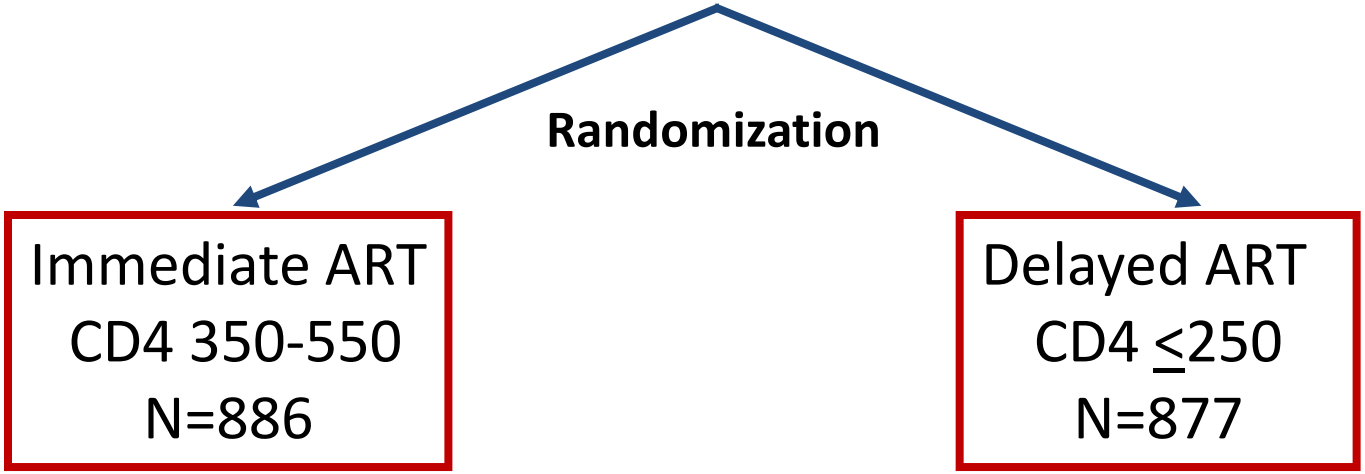
Quinn et al. N Engl J Med 2000;342:921-9



HPTN 052 HIV DISCORDANT COUPLE STUDY

HPTN 052 Study Design

Stable, healthy, serodiscordant couples, sexually active
CD4 count: 350 to 550 cells/mm^3



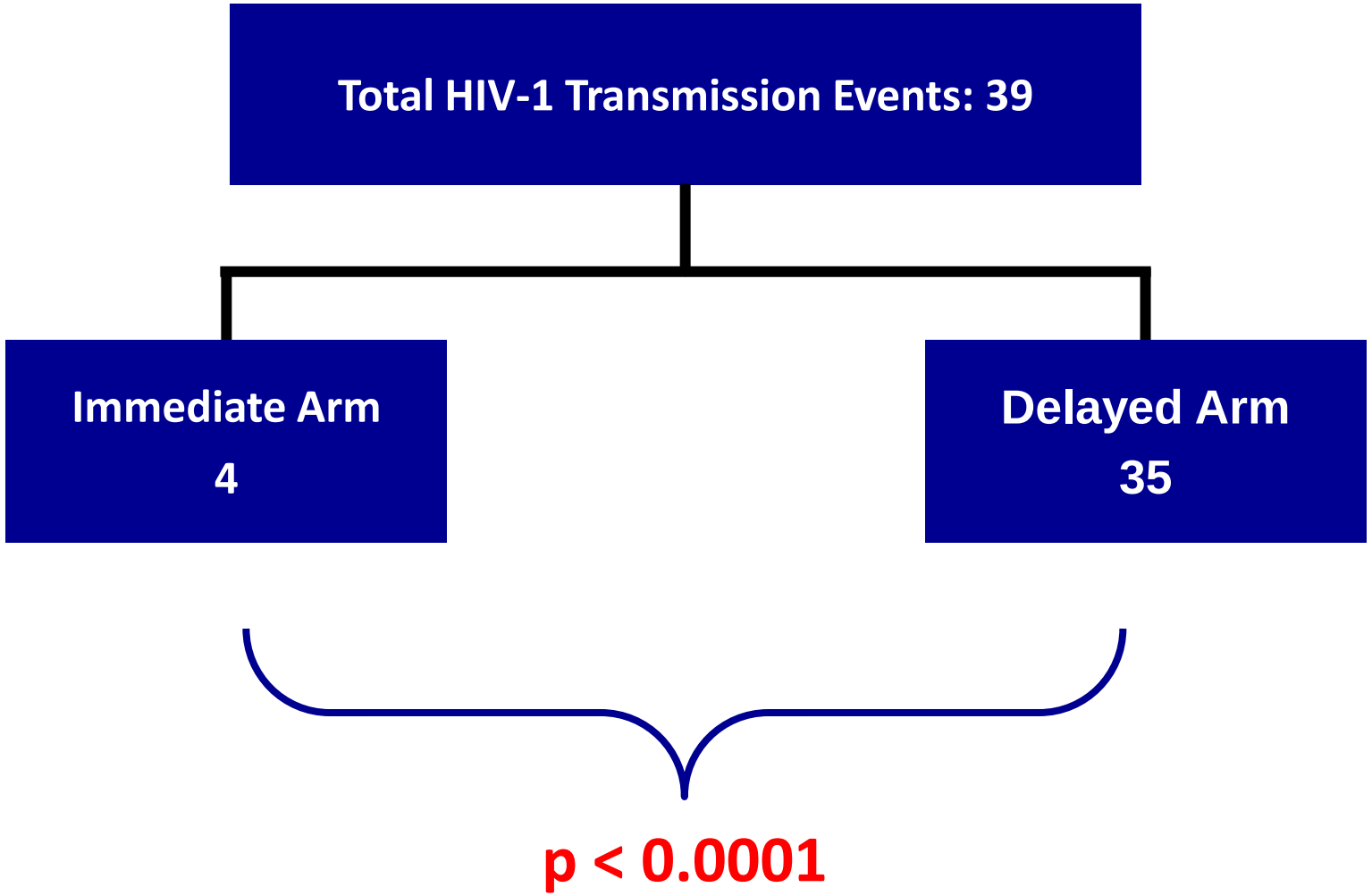
Primary Transmission Endpoint

Virally linked transmission events

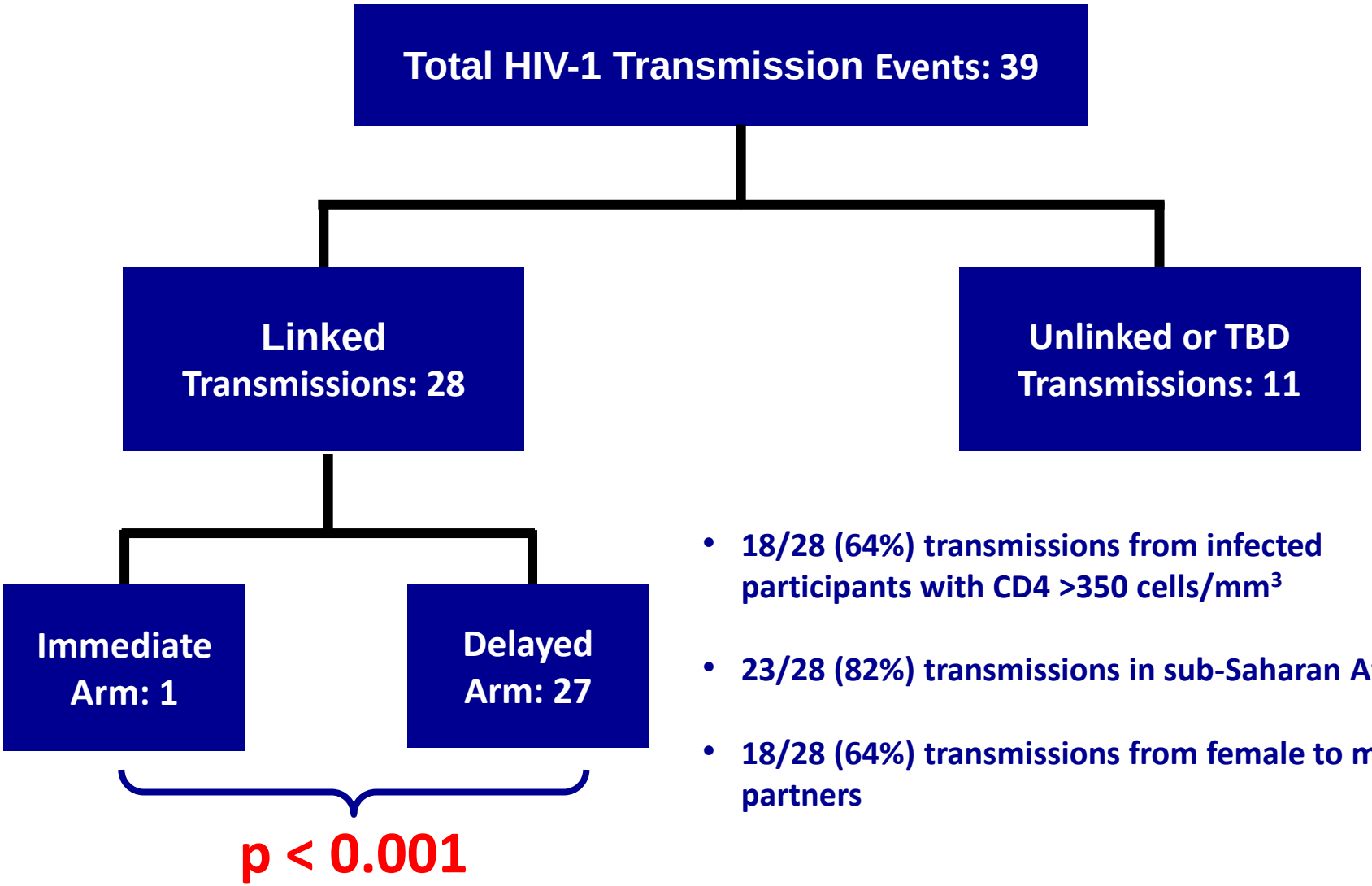
Primary Clinical Endpoint

WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

HPTN 052: HIV-1 Transmission



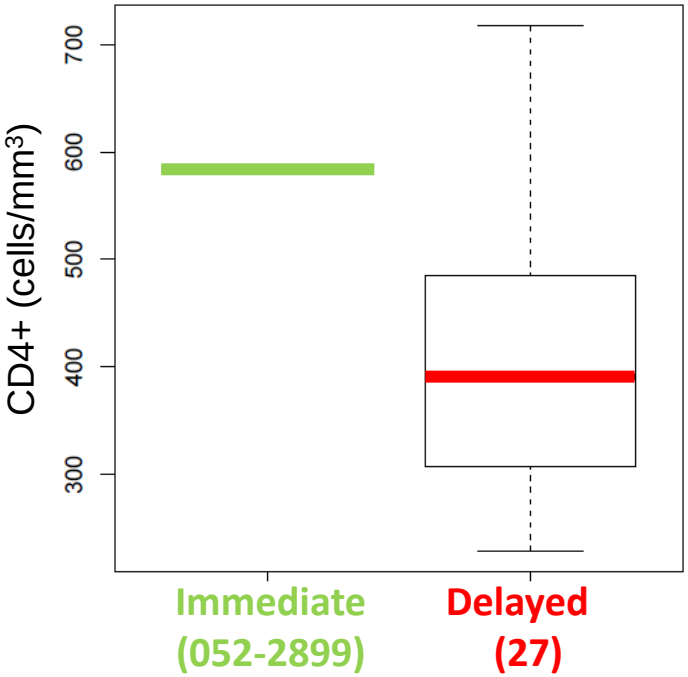
HPTN 052: linkage of HIV-1 Transmission

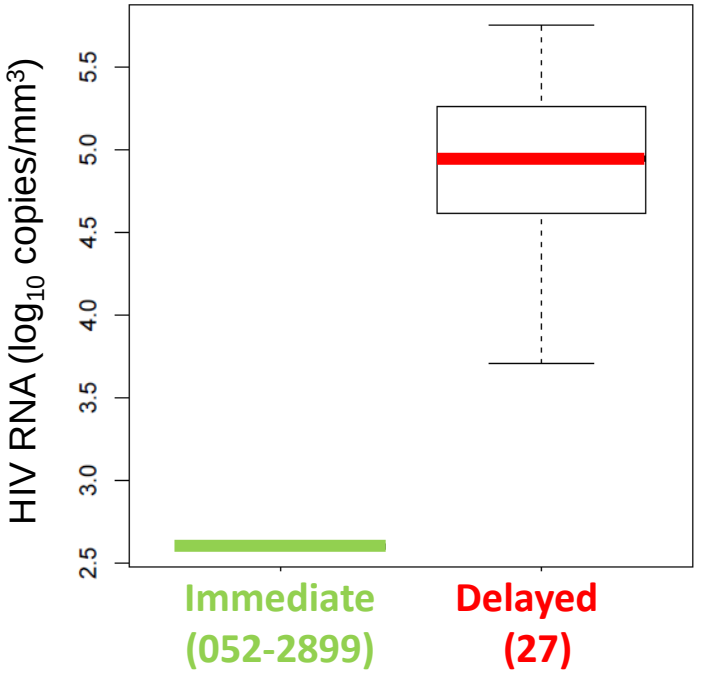


- 18/28 (64%) transmissions from infected participants with CD4 >350 cells/mm^3
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

HIV Transmission and Viral Load

28 Linked Transmissions





Median proximal CD4 (range): 400 (229-858)
Immediate arm: 584 (584-584)
Delayed arm: 391 (229-858)

Median proximal $\log_{10}$ VL (range): 4.9 (2.6-5.8)
Immediate arm: 2.6 (2.6-2.6)
Delayed arm: 4.9 (2.6-5.8)

HPTN 052 Clinical Results

- 105 morbidity and mortality events (p<.01)
  - 65 in delayed arm
  - 40 in immediate arm
- 20 cases of extrapulmonary TB (p= 0.0013)
  - 17 in delayed arm
  - 3 in immediate arm
- 23 deaths (NS)
  - 13 in delayed arm
  - 10 in immediate arm

Results

3 heterosexual discordant couple studies in Africa

	Study A*	Study B**	Study C*** « before »	Study C*** « after »
Condoms	✓	✓	✓	✓
HAART	-	✓	-	✓
Infections %/year	12	0.5	2.23	0.39

Wawer M et al. Lancet 2009; 374:229-37

** *Bunnell R et al. Abstract 29, 15th CROI, 2009*

*** *Donnell D, Lancet 2010*

Couples studies

- **Rwanda/Zambia**
- **2,993 couples studied 2002-2008**
- **512 days follow-up (mean)**
- **ART use was not associated with increase sexual risk**
- **175 transmission events,**

4/175 from subjects receiving ART

80% reduced risk of HIV transmission

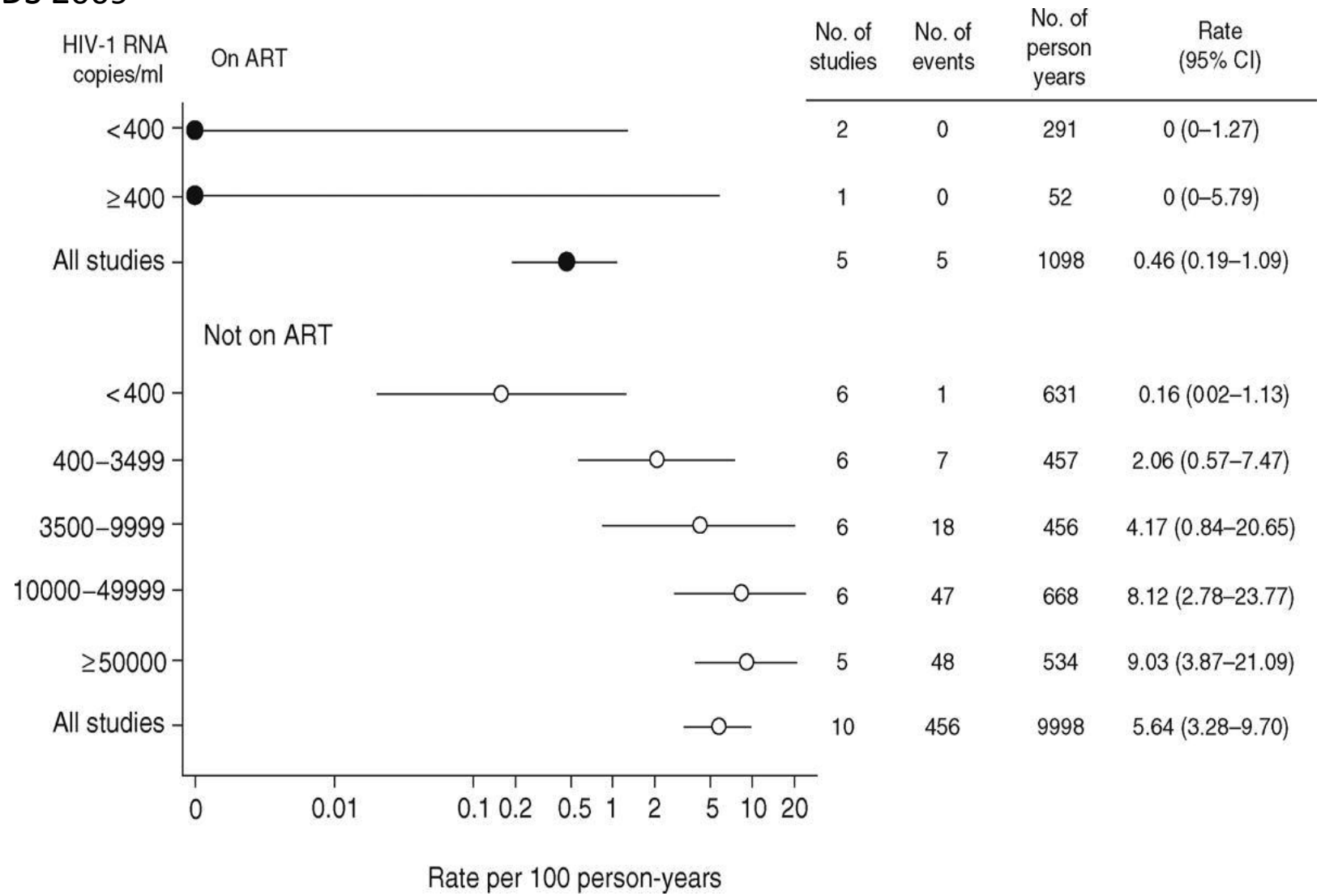
Sullivan et al. CROI 2009 **#52bLB**
IAS 2009

- Chinese couple study
- **1,927 discordant couples in Henan followed 2006-2008**
- **1,396 index cases receiving FREE ART**
- ***84 seroconversions distributed equally among subjects on and off ART***

Wang Lu et al. IAS 2010, JAIDS in press

Wang ThPDC102, IAS 2010

Attia AIDS 2009



Meta-analysis of 47 studies of HIV heterosexual discordant couples

showed zero transmissions for HIV pVL < 400 copies HIV RNA/ml

but were compatible with 1 transmission / 79 person years

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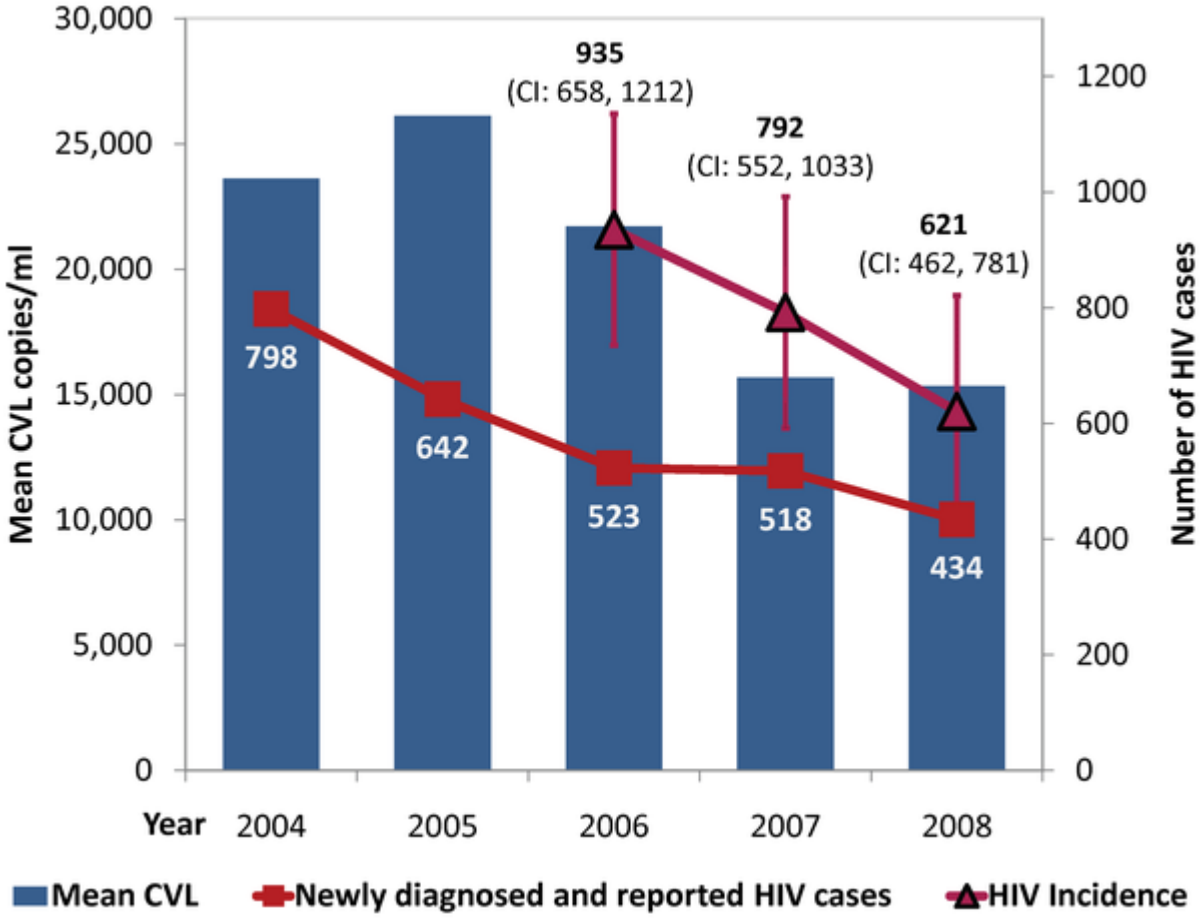
Ecological Studies of expanded HIV VCT and ART

- **Proposed Benefit from Introduction of ART:**
  San Francisco (Das PloS One, 2010)
  British Columbia (Montaner Lancet, 2010)
  Denmark (IAS, 2010)
  Sullivan (IAS 2008)
  Donnell (Lancet, 2010)
  Romero (BMJ, 2010)

- **No benefit from Introduction of ART**
  Amsterdam (CROI, 2010)
  France (CROI 2010)
  Australia (Sexual Health, 2008)

Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco.

Das et al PlosOne 2010



Mean CVL was calculated as the mean of the most recent viral load of all reported HIV-positive individuals in a particular community

HIV VCT 72%

ART uptake 90%

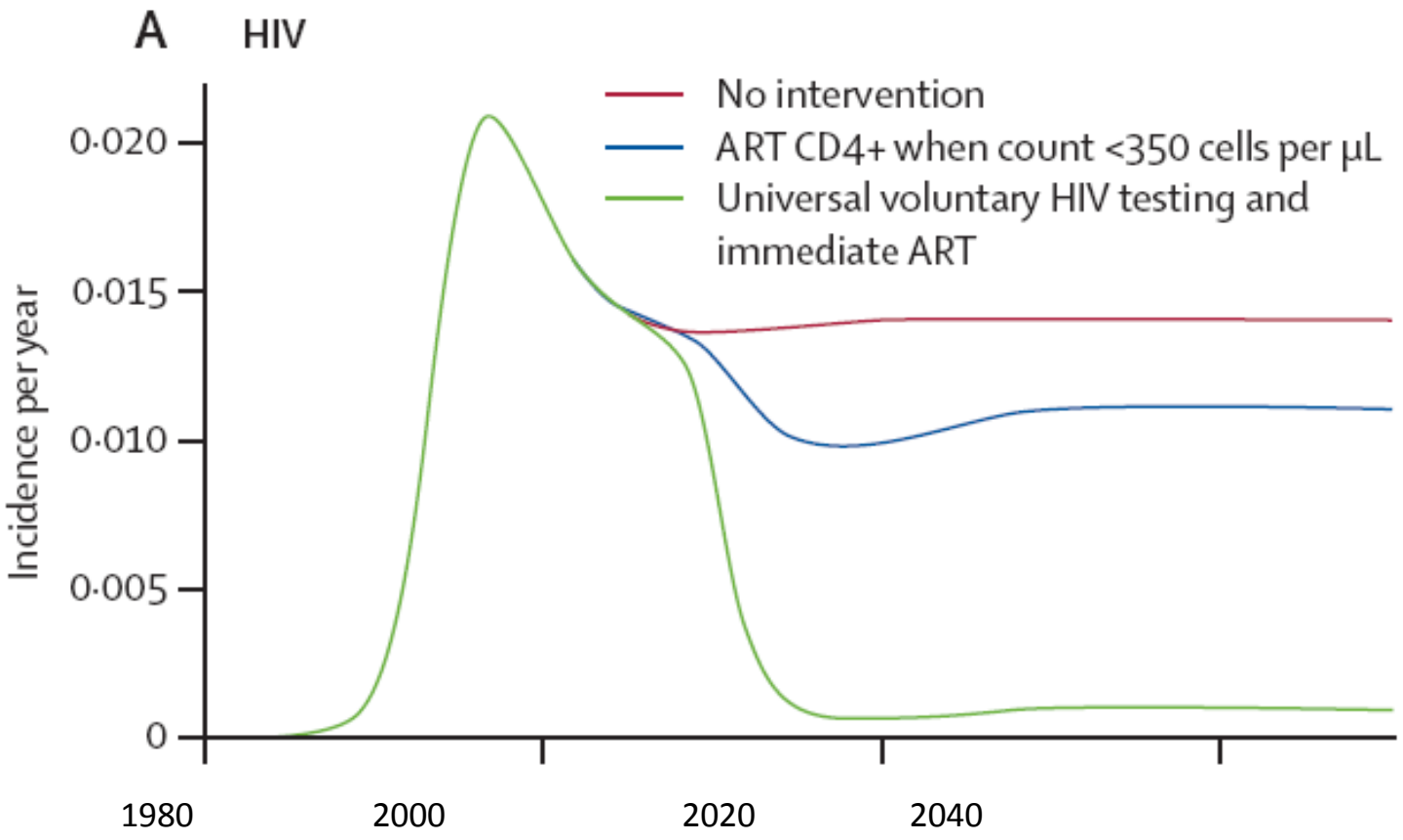
Setting the scene

Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

www.thelancet.com Vol 373 January 3, 2009

HIV Universal test and Treat



ART for Prevention: Assumptions=Results

Cohen and Gay, 2010

1st author (yr)	Key assumptions	Results
Blower (2000)	Steady risk behavior levels; low resistance rate; 50% - 90% ART coverage	substantial ↓in HIV incidence
Lima (2008)	75% - 100% ART coverage when CD4 < 200; stable adherence	37% - 62% ↓ in HIV incidence
Law (2001)	2X-10X ↓ in infectiousness; 40% - 70% ↑ in unsafe sex	Behavioral disinhibition could limit preventive benefit
Fraser (2004)	Viral load suppression on ART limits transmission; 66% ↑ in risk behavior	Behavioral disinhibition could limit preventive benefit
Wilson (2008)	Effective ART reduces viral load to < 10 copies / mL; decreased condom use	Behavioral disinhibition could limit preventive benefit
Baggaley (2006)	Treatment of all w/ AIDS & pre-AIDS; decreased risk-taking	Only small number of infections averted
Granich (2009)	Universal annual HIV testing & immediate treatment	African HIV epidemic could be ended

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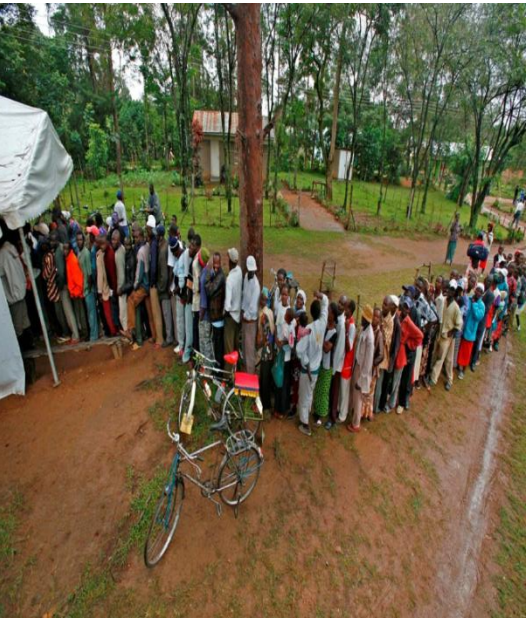
Implementation of testing

Currently
80-90% of PLWHA in SSA **DON'T** know their status
27% of PLWHA in UK don't know their status

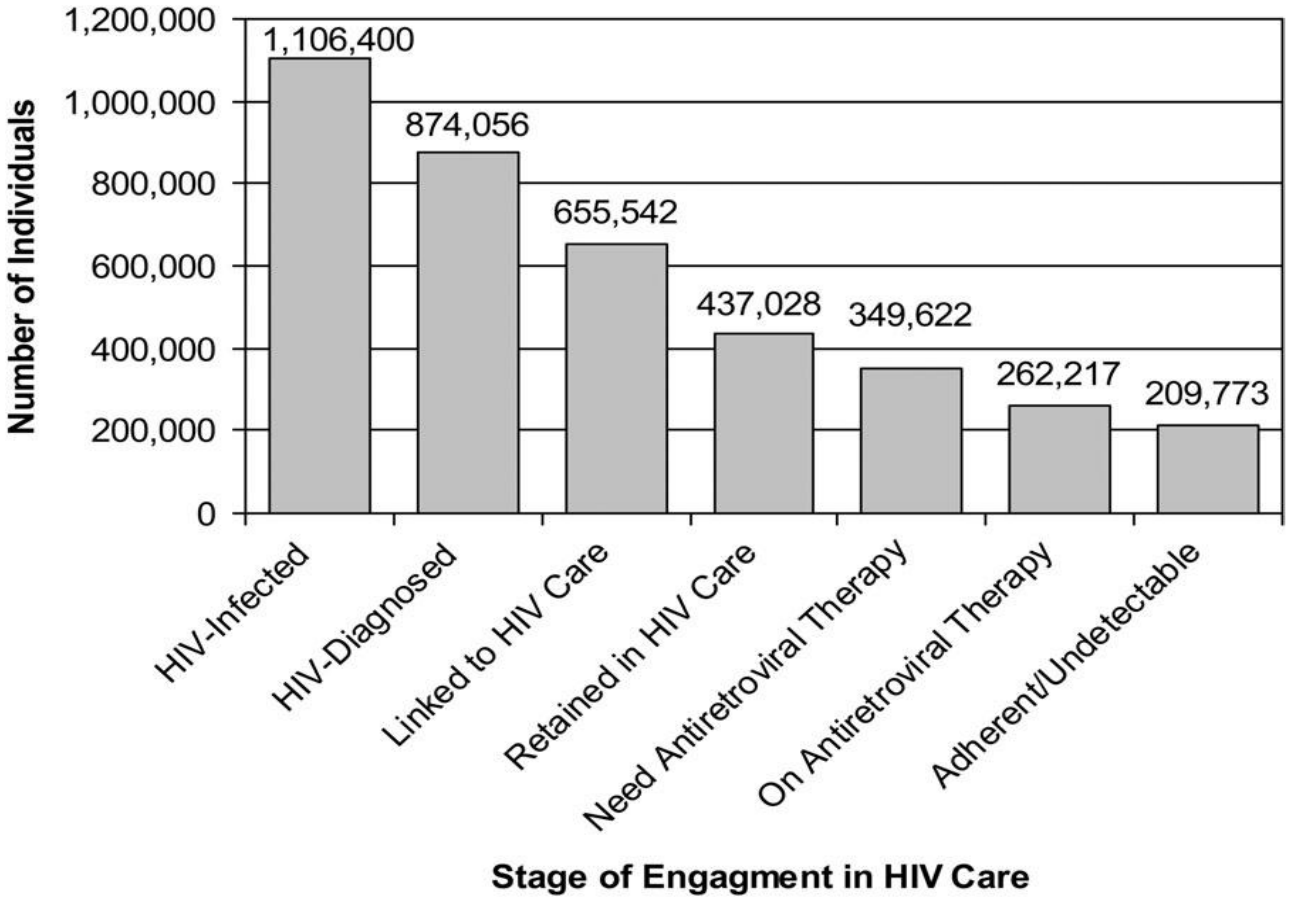


Uptake of HIV testing

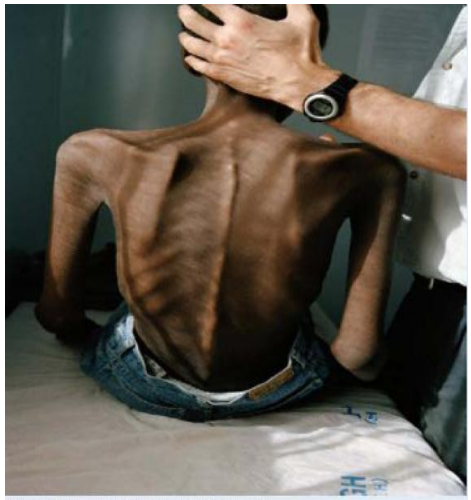
- **“Treat and we will test”**
- What frequency of testing is needed to prevent transmission? Annual 2-5 years (Dodd 2010 AIDS)
- How best to deliver testing?
  - POCT,
  - self testing
  - work place,
  - house-to-house,
  - linkage with other services- TB, Malaria, Vaccination, GUM screens, opt out hospital settings

Test, Link and Treat: The Reality

Gardner et al CID, 2011



Treatment

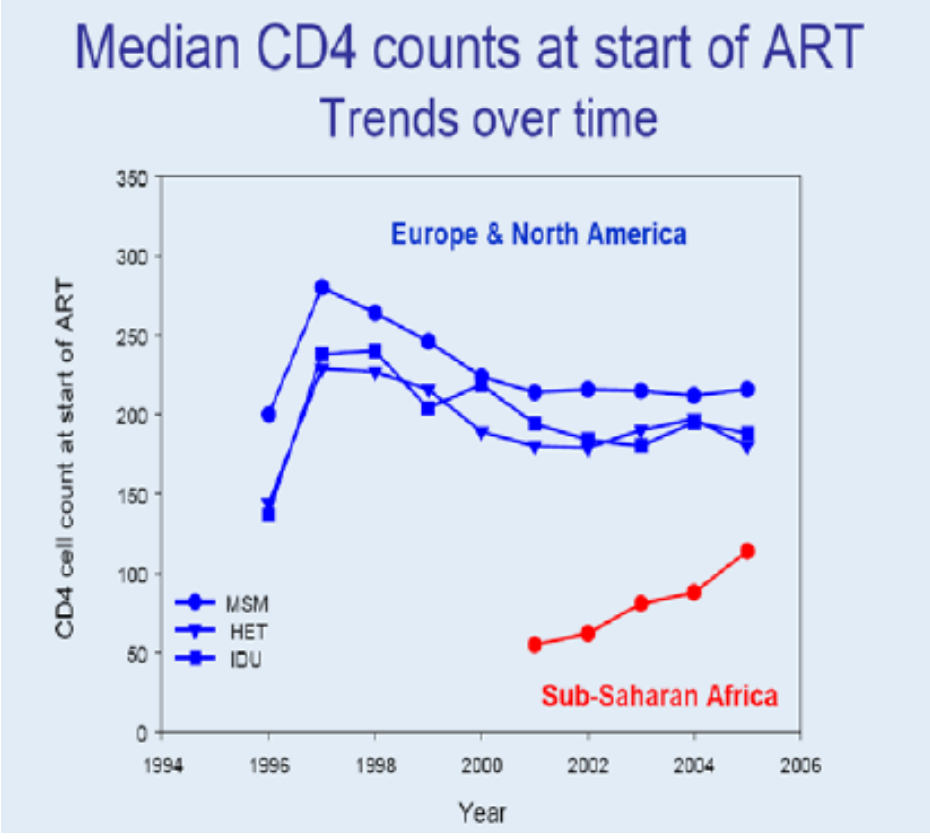


2010 WHO treatment guidelines recommend ART for CD4 <350
Universal access for pregnant and breast feeding women

BUT
Inability to deliver ART for 5 million people now living in need of immediate ART

When to Start?
START trial CD4 > 500
immediate or defer

Risks vs benefit of earlier ART are unknown



Do we really understand all the issues of early ART?

- **Pros**
- Earlier treatment maybe beneficial to the individual
- Reduces the rates of TB (rate of TB increases by 0.42 cases/100PYs per 100 fall in CD4 count Lawn et al CROI 2009)
- Automatically takes care of PMTC programs as all HIV+ve women are on ART
- Reduces sexual transmission in monogamous HIV serodiscordant relationships

- **Cons**
- Lack of data on long-term risk of drug resistance
- Lack of data on risk of toxicity vs clinical benefit of longer ART exposure (START trial)
- Acceptability within communities where HIV status remains stigmatising
- Feasibility of operationally delivering ART to almost all the HIV+ve population (San Francisco MSM achieved >90% ART coverage to confer a reduction in incidence)
- Is this best use of resources?

Monitoring

Monitoring /safety

– renal, liver, bone marrow (blood/urine) function

Efficacy tests (CD4, RNA VL)

– Need for roll-out of low-cost point-of-care tests

– CD4, RNA VL, resistance testing

- Cost
- Lab capacity
- Impact on pace of roll-out
- Need for evidence-based monitoring

How to do the monitoring

Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial

DART Trial Team*

DART

Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial

Ian Sanne, Catherine Orrell, Matthew P Fox, Francesca Conradie, Prudence Ive, Jennifer Zeinecker, Morna Cornell, Christie Heiberg, Charlotte Ingram, Ravindre Panchia, Mohammed Rassool, René Gonin, Wendy Stevens, Handré Truter, Marjorie Dehlinger, Charles van der Horst, James McIntyre, Robin Wood, for the CIPRA-SA Study Team*

CIPRA
S. Africa

Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial

Shabbar Jaffar, Barbara Amuron, Susan Foster, Josephine Birungi, Jonathan Levin, Geoffrey Namara, Christine Nabiryo, Nicaise Ndembi, Rosette Kyomuhangi, Alex Opio, Rebecca Bunnell, Jordan W Tappero, Jonathan Mermin, Alex Coutinho, Heiner Grosskurth, on behalf of the Jinja trial team*

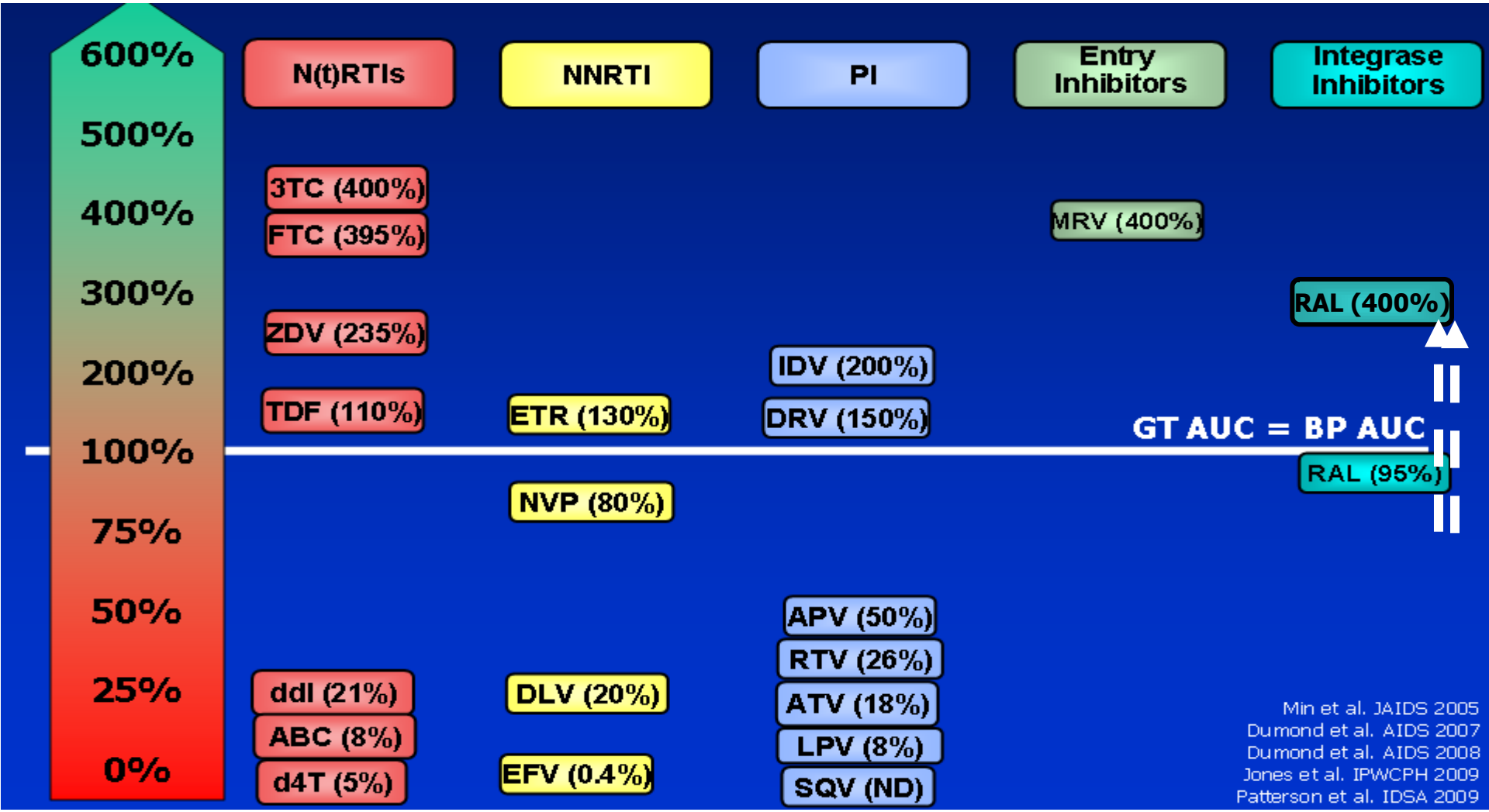
Jinja
Uganda

But not all ART are equal… What should we treat with?

Sexual transmission requires drug genital tract penetration and reduction in genital tract viral loads to < 400 copies HIV RNA/ml

Concentration of ART in the Female Genital Tract

Results Depend on Drug Class



Min et al. JAIDS 2005
Dumond et al. AIDS 2007
Dumond et al. AIDS 2008
Jones et al. IPWCPH 2009
Patterson et al. IDSA 2009

Summary-much to do…

- **ART has the power to reduce transmission of HIV, but the exact magnitude of ART transmission suppression and its durability are unknown**
- **ART combinations designed for HIV prevention can be developed**
- **The population benefit of ART depends on**
  - **durable transmission suppression**
  - **the contribution of acute HIV infection**
  - **Sexual mixing within a population**
  - **Frequency of testing**

Goals of this lecture

- Reminder of the biology of HIV infection
- Summary of HIV transmission
- The global HIV epidemic
- The universal test and treat concept
- Evidence to support the idea
- Could it work- data from ecological studies
- How to test the hypothesis- PopART
- ***Should we try it? The ethics***

The Economist June 4, 2011

" Thirty years on, it looks as though the plague can now be beaten, if the world has the will to do so"

Should we?

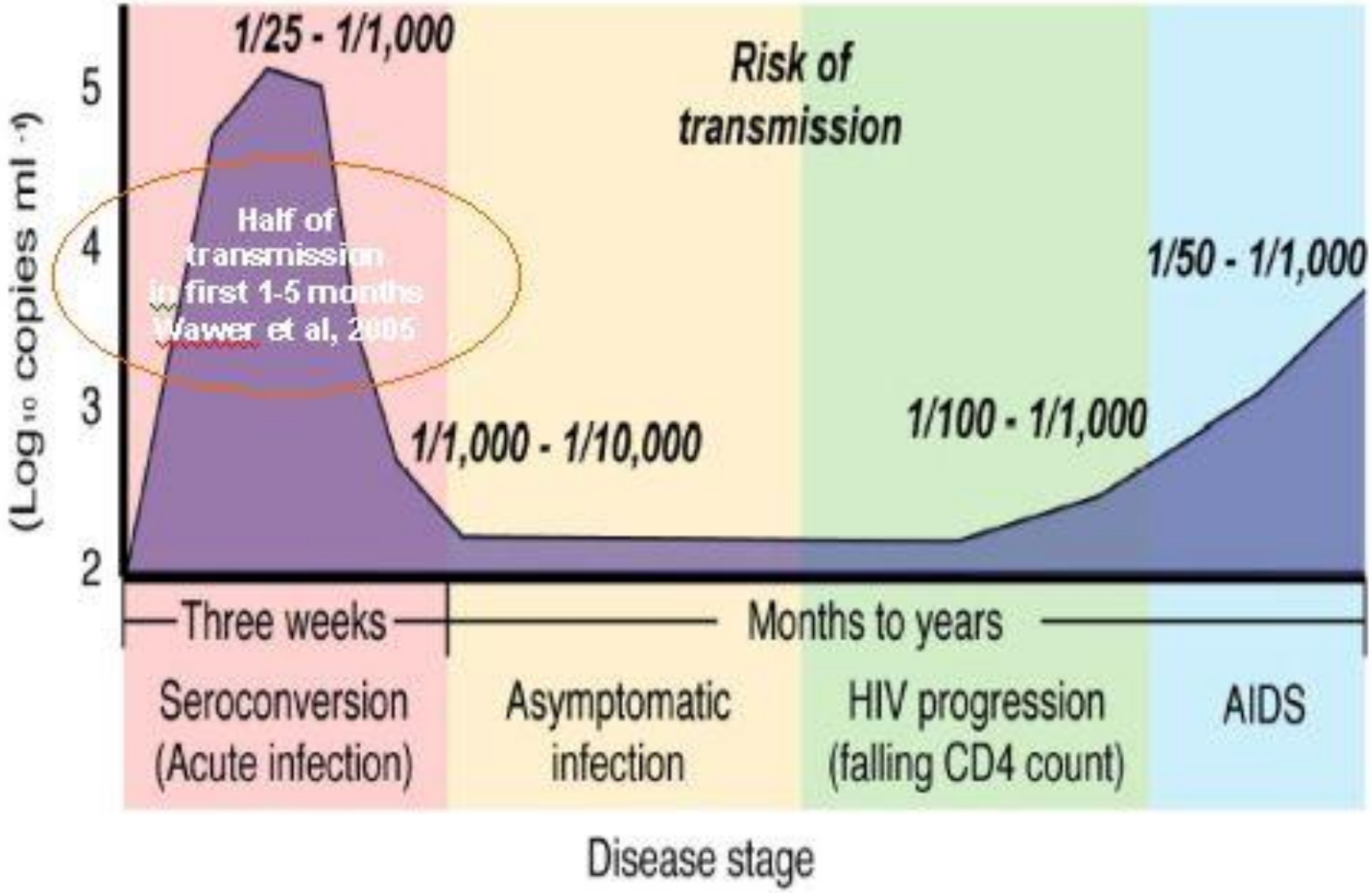
It is disappointing to frame HIV/AIDS intervention as an issue of "cost-effectiveness."
When people put forward the cost-effectiveness argument regarding access to health care it seems a thinly veiled way of saying that some lives are simply not worth saving.

- How do you really calculate the costs of not intervening any ways?
- Have you factored in the number of children who are orphaned because of HIV/AIDS?
- The communities that are utterly decimated by it?
- What about all the other human costs? If 20% of all economically reproductive age group in the developed world had HIV would we behave the same?

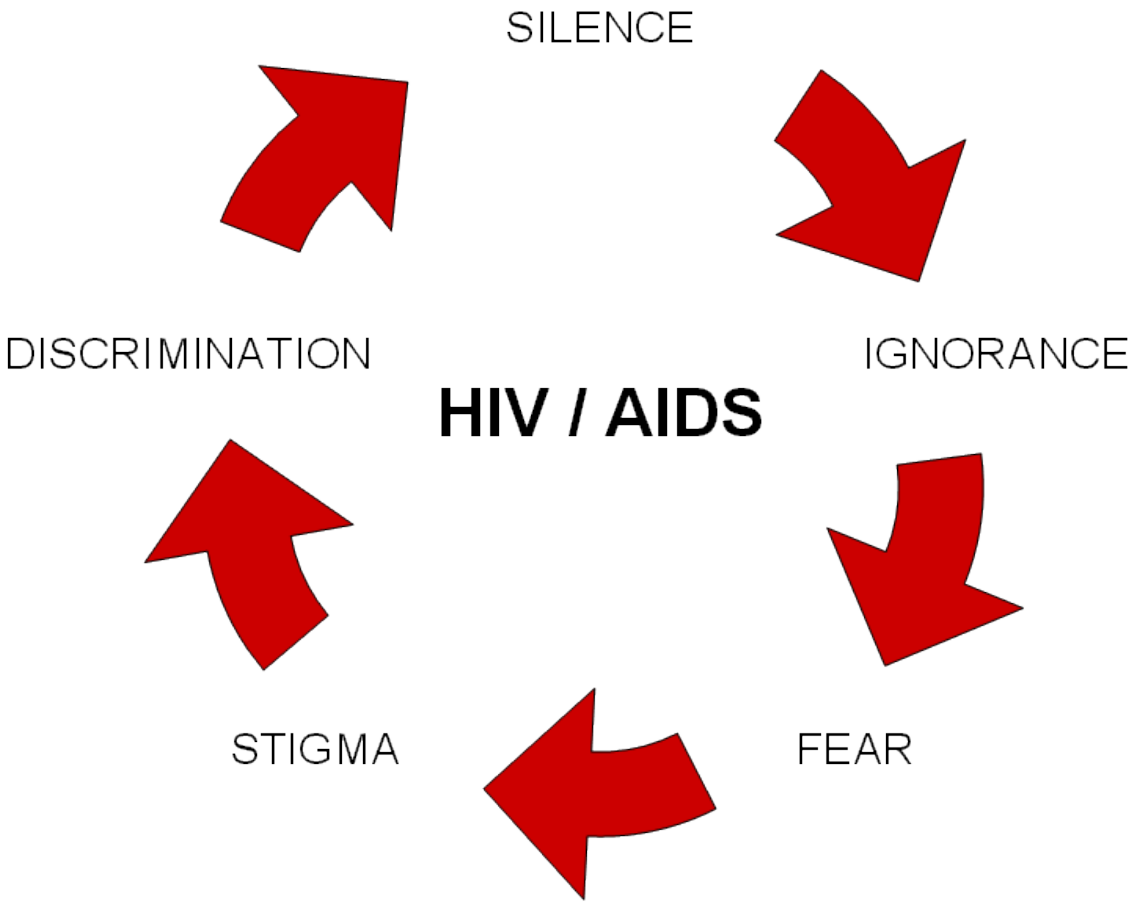
A paradigm shift is needed. If we are to truly overcome HIV/AIDS we, as a global community, must acknowledge that ***every human being has a right to adequate health care and that no lives are more or less "cost-effective" to save then others.***

What are the problems of a Universal HIV test and treat model?

- Ignores:
  - Human rights issues: coercion, marginalisation of groups choosing not to comply or adhere or test
  - Compensatory increased sexual disinhibition may counteract benefit
  - Increased life expectancy on ART will lead to ‘treatment fatigue’ poor adherence to treatment and maybe a worse public health disaster untreatable infection with drug resistant virus



Source: Galvin, S.R. & Cohen, M.S. (2004) The role of sexually transmitted diseases in HIV infection. Nature Reviews Microbiology, 2(1).


SILENCE
IGNORANCE
FEAR
STIGMA
DISCRIMINATION
HIV / AIDS

Comparison of mortality in low and high income countries

- **57 million people die each year**
- Cardiovascular diseases kill more people each year than any others. In 2008, 7.3 million people died of ischaemic heart disease, 6.2 million from stroke or another form of cerebrovascular disease.
- **In high-income countries**
  - **> 66%** of all people live beyond the age of 70
  - Predominant cause of death is chronic diseases: cardiovascular disease, chronic obstructive lung disease, cancers, diabetes or dementia.
- **In low-income countries**
  - **<20%** reach the age of 70,
  - **>30%** of all deaths are among children under 15.
  - Predominant cause of death is infectious diseases: lung infections, diarrhoeal diseases, HIV/AIDS, tuberculosis, and malaria.
  - Other causes: Complications of pregnancy and childbirth together continue to be leading causes of death, claiming the lives of both infants and mothers.

Causes of death lower income countries WHO figures June 2011

Causes of death	Deaths in millions	% of deaths
Lower respiratory tract infection	1.05	11.3%
Diarrhoea	0.75	8.2%
HIV/AIDS	0.72	7.8%
Ischaemic heart disease	0.57	6.1%
Malaria	0.48	5.2%
Stroke CVD	0.45	4.9%
TB	0.40	4.3%

ART:

Potentially more efficacious

than any of the previously evaluated prevention methods

Are the underlying assumptions of the models correct?

But where will the money come from- and where does it go?

- http://www.youtube.com/watch?v=MkWoKgLhDVs

Triage

How do we allocate resources fairly and with the best effect?

- **TRIAGE: Dr. James Orbinski's Humanitarian Dilemma**
  RSM Global Health and Human Rights Film Club
- **Thursday 24 November 2011, 6.00pm**
  at the Royal Society of Medicine
  organised by the RSM Global Health and Human Rights Film Club
- http://www.youtube.com/watch?v=TMPCjy_Arbo