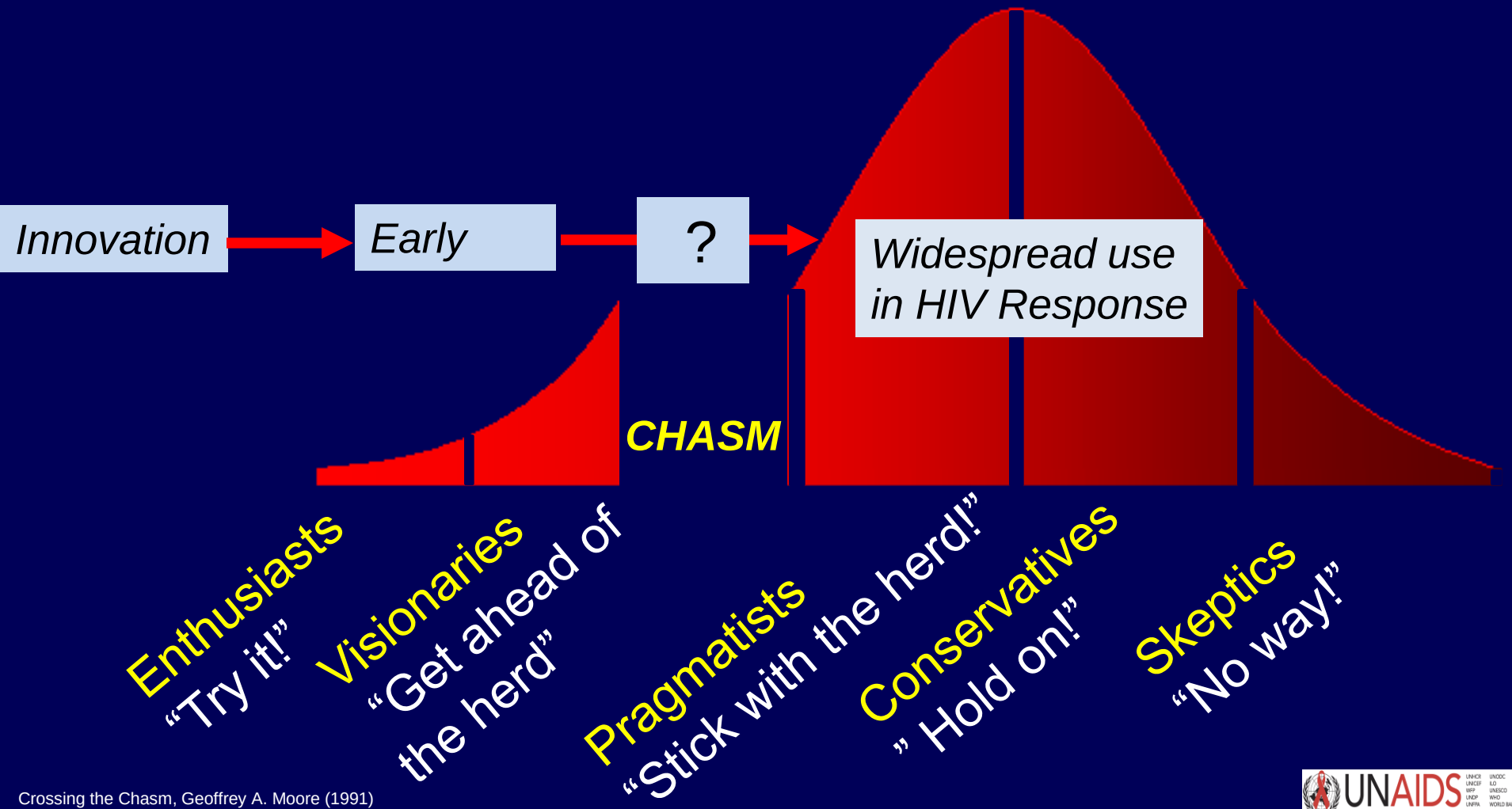
EATG TasP Webinar

Harnessing treatment as prevention

November 2014

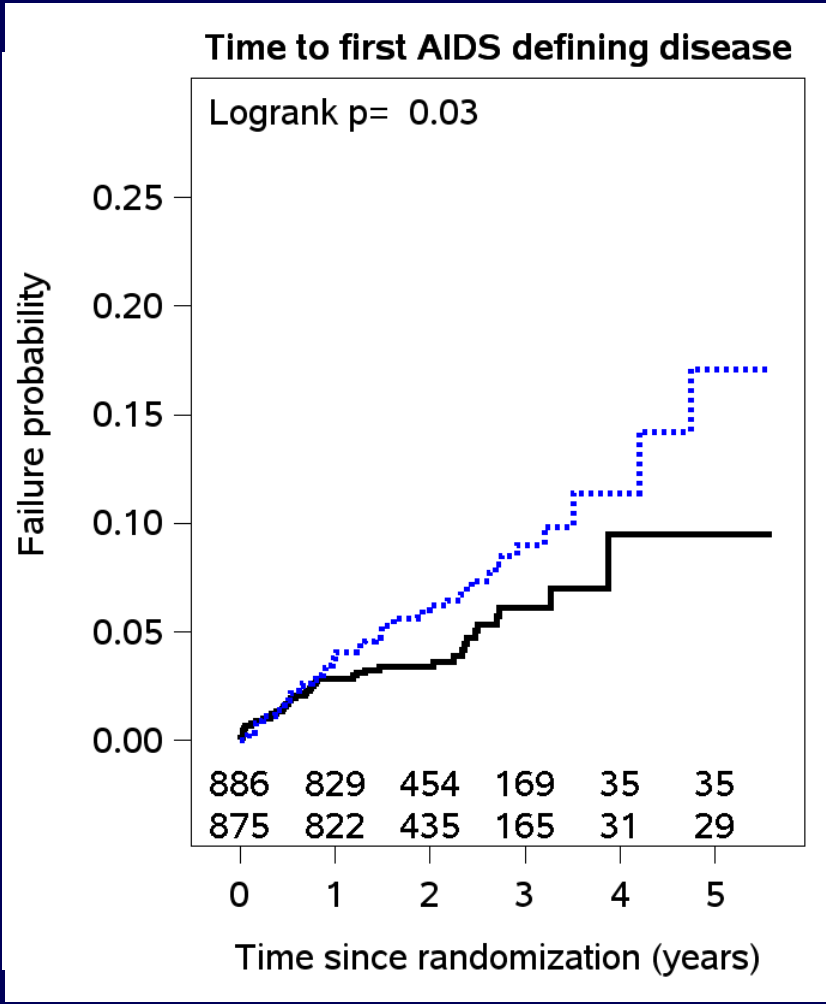
Reuben Granich, MD, MPH
Senior Advisor, Care and Treatment
UNAIDS

To end AIDS we will need to bridge the "innovation to scale" chasm



Crossing the Chasm, Geoffrey A. Moore (1991)

HPTN 052 showed clinical benefit for earlier ART at <550 CD4 cell count



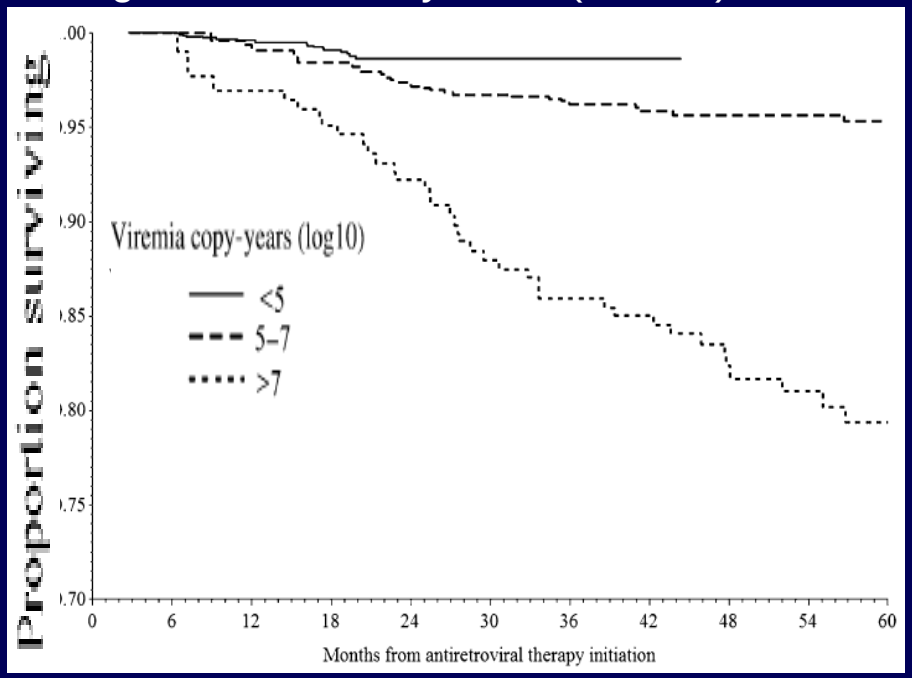
Number of subjects experiencing ≥1 event	Delayed	Immediate
Tuberculosis	**34 (4%)**	**17 (2%)**
Serious bacterial infection	**13 (1%)**	**20 (2%)**
WHO Stage 4 event	**19 (2%)**	**9 (1%)**
Oesophageal candidiasis	2	2
Cervical carcinoma	2	0
Cryptococcosis	0	1
HIV-related encephalopathy	1	0
Herpes simplex, chronic	8	2
Kaposi's sarcoma	1	1
CNS Lymphoma	1	0
Pneumocystis pneumonia	1	0
Septicemia	0	1
HIV Wasting	2	0
Bacterial pneumonia	1	2

Source: Grinsztejn B, et al, Lancet Infectious Diseases, 4 March 2014

UNAIDS

Unchecked viral replication impacts disease progression independent of CD4 count

Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort

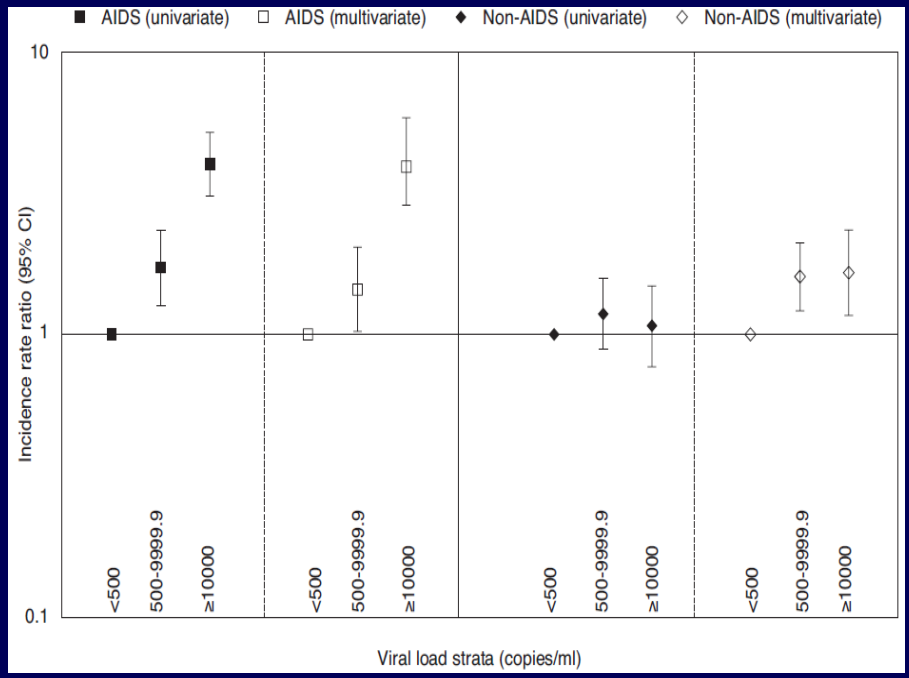


- Cumulative exposure to replicating virus independently associated with mortality.
- Multivariable model (HR 1.44 per log10 copy-year/mL; 95% CI: 1.07–1.94).

Mugavero et al. Clin Infect Dis. 2011

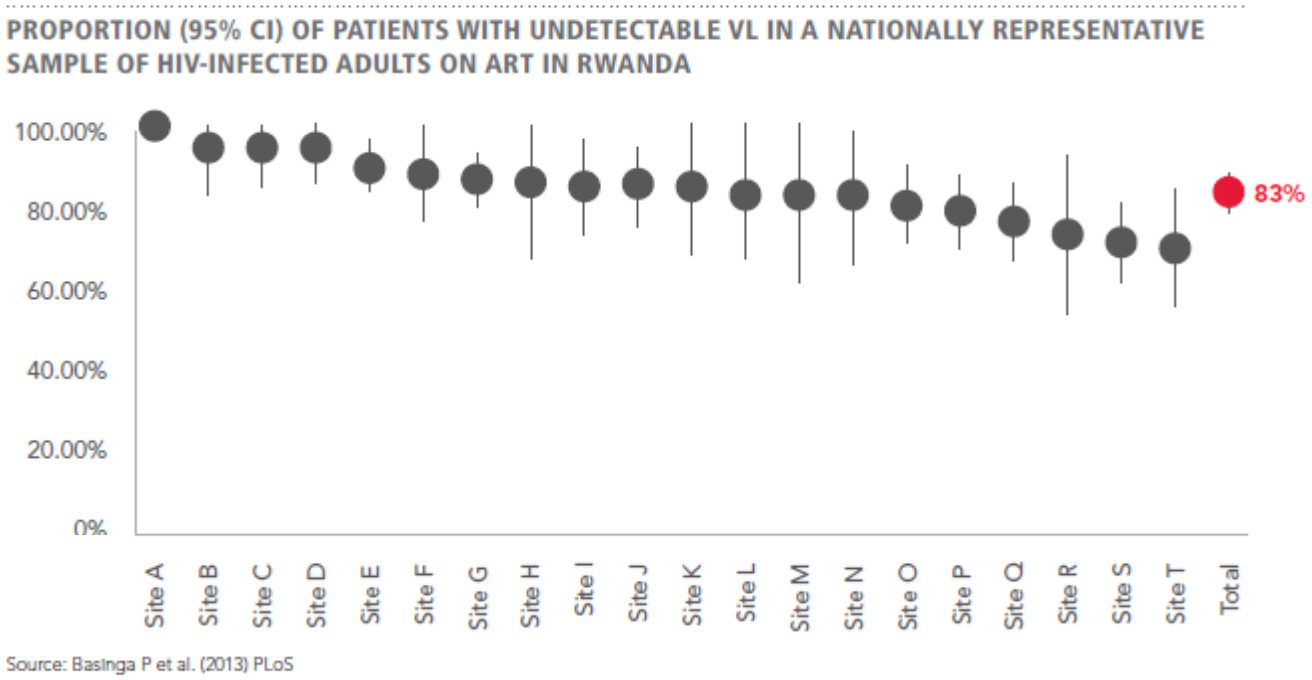
Reekie et al. AIDS 2011

EURO SIDA



- Impact of VL on fatal and non-fatal AIDS-related and non-AIDS-related events.
- After adjustment, **rates of non-AIDS events were 61% (*P*=.001) and 66% (*P*=.004) higher** in those with VLs 500-9,999 and >10,000, respectively, than in those with VLs <500.

Scaling high viral suppression is feasible: population based data from Rwanda



Basina P, Plos 2013

HIV treatment reduces viral load and heterosexual transmission (2003)

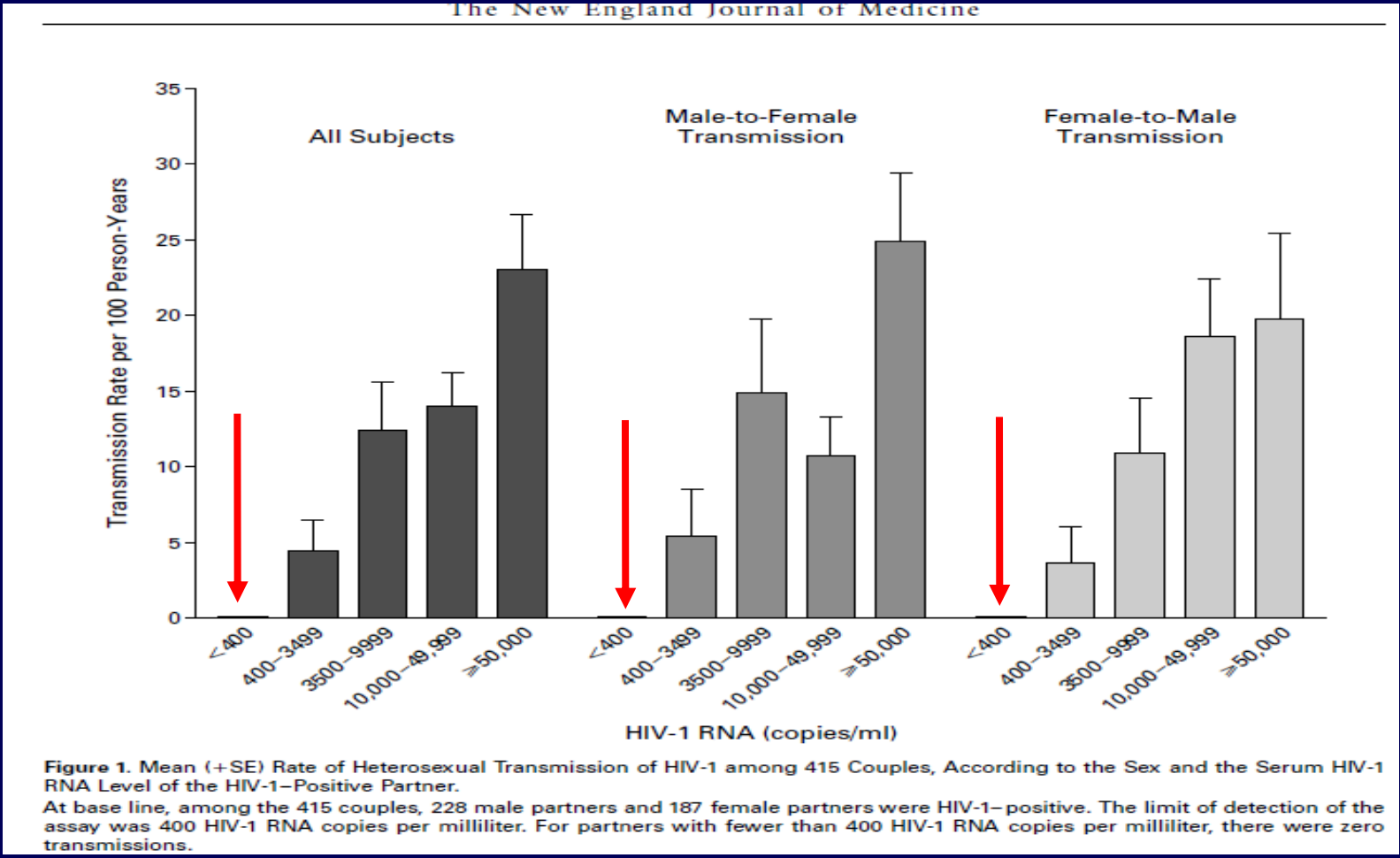
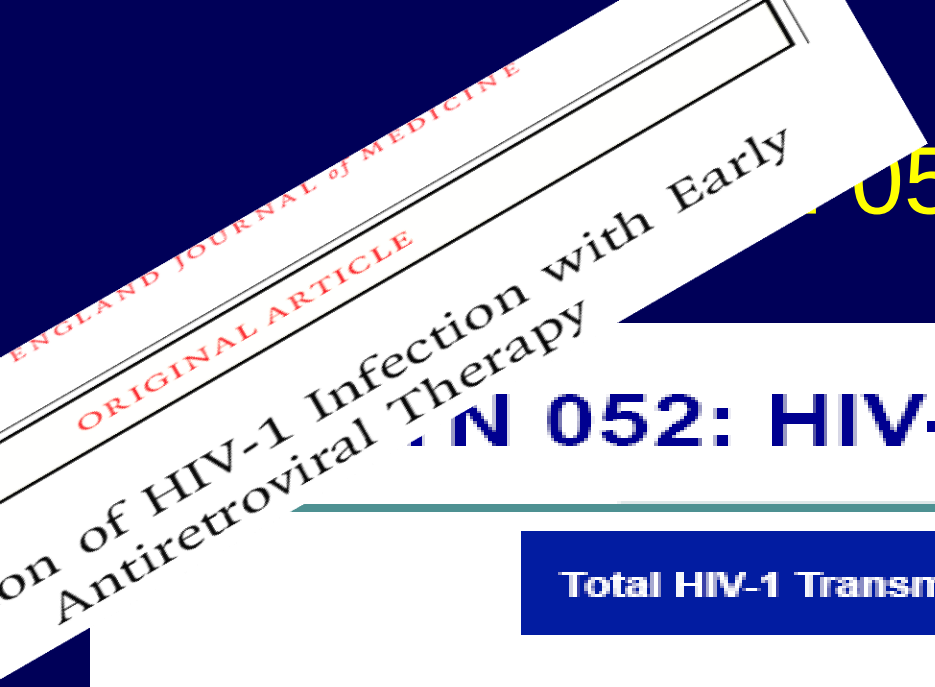


Figure 1. Mean (+SE) Rate of Heterosexual Transmission of HIV-1 among 415 Couples, According to the Sex and the Serum HIV-1 RNA Level of the HIV-1–Positive Partner.

At base line, among the 415 couples, 228 male partners and 187 female partners were HIV-1–positive. The limit of detection of the assay was 400 HIV-1 RNA copies per milliliter. For partners with fewer than 400 HIV-1 RNA copies per milliliter, there were zero transmissions.

Quinn et al. NEJM. 2003;342(13):921-929.



052 Results

N 052: HIV-1 Transmission

Total HIV-1 Transmission Events: 39

- **Linked Transmissions: 28**
  - **Immediate Arm: 1**
  - **Delayed Arm: 27**
  - $p < 0.001$
- **Unlinked or TBD Transmissions: 11**

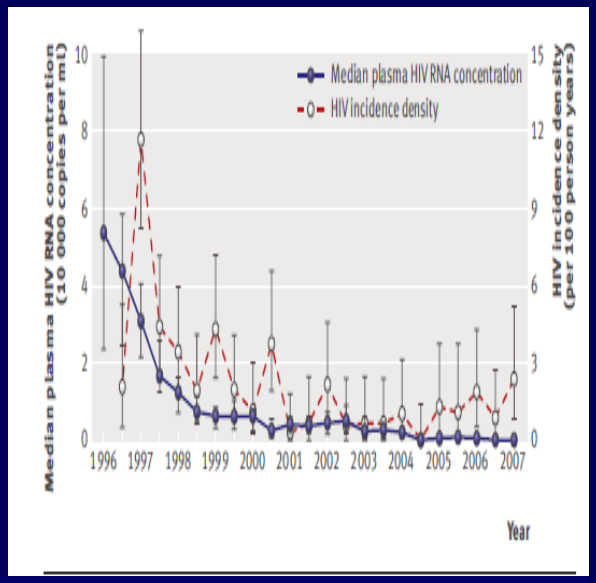
- 18/28 (64%) transmissions from infected participants with CD4 >350 cells/mm^3 and VL >50,000 copies/ml at transmission
- 23/28 (82%) transmissions in sub-Saharan Africa
- 18/28 (64%) transmissions from female to male partners

Cohen NEJM 2011

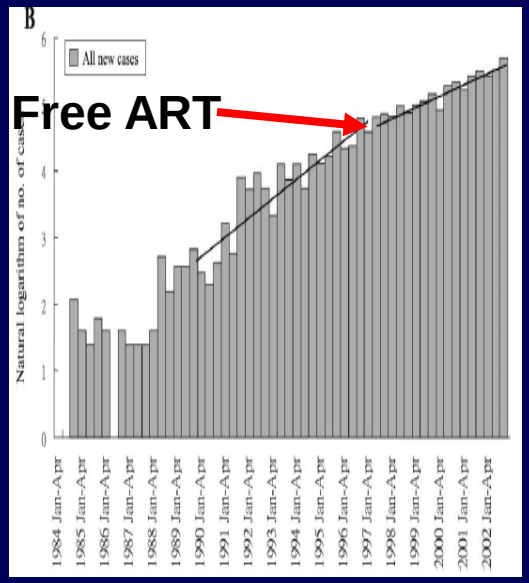
UNAIDS

Scaling treatment has an impact on community HIV transmision

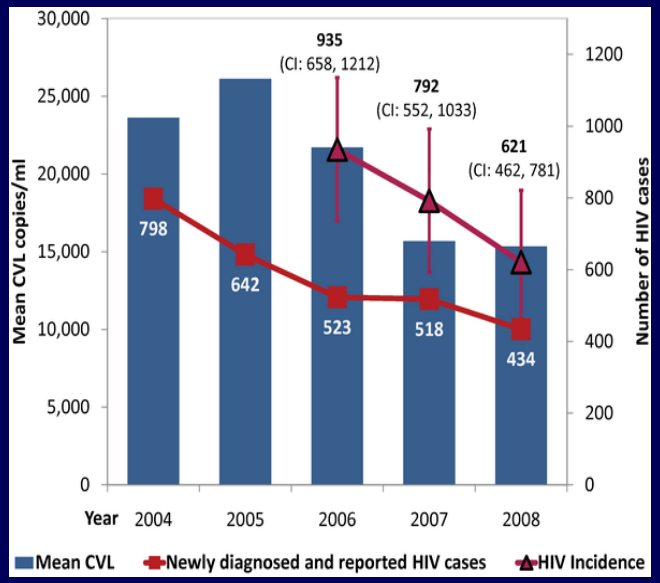
BC Canada



Taiwan



San Francisco

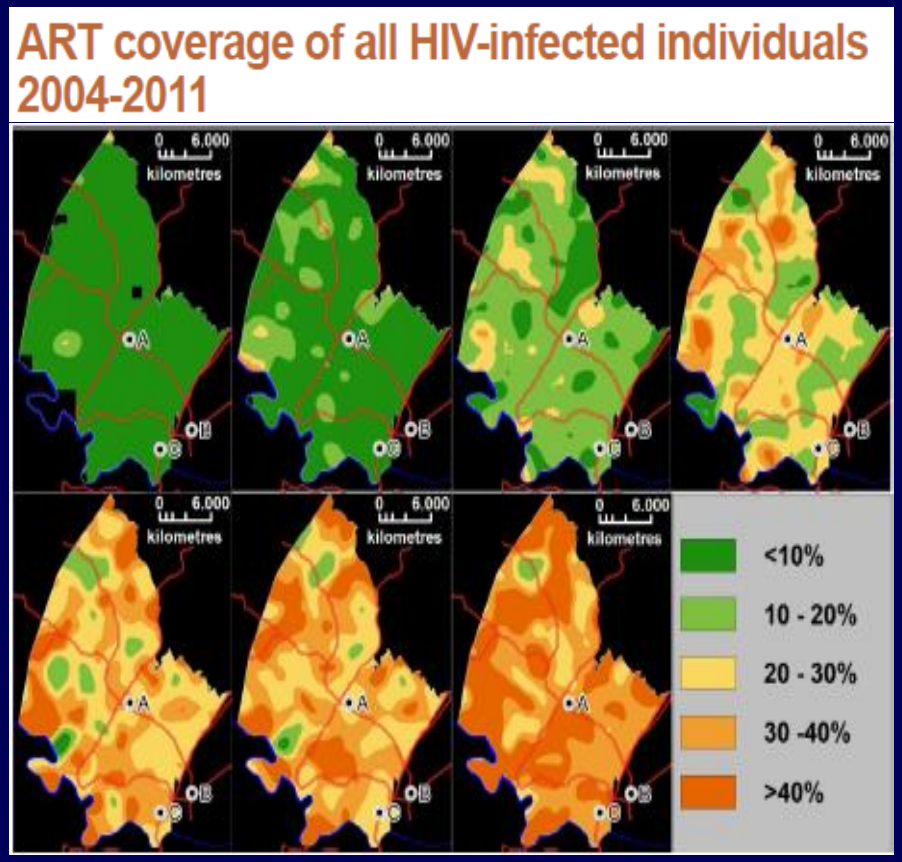


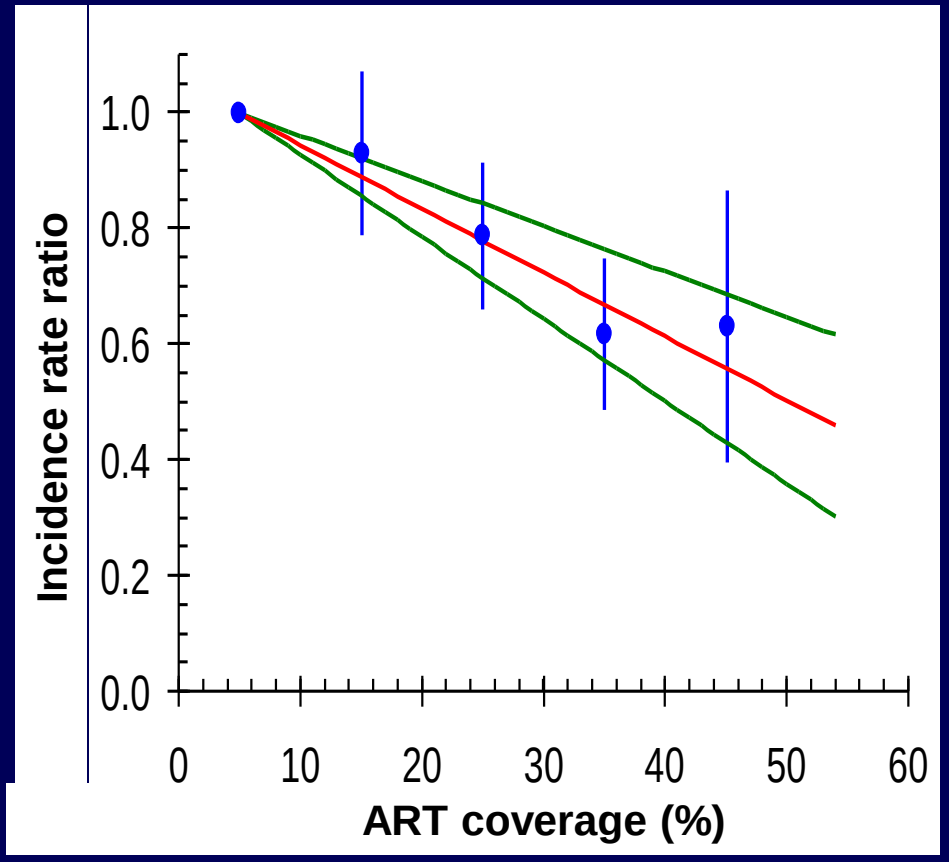
Wood et al. BMJ 2009;338b:1649

Fang et al. JAIDS 2004;190:879-85

Das et al. PlosOne 2010

Community scaling of ART coverage reduces individual risk of transmission: KZN South Africa





Incidence falls by 1.1% (0.8%-1.4%) for each 1% increase in coverage

Tanser Science 2013; Williams 2013

WHO 2013 Guidelines
Using new science to optimize TasP

- Earlier Initiation of ART (CD4 ≤ 500):
  - Strategic use to maximize treatment & prevention benefits
  - Symptomatic and CD4 ≤ 350 as a priority
  - CD4-independent situations for ART initiation:
    - TB-HIV and HBV-HIV
    - pregnant women (*Option B+*)
    - sero-discordant couples
    - children < 5 years of age
- No specific recommendations for key populations

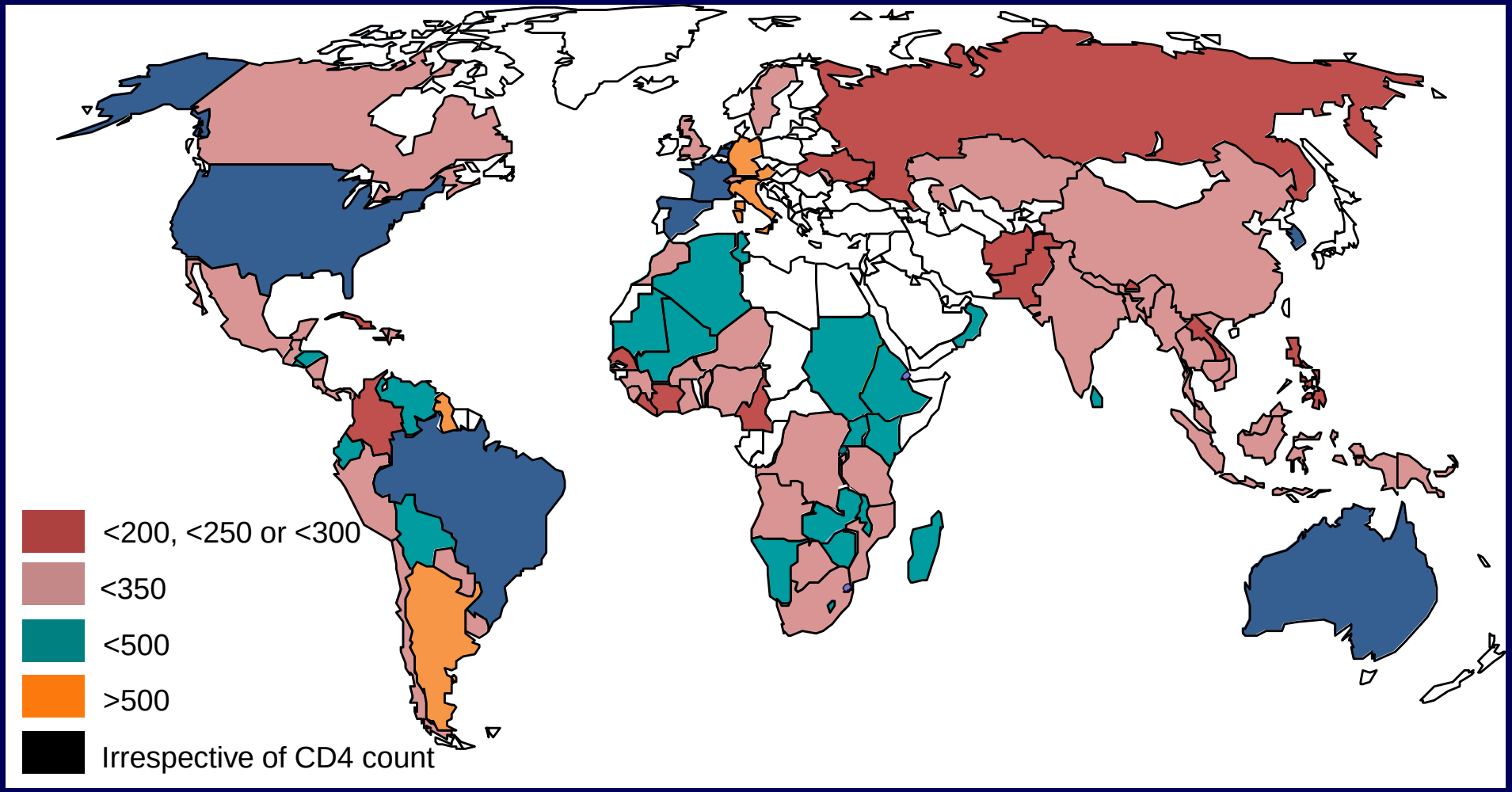
ART initiation for asymptomatic people

ART initiation criteria	No. of Countries	People with HIV (2013)	Countries
Irrespective of CD4 count	**7**	908,000 (2.6%)	Australia, Brazil, British Columbia (Canada), France, Korea, the Netherlands, Spain, United States, Thailand (reported)
Consider for CD4 >500	**6**	127,700 (0.3%)	Argentina, Austria, Germany, Guyana, Hong Kong, Italy
≤500	**22**	8,878,300 (25%)	Algeria, Bolivia, Ecuador, El Salvador, Ethiopia, Honduras, Kenya, Lesotho, Mali, Madagascar, Malawi, Namibia, Oman, Rwanda, Sri Lanka, South Sudan, Sudan, Tunisia, Uganda, Venezuela, Zambia, Zimbabwe
≤350 (consider for CD4 ≤ 500)	**5**	334,900 (1%)	Belize, Costa Rica, Guinea, Mexico, Uruguay, Europe
≤350	**42**	18,769,800 (54%)	Angola, Bangladesh, Benin, Botswana, Britain, Burkina Faso, Burundi, Cambodia, Canada, Chile, China, Democratic Republic of Congo, Djibouti, Dominican Republic, Ghana, Guatemala, Haiti, India, Indonesia, Jamaica, Kazakhstan, Malaysia, Moldova, Morocco, Mozambique, Myanmar, Nepal, Nicaragua, Niger, Nigeria, Panama, Papua New Guinea, Paraguay, Peru, Sierra Leone, South Africa, Swaziland, Sweden, Switzerland, Tanzania, Thailand, Vietnam
≤250 (consider for CD4 ≤ 350)	**1**	140,000 (0.4%)	Colombia
≤200 (consider for CD4 ≤ 350)	**5**	232,000 (1%)	Afghanistan, Cape Verde, Cuba, Russia, Ukraine
≤200	**10**	1,113,800 (3%)	Bhutan, Cameroon, Comoros, Ivory Coast, Lao PDR, Liberia, Mauritania, Pakistan, Philippines, Senegal

Source: published policy

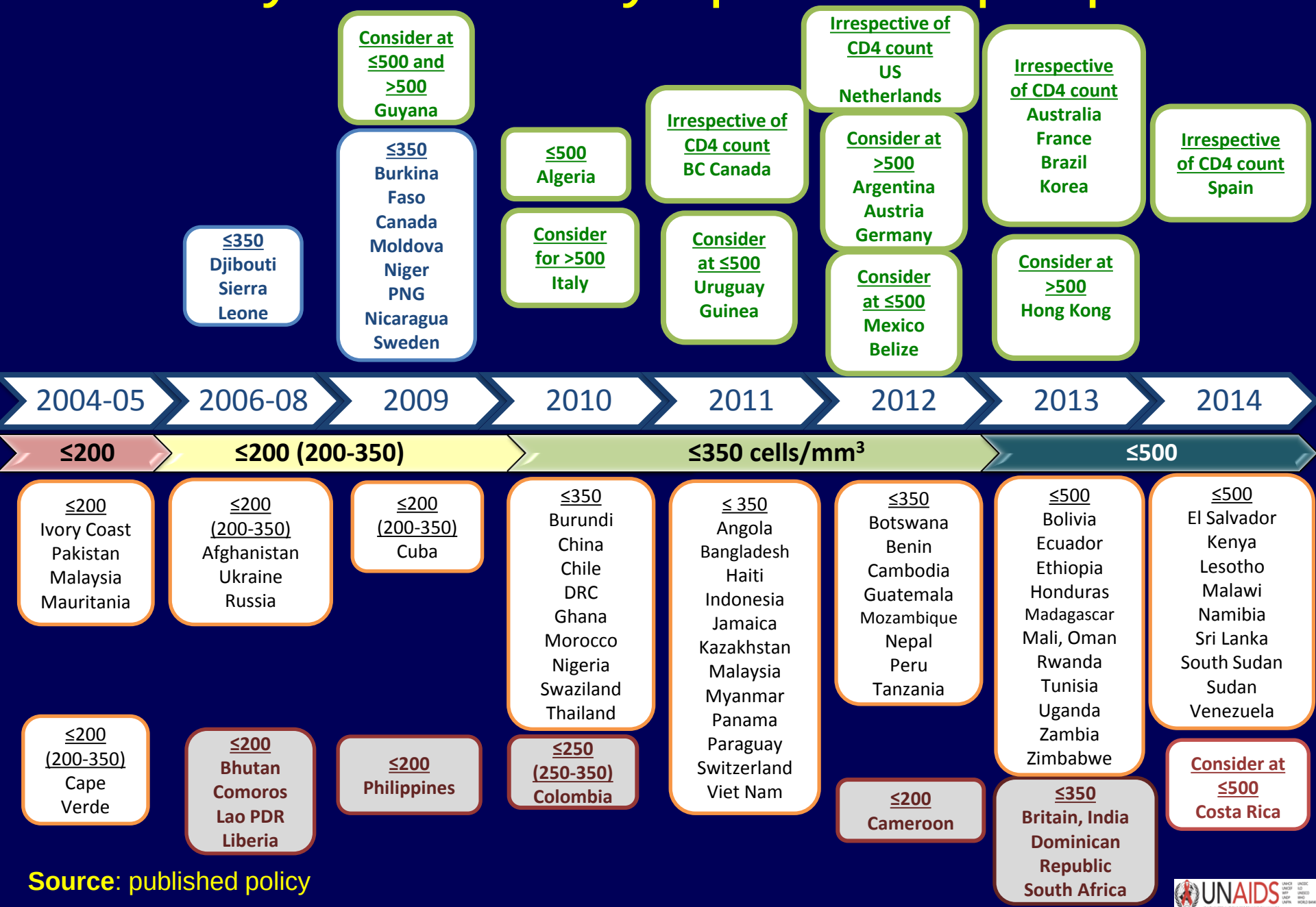
UNAIDS

ART initiation for asymptomatic people



Source: published policy

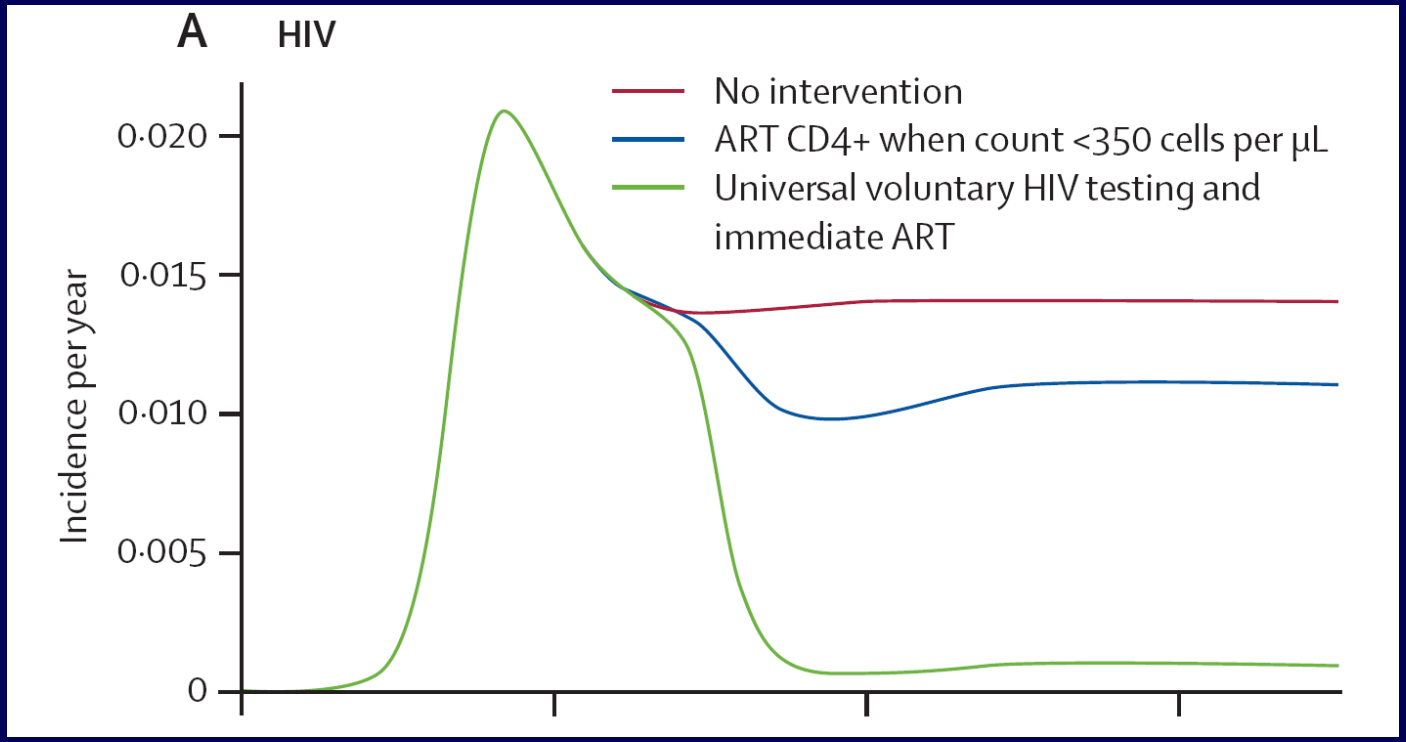
Early ART for asymptomatic people



Source: published policy

UNAIDS

ART as prevention

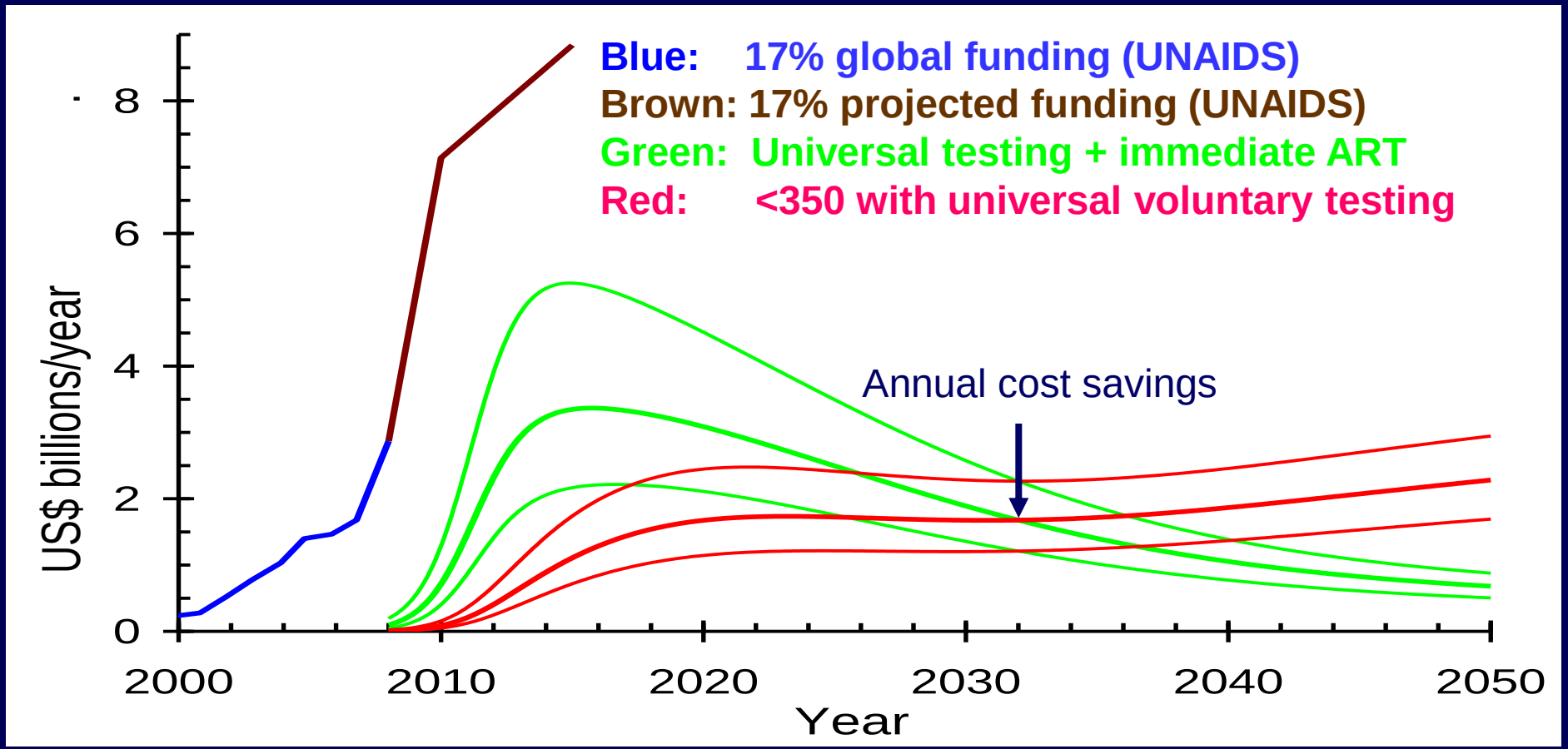


- Testing and ART impacts HIV incidence and survival
- Elimination is feasible

Granich, Gilks, Dye, De Cock, Williams *Lancet* 2008

UNAIDS

Available funding and costs: We appear to be in the right ball park….



Cohen J. HIV/AIDS. The great funding surge. Science **2008** Jul 25;321(5888):512-9.

UNAIDS. Financial resources required to achieve universal access to HIV prevention, treatment, care and support.

UNAIDS Report (2007). http://data.unaids.org/pub/Report/2007/20070925_advocacy_grne2_en.pdf.

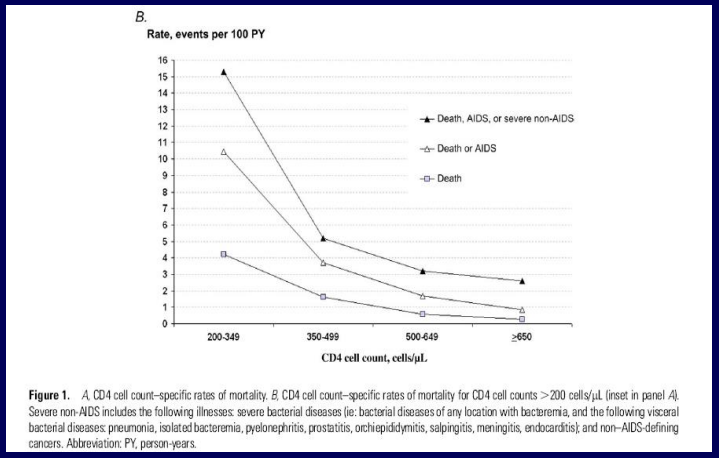


Figure 1. *A*, CD4 cell count–specific rates of mortality. *B*, CD4 cell count–specific rates of mortality for CD4 cell counts >200 cells/μL (inset in panel *A*). Severe non-AIDS includes the following illnesses: severe bacterial diseases (ie: bacterial diseases of any location with bacteremia, and the following visceral bacterial diseases: pneumonia, isolated bacteremia, pyelonephritis, prostatitis, orchiepididymitis, salpingitis, meningitis, endocarditis); and non–AIDS-defining cancers. Abbreviation: PY, person-years.

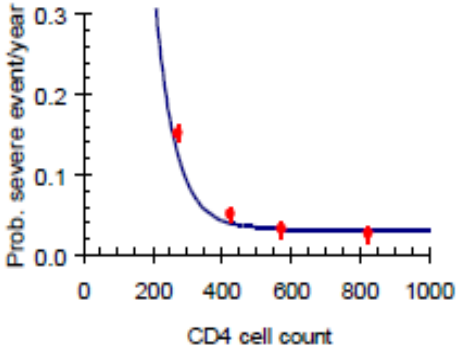


Figure 1. Line fitted to the risk of a severe event.

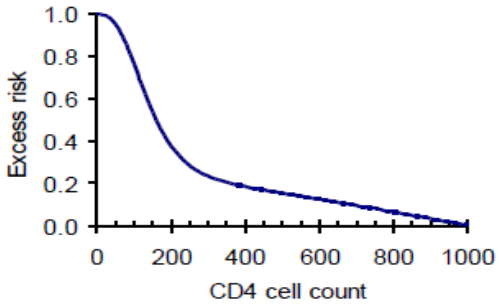


Figure 2. Excess risk of AIDS and non-AIDS morbidity and mortality as a function of the $CD4^+$ cell count at which people start treatment.

Significant cumulative risk?

Risk of AIDS, serious non-AIDS or death (Anglaret 2012)

Fitted risk of event to CD4 data

Cumulative risk of adverse events while Waiting to be eligible:

<200 38%

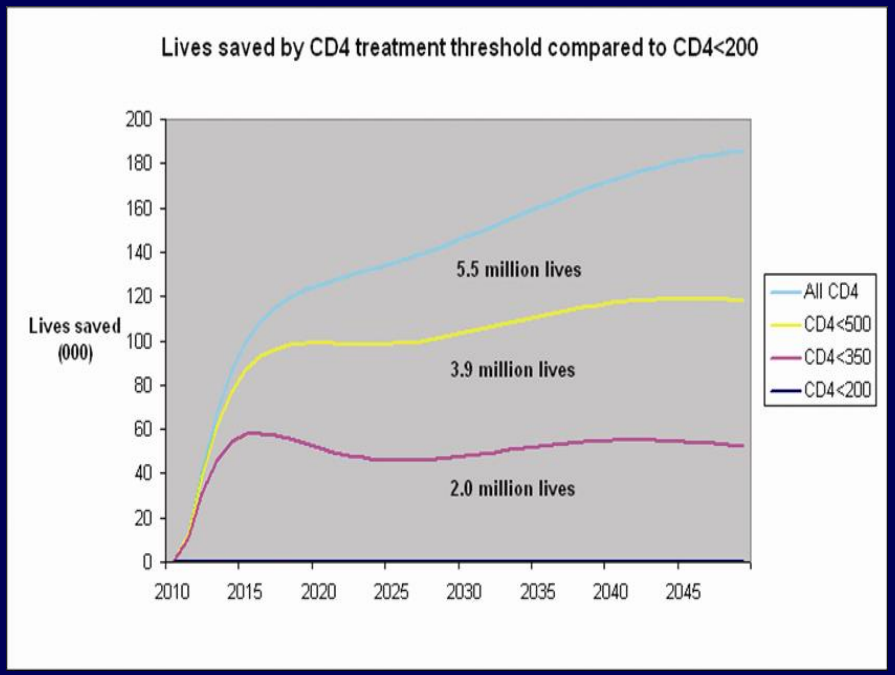
<350 21%

<500 15%

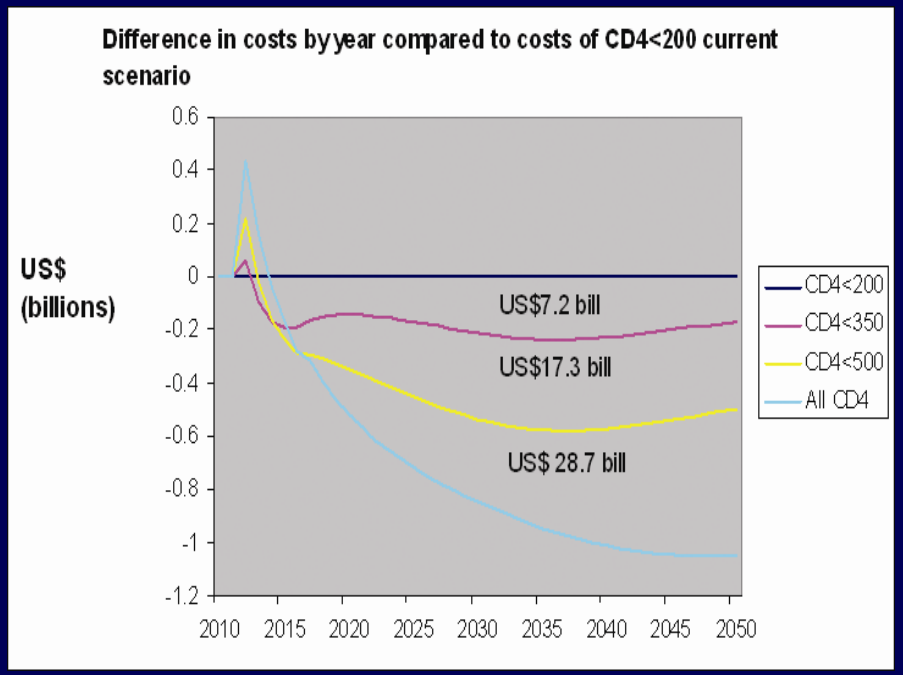
<950 2%

Anglaret, et al, CID 2012; Williams, Archives 2013

Projected impact of scaling ART access suggests that it would save lives and costs



Lives saved (millions)

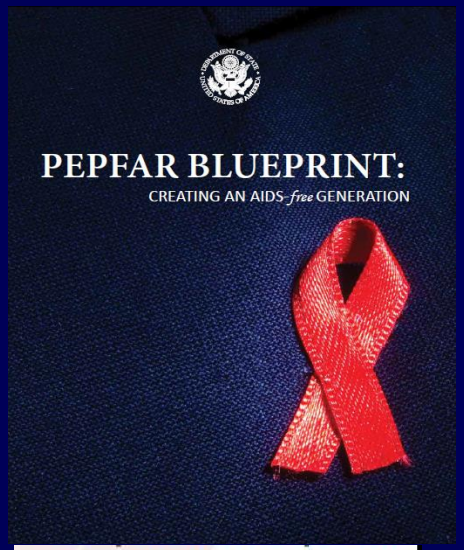


Cost savings (billions)

Granich et al. Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050. Plos Med

UNAIDS

Re-think focus: eMTCT, Testing. ART, VMMC



November 29, 2012

As a nation, we are firmly committed to turning the tide on the 30-year-old fight against AIDS. That's why I proudly announced last year that creating an AIDS-free generation is a new policy imperative for the United States.

To be clear, we still face enormous challenges. Far too many people are dying from this disease. We need to reach more people with both prevention and treatment services. But today, thanks to remarkable scientific discoveries and the work of countless individuals, organizations and governments, an AIDS-free generation is not just a rallying cry—it is a goal that is within our reach.

At the International AIDS Conference this past July, I asked our Global AIDS Coordinator, Ambassador Eric Goosby, to prepare this blueprint outlining our path to helping create an AIDS-free generation. I want the next Congress, the next Secretary of State, and all of our partners here at home and around the world to understand everything we've learned and to have a road map for how the United States will contribute to an AIDS-free generation.

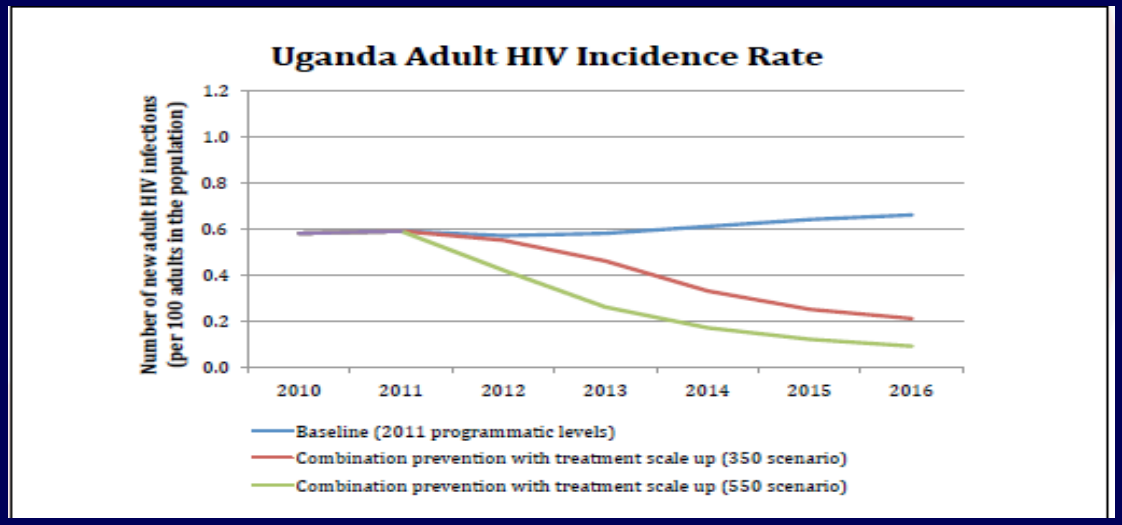
This blueprint should make one thing clear: the United States is and will continue doing our part. But creating an AIDS-free generation is too big a task for one government or one country. It requires the world to share in the responsibility. We call on partner countries, other donor nations, civil society, faith-based organizations, the private sector, foundations, multilateral institutions and people living with HIV to join us as we each do our part.

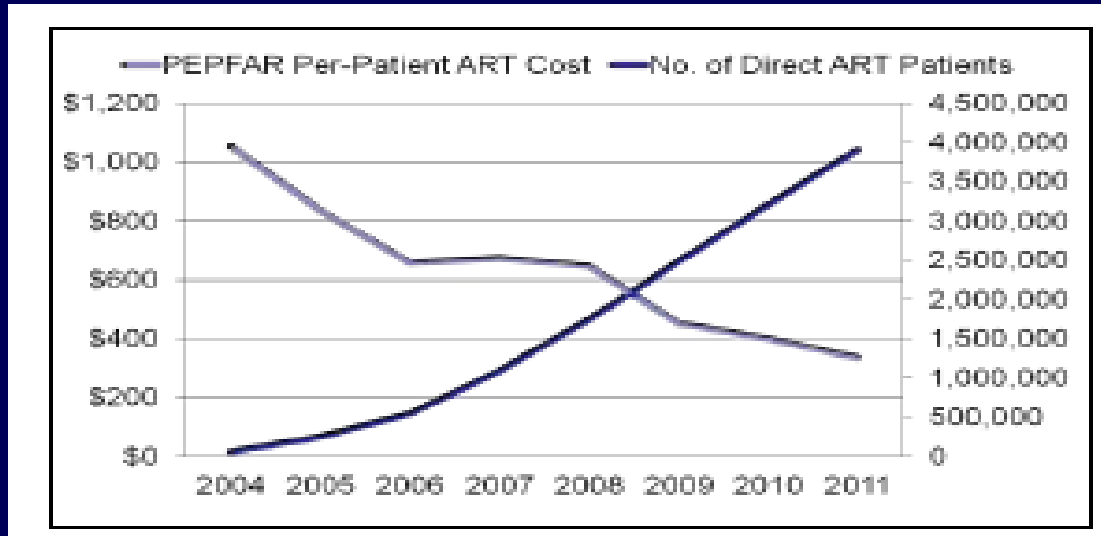
Together, we can deliver a better future to millions across the globe. A future where children are not born with HIV… where teenagers and adults are at far lower risk of contracting the virus… where those who do have the virus get lifesaving treatment. A future where every child has the chance to live up to his or her God-given potential.

That's a future worth fighting for, together.

Sincerely,

Hillary Rodham Clinton
Secretary of State

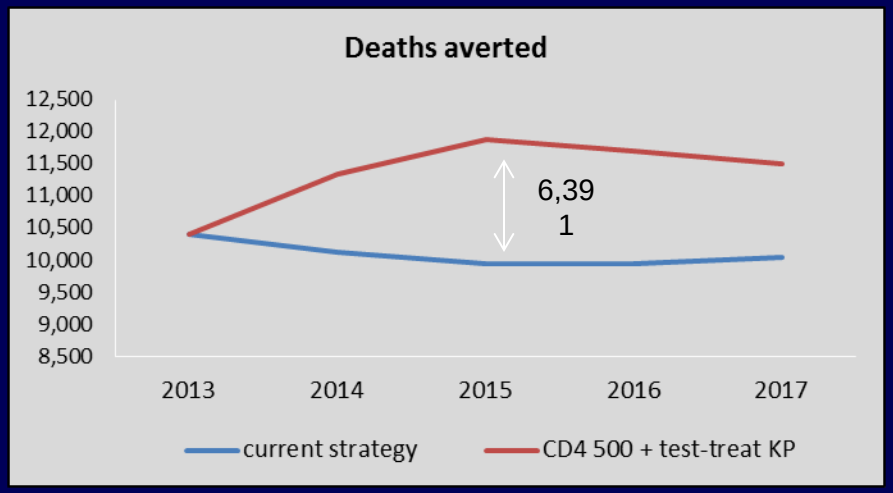


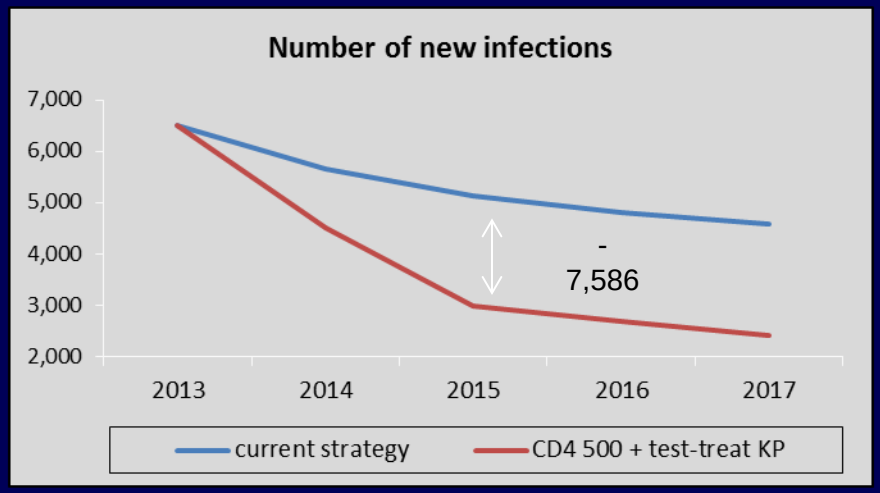


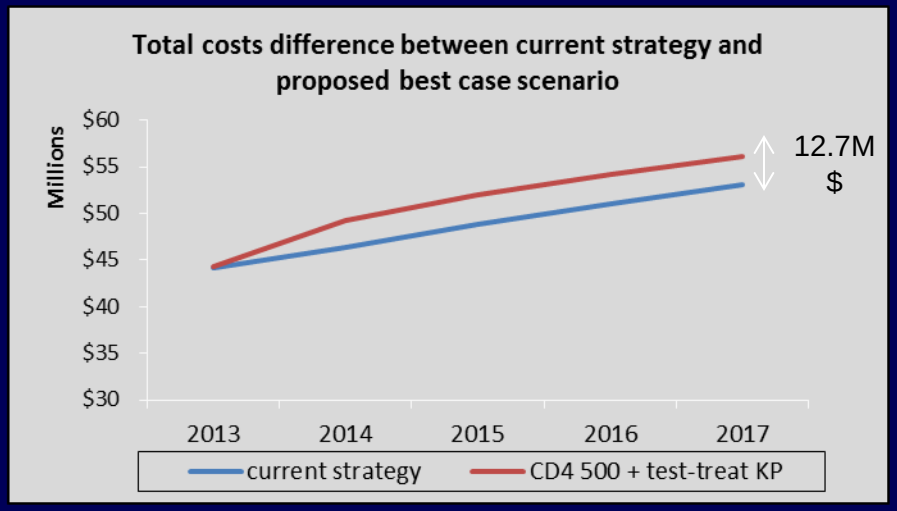
UNAIDS

Re-think when to start ART: test and treat for key populations or everyone?

Over a 5 year period, a 5.2% increase in costs* would results in 12.7% additional deaths averted and a 28.4% decrease in new infections**







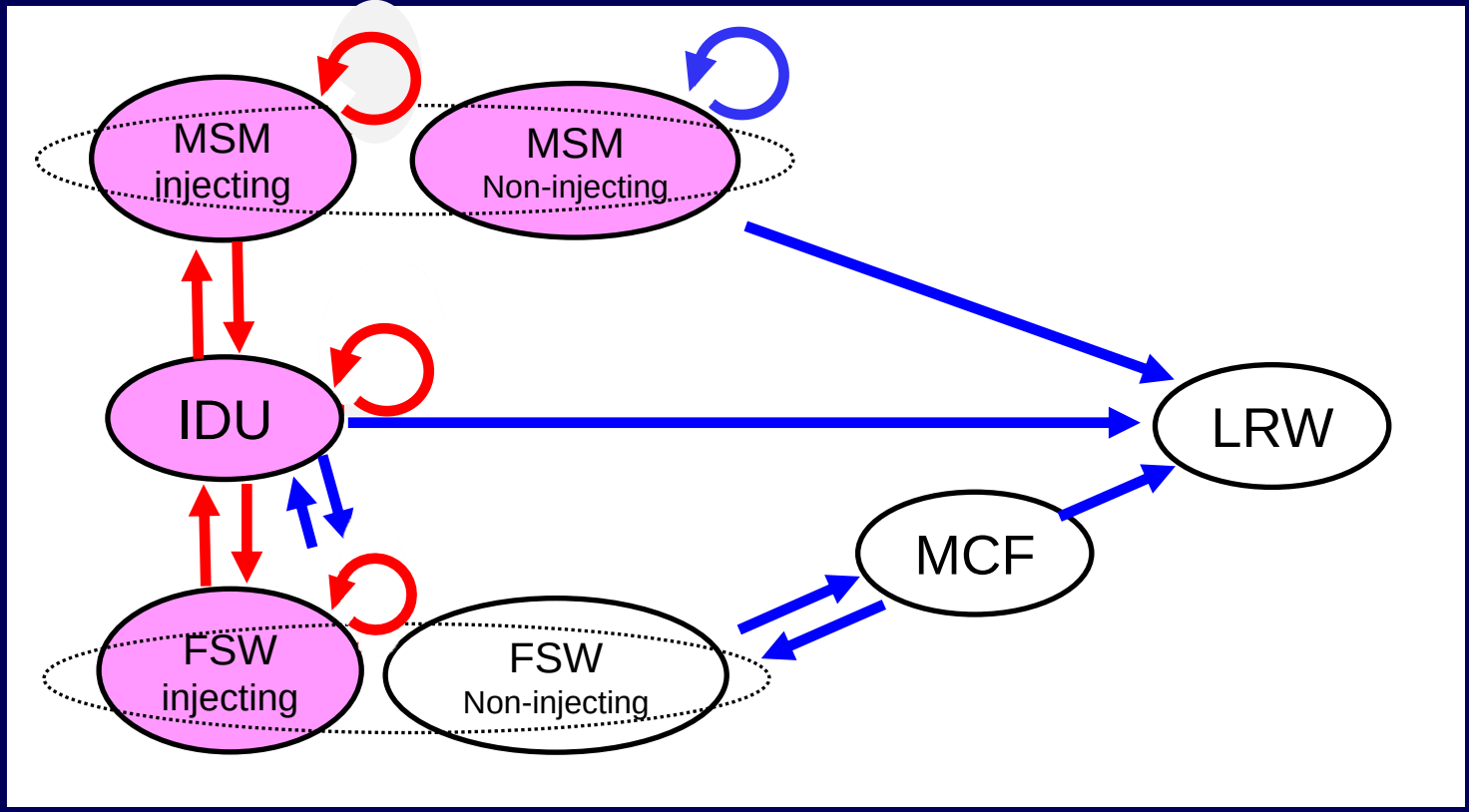
Investing an additional 12.7M $ would results in

6,391 deaths averted and

7,586 fewer new infections

- Additional costs may be underestimated as current resources were assumed to be able to absorb the new ART and pre-ART patients. *
- * EPI impact calculated with Spectrum, with conservative assumptions

7 sub-populations in the Viet Nam model



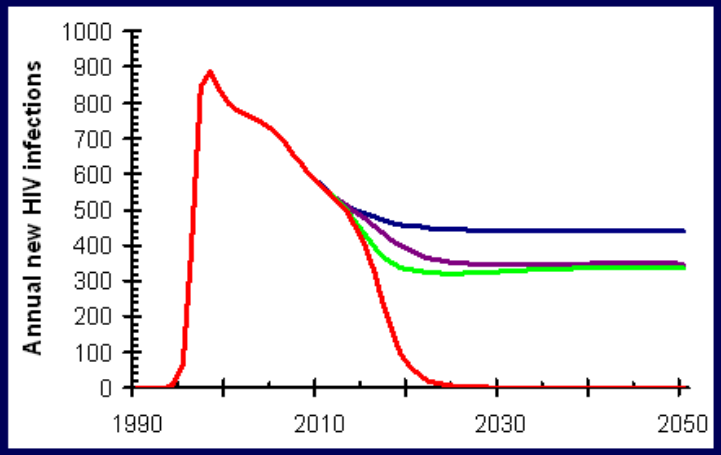
IDU: Injection drug users
MSM: Men having sex with men
FSW: Female sex workers
MCF: Male clients of FSW
LRW: Low risk women

Red arrow: Transmission via needle sharing
Blue arrow: Sexual transmission
Pink circle: Transmission within group

Re-think strategy for “concentrated epidemics” and key populations

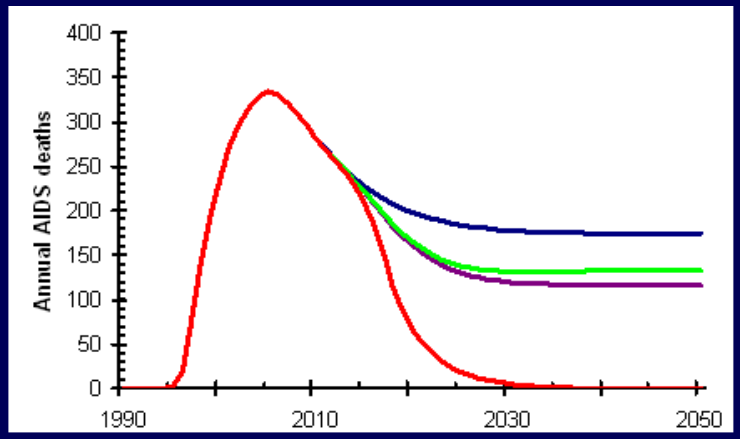
A

Annual new HIV infection



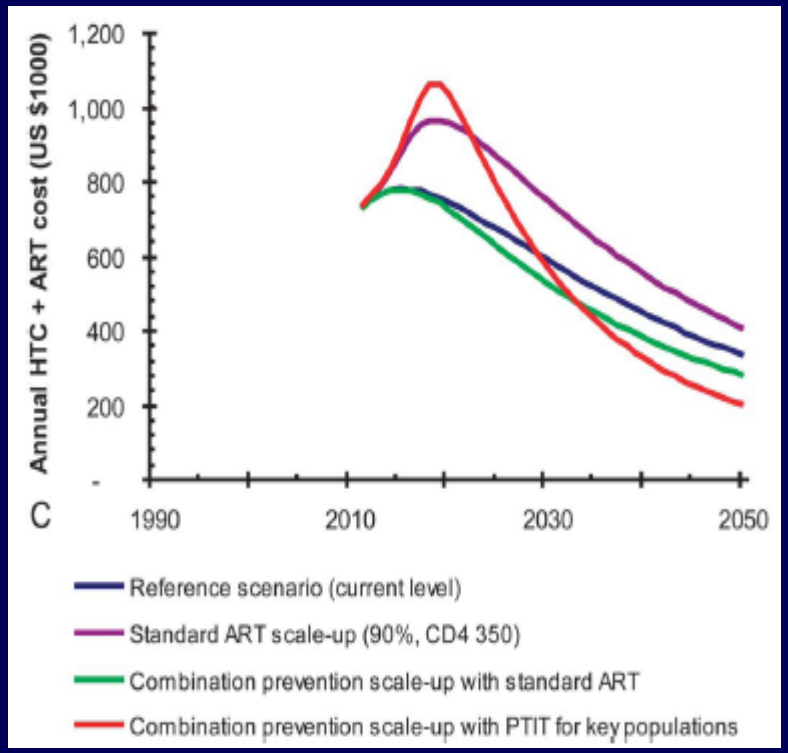
B

Annual AIDS death



C

ART and HTC cost



Periodic testing and immediate treatment (PTIT)

Kato M et al . JAIDS Vol 63(5) 2013

However beautiful the strategy, you should occasionally look at the results

--Winston Churchill

Are we on track to scale?

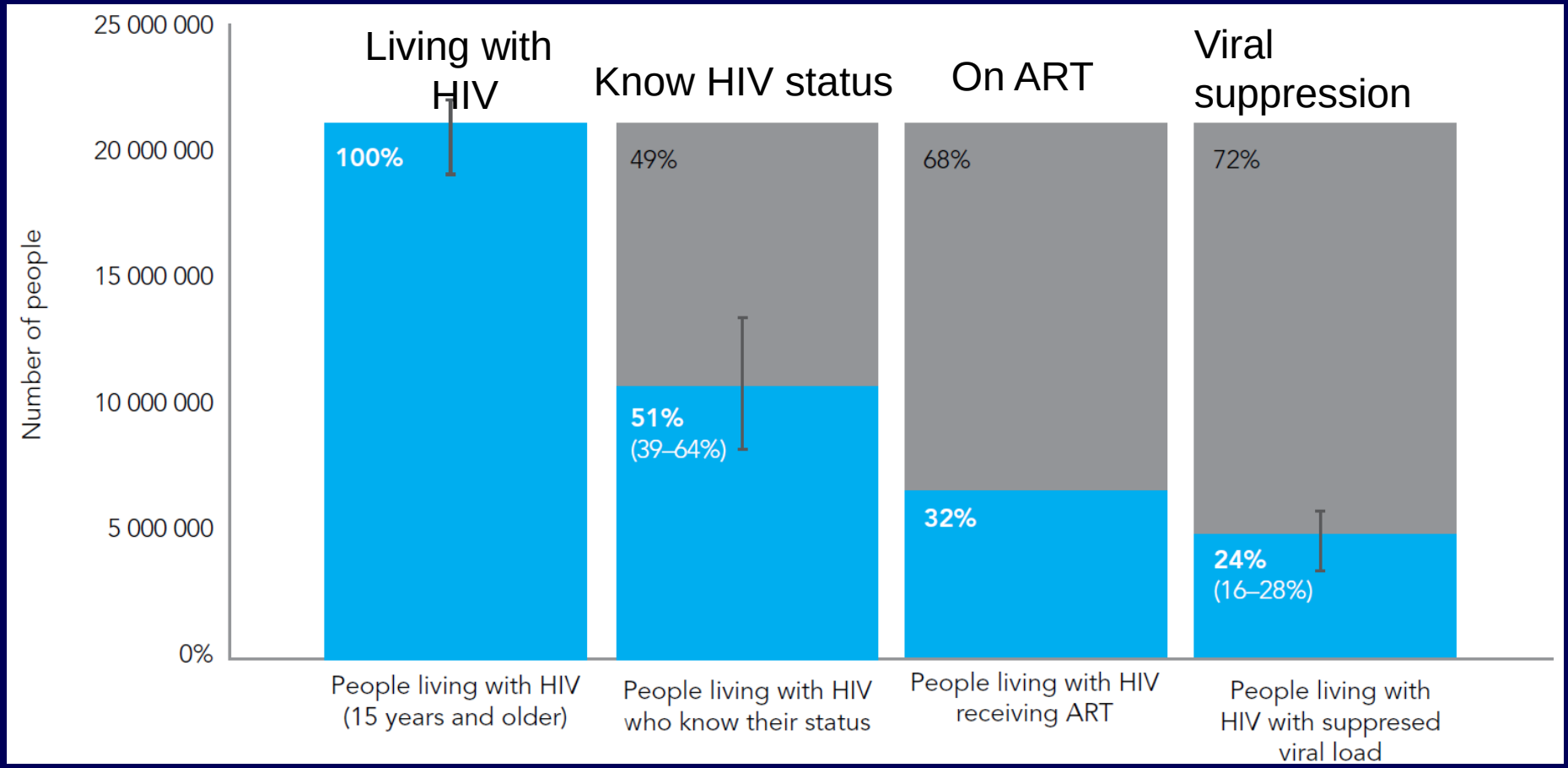
By end of 2013:

- ~52% of people living with HIV do not know their status
- ~22 million (63%) are not on treatment (76% for children)
- ~1.5 million deaths
- ~2.1 million new infections (5753 per day; 240 per hour)

Bottom line:

- Everyone living with HIV will need ART to survive
- Treatment expansion is part of solution to preventing illness, death, transmission, and costs.

Accountability: measuring diffusion and scale

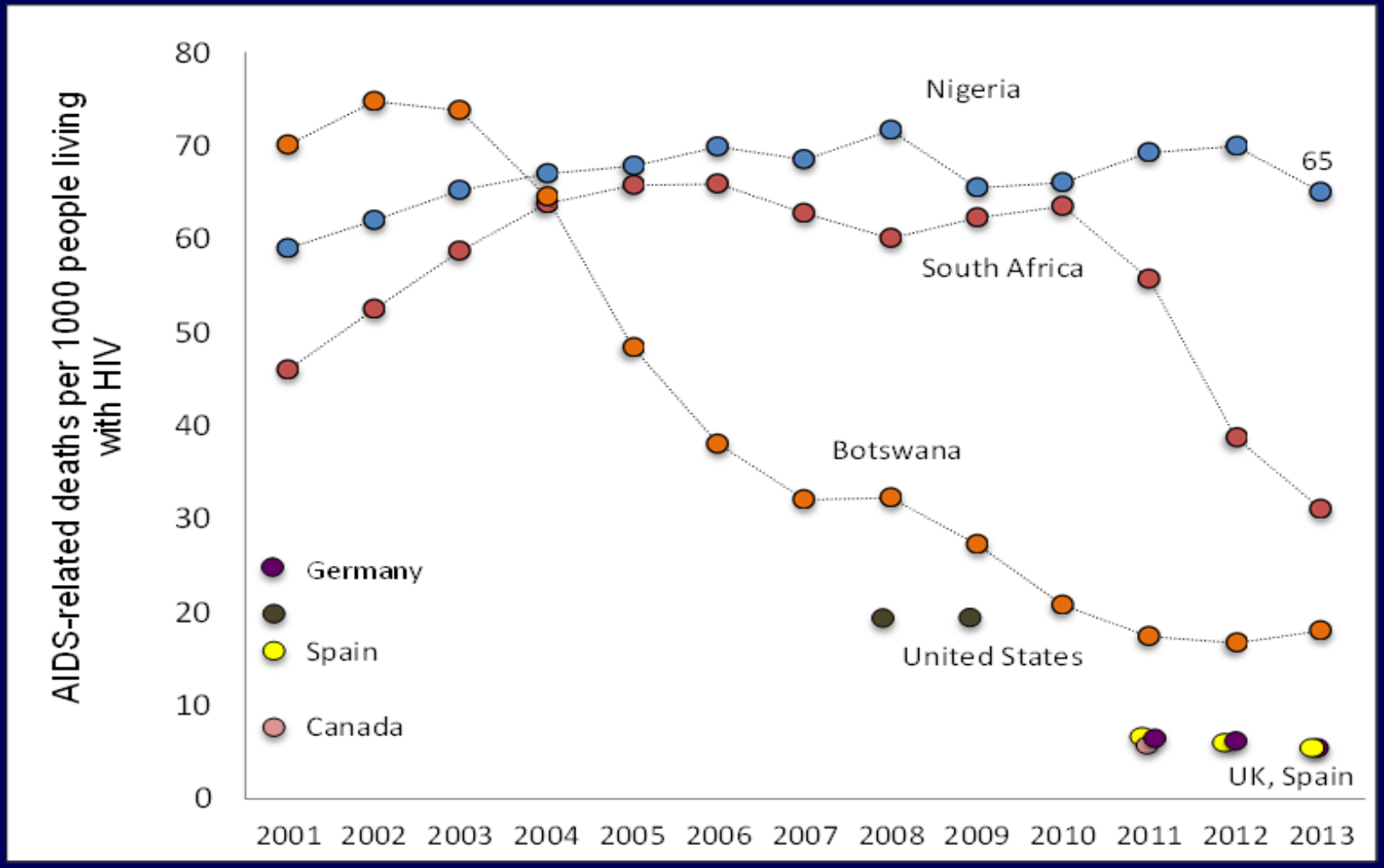


HIV treatment cascade for sub-Saharan Africa, 2012

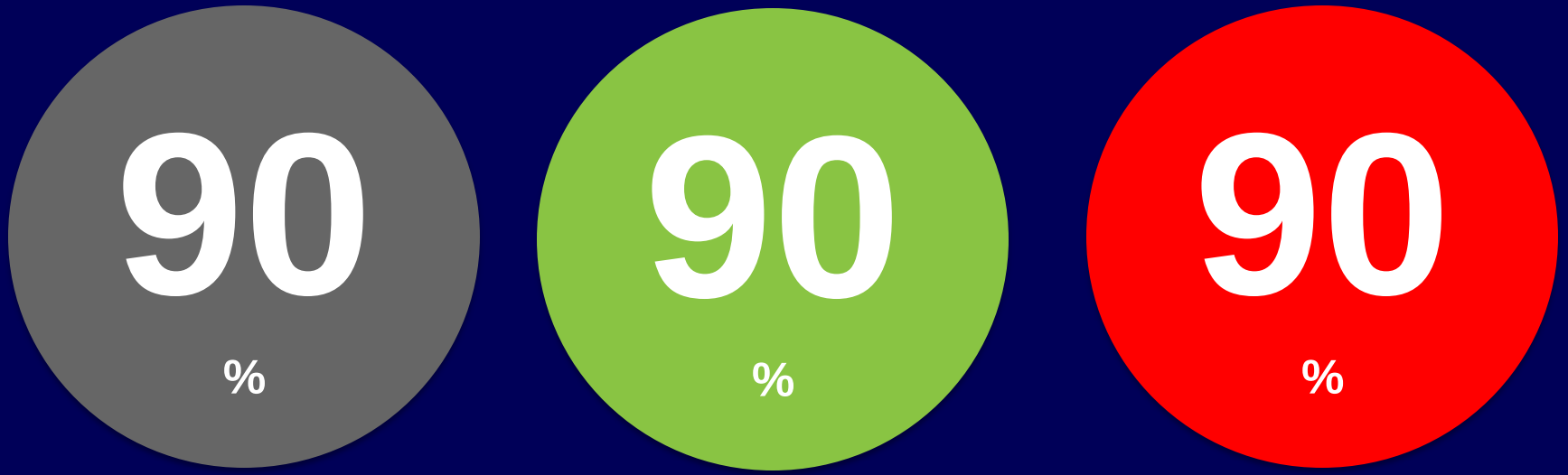
Notes: No systematic data are available for the proportion of people living with HIV who are linked to care, although this is a vital step to ensuring viral suppression in the community.

Sources: 1. UNAIDS 2012 estimates; 2. Demographic and Health Surveys, 2007–2011 (www.measuredhs.com); 3. Kranzer, K., van Schaik, N., et al. (2011), PLoS ONE; 4. CAPRR 2012; 5. Barth R E, van der Loeff MR, et al. (2010), Lancet Infect Disease.

Estimated annual AIDS deaths per 1000 people living with HIV



UNAIDS treatment targets: getting to scale



tested

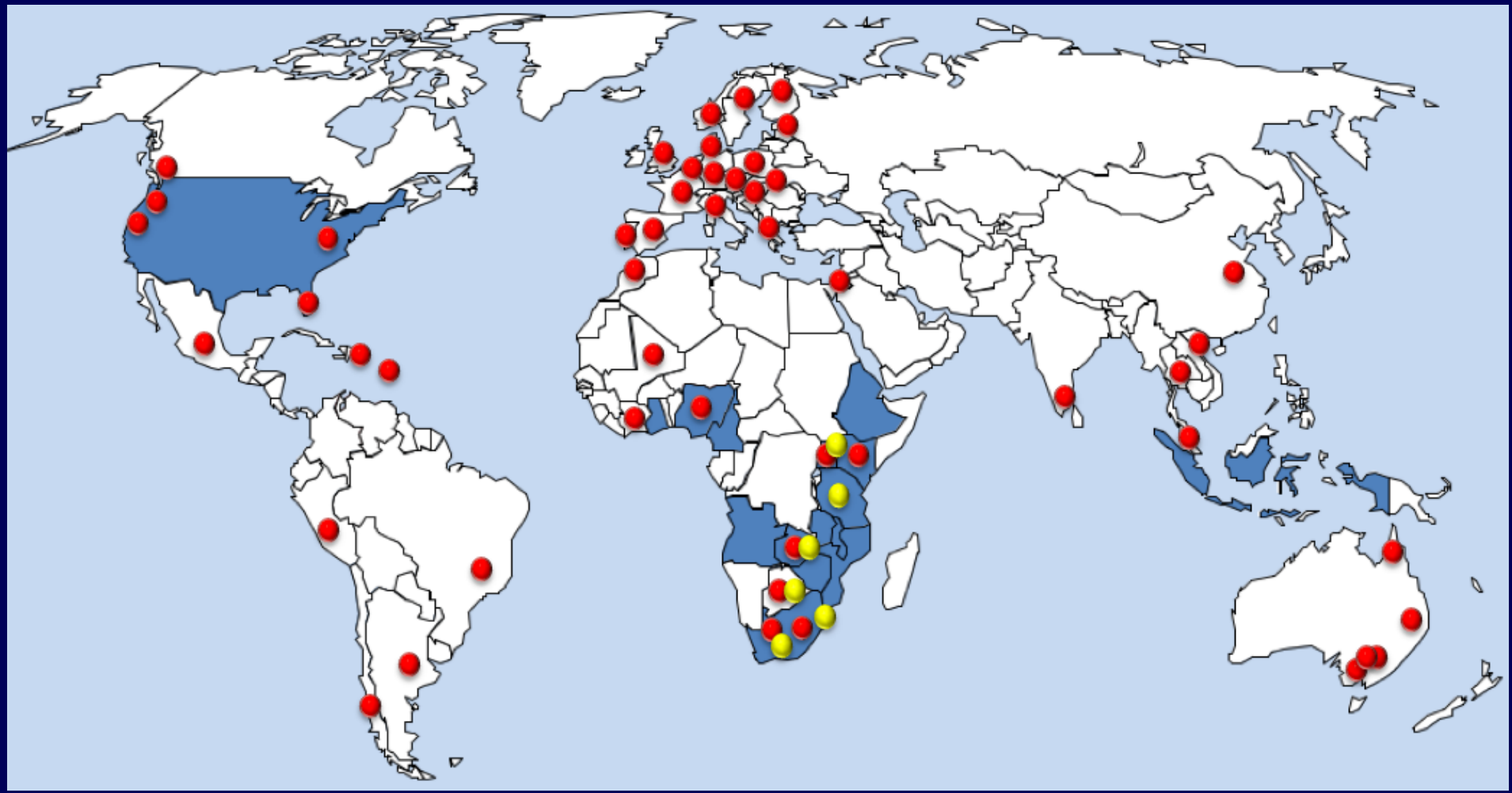
on treatment

virally suppressed

Thank You

Views expressed in this presentation are those of the author and do not necessarily represent the views of the Joint United Nations Programme on HIV/AIDS (UNAIDS).

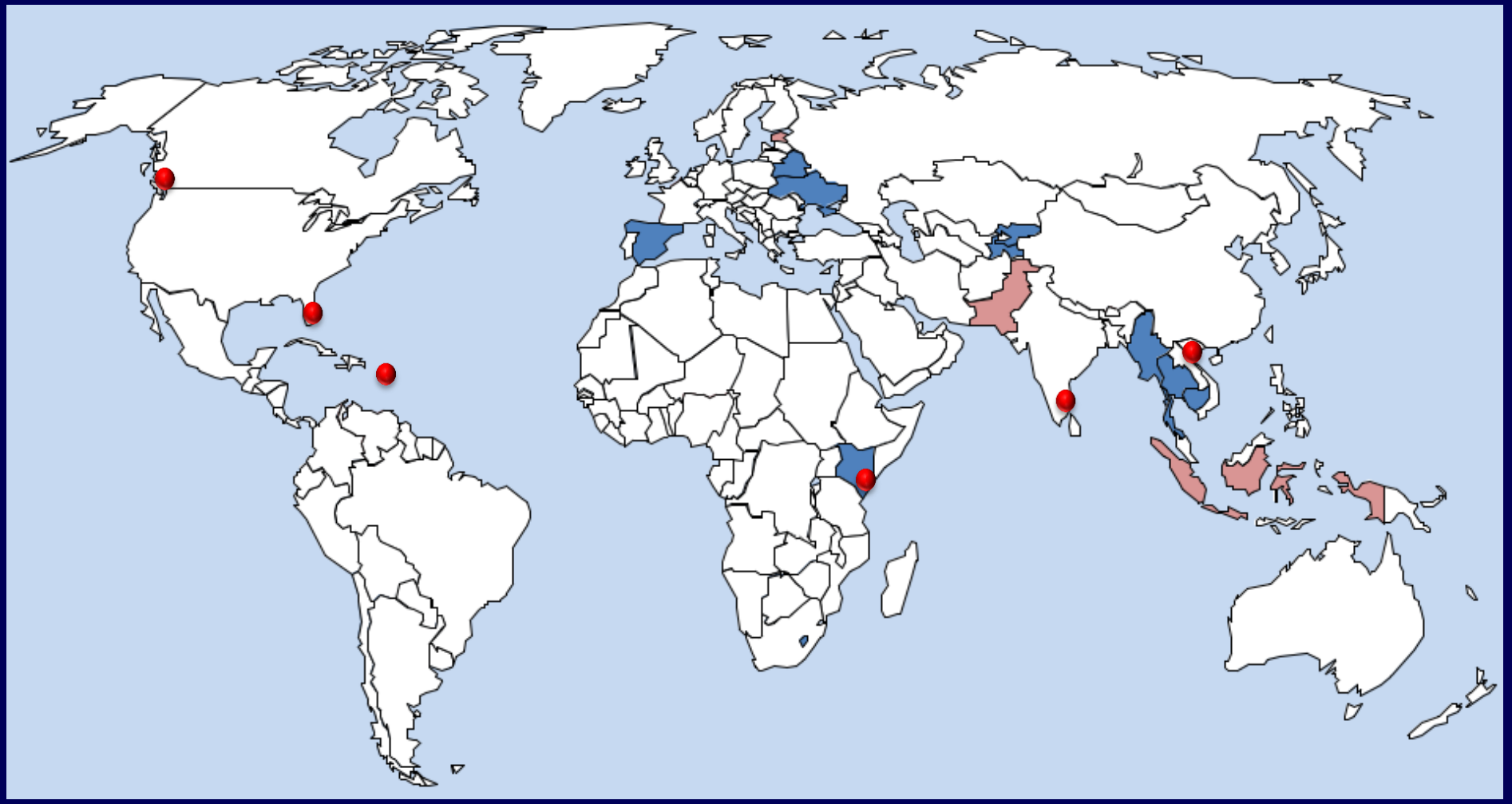
Ongoing and planned TasP studies: feasibility, impact and key populations



- Countries in blue are high HIV incidence countries (2011)
- Red dots represent countries with ongoing/planned research on early ART and the yellow dots represent countries with research on combination HIV prevention strategies

UNAIDS

Countries with studies on TasP for PWID



Dark blue represents countries where 15-25% of IDUs are living with HIV (2011); pink represents countries where >25% of IDUs are living with HIV (2011) and the red dots represent countries conducting research

UNAIDS

Community based delivery can lead to high uptake of ART (83%)

OPEN ACCESS Freely available online

PLOS | ONE

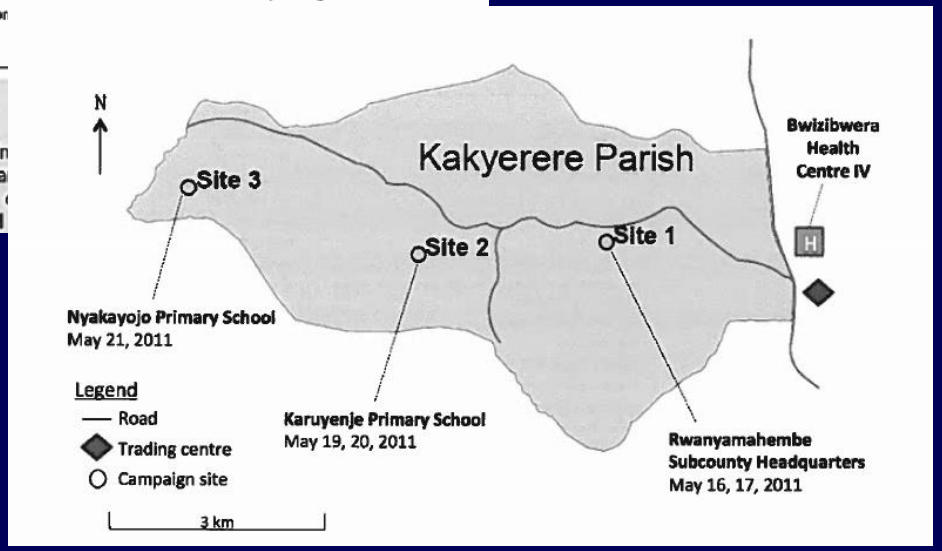
Leveraging Rapid Community-Based HIV Testing Campaigns for Non-Communicable Diseases in Rural Uganda

Gabriel Chamie[1,2]*, Dalsone Kwarisiima[3], Tamara D. Clark[1,2], Jane Kabami[2], Vivek Jain[1,2], Elvin Geng[1,2], Maya L. Petersen[4], Harsha Thirumurthy[5], Moses R. Kamya[2,6], Diane V. Havlir[1,2], Edwin D. Charlebois[2,7], and the SEARCH Collaboration

1 HIV/AIDS Division, Department of Medicine, San Francisco General Hospital, University of California San Francisco, San Francisco, California, United States of America, 2 Makerere University-University of California San Francisco (MU-UCSF) Research Collaboration, Mbarara, Uganda, 3 Mulago-Mbarara Joint AIDS Program, Kampala and Mbarara, Uganda, 4 School of Public Health, University of California, Berkeley, California, United States of America, 5 Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America, 6 Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda, 7 Center for AIDS Prevention Studies, Department of Medicine, University of Califor
of America

Abstract

Background: The high burden of undiagnosed HIV in sub-Saharan Africa lin
Community-based HIV testing campaigns can address this challenge and provide a
communicable diseases (NCDs). We tested the feasibility and diagnostic yield
diseases into a rapid HIV testing and referral campaign for all residents of a rural



Chamie Plos One 2012

Re-think delivery: SEARCH Uganda community trial of test and treat

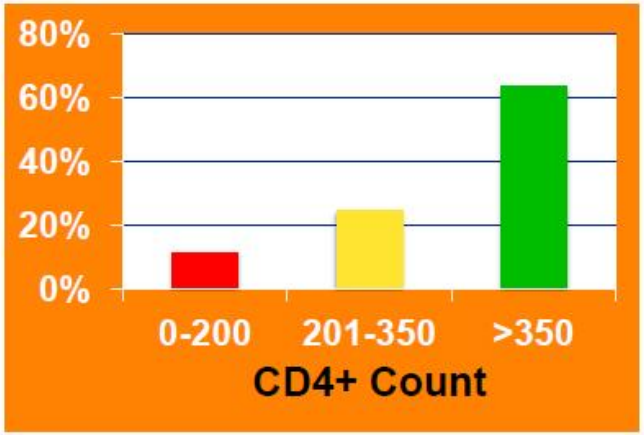
Approach: Multidisease "Community Health Campaign" HIV + other diseases

Principles:

- community led
- high throughput
- health services for children/ adults

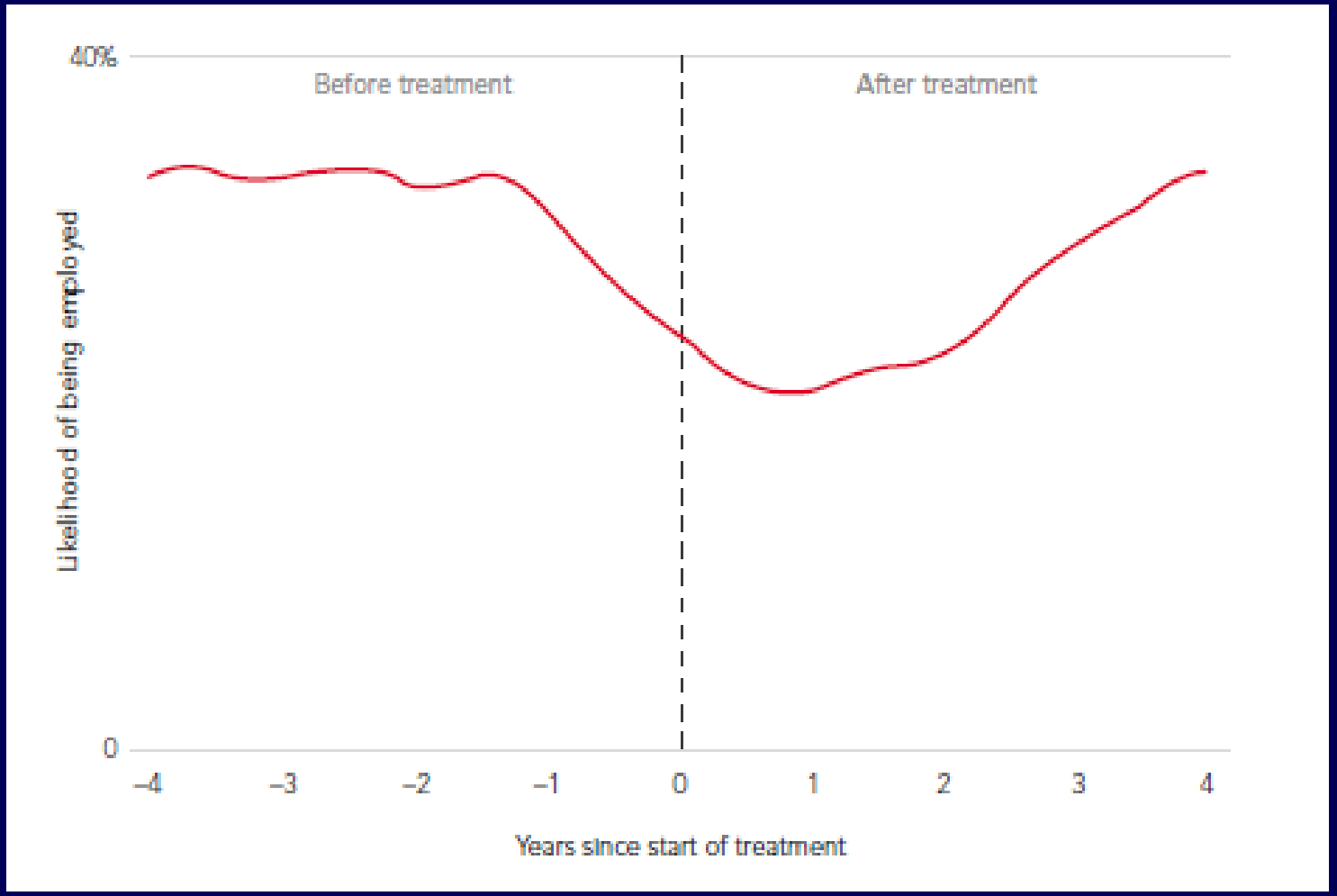
Findings:

- Adults with HIV 8%
- Hypertension 12%
- Diabetes 3.5%



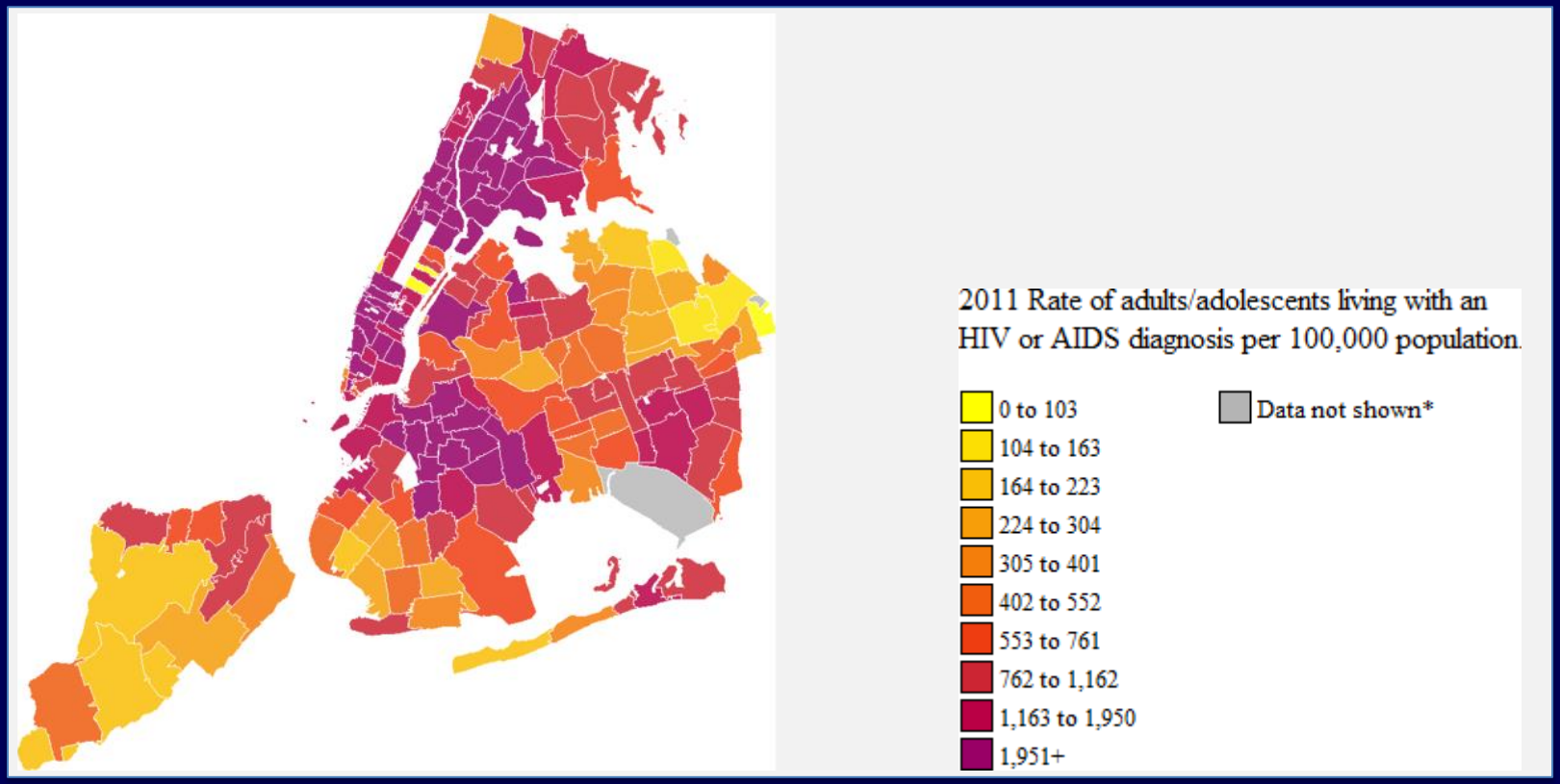
Chamie, PLOS Med, 2012

Treatment has a positive economic impact: healthy people go back to work



Source: Bärnighausen T et al. The economic benefits of ART: evidence from a complete population cohort in rural South Africa. *2nd International HIV Workshop on Treatment as Prevention, Vancouver, Canada, 22–25 April 2012.*

Mash-up to drive implementation and health outcomes: 90-90-90



Rates of people living with HIV or AIDS diagnosis by zip code, New York City 2011

AIDSVu http://aidsvu.org/resources/downloadable-maps-and-resources/ Sept 11 2014

Conceptual diagram of CD4+ response on ART: starting later translates in lower CD4 levels (and higher risk)

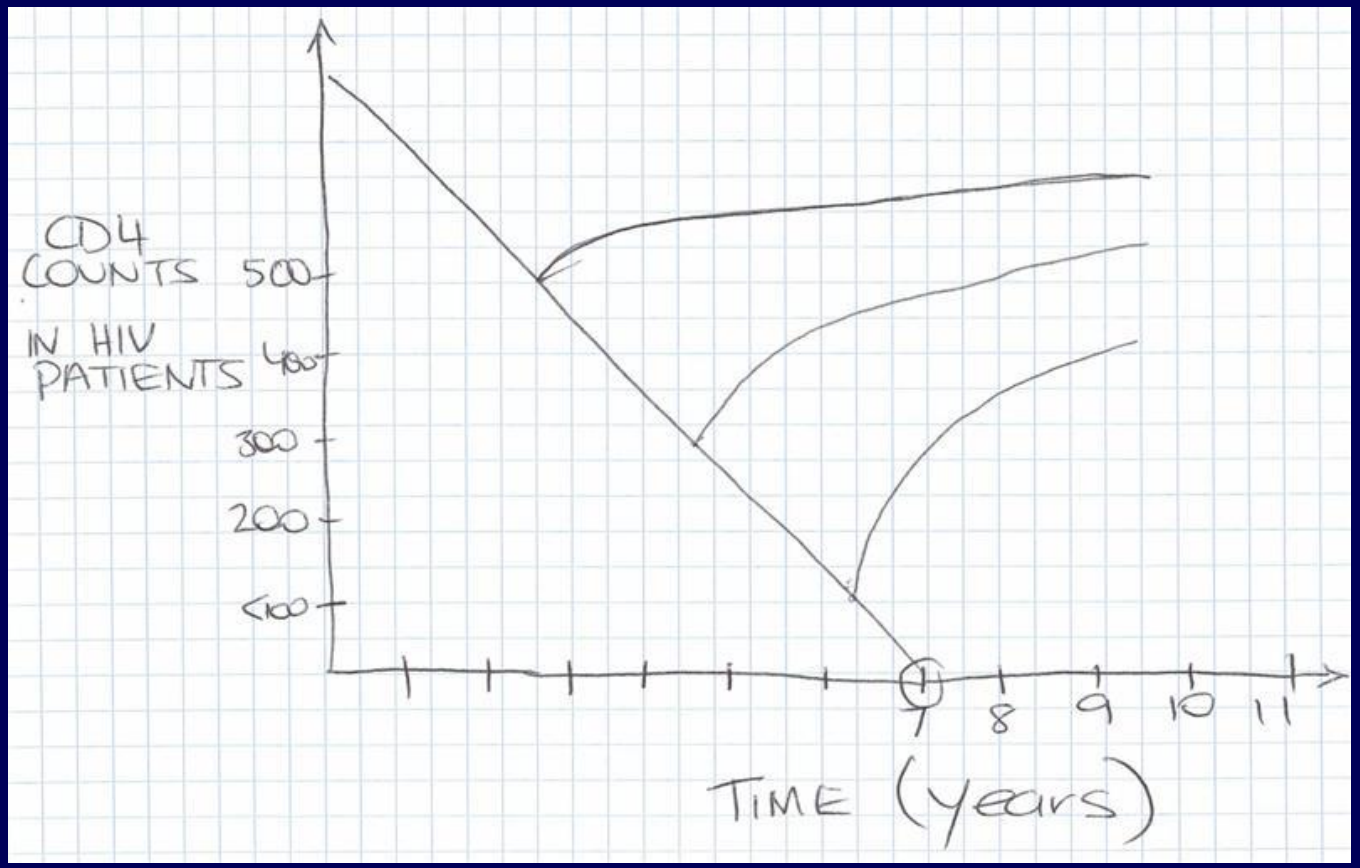
5-7 YEARS

Le Moing et al. HIV Med 2007;8:156.

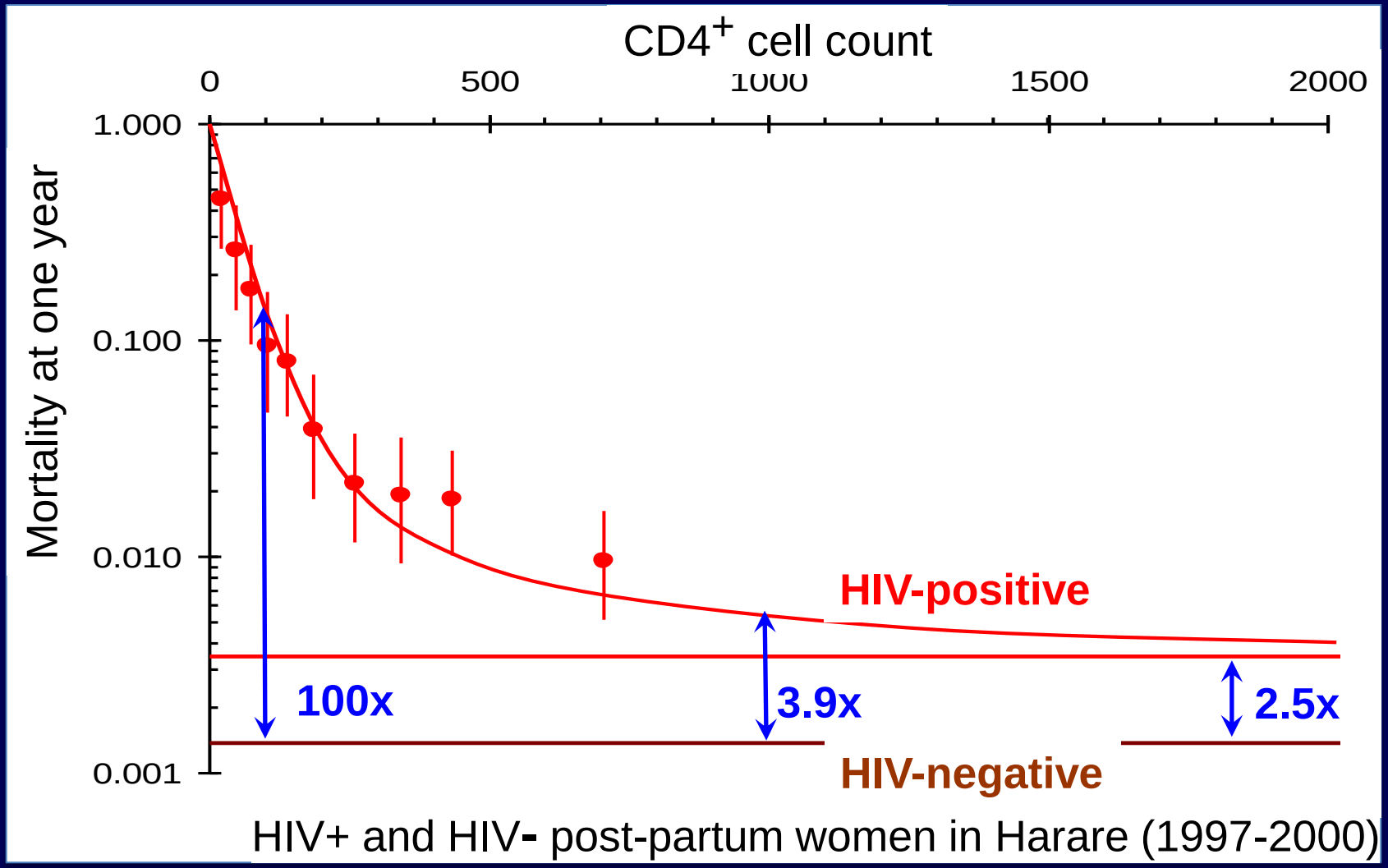
Micheloud et al. J Infection 2008;56:130.

Mocroft et al. Lancet 2007;370:407.

Vrisekoop et al. J Immunol 2008;181:1573.



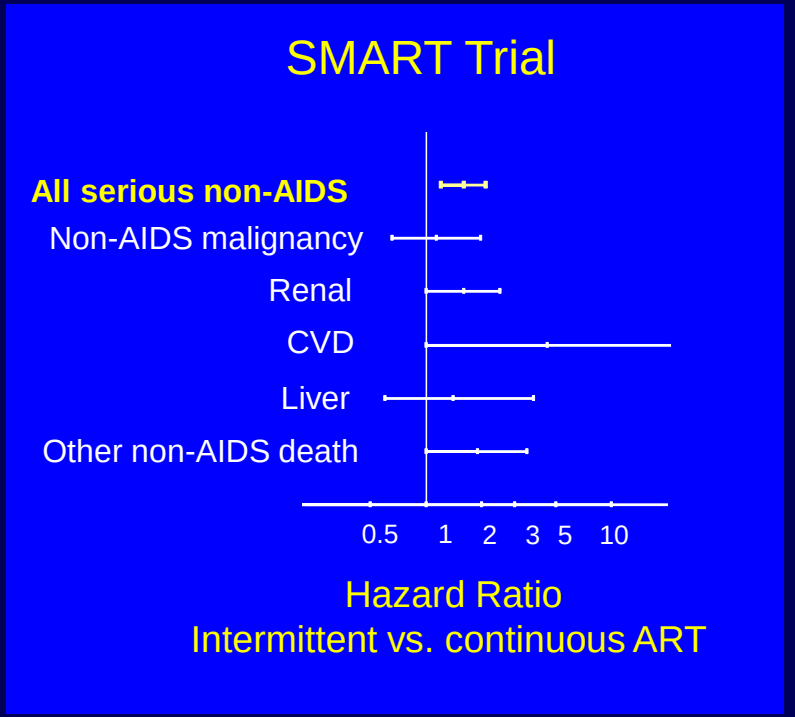
Higher mortality for mothers in Zimbabwe even when their CD4 cell counts are at higher level (ZIVTAMBO study)



Data: Hargrove *AIDS* 2010; Model: Williams *JID 2006*

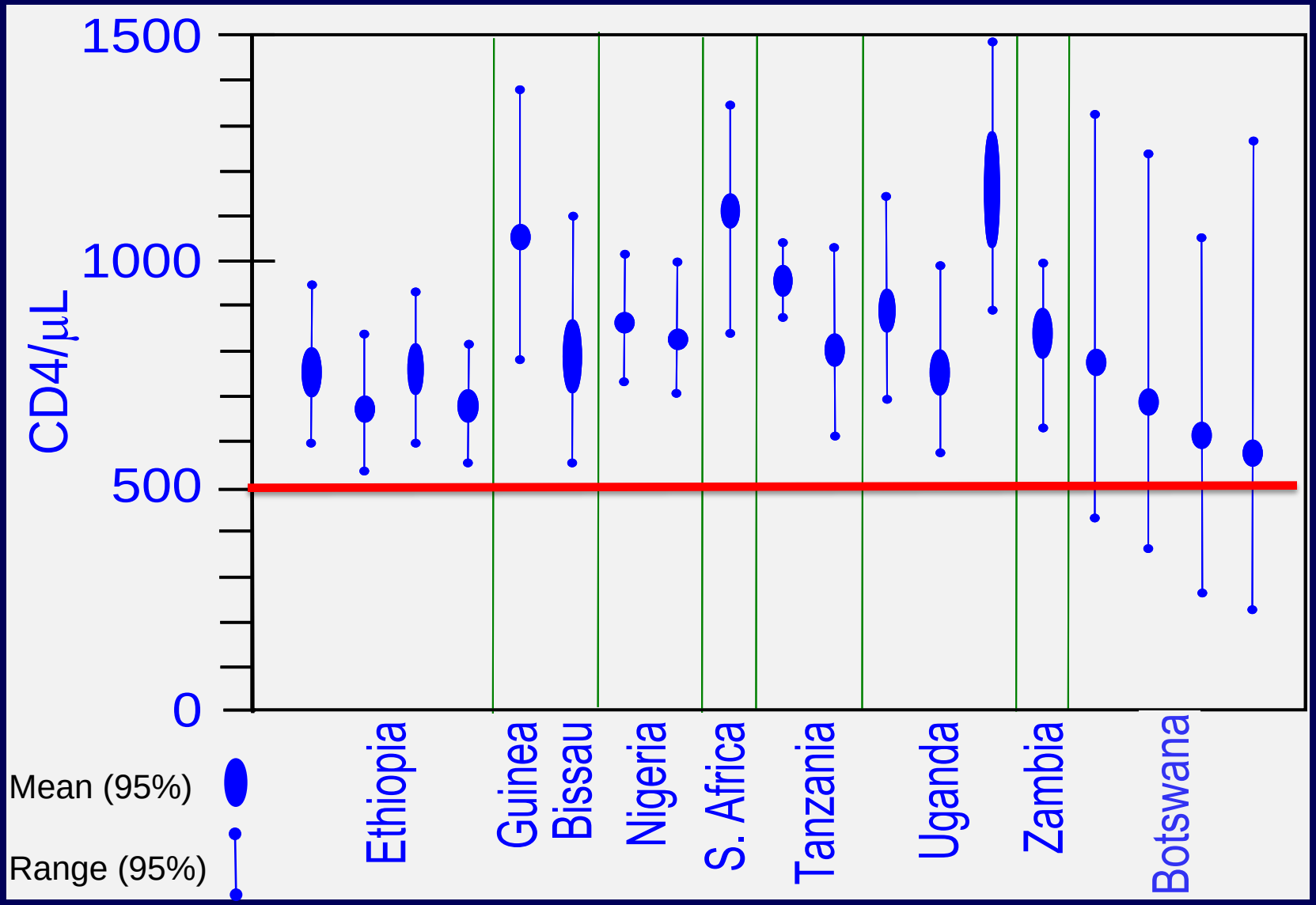
Risk of non-AIDS morbidity and mortality

- HIV may be associated with serious non-AIDS defining events
  - Cardiovascular
  - Renal
  - Liver
  - Non-AIDS malignancies
- At higher CD4 counts non-AIDS events are much more common than AIDS events
- Does ART use reduce risk of some serious non-AIDS events?



SMART Study Group, NEJM 2006 & Neaton et al, Current Opinion in HIV/AIDS 2008
Slide courtesy of A Phillips

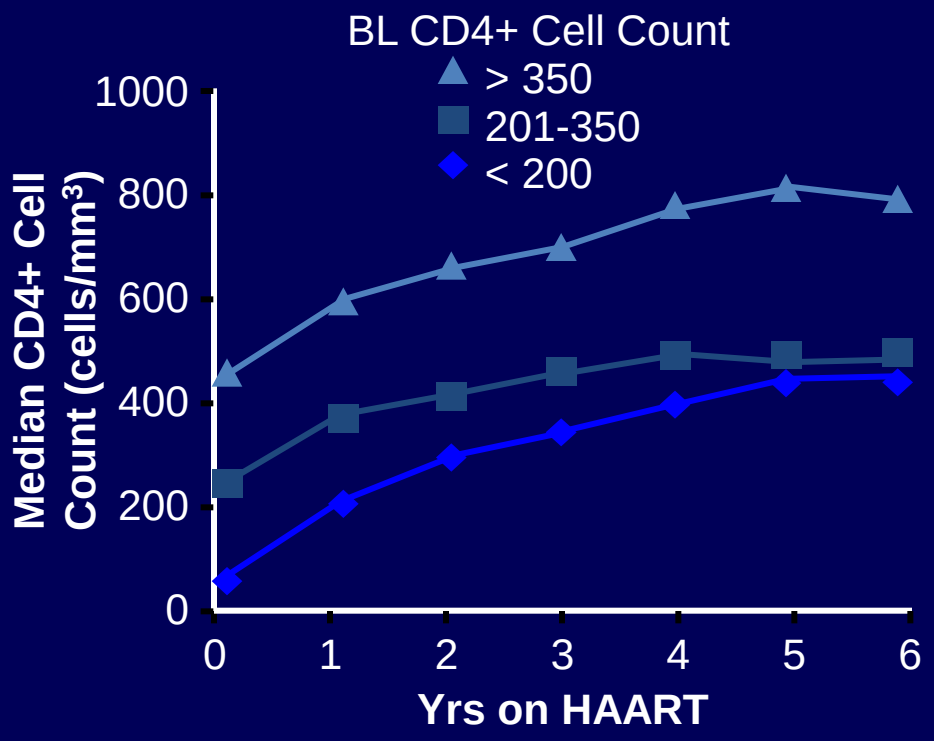
CD4 highly variable in **HIV-negative** people



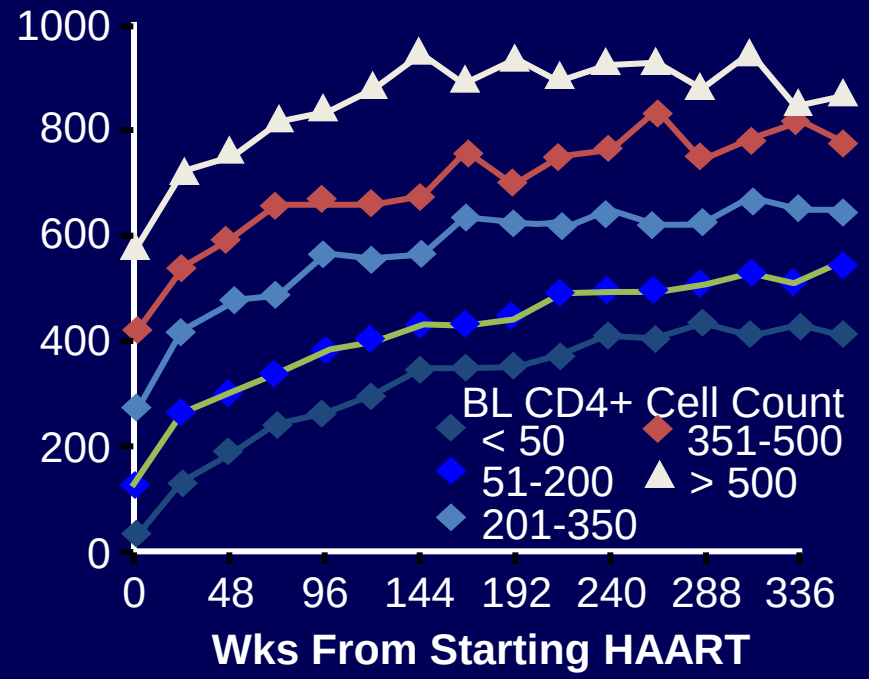
Williams *et al. J Infect Dis.* 2006; 194: 1450-8; Bussman *et al. Clinical and Diagnostic Laboratory Immunology* 2004

Likelihood of achieving normal CD4+ cell count on ART depends on baseline level

Johns Hopkins HIV Clinical Cohort[1]



ATHENA National Cohort[2]

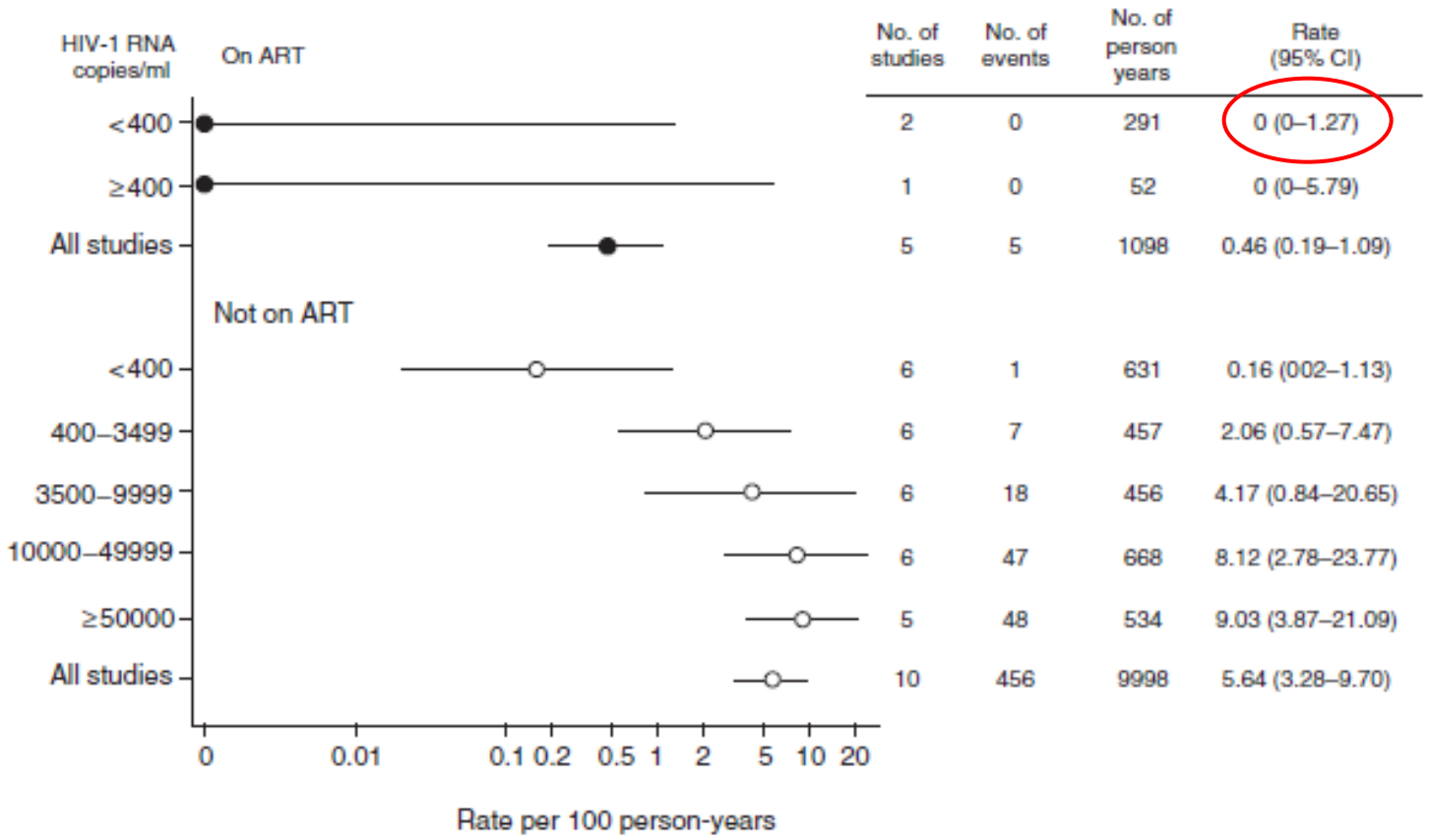


1. Moore RD, et al. Clin Infect Dis. 2007;44:441-446. Published by The University of Chicago Press. Copyright ©2009. University of Chicago Press. All rights reserved. http://www.journals.uchicago.edu/toc/cid/current.
2. Gras L, et al. J Acquir Immune Defic Syndr. 2007;45:183-192. Reproduced with permission.

ART reduces sexual transmission of HIV: meta-analysis shows no transmission <400 copies per ml

2009

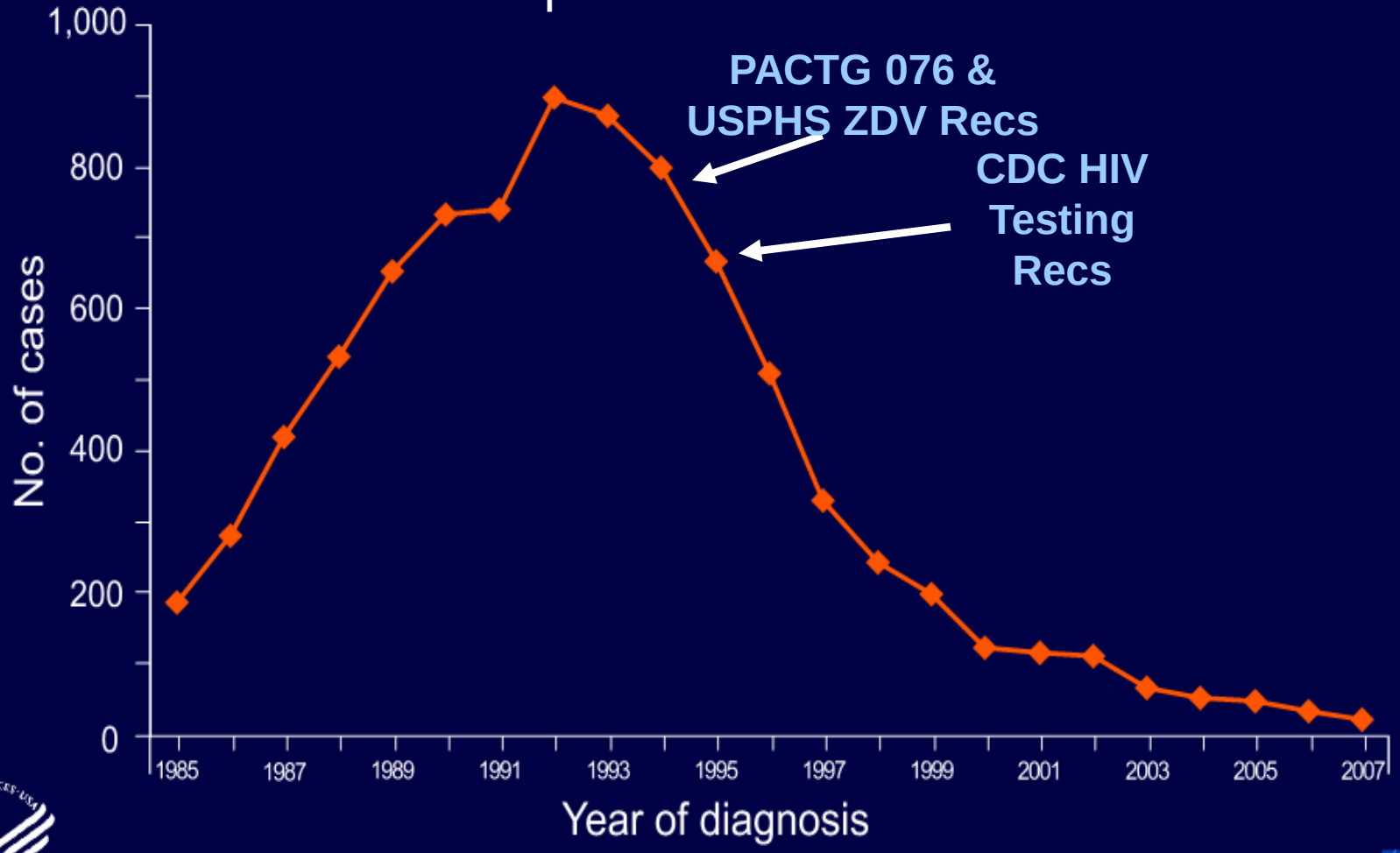
Sexual transmission of HIV Attia *et al.*



	No. of studies	No. of events	No. of person years	Rate (95% CI)
On ART, <400	2	0	291	0 (0–1.27)
On ART, ≥400	1	0	52	0 (0–5.79)
On ART, All studies	5	5	1098	0.46 (0.19–1.09)
Not on ART, <400	6	1	631	0.16 (002–1.13)
Not on ART, 400–3499	6	7	457	2.06 (0.57–7.47)
Not on ART, 3500–9999	6	18	456	4.17 (0.84–20.65)
Not on ART, 10000–49999	6	47	668	8.12 (2.78–23.77)
Not on ART, ≥50000	5	48	534	9.03 (3.87–21.09)
Not on ART, All studies	10	456	9998	5.64 (3.28–9.70)

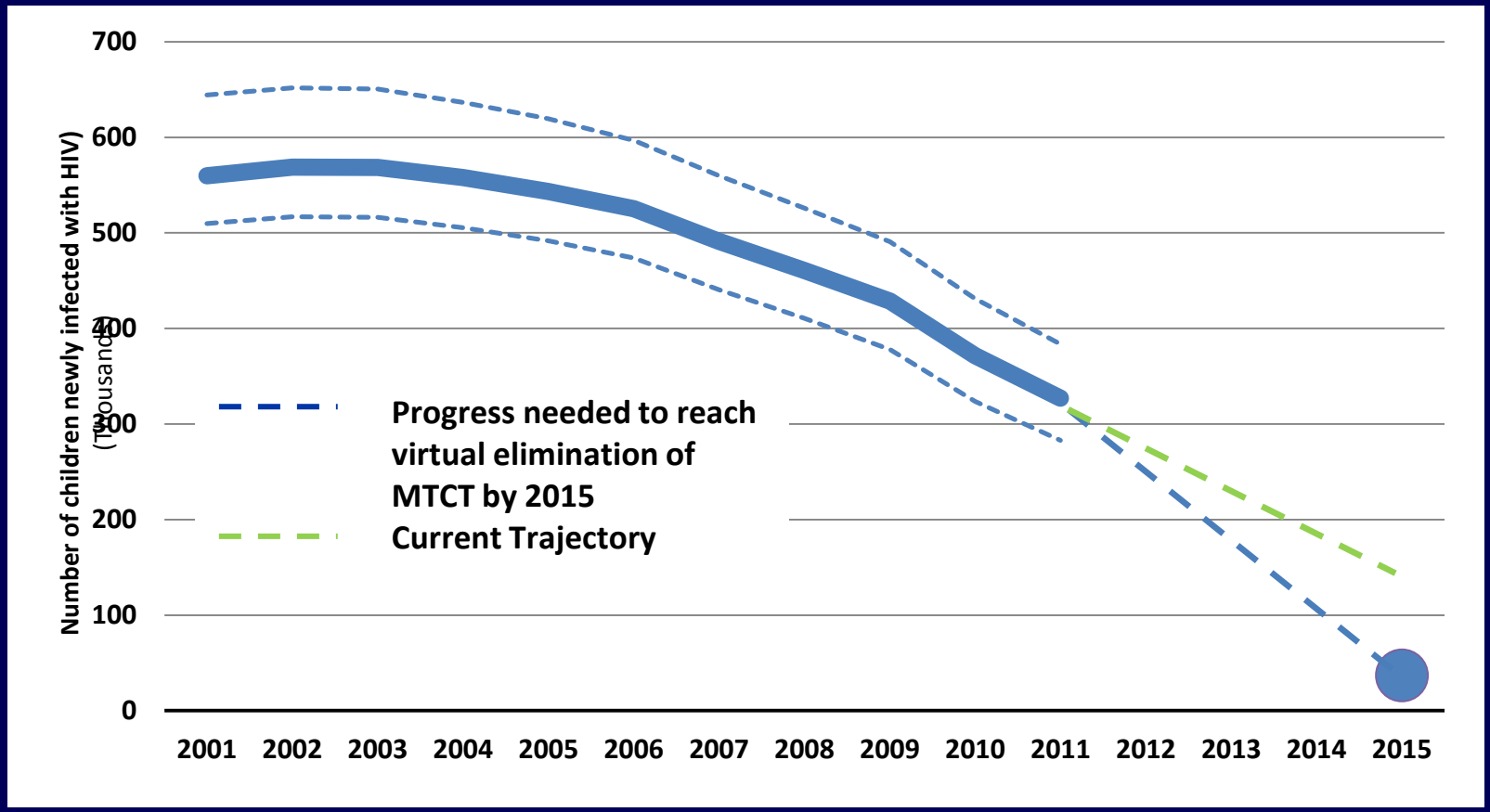
Attia S, et al.AIDS 2009 Jul 17;23(11):1397-404.

Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas



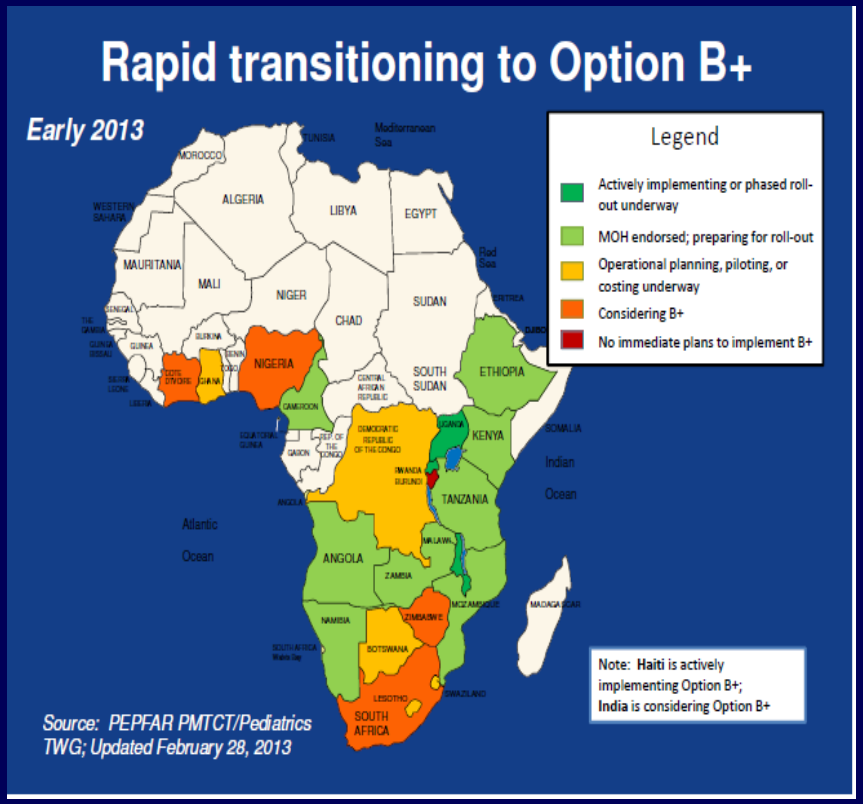
Note. Data have been adjusted for reporting delays and missing risk-factor information.

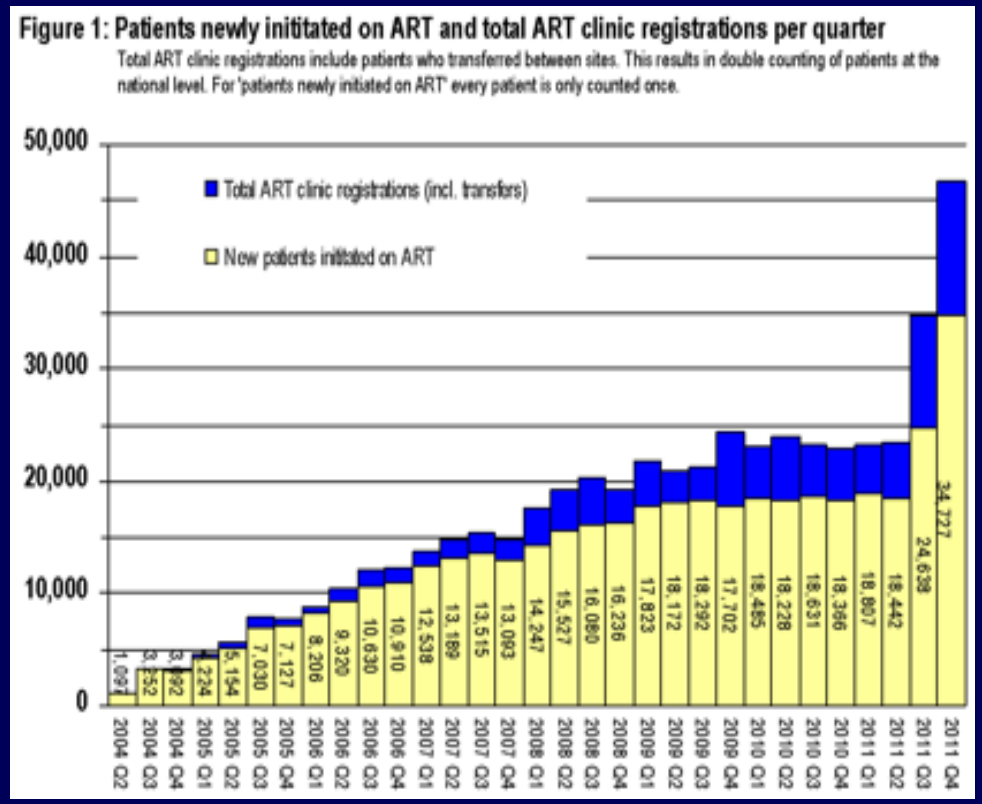
Impact of ART: Significant Decrease in Mother-to-Child Transmission of HIV since 2010



UNAIDS Global Report 2012

One size does not fit all….



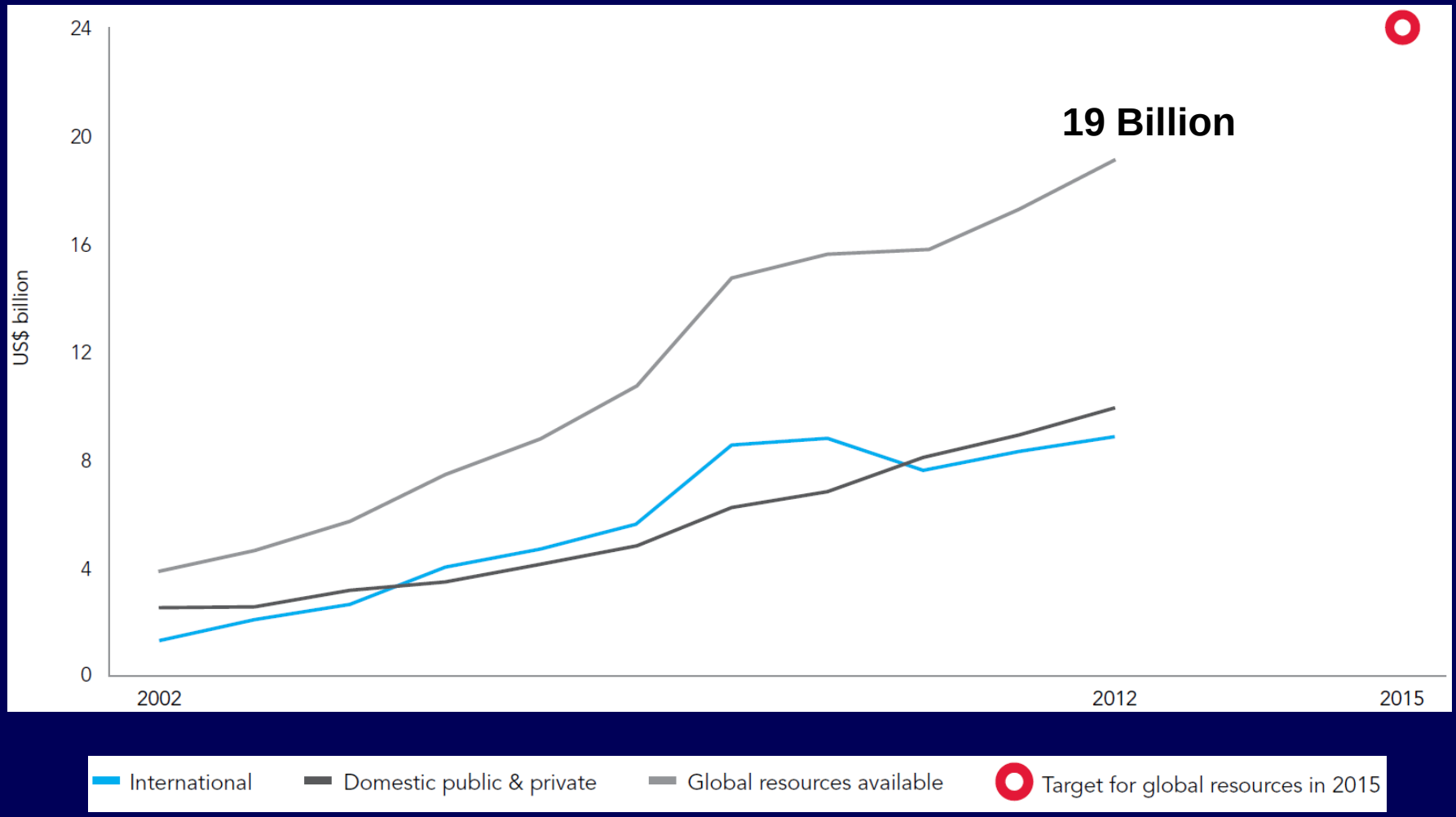


Option B+: early 2013

Slide courtesy of CDC

UNAIDS

Resources available for HIV in low- and middle-income countries, 2002–2012 and 2015 target*

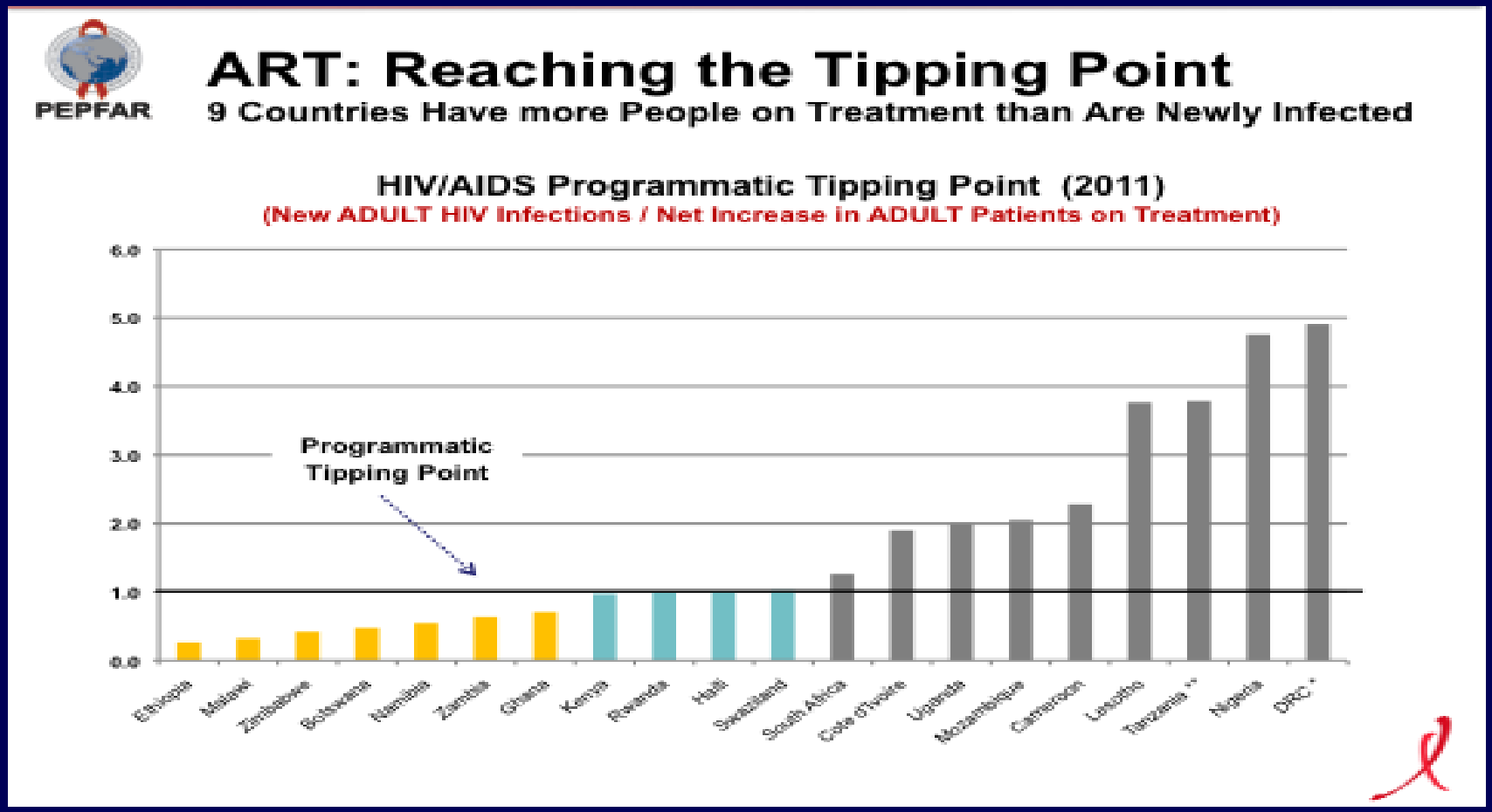


* The UN General Assembly 2011 Political Declaration on HIV and AIDS set a target of US$ 22bn – 24bn by 2015.

Source: UNAIDS estimates.

Re-think how we spend the money

Re-think targets*: programmatic tipping point*: on treatment equals new infections



Slide courtesy of PEPFAR

Conclusion

- Prevention matters—combination will be required
- Treatment prevents illness, death, transmission
- Global testing and treatment scale-up plan with practical measurable milestones (think end game)
- Speed—slow scale up is not an option for millions, remove complexity and barriers to access
- Innovation—community delivery, consider standardized franchise model
- People first, community engagement

Public health is purchasable. Within a few natural and important limitations any community can determine its own health.

--Hermann M. Biggs

(29 Sep 1859 - 28 Jun 1923)
New York City's Public Health Officer and public health pioneer

PARTNERS Study: CROI 2014

Press conference at CROI 2014.

Photo by Liz Highleyman, hivandhepatitis.com.

- 16,400 occasions of sex in the gay men and 28,000 in the heterosexuals
- Zero transmissions within couples from a partner with an undetectable viral load
- Upper bounds of confidence intervals suggest that risk is not zero

Rodger A et al. *HIV transmission risk through condomless sex I f HIV+ partner on suppressive ART: PARTNER study.* 21st CROI, Boston, abstract 153LB, 2014.

Significantly higher employment at CD4≥500 among adults

- Compared to CD4<200, CD4≥500 associated with
  - 5.8 more days/month
  - 2.2 more hours/day (40% more than ref. mean of 5.5)

Regression model coefficients		
	(1)	(2)
Outcome:	Days worked in the past month	Hours worked on usual day in past
CD4<200	Reference	Reference
CD4 200-349	2.7	1.8
CD4 350-499	4.8	0.9
CD4 ≥500	5.8**	2.2*
Observations	107	107

- Linear regression model with age, age-squared, and sex included as controls
- ** p<0.05, * p<0.10
- Reference group has CD4<200

Those with CD4≥500 worked nearly 1 week/month more than those with CD4<200, and as much as HIV-uninfected adults

Thirurmurthy, Health Affairs, 2012

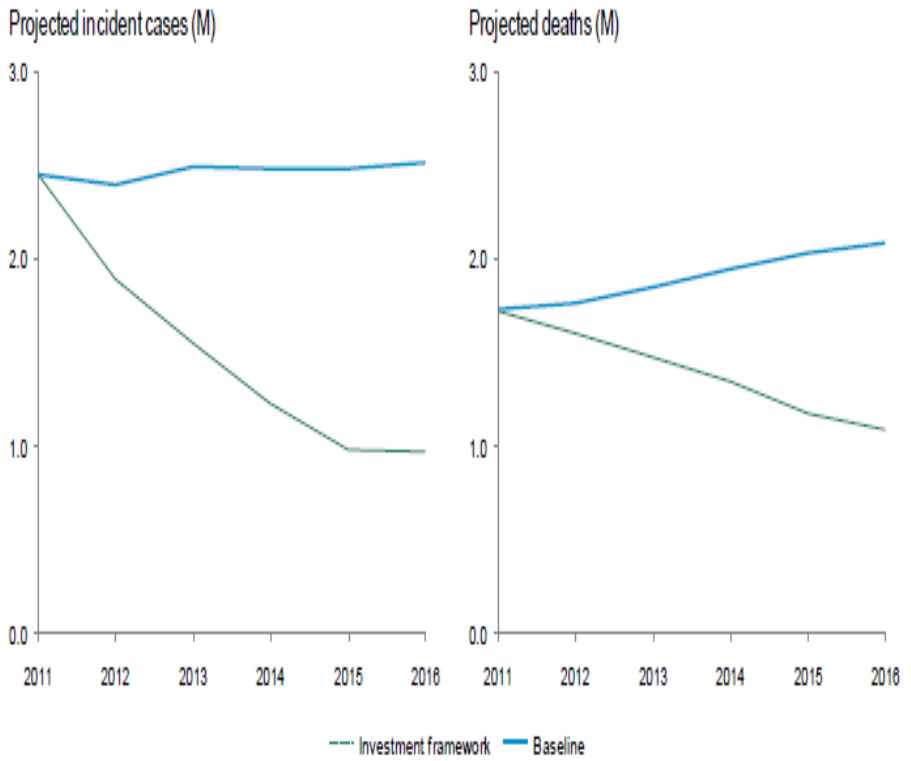
The Global Fund
To Fight AIDS, Tuberculosis and Malaria

REVIEW OF HIV/AIDS, TUBERCULOSIS AND MALARIA LANDSCAPE FOR THE GLOBAL FUND STRATEGY 2012-2016

Exhibit 5: HIV/AIDS – Likelihood and impact of new interventions[12]

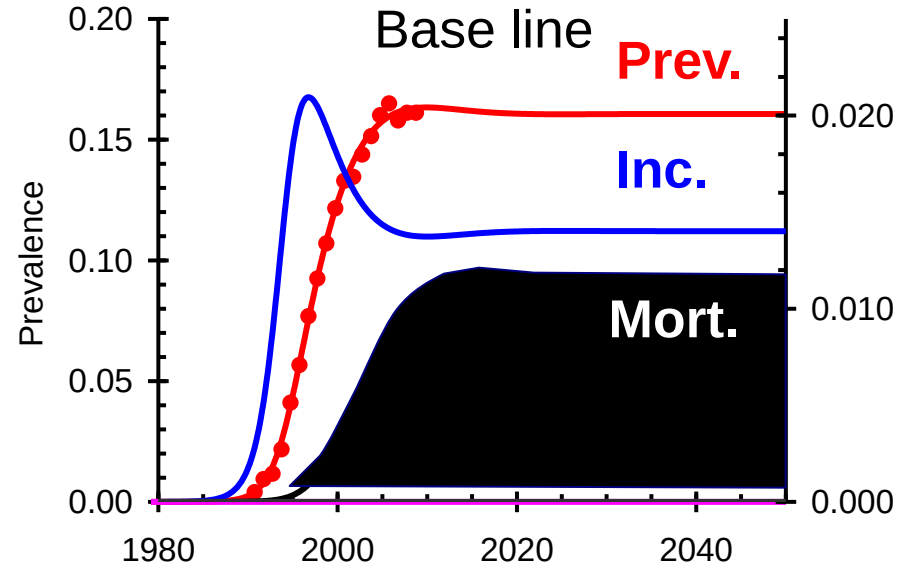
Type	Existing	Anticipated	Timing	Likelihood	Impact
Vaccine	N/A	RV144, HVTN 505	2020+		
Prevention	Condoms, Male Circumcision	Treatment as Prevention (discordant couples)	2011		
		Oral PReP (for MSMs)	2011		
		Male circumcision devices	2012		
Treatments	ARV	Treatment. 2.0	2011		
Diagnostics	CD4, viral load	Point of care	2011		
		Couples testing	2011		

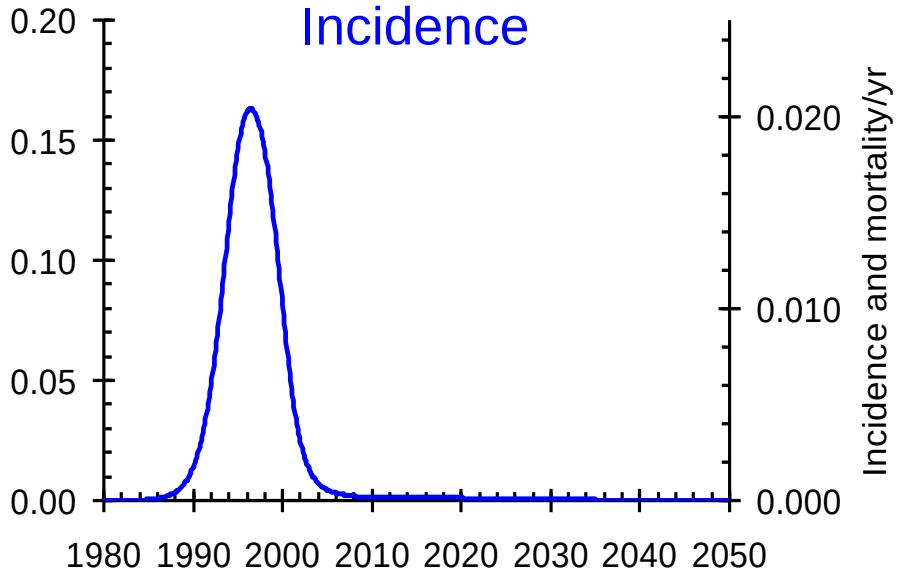
Exhibit 3: *HIV/AIDS – Projected incidence and deaths (2011-2016)*[6]

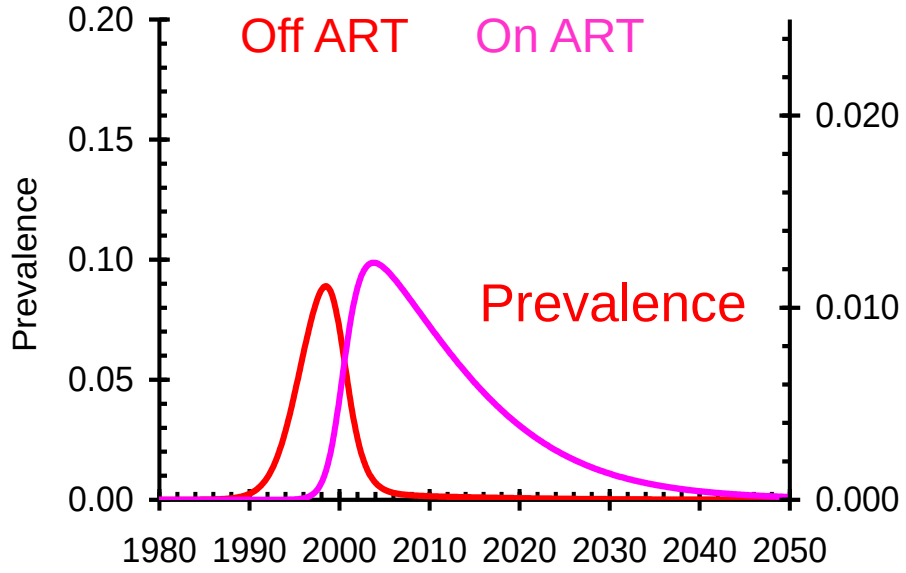


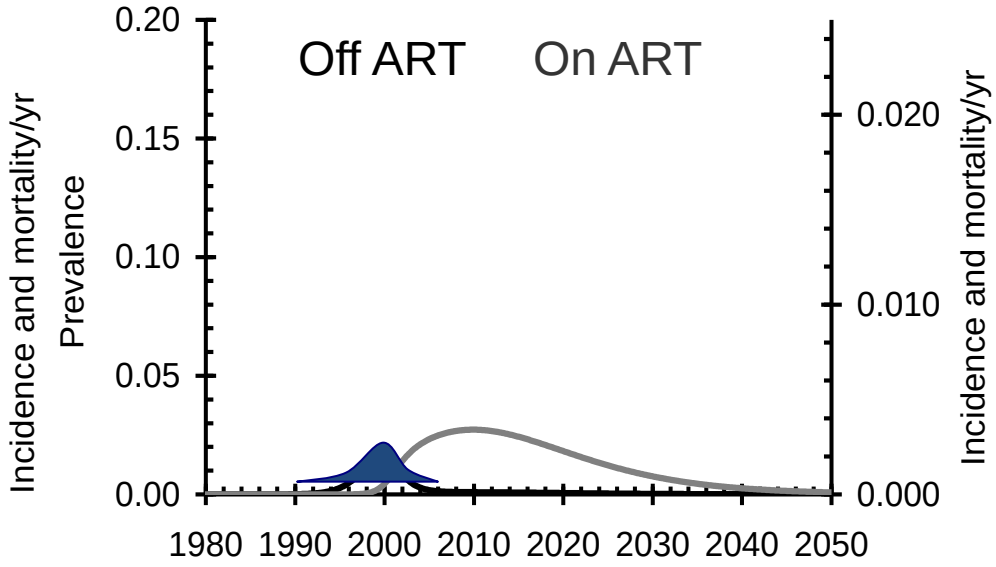
Global Fund website http://www.theglobalfund.org/en/about/strategy/ accessed September 19th 2013

Accountability and the dreaded retrospectoscope









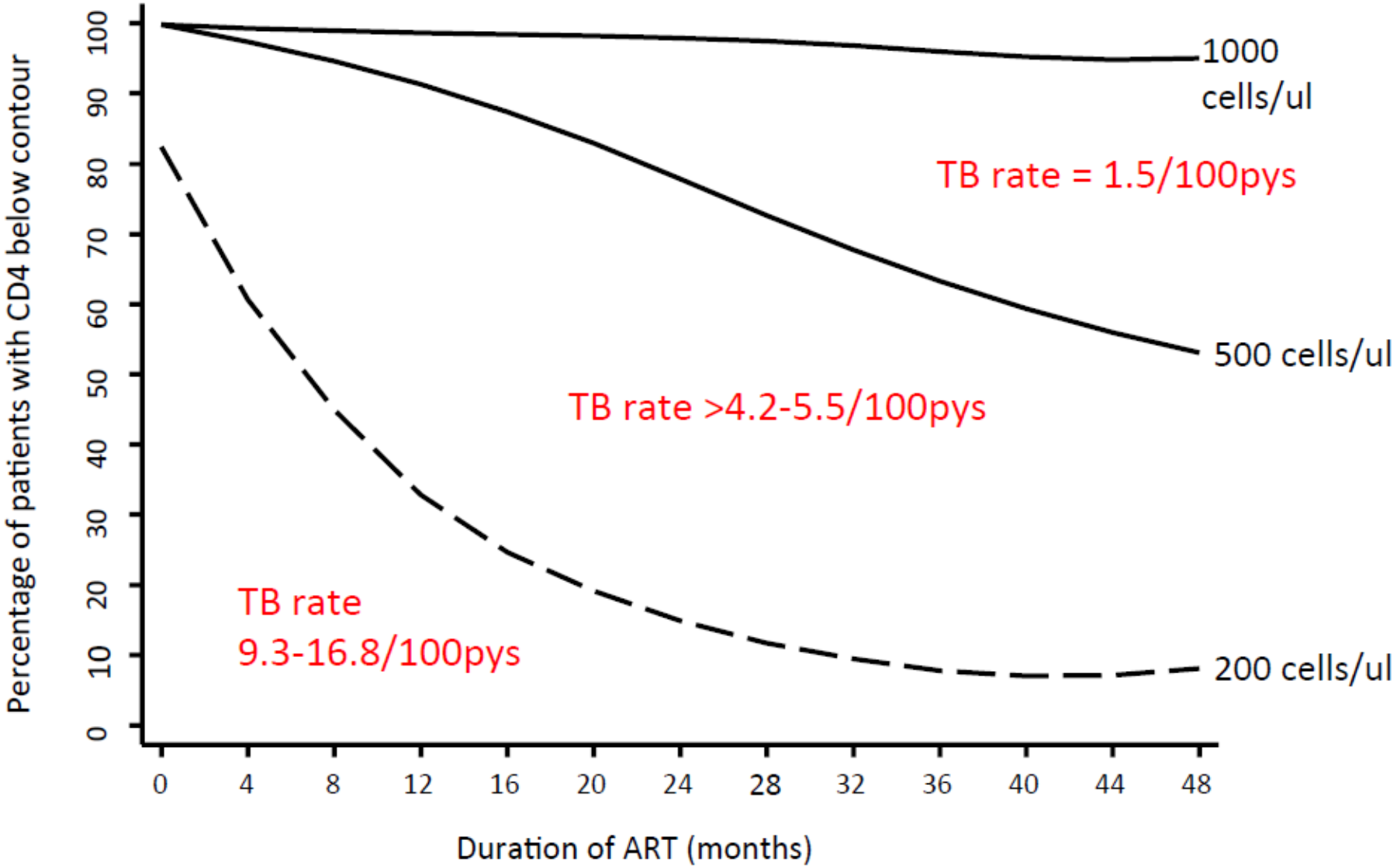
HIV in South Africa: test and treat starting in 1995

Williams 2010

HIV control: challenges

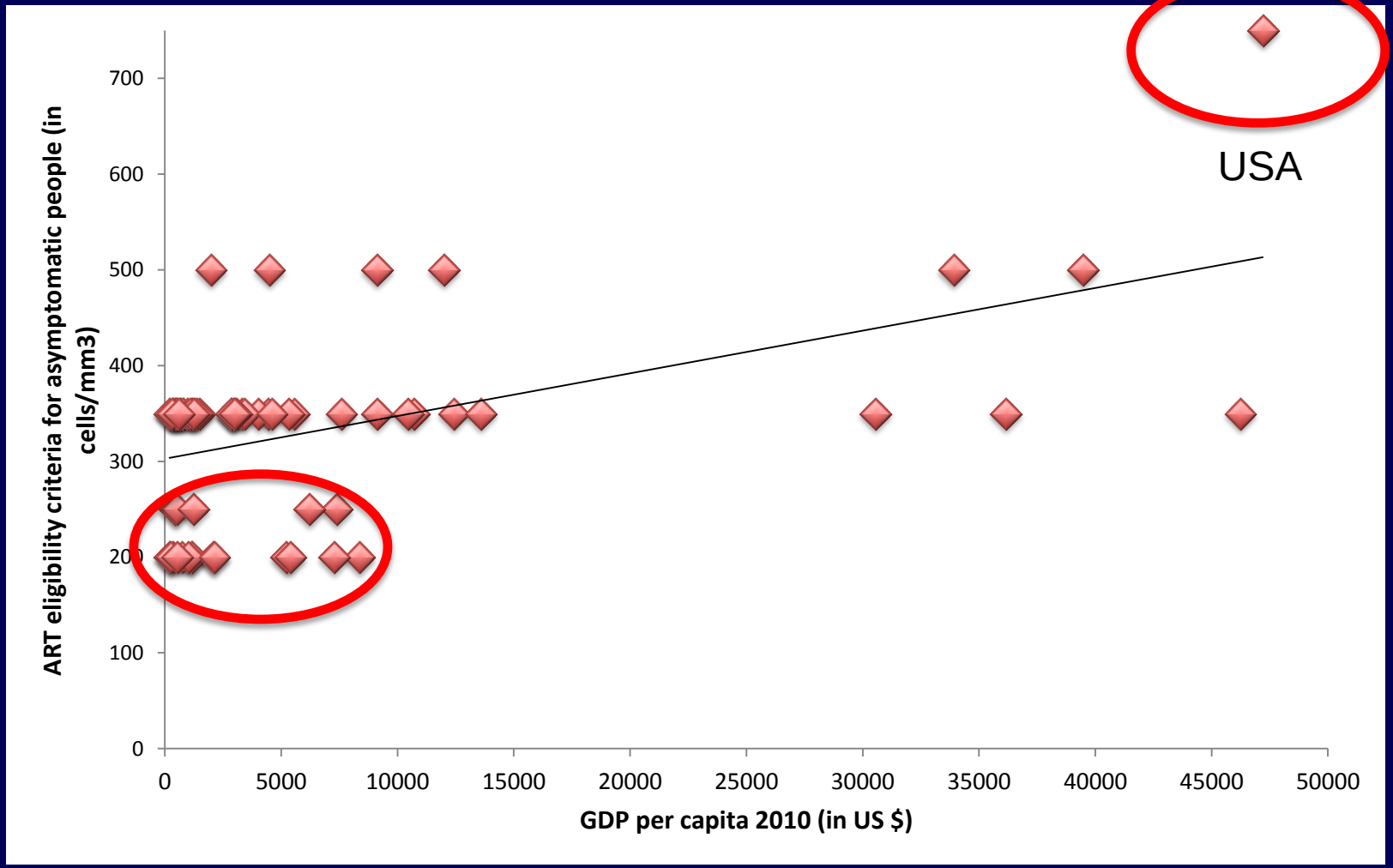
- Political will—leadership and funding
  - “Coordination”—simplify current complexity
- Scale-up plan with practical measurable milestones
- Focus—prioritize interventions, geography/people
- Speed—slow scale up is not an option for millions
- Innovation—private sector, community delivery, franchise model
- Delivery—standardized approach, clear practical guidelines, people first, community engagement
- Robust supply chain, simplify commodities
- Better M and E and surveillance

CD4 Count Profile of Cohort and TB Risk



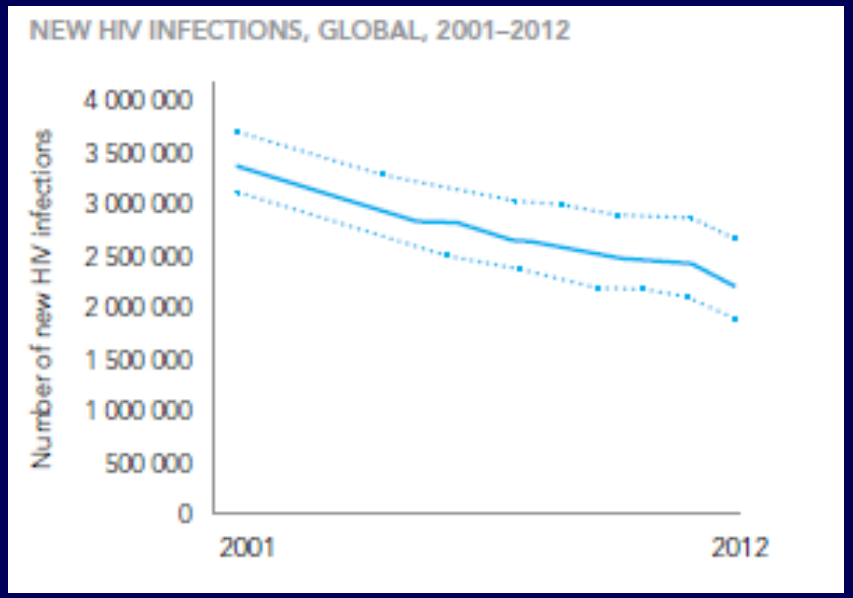
Slide courtesy of Steve Lawn

2010 GDP per capita and ART eligibility for asymptomatic people living with HIV

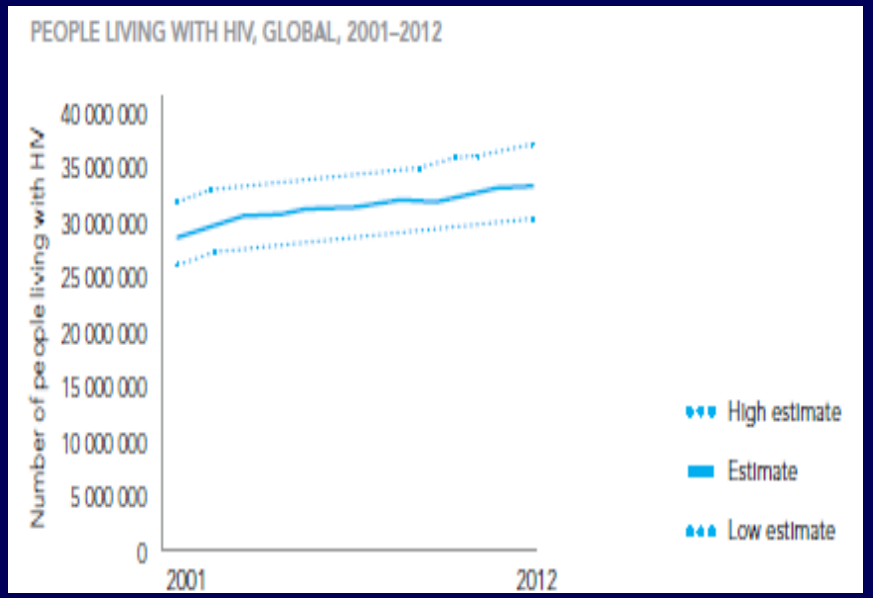


Positive but low correlation between GDP per capita and ART eligibility criteria for asymptomatic people

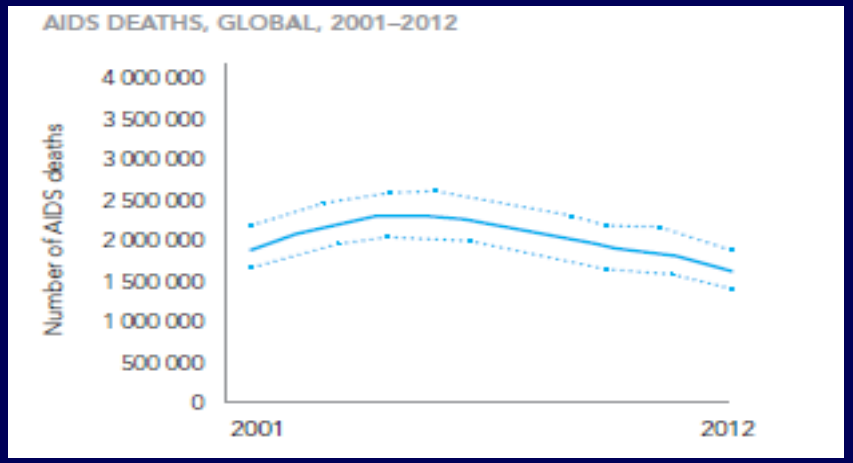
Numbers of people living with HIV, new HIV infections, and AIDS deaths, 2001-2012



New infections

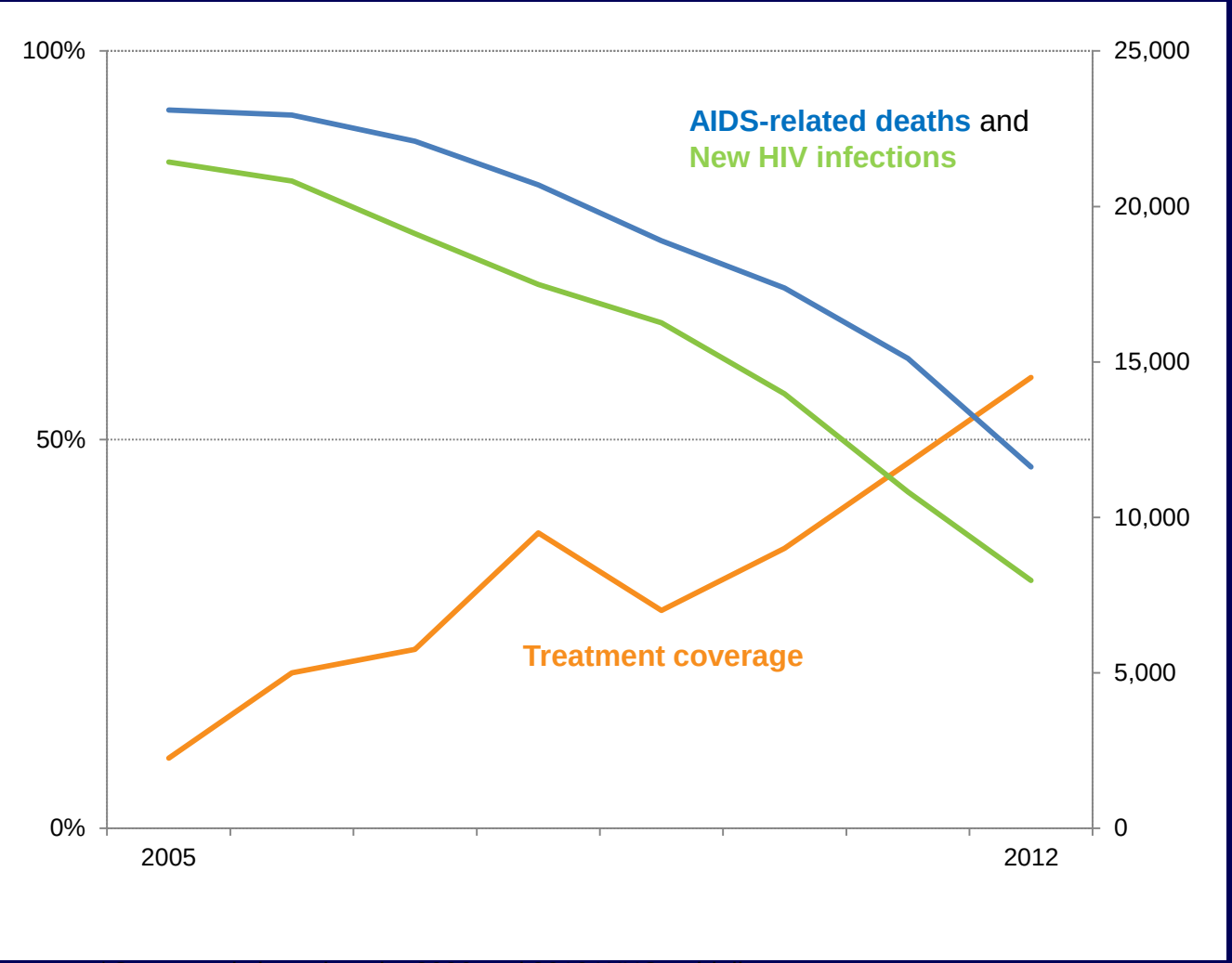


People living with HIV



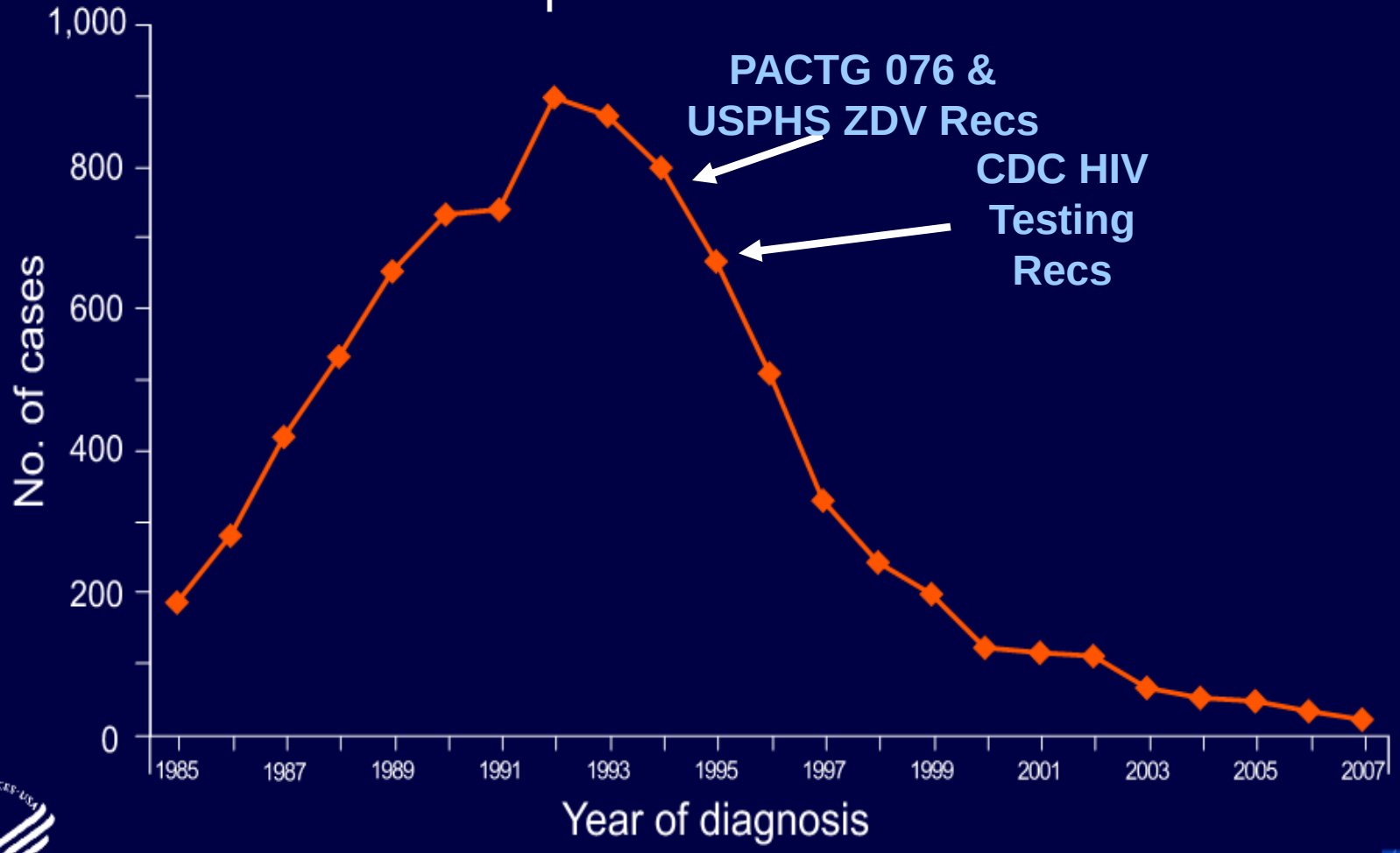
Deaths

Ghana: As HIV treatment coverage rose, new HIV infections and AIDS-related deaths fell, 2005-2012



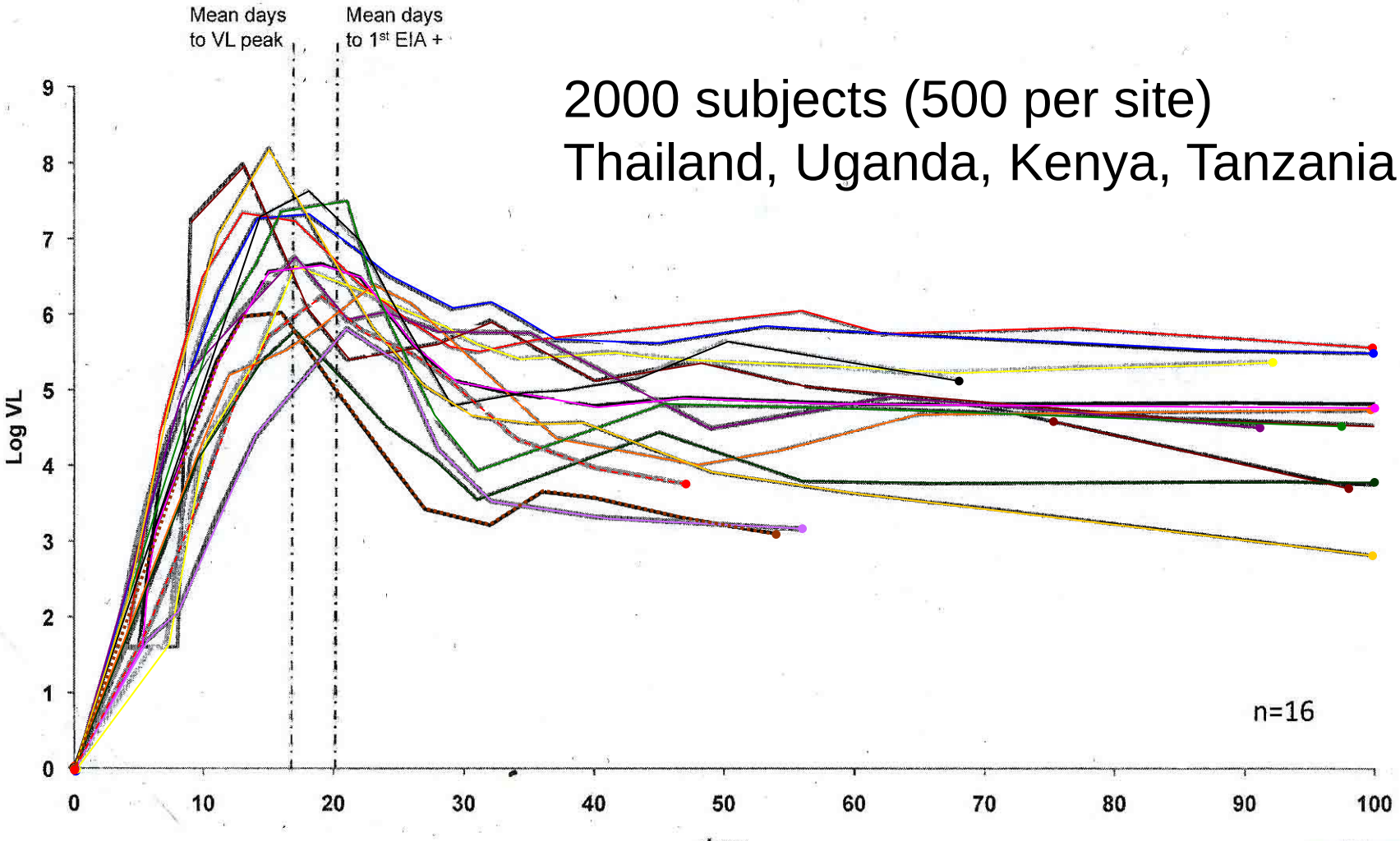
*Coverage is based on the 2006 and 2010 WHO guidelines

Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas



Note. Data have been adjusted for reporting delays and missing risk-factor information.

Aggregate Priority 1 Viral Loads- 1st 100 days

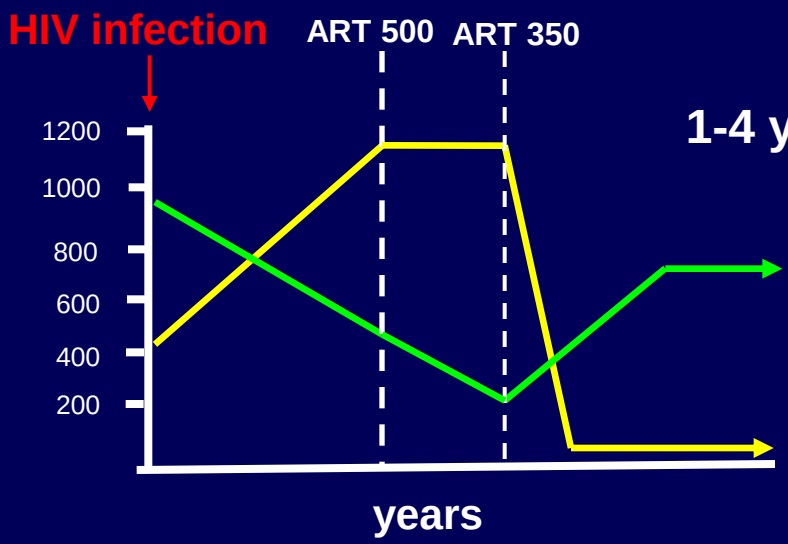


2000 subjects (500 per site)
Thailand, Uganda, Kenya, Tanzania

Mean # timepoints before peak = 4 (range: 3-6)
Mean # timepoints after peak = 8 (range: 6-11)

Robb ML. AIDS Vaccine 2012 Conference; 2012

When to start ART?
A matter of perspective



1-4 years earlier significant period

CD4 Count

Viral Load

1-4 years earlier now appears like a short period

CD4 Count

Viral Load

Slide adapted from Julio Montaner

UNAIDS

When to start?

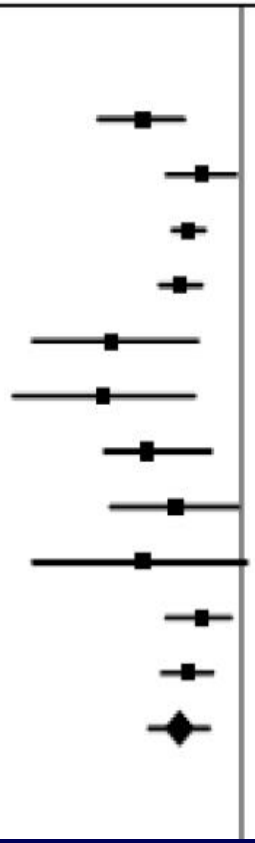
- **Advantages**:
  - Reduces mortality and extends lifespan
  - Prevents AIDS-related events and OIs
  - Reduces non-AIDS related events
  - Improves immune function
  - Reduces transmission
- **Disadvantages**:
  - Does not cure HIV
  - Side effects and toxicity
  - Pill burden/quality of life
  - Lifelong adherence
  - Resistance may develop
  - Cost ($$) – for drugs and for monitoring

Slide courtesy of D. Riedel

Morbidity prevention: Providing ART decreases the risk of TB by 65% across all CD4 levels

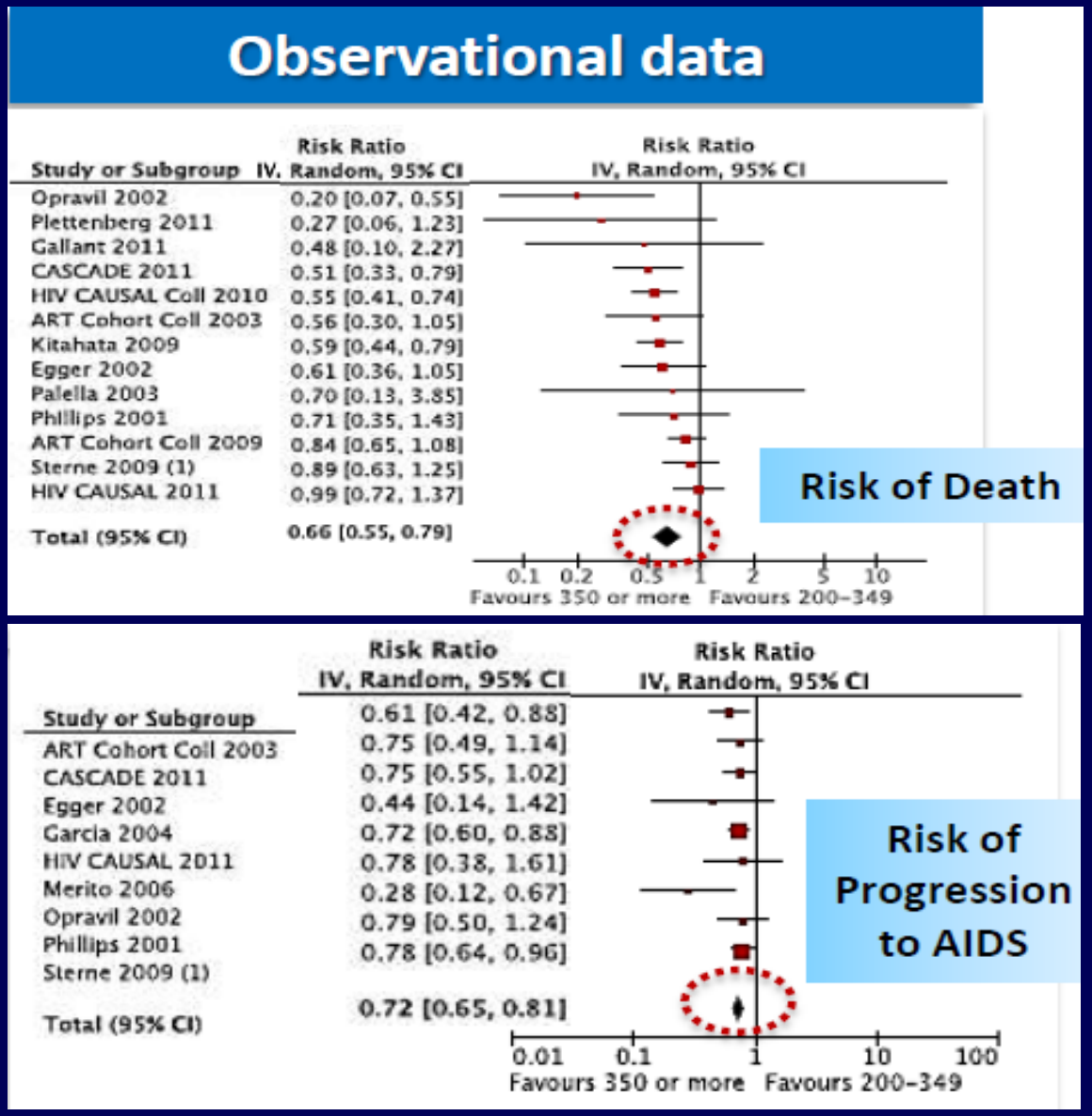
	ART		Control		IRR (95% CI)
	TB cases	PY at risk	TB cases	PY at risk	
All baseline CD4 counts					
Badri (2002)	9	375.1	82	848.2	0.19 (0.09 - 0.38)
Cohen (2011)	17	1661.9	33	1641.8	0.51 (0.28 - 0.91)
Golub (2007)	221	11627	155	3865	0.41 (0.31 - 0.54)
Golub (2009)	44	952	200	2815	0.36 (0.25 - 0.51)
Jerene (2006)	6	162.6	9	80.9	0.11 (0.03 - 0.48)
Lannoy (2008)	-	-	-	-	0.10 (0.02 - 0.45)
Miranda (2007)	-	-	-	-	0.20 (0.10 - 0.60)
Samandari (2011)	-	-	-	-	0.33 (0.11 - 0.94)
Santoro-Lopes (2002)	1	-	42	-	0.19 (0.03 - 1.09)
Severe (2010)	18	-	36	-	0.50 (0.28 - 0.83)
Zhou (2009)	57	5186	40	985	0.40 (0.26 - 0.61)
All studies					**0.35 (0.28 - 0.44)**

Effect: Z = 9.19, p < 0.001; Heterogeneity: I^2 = 31% (22% - 44%), p = 0.151



Suthar et al 2012 ,Plos Med

When to start ART….or how late is too late?



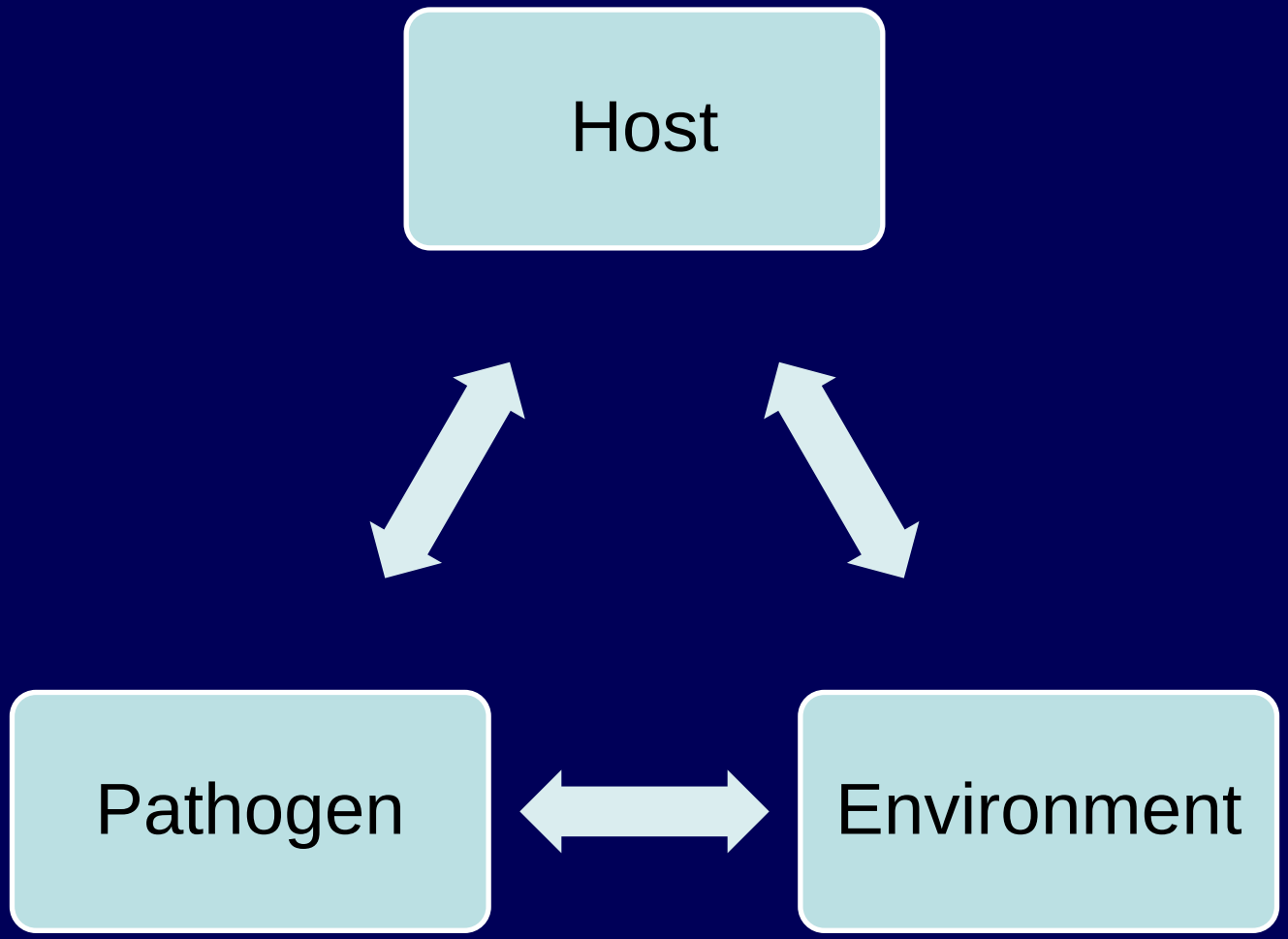
KL 2013 Critical issues for Adults with HIV: Presentation of Systematic reviews and Main recommendations. Doherty. WHO 2013 ARV Guidelines Launch

When to start?

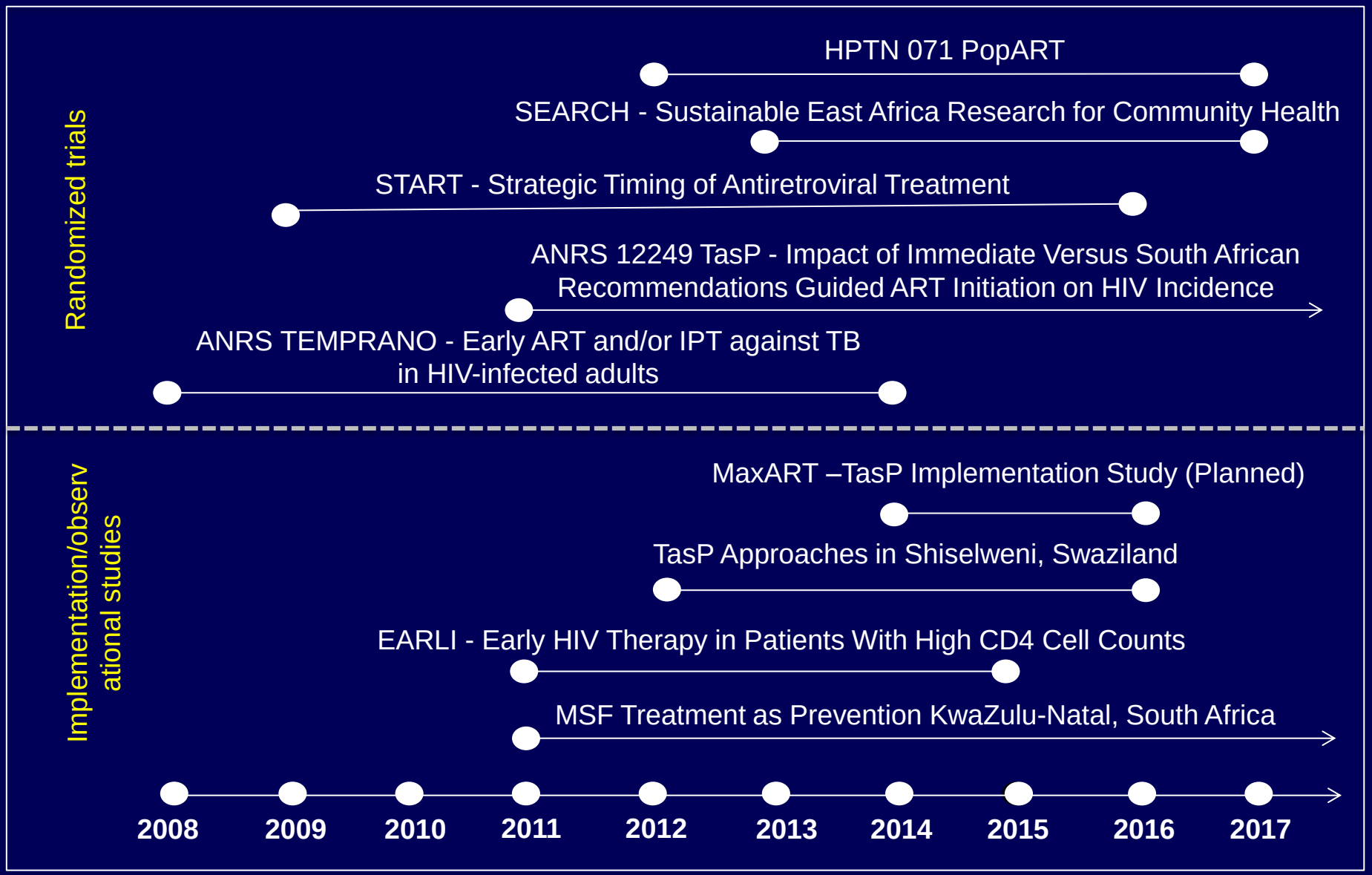
- **Advantages**:
  - Reduces mortality and extends lifespan
  - Prevents AIDS-related events and OIs
  - Reduces non-AIDS related events
  - Improves immune function
  - Reduces transmission
- **Disadvantages**:
  - Does not cure HIV
  - Side effects and toxicity
  - Pill burden/quality of life
  - Lifelong adherence
  - Resistance may develop
  - Cost ($$) – for drugs and for monitoring

Slide courtesy of D. Riedel

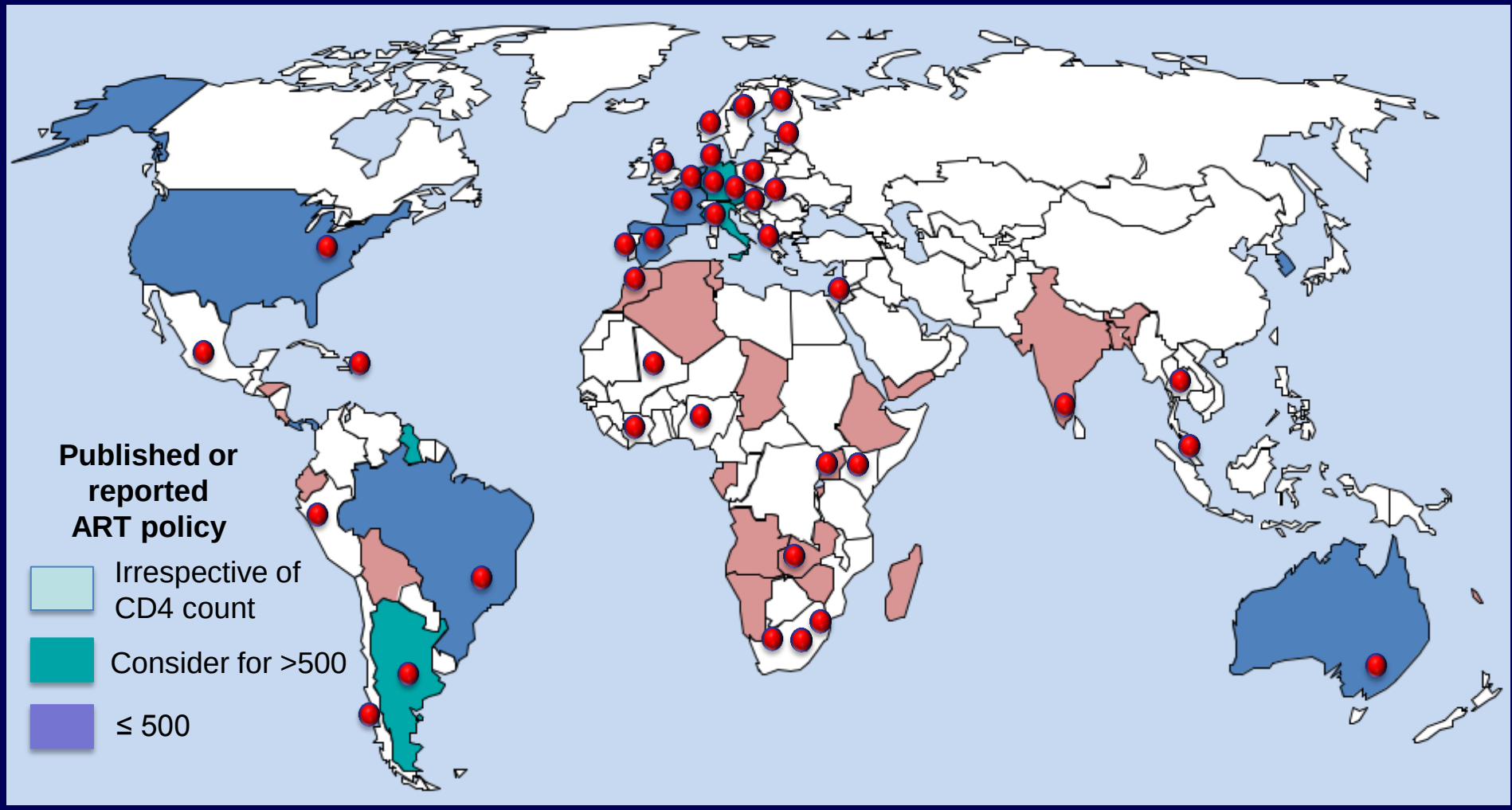
ART addresses all parts of classic infectious disease triangle



Timeline on projects with early ART (≥500)



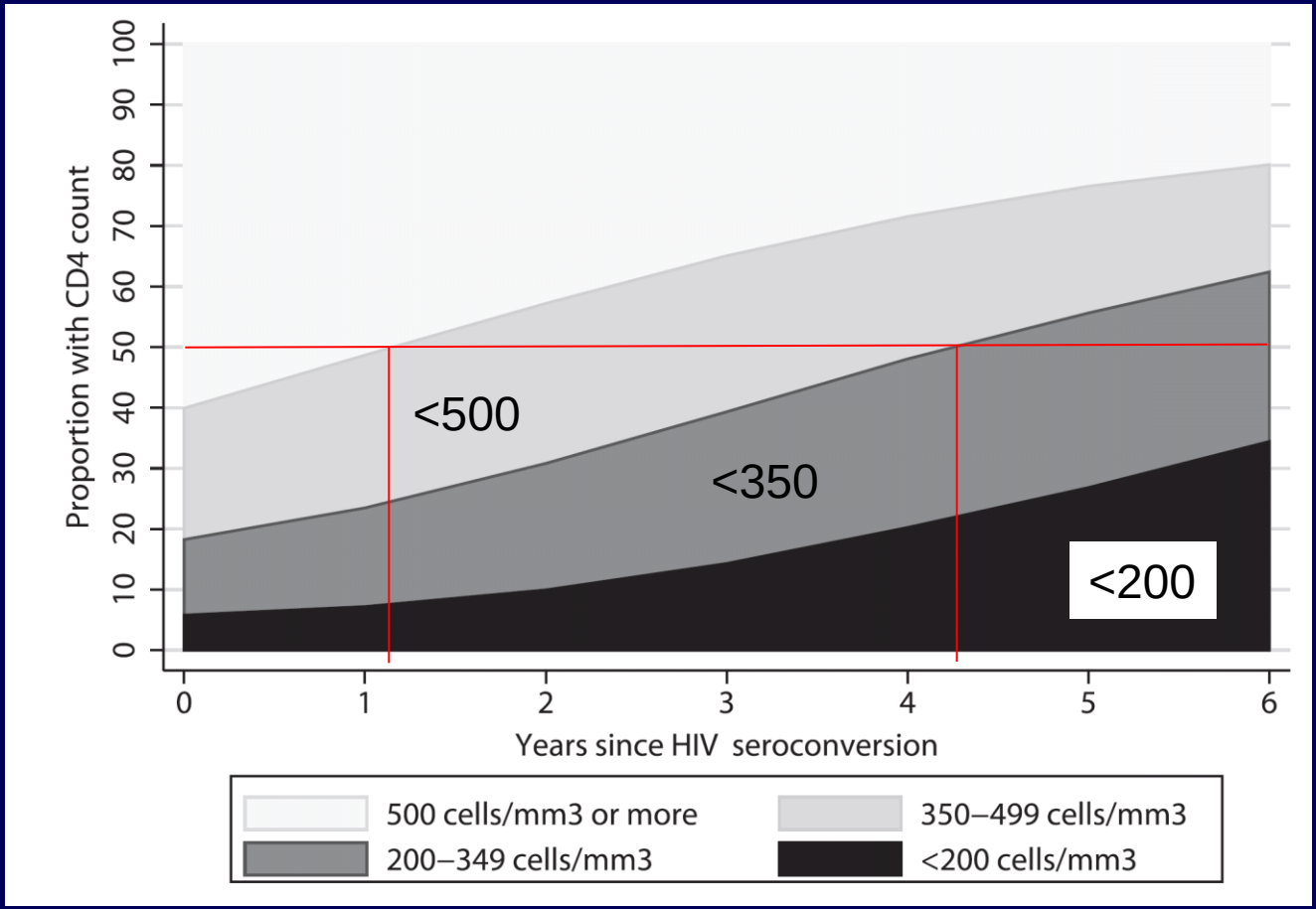
Countries with studies on early ART (≥ 500)



Red dots represent the countries with research on early ART

UNAIDS

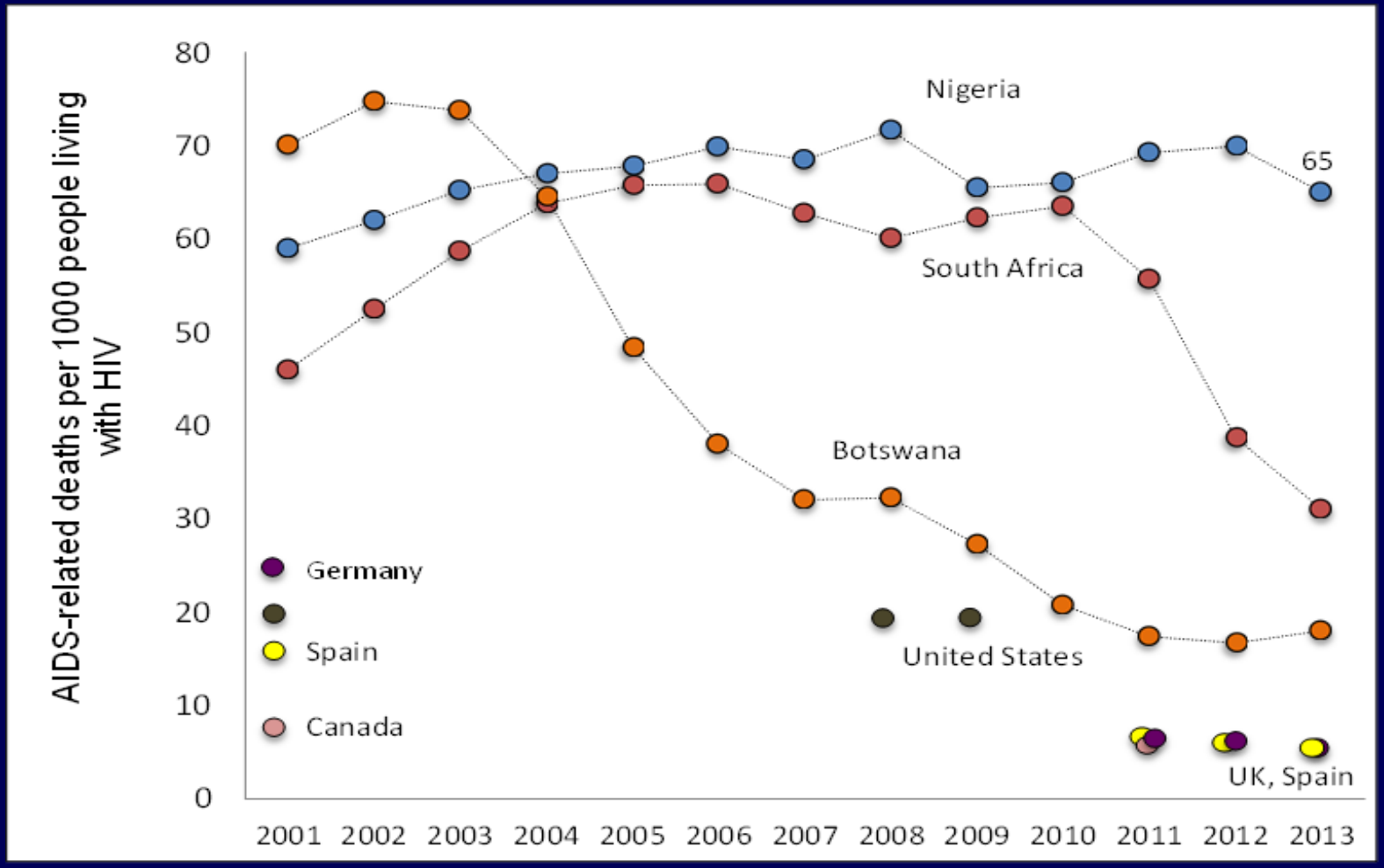
Time from HIV seroconversion to CD4 <500 is median of 1.2 years



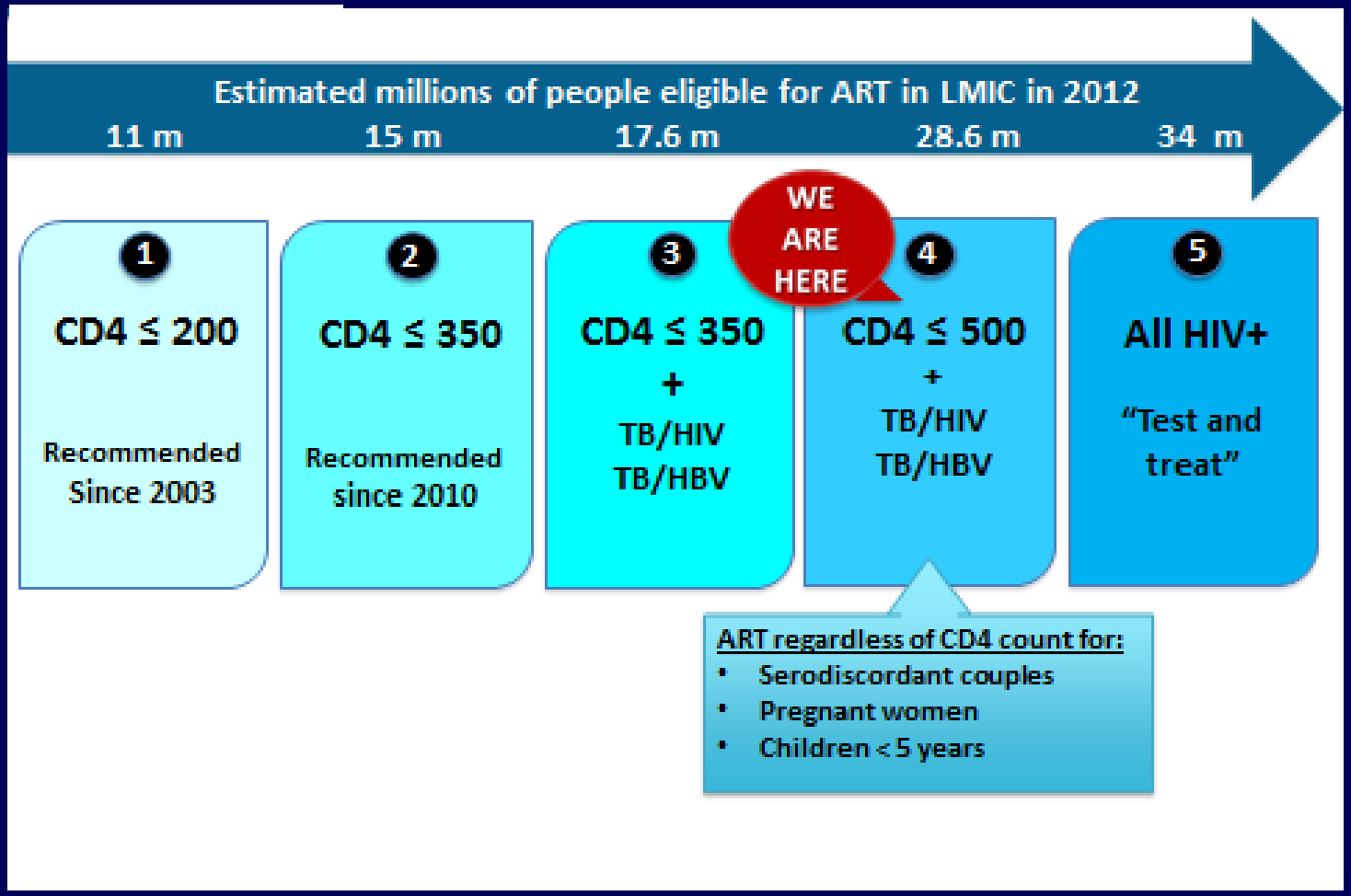
Median year (95% CI):
< 500: 1.19 (1.12-1.26)
<350: 4.19 (4.09-4.28)
<200 : 7.93 (7.76-8.09)

CASCADE: Lodi *et al*, CID 2011

Estimated annual AIDS deaths per 1000 people living with HIV

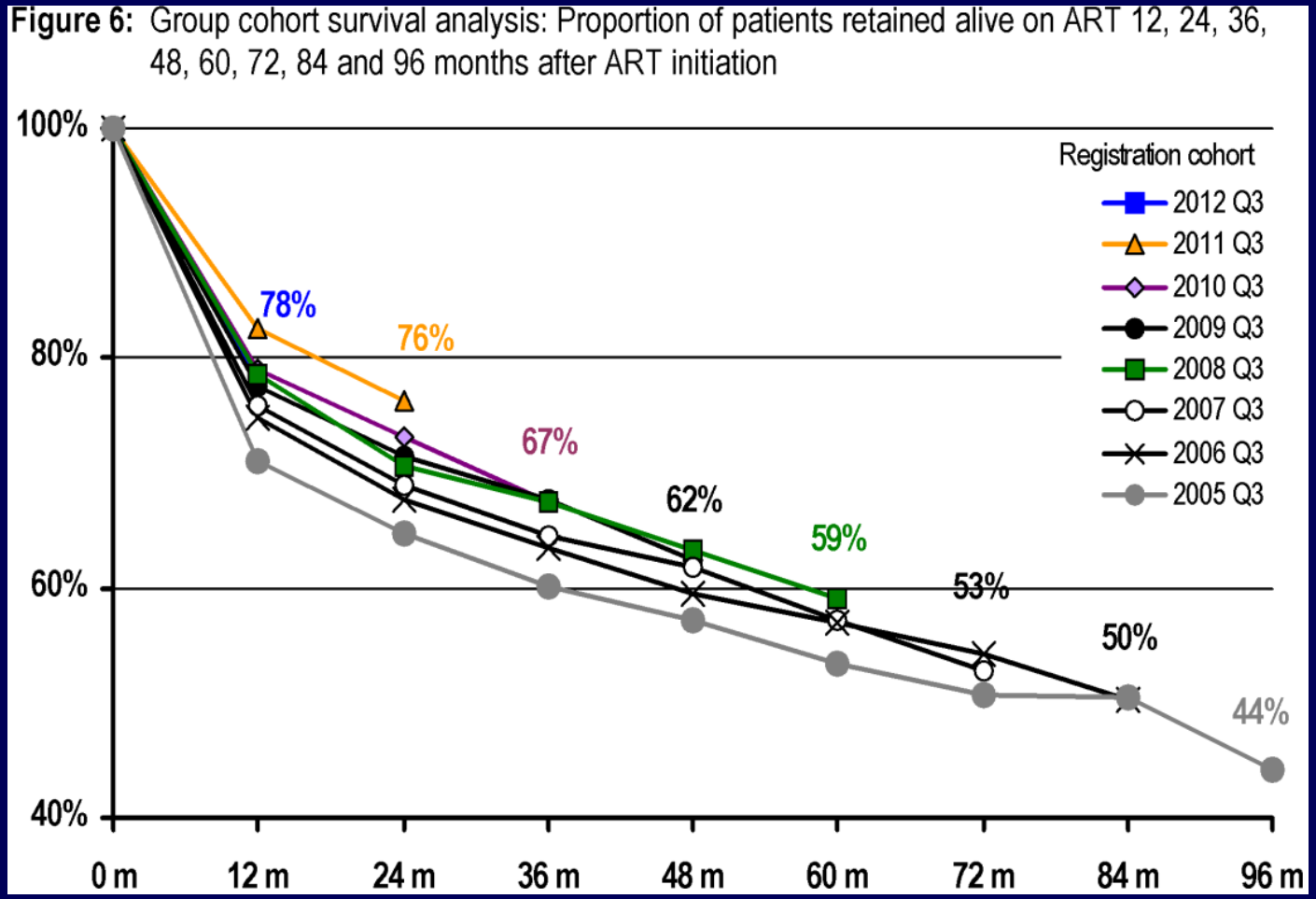


Scenarios of ARV eligibility: WHO vision

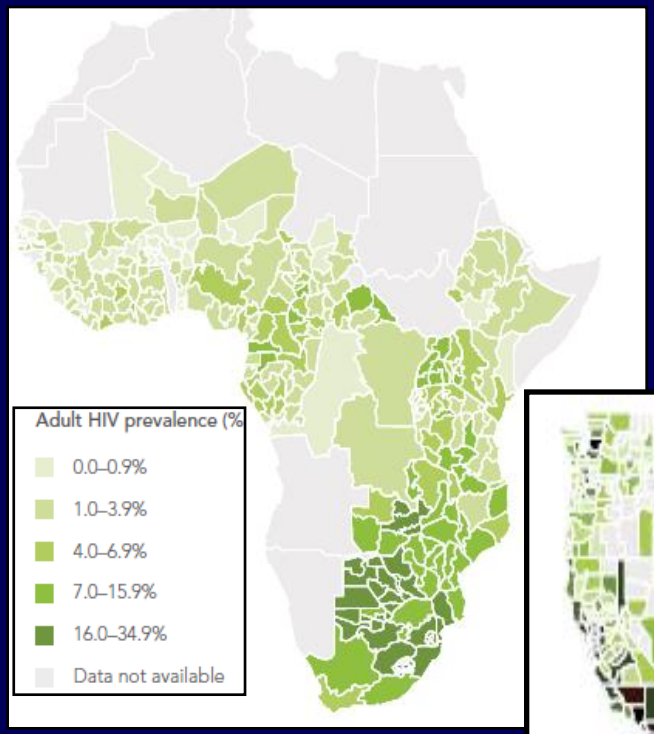


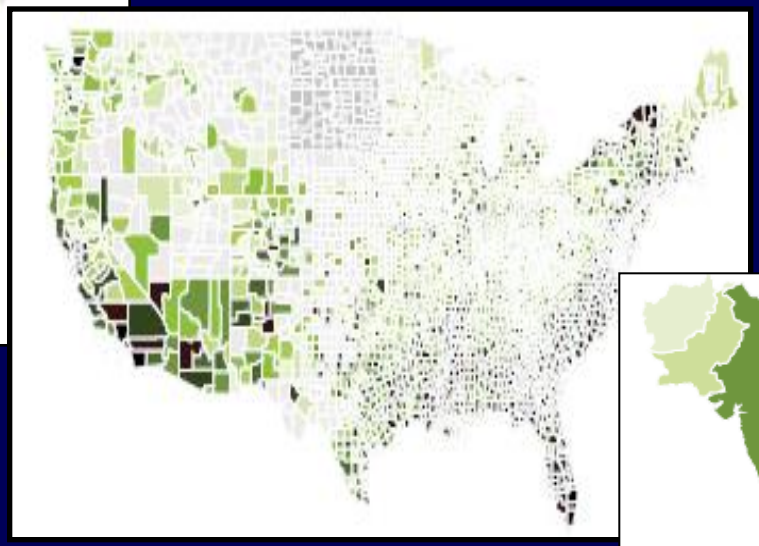
Source: WHO 2014

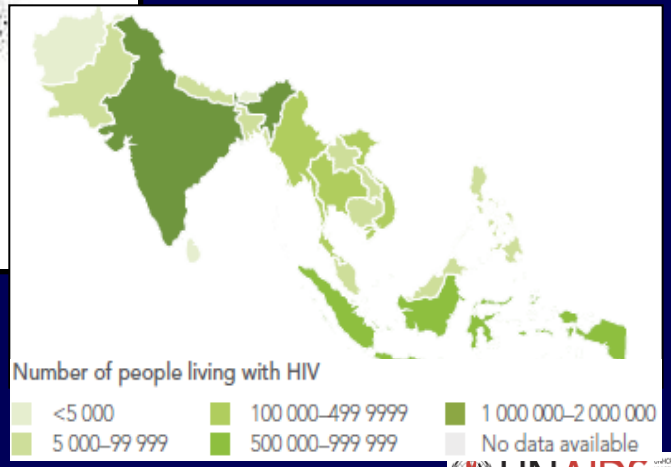
Malawi: each cohort is doing better than the last



Mapping local epidemiology, interventions and financing to monitor impact

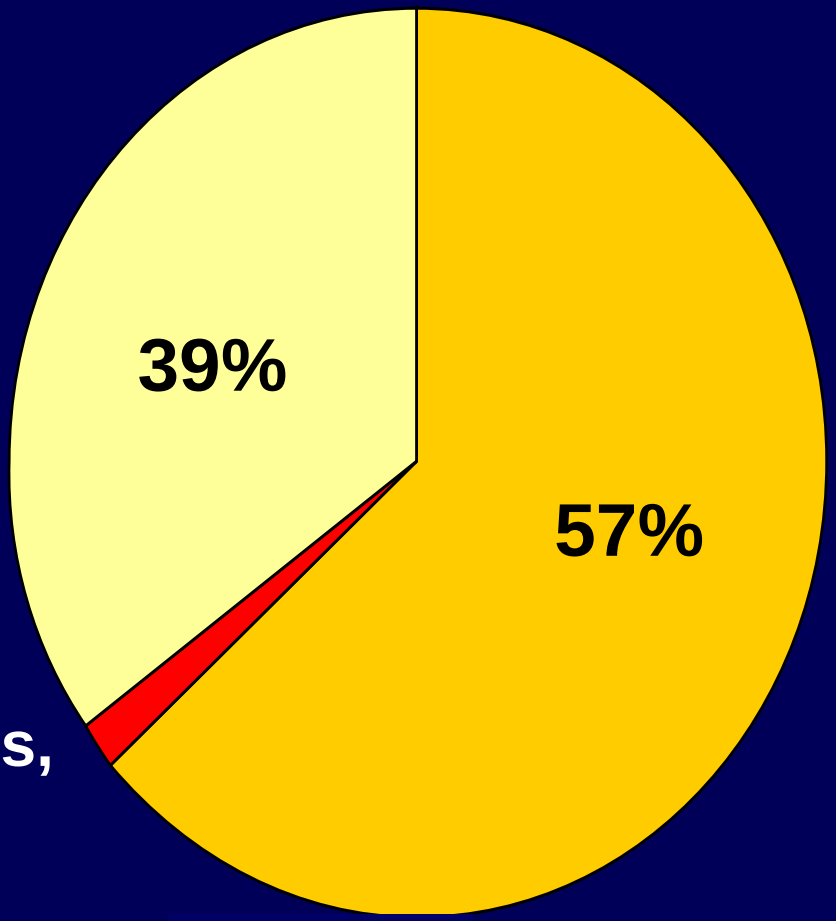






UNAIDS

Coverage of ART among eligible people living with HIV Kenya (2007 KAIS)

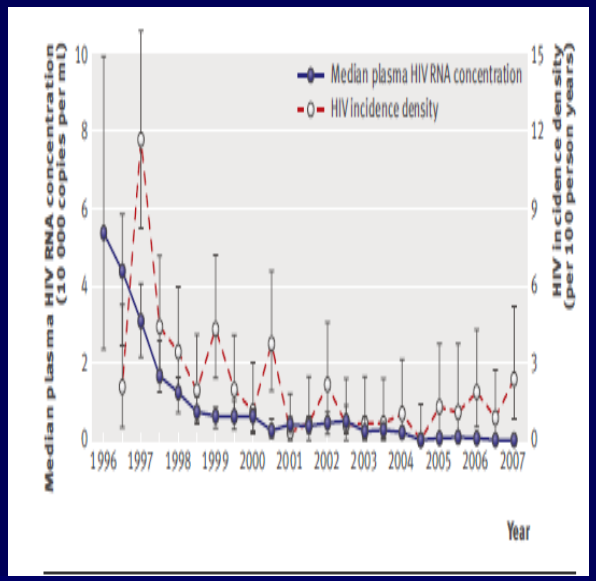


Among those who knew status and were eligible 92% were on ART

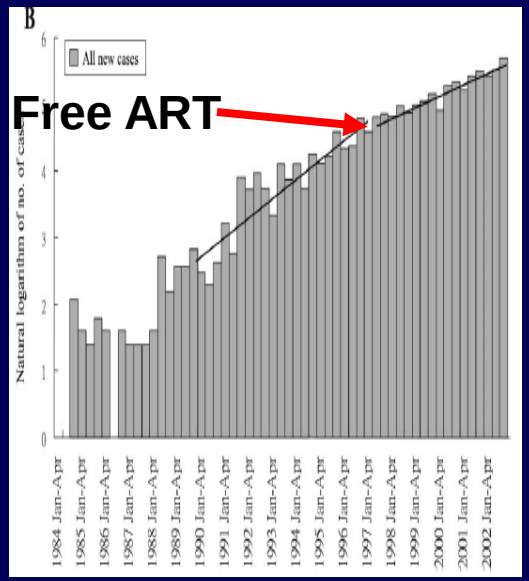
Mohammed, CROI 2009

Community studies suggest population-level impact of ART

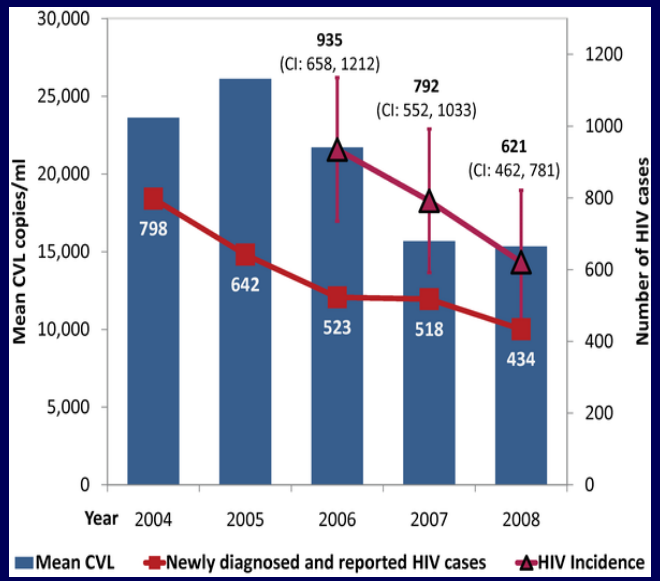
BC Canada



Taiwan



San Francisco

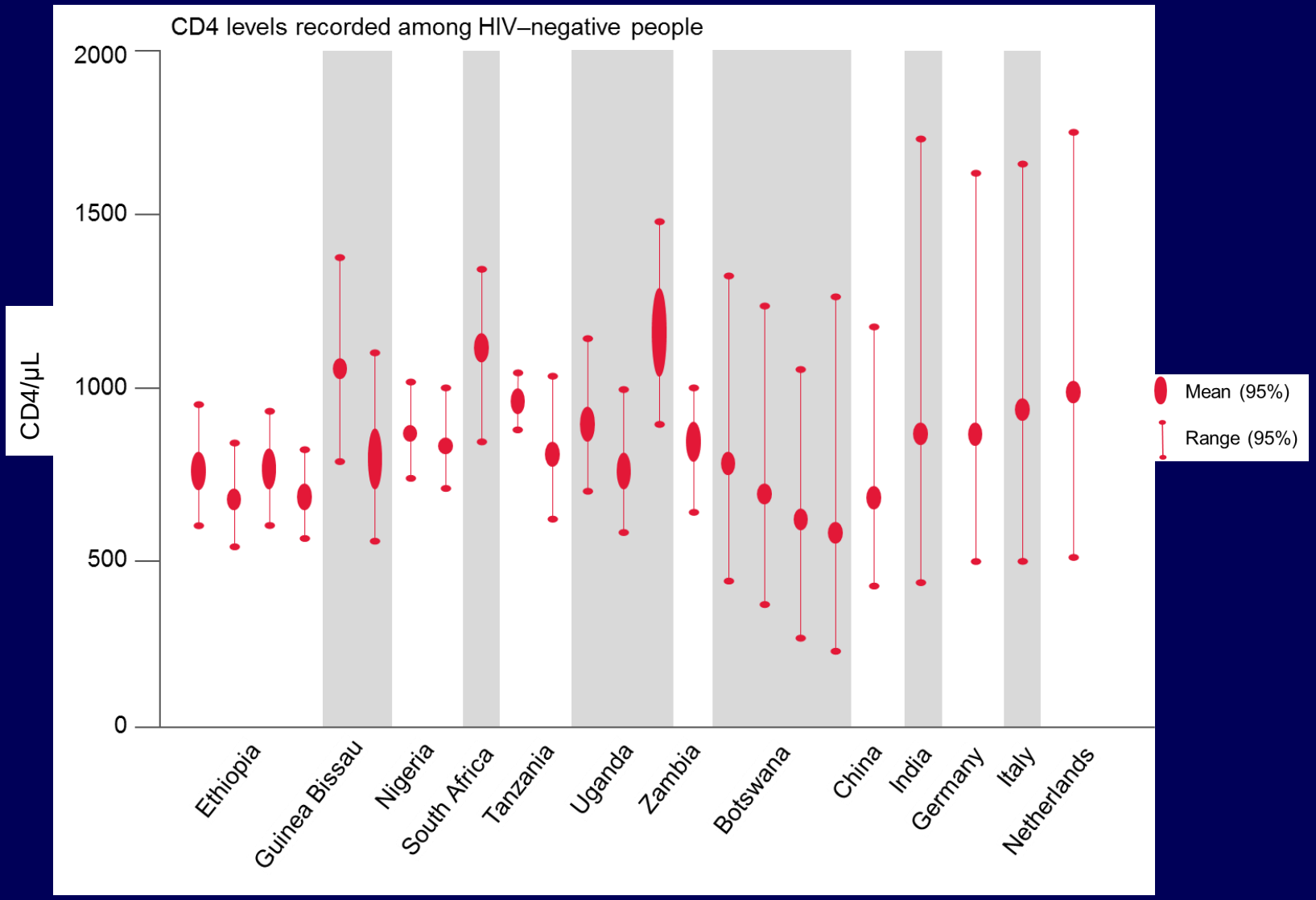


Wood et al. BMJ 2009;338b:1649

Fang et al. JAIDS 2004;190:879-85

Das et al.

Mean CD4 is highly variable across populations



Sources: Williams *et al.* 2006; 194: 1450-8; Bussman *et al.* 2004; Messele *et al*, 1999; Levin *et al*, 1996; Aina *et al*, 2005; Zekeng *et al*, 1997; Jiang *et al*, 2004; Uppal *et al*, 2003; Jentsch-Ullrich *et al*, 2005; Santagostino *et al*, 1999; Tsegaye *et al*, 1999.

Kenya Multidisease Prevention Campaign

September 16-22, 2008

Kenya Multi-disease Prevention Campaign

September 16-22, 2008

Over 7 day period more than 47,000 (80%) of the 15-49 population attended the campaign and 41,040 were tested for HIV. Over 18,000 men received an HIV test….

PARTNERS Study: CROI 2014

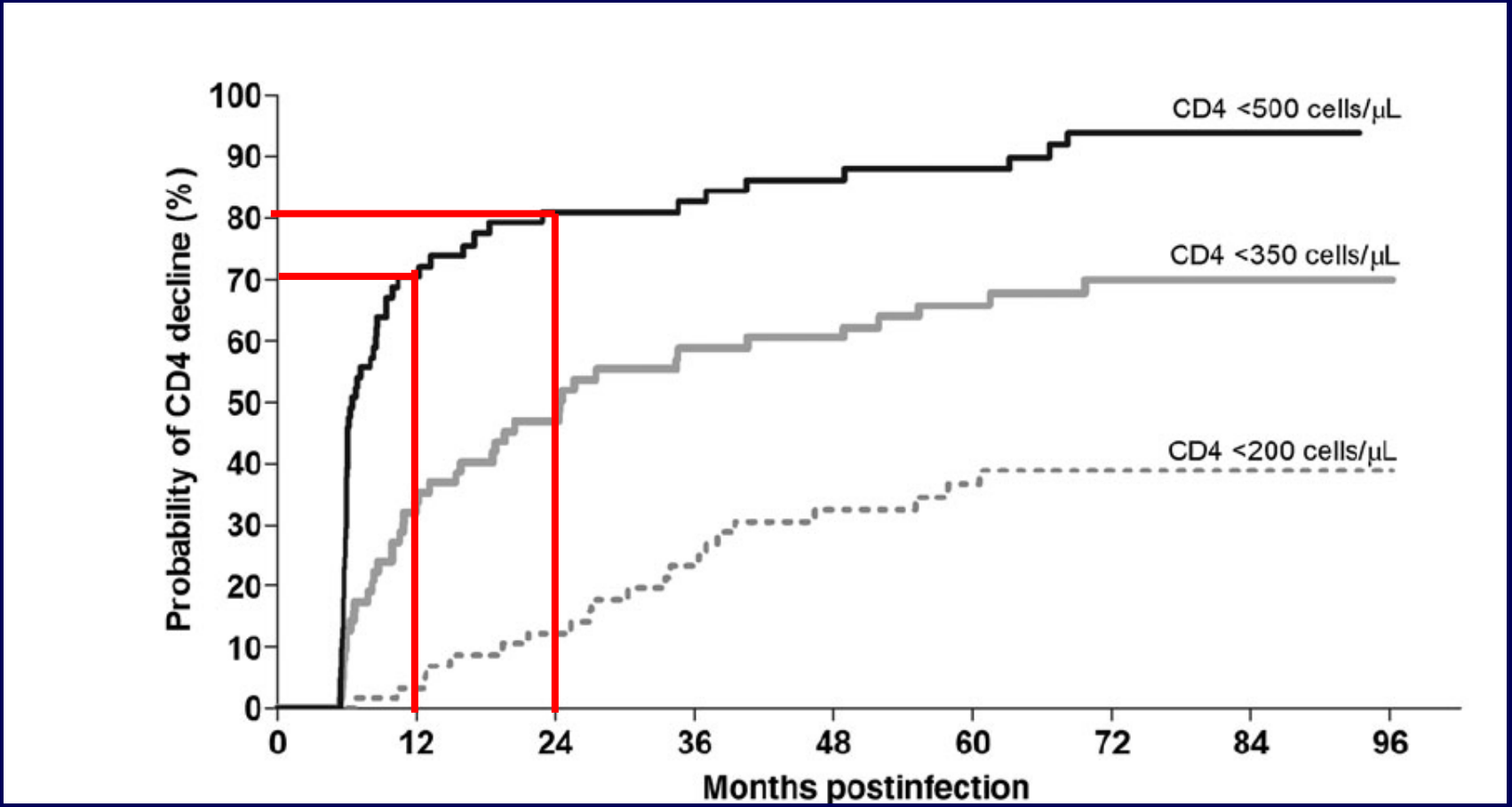
Press conference at CROI 2014.

Photo by Liz Highleyman, hivandhepatitis.com.

- 16,400 occasions of sex in the gay men and 28,000 in the heterosexuals
- Zero transmissions within couples from a partner with an undetectable viral load
- Upper bounds of confidence intervals suggest that risk is not zero

Rodger A et al. *HIV transmission risk through condomless sex I f HIV+ partner on suppressive ART: PARTNER study.* 21st CROI, Boston, abstract 153LB, 2014.

Time to CD4 cell count: South African women infected with sub-type C



Mlisana CID 2014

WOMEN, CARE, TREATMENT, PREVENTION & HIV

Silvia Petretti
Deputy CEO
Positively UK

10 November 2014
EATG TasP Webinar

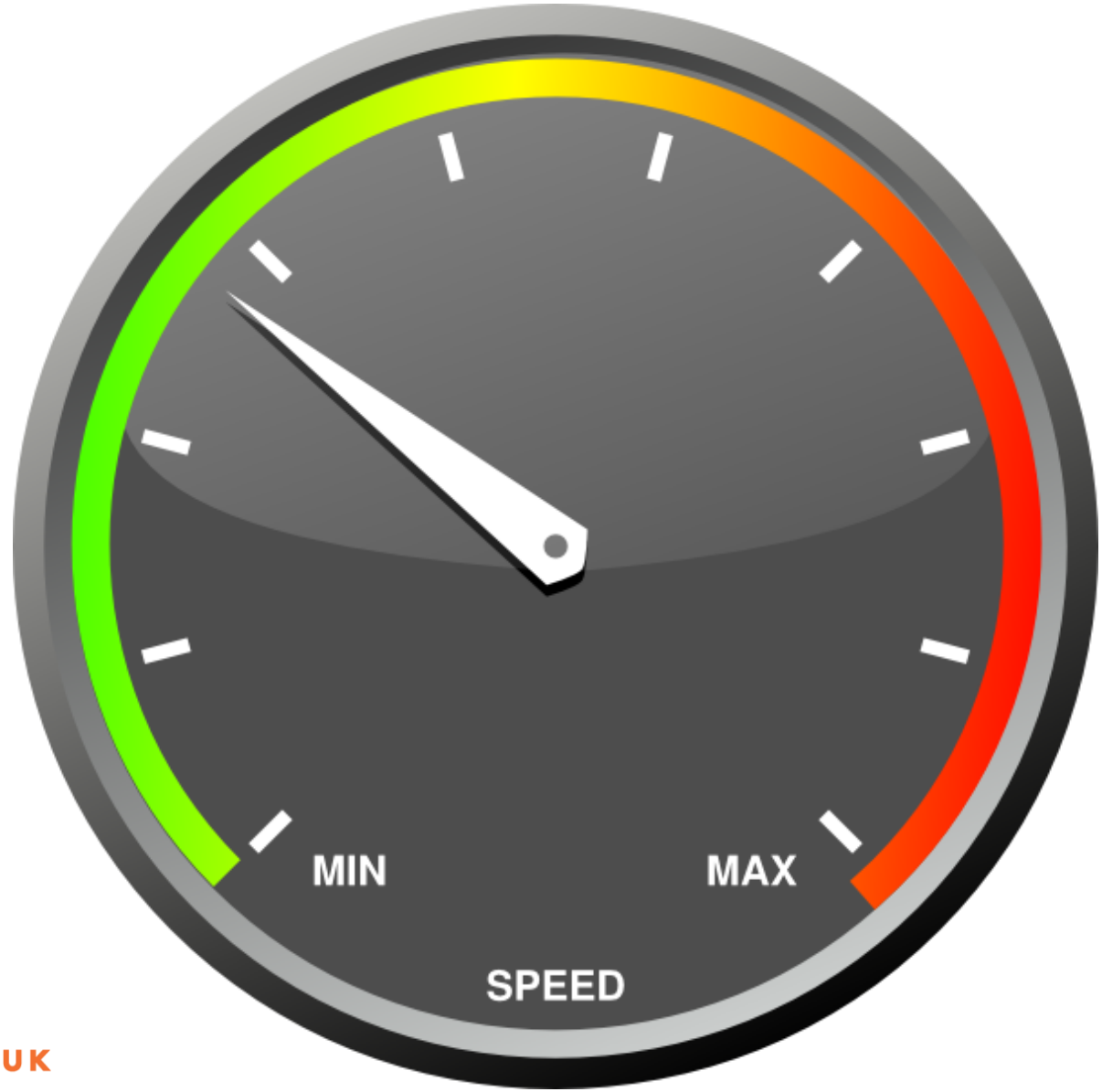
POSITIVELY UK

DISCLOSURE

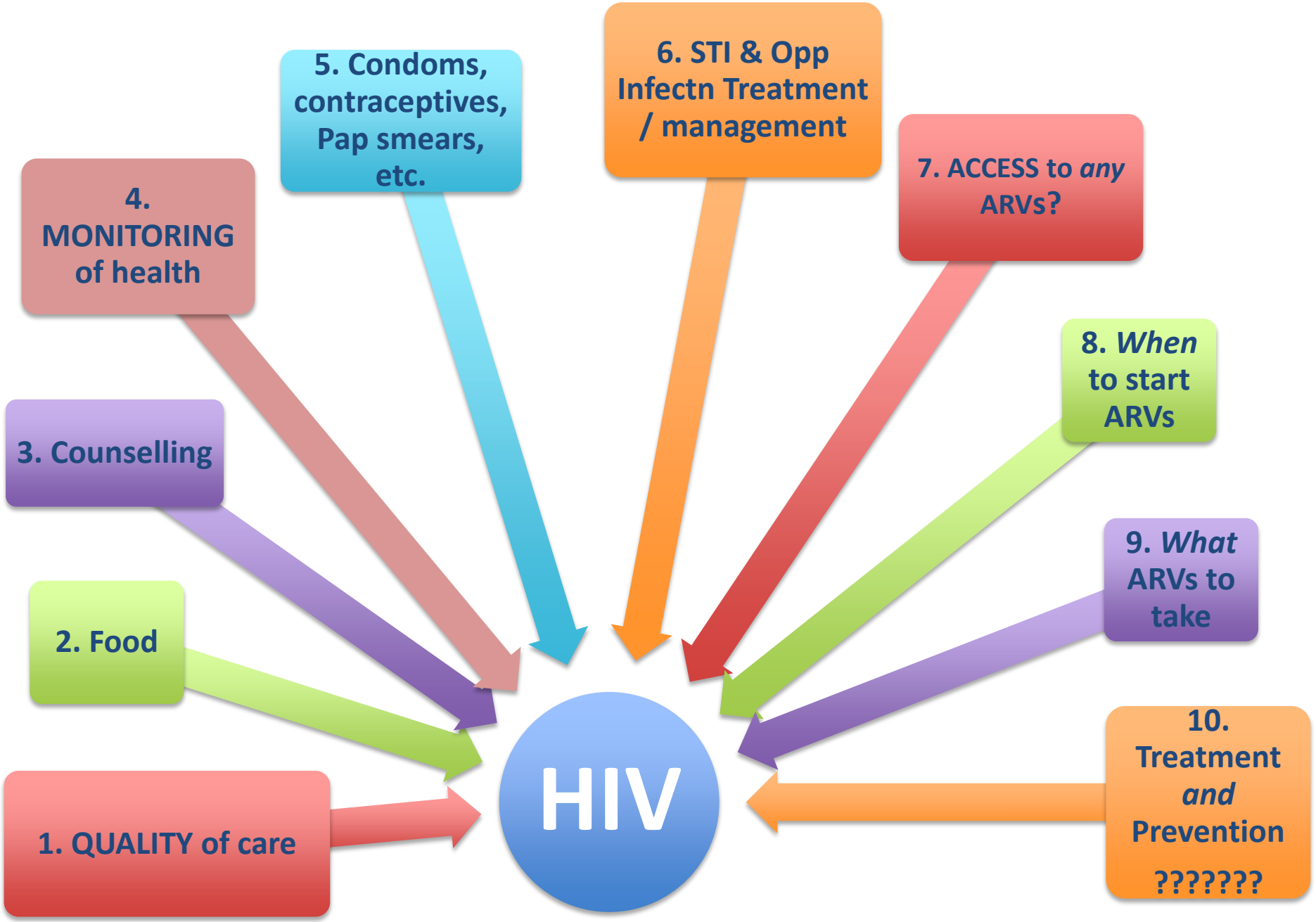
- Diagnosed in 1997 aged 30
- Started treatment in 1998
- I have taken: AZT, DDI, D4t, Indinavir, Sequinavir, Ritonavir, Nevirapine, Efavirenz, Tenofovir, FTC, 3TC, Lopinavir, Darunavir and Raltegravir …in various combinations
- VL undetectable
- CD4 >500

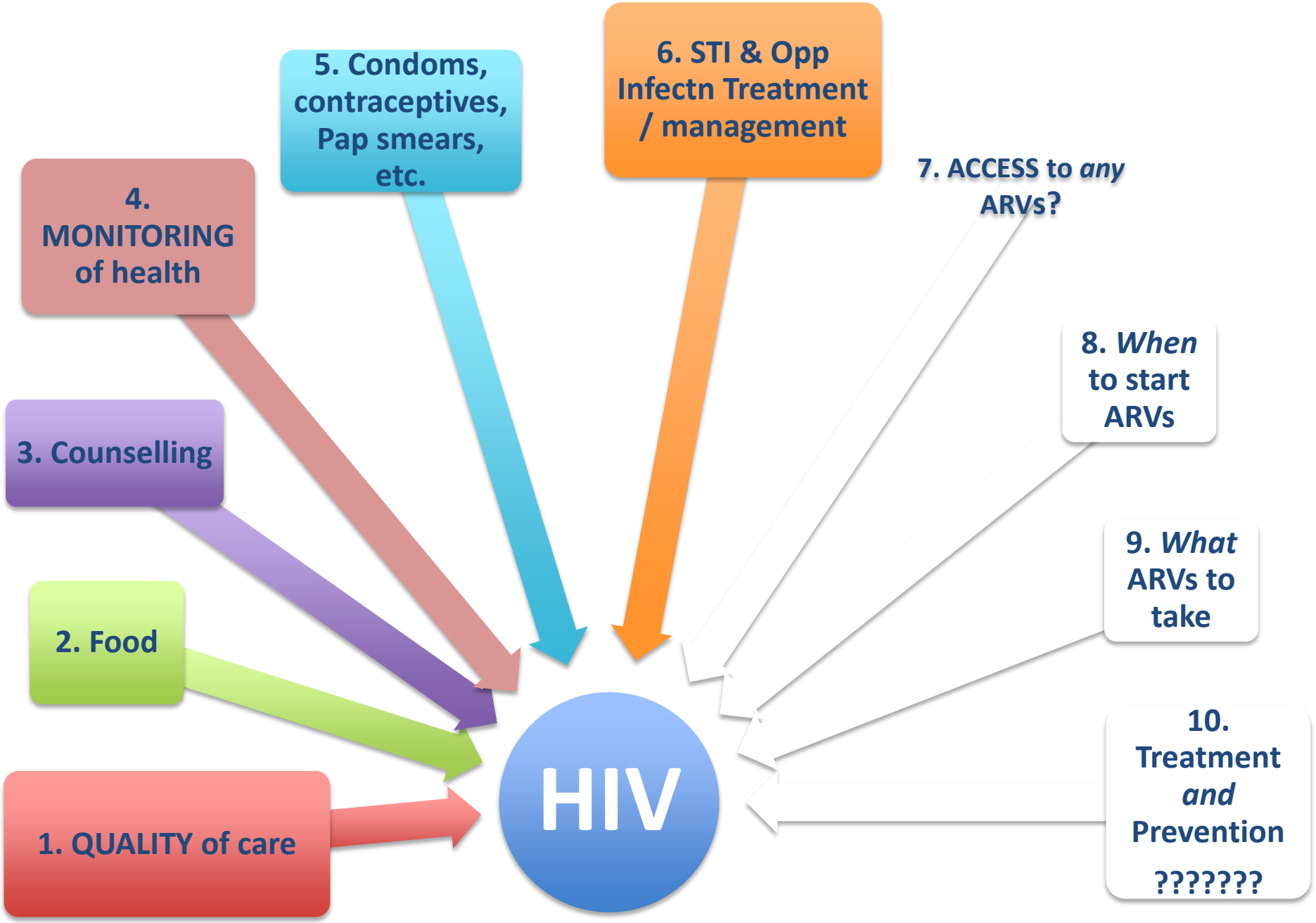
WITHOUT ARV'S I WOULD BE DEAD

POSITIVELY UK



POSITIVELY UK


5. Condoms, contraceptives, Pap smears, etc.
6. STI & Opp Infectn Treatment / management
4. MONITORING of health
7. ACCESS to *any* ARVs?
8. *When* to start ARVs
3. Counselling
9. *What* ARVs to take
2. Food
HIV
1. QUALITY of care
10. Treatment *and* Prevention
???????


5. Condoms, contraceptives, Pap smears, etc.
6. STI & Opp Infectn Treatment / management
4. MONITORING of health
7. ACCESS to *any* ARVs?
8. *When* to start ARVs
3. Counselling
9. *What* ARVs to take
2. Food
HIV
10. Treatment *and* Prevention ???????
1. QUALITY of care

Some basic ethical principles: 1

Doctors' duties are primarily to the **individual** in the **trusting** "doctor-patient" relationship where the doctor **puts the individual's interest first**.

Their duty is to prevent death & relieve suffering.

First of all, do no harm a strong, traditional tenet.

POSITIVELY UK

All Care *includes*:

1. Discussions with provider(s) (case history)

2. Tests (eg blood tests for CD4, VL, scans, ultra-sound, pap smear…..)

3. Unbiased Information about pros and cons of different options

4. Q and As

5. On-going monitoring and evaluation

6. Suggest joining support group (if wanted)

7. More appointments (so client can go away and think/discuss etc)

8. Decisions – all as INFORMED CHOICE:

-Watch and Wait ("watchful waiting" (http://en.wikipedia.org/wiki/Watchful_waiting)

-Option of Counselling – alone or as couple if wanted

-Medication – "Treatment" (eg for Opp Infectns, contraception, condoms…..ARVs,)

-Surgical intervention

-Combination of these

9. ON-GOING MONITORING AND EVALUATION

POSITIVELY UK

"CARE" DOES *NOT* JUST MEAN "TREATMENT"

“INFORMED CHOICE”?

The individual is given ***non-judgmental information***

It is the ***individual’s choice*** – *not* the healthcare provider’s

Choice should be over ***whether*** or not to take medication

Choice should then be over ***which*** medication to take

The individual is offered time to *think through options* and *discuss with others* before making a decision

POSITIVELY UK

CATIE QUESTIONS

The Canadian AIDS Treatment Information Exchange (CATIE) suggests ten questions for assessing a new therapy (actually re complementary therapies but an equally valid set of questions for *any* medication):

What am I hoping to get out of this therapy?

Do other HIV positive people use it?

Am I able to talk to any of these other people about their experiences?

Is there any research or additional information about this therapy?

What are the side effects, if any?

What sort of commitment do I have to make to use this treatment?

Where can I get this treatment, and will it be regularly available?

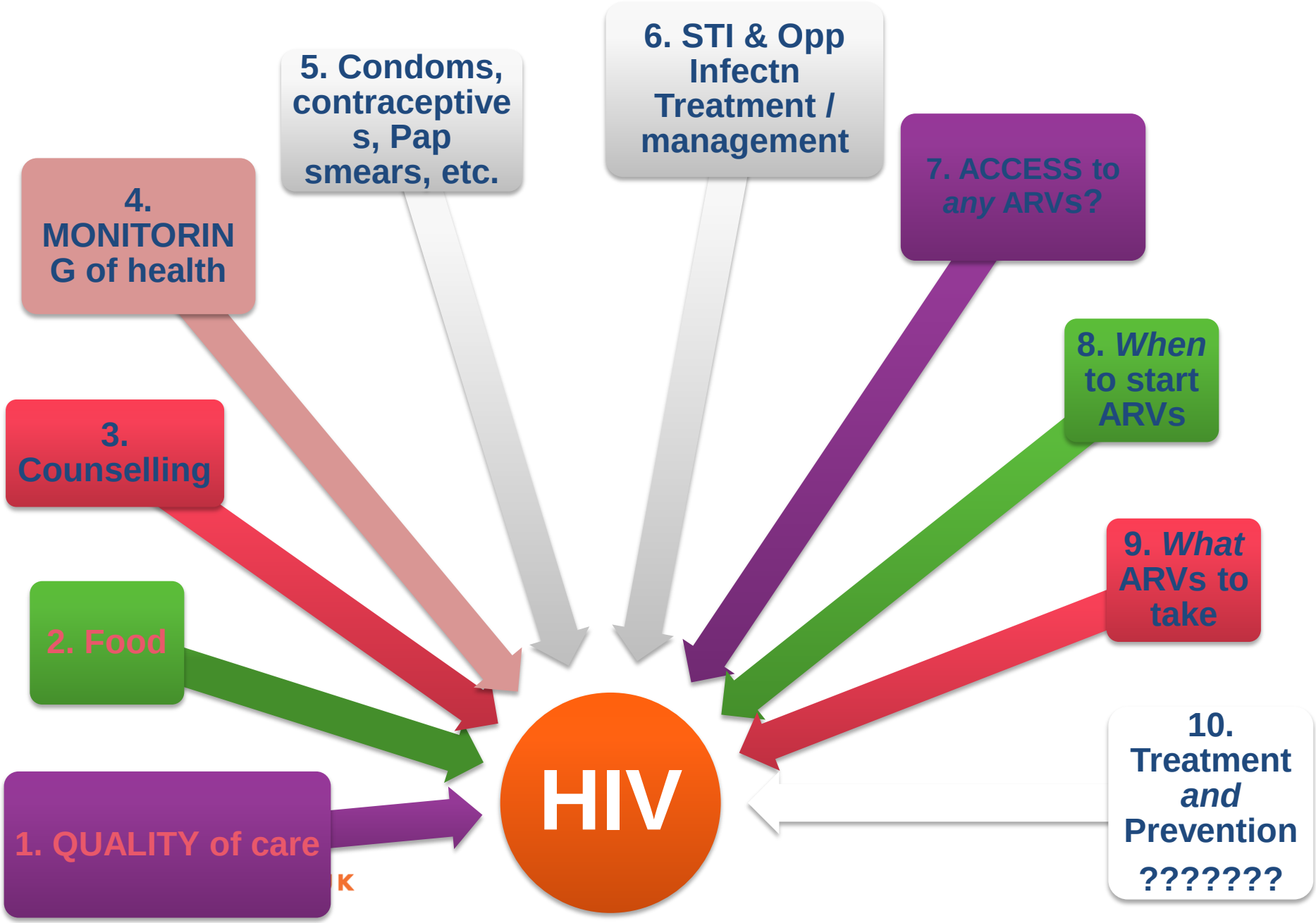
How much of this treatment is too much and what are the early signs of taking too much?

Does this treatment interact with anything else I'm taking?

How much does it cost?

POSITIVELY UK

See more at: http://www.avert.org/alternative-hiv-treatment.htm#sthash.5sG1bHWE.dpuf


5. Condoms, contraceptives, Pap smears, etc.
6. STI & Opp Infectn Treatment / management
4. MONITORING of health
7. ACCESS to *any* ARVs?
8. *When* to start ARVs
3. Counselling
9. *What* ARVs to take
2. Food
HIV
1. QUALITY of care
10. Treatment *and* Prevention
???????

Basic pharmacological principles

Drugs:

Chemicals with beneficial &harmful effects

Should be avoided unless **benefit > harm**

To avoid harm:

Used for a recognised medical indication for the individual's benefit

Minimum dose should be used

Minimum time should be used

Patient should be fully informed about

why, when& how to use the medication

POSITIVELY UK

DRUGS AND FDA APPROVAL

FDA approves medication for USA use

Then generally considered to be “safe for use”

FDA nowadays 80% funded by pharma

“For most drugs, companies must show [the FDA] only that their products are as safe as & more effective than a placebo” (Brownlee S, 2007)

POSITIVELY UK

A wonder-drug?

Viagra was promoted as a wonder-drug to deal with “erectile dysfunction” in men after it was approved by the FDA in 1998

“In 2005, Pfizer was ordered by the FDA to put a warning on its Viagra labels that the drug can cause irreversible vision damage, and in rare cases, blindness” (Brownlee S, 2007)

Note: it may be that the **side-effects only emerged over time** – but this is how difficult it can be to say that *any* medicine is “safe”

POSITIVELY UK

ALL-TRIALS CAMPAIGN

Viagra one of many where side-effects only became known later

Pharma are not legally bound to publish any negative information which they may know about their products

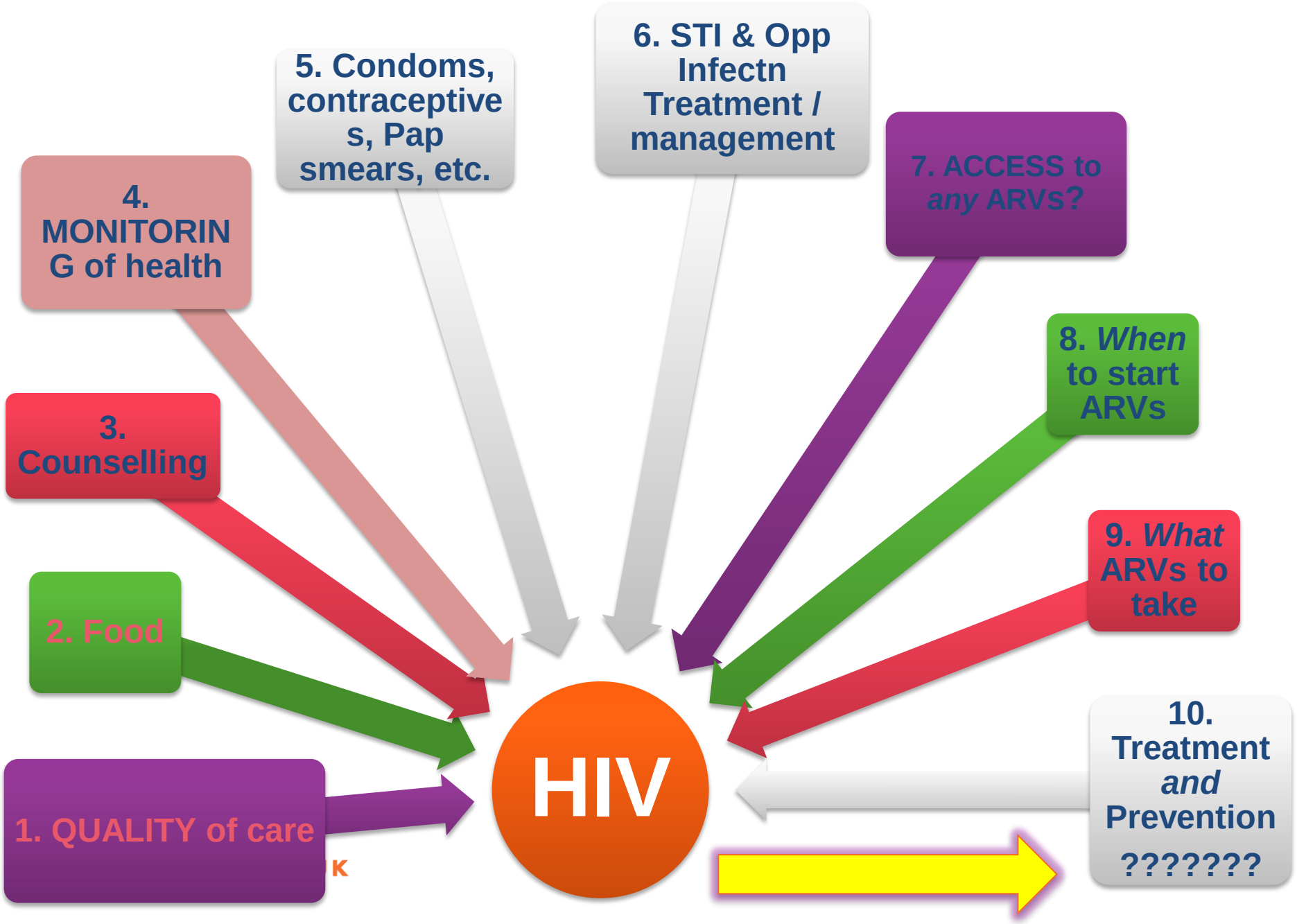
So many drugs reach public without even doctors knowing their side-effects

Why the “All Trials” campaign, which calls for *all* information from trials to be published, is so important for us all:

AllTrials is an initiative of many different organisations*

POSITIVELY UK

YOU CAN SIGN ON TO THIS CAMPAIGN ALSO IF YOU WANT


5. Condoms, contraceptives, Pap smears, etc.
6. STI & Opp Infectn Treatment / management
4. MONITORING of health
7. ACCESS to *any* ARVs?
8. *When* to start ARVs
3. Counselling
9. *What* ARVs to take
2. Food
HIV
10. Treatment *and* Prevention ???????
1. QUALITY of care

WHEN TO **START** TREATMENT

TEST & TREAT	USA
< 500	WHO
< 350	UK; and most countries*

START Trial: results 2016. To ***inform*** us re pros and cons of when to start ARVs.

NB: when to start should still be our own ***choice*** after the results are released…..

http://i-base.info/start-study/

POSITIVELY UK

“Treatment as Prevention” - Some basic ethical principles: 2

- If *one* person must take medication (thereby risking harm to themselves) in order to benefit someone *else*, unbalanced equation.
- ‘offloading’ of risk is not what doctors should be encouraging.
- Acceptable if this only happens in pregnancy (understandably fo the ‘my risk : your benefit’ to the baby which is *inside* the mothe
- When it is aimed to women with HIV because of possible transmission to men then it is gender-based discrimination, because men are not being asked or told to take “Option B+” also

POSITIVELY UK

Option B+: ethical issues

(Coutsoudis et al, 2013, The Lancet)

- Should pregnant women be prioritised for treatment for reasons other than immediacy of their medical condition?

- Have the implications of introduction or exacerbation of intrahousehold and community tensions because of different treatment access been adequately considered?

- Should selective test-and-treat interventions be considered ahead of achieving universal access for patients with CD4 cell counts <350 cells per µL?

-

POSITIVELY UK

Option B+: ethical issues
(Coutsoudis et al, 2013, The Lancet)

- Is it ethical to give women with high CD4 cell counts treatment for life without fully understanding the long-term benefits and risks?
- Will the roll-out of antiretrovirals for a selected group in the population compromise the provision of antiretrovirals for other groups who need it for their own health in resource-limited settings or settings with drug-supply restrictions?

POSITIVELY UK

Option B+: medical issues (Coutsoudis et al 2013, The Lancet)

- Are there benefits for mother-to-child transmission and long-term infant HIV-free survival?
- Are the benefits for maternal health worth the potential increase in drug resistance?
- Will long-term exposure to antiretrovirals in mothers reduce horizontal transmission and change the trajectory of the HIV epidemic?
- Do we have enough evidence to suggest that pregnant women and new mothers are a risk group who have discordant relationships and contribute to the HIV epidemic?

POSITIVELY UK

Option B+: Programmatic issues

(Coutsoudis et al 2013, The Lancet)

- Can B+ be implemented in strained health systems without disruption of the introduction of treatment programmes?
- Will the implementation of B+ need scarce resources such as personnel, laboratory support, and drugs to be diverted from the drive towards universal access to HIV treatment or universal access to treatment for other non-HIV life-threatening or infectious diseases?
- Will the necessary levels of adherence be maintained?

POSITIVELY UK

Option B+: Economic issues

(Coutsoudis et al 2013, The Lancet)

- Is the assumption valid that economies of scope will favour this three-in-one intervention (ie, prevention of mother-to-child transmission, treatment, and treatment-as-prevention)?

- If retention rates are not high, will the economic argument in favour of B+ be invalid?

POSITIVELY UK

TAKING MEDICATION FOR ANOTHER'S BENEFIT

An Unusual Indication – eg. women taking drugs to change fetal heart rhythm

Research participants taking drugs in trials to benefit future patients

Very occasionally people take drugs/vaccination as part of preventing spread of diseases and the pharmacology and ethics have not been discussed so much

POSITIVELY UK

TAKING RISKS FOR OTHERS…

We do know that some people will undergo risks for others, such as kidney donation

However usually it has more safeguards in place

But it is seen as altruistic, with more time insisted upon for such a serious decision, and higher standards of informed consent, with independent counsellors

Safeguards like these could be put into place to make Option B+ a bit more ethical

All this has to be spelled out

POSITIVELY UK

OPTION B+, TOXIXCITIES and MONITORING

TasP regimens include potentially toxic drugs for eg tenofovir

Tenofovir is already known to have side-effects, including harm to kidneys and bone density

http://i-base.info/guides/3541 lists issues *already known*

Few sites have CD4 or VL tests in place

Even fewer have kidney or bone density tests

HOW can women be *safely* monitored when put on Option B+?

POSITIVELY UK

Treatment *as* Prevention…..?

Or Treatment *and* Prevention

For women **offer** of condoms, of contraception, and of couple counselling, STI control (and food) should go at least *with* – and preferably *before* ARVs

Are these routinely being offered also?

POSITIVELY UK

“Option B” is *not* an option…..

Countries that have adopted Option B+ are rolling it out to all women with HIV after pregnancy.

It is *not* an option. Women are criticized and ostracized by health workers if they do not take it.

POSITIVELY UK

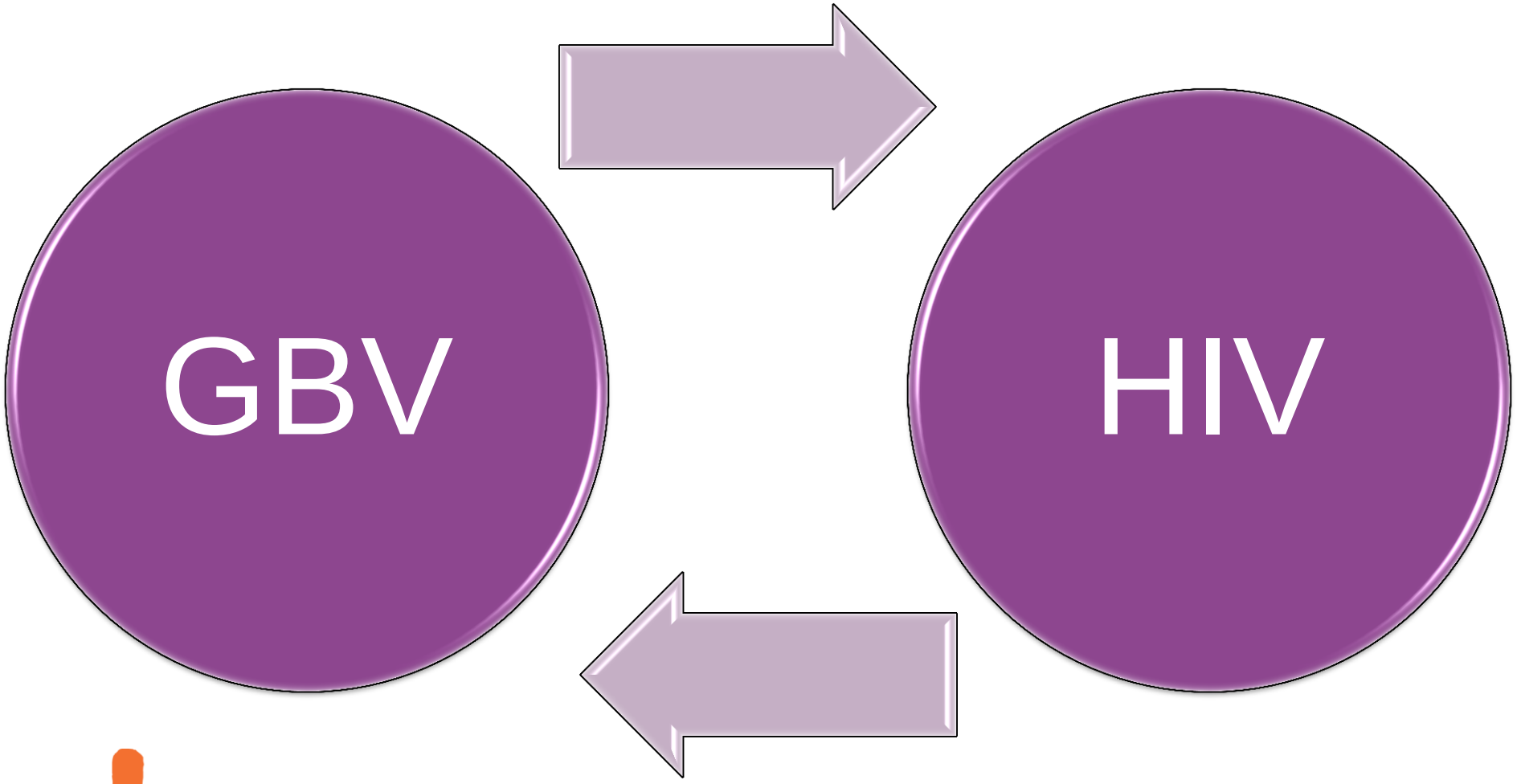
Gender Based Violence and HIV

Intimate Partner Violence as a consequence of HIV diagnosis with ARV uptake, ARV adherence & depression as first casualties (COWLHA baseline study)

Women experiencing fear of disclosure through having Option B+

Women experiencing guilt through having Option B+ when children/partner/others don't

POSITIVELY UK



POSITIVELY UK

Good practice:

Positively UK From Pregnancy and Beyond Project – peer-led grassroots, sustainable “mentor mothers” programme: http://positivelyuk.org/wp-content/uploads/2014/11/Pos-UK-Pregnancy-Project-Evaluation-Report-Aug11.pdf

Mama’s Club Uganda – similar grassroots programme:

Couple-counseling Zambia: couple counselling shown to be better at HIV transmission than ARVs alone: http://pag.aids2014.org/Abstracts.aspx?SID=1118&AID=3923

POSITIVELY UK

CONCLUSIONS

- We need funding and capacity building to advance the rights and meaningful involvement of women living with HIV and their networks to:
- address structural power imbalances
- address gender based violence
- increase quality of care, including treatment & prevention
-

POSITIVELY UK

Treatment as Prevention

Current research trials

Webinar November 2014

Sarah Fidler

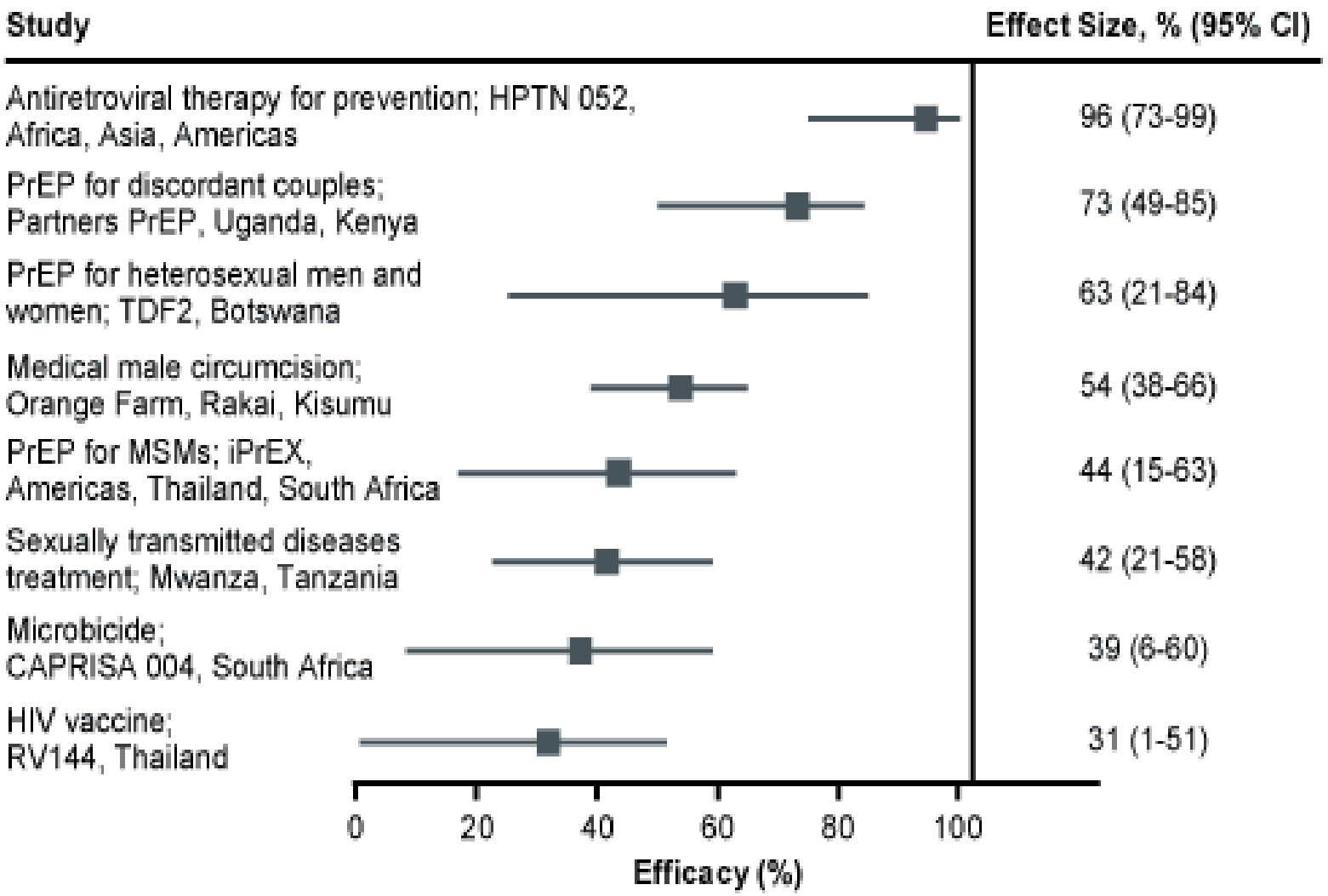
Problem statement

- Reductions in HIV incidence in many countries

BUT HIV incidence remains too high

- Number of new HIV infections greatly exceeds number of HIV-related deaths (thanks to ART!)
- This means that HIV prevalence continues to increase every year
- ...and that unless HIV incidence can be reduced steeply it will be increasingly difficult to sustain HIV treatment services for all who need them

Combination Prevention: Evidence



Abdool Karim, Lancet 2011

Can ART prevent onward HIV transmission?

Evidence

- HPTN052 study
- PARTNER study
- TasP demonstration projects
- TasP Community Randomised controlled population level trials ; HPTN071-PopART, SEARCH, Botswana CPPT, TasP,

Unanswered questions?

- What about different sexual exposures? Anal sex?
- Actual range of risk
- Can ART as prevention impact HIV incidence at a population level?
- How should ART as prevention be delivered?

Why is more research needed on TasP?

- Can TasP prevent transmission through anal sex
- How can TasP be delivered most effectively?
- What coverage can be achieved on the ground at each step of the cascade?
- How can other prevention modalities be incorporated in TasP programmes (e.g. MC, PrEP)?
- What are the adverse effects of TasP programmes?
  - Drug resistance
  - Toxicity
  - Sexual risk disinhibition
  - Stigma
  - Overload of health services

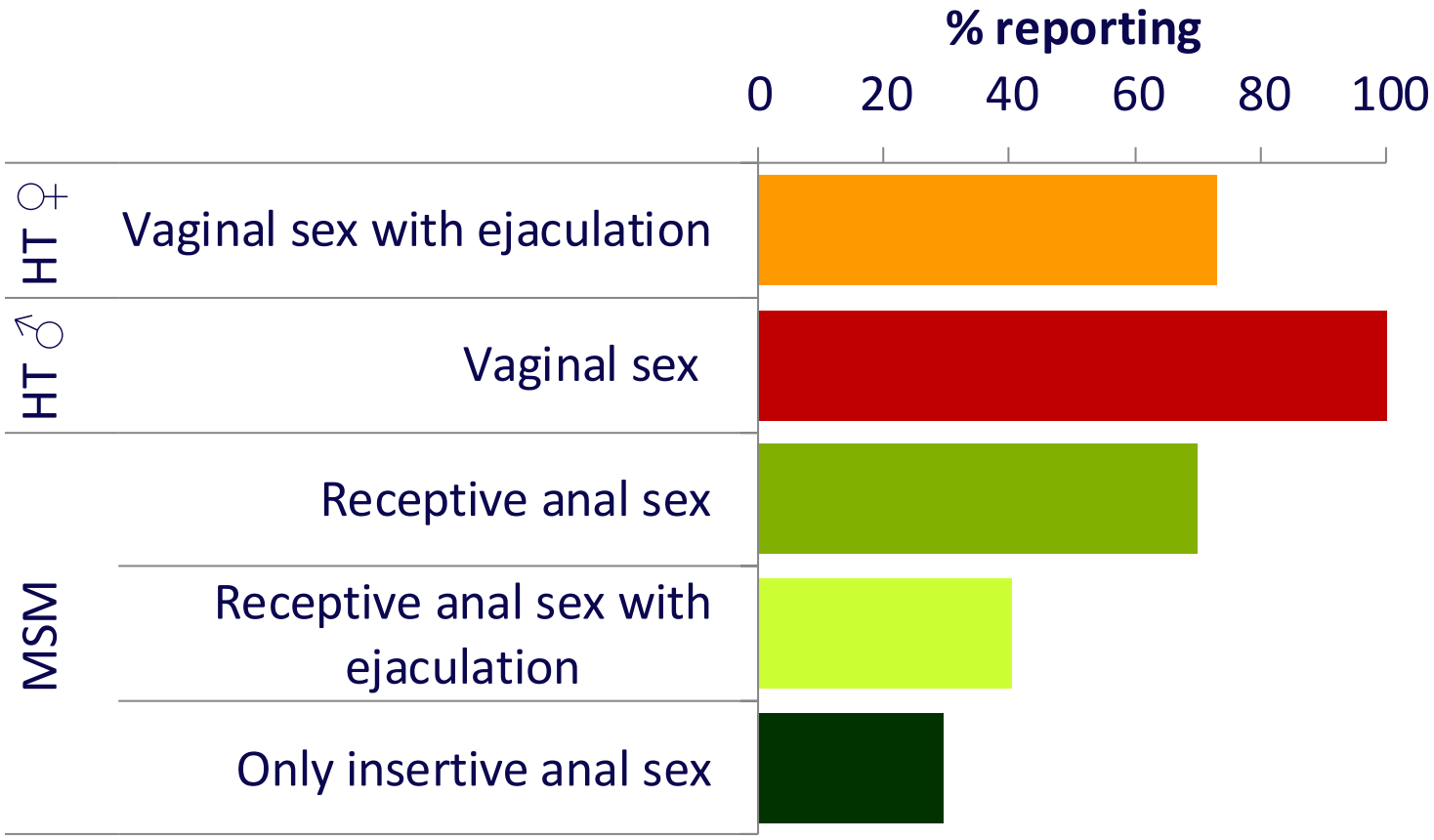
PARTNER Study

The PARTNER study is an observational multi-centre study of HIV serodifferent couples in which the positive partner is on ART, taking place in 75 European sites

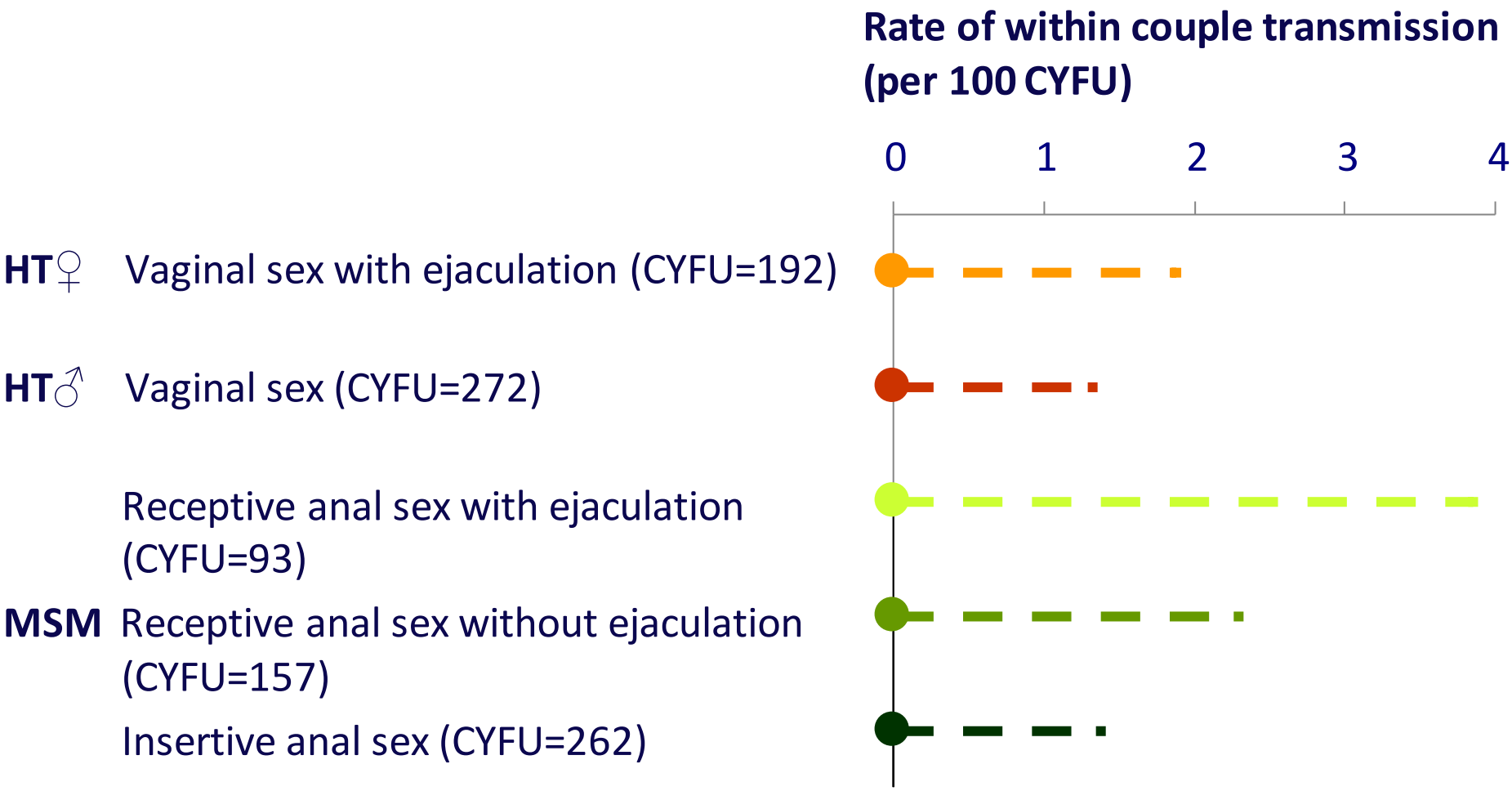
Aim

To evaluate the risk of within-couple HIV transmission (HT and MSM) during periods where condoms are not used consistently and the HIV positive partner is on suppressive ART

HIV-ve partners reporting condomless penetrative sex during eligible CYFU



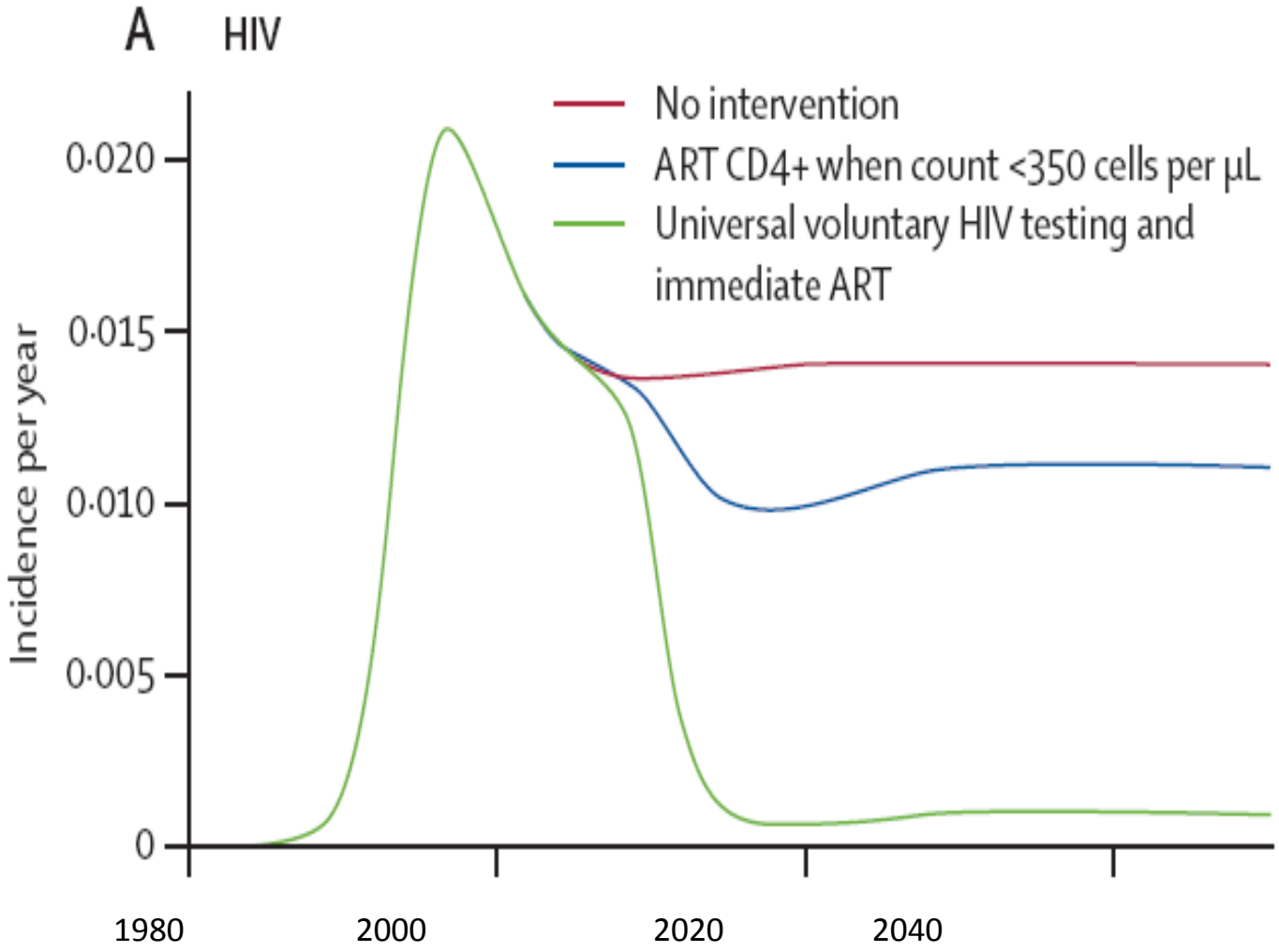
Rate of HIV transmission according to sexual behaviour reported by the negative partner



Conclusions

- Interim results after 894 eligible CYFU report an overall HIV transmission rate of zero through condomless sex with a plasma VL < 200 copies/mL on ART, despite a significant number of sexual acts.
- However uncertainty over the upper limit of risk remains, particularly over receptive anal sex with ejaculation
- Additional follow-up in MSM is needed through PARTNER2 (2014-2017) to provide more precise estimates for transmission risk to inform policy and also individual choice on condom use

‘Test and Treat concept’



Granich et al 2009 Lancet

HIV Prevention Trials Network

HPTN 071 - PopART

UNIVERSAL TESTING, LINKAGE TO CARE AND IMMEDIATE TREATMENT TO REDUCE POPULATION LEVEL HIV INCIDENCE IN A GENERALISED EPIDEMIC

National Institute of Allergy and Infectious Diseases

NIMH National Institute of Mental Health

National Institutes of Health

U.S. Department of Health and Human Services

National Institutes of Health

NIDA National Institute on Drug Abuse

3 arm cluster-randomised trial with 21 communities

Arm A

Full PopART intervention

including

immediate ART irrespective of CD4 count

Arm B

PopART intervention

except

ART initiation according to current national guidelines

Arm C

Standard of care at current service provision levels

including

ART initiation according to current national guidelines

7 communities per arm (N=21)

12 in Zambia
9 in S. Africa

2,500 random sample from each community :
Population Cohort
N = 52,500

Primary outcome:
HIV incidence at 36 months

PopART intervention package

- Annual rounds of Home Based Voluntary HIV Testing by Community HIV-care Providers (CHiPs)
- Health promotion, Active Referral and/or Retention in Care support by CHiPs for the following:
  - Voluntary Medical Male Circumcision (VMMC) for HIV negative men
  - Prevention of Mother to Child Transmission (PMCT) for HIV positive women
  - HIV treatment and care for all HIV positive individuals
  - Promotion of sexual health and TB services
  - Condom provision
- ART irrespective of CD4-count or immune-status provided at the local health centre in Arm A

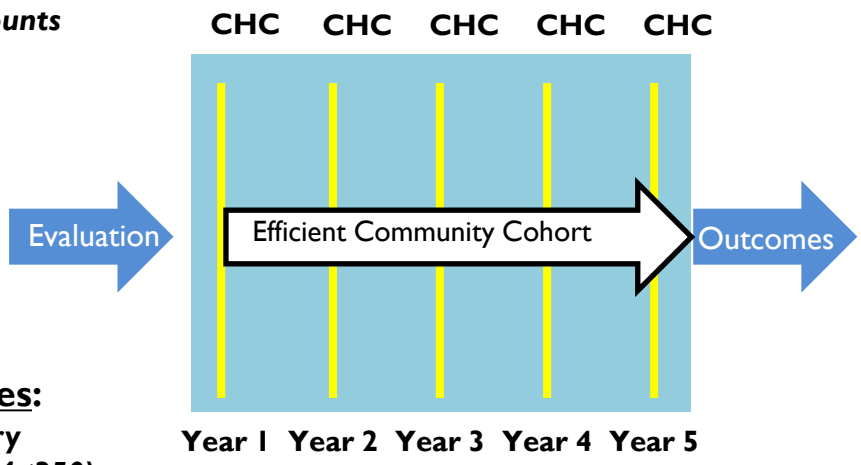
SEARCH Consortium 2013

SEARCH

Community Health Campaigns (CHC): HIV Testing/Linkage

Intervention Communities:
ART at all CD4 counts
16 villages
n = 10,000 each

Control Communities:
ART via country guidelines (CD4<350)
16 villages
n = 10,000 each

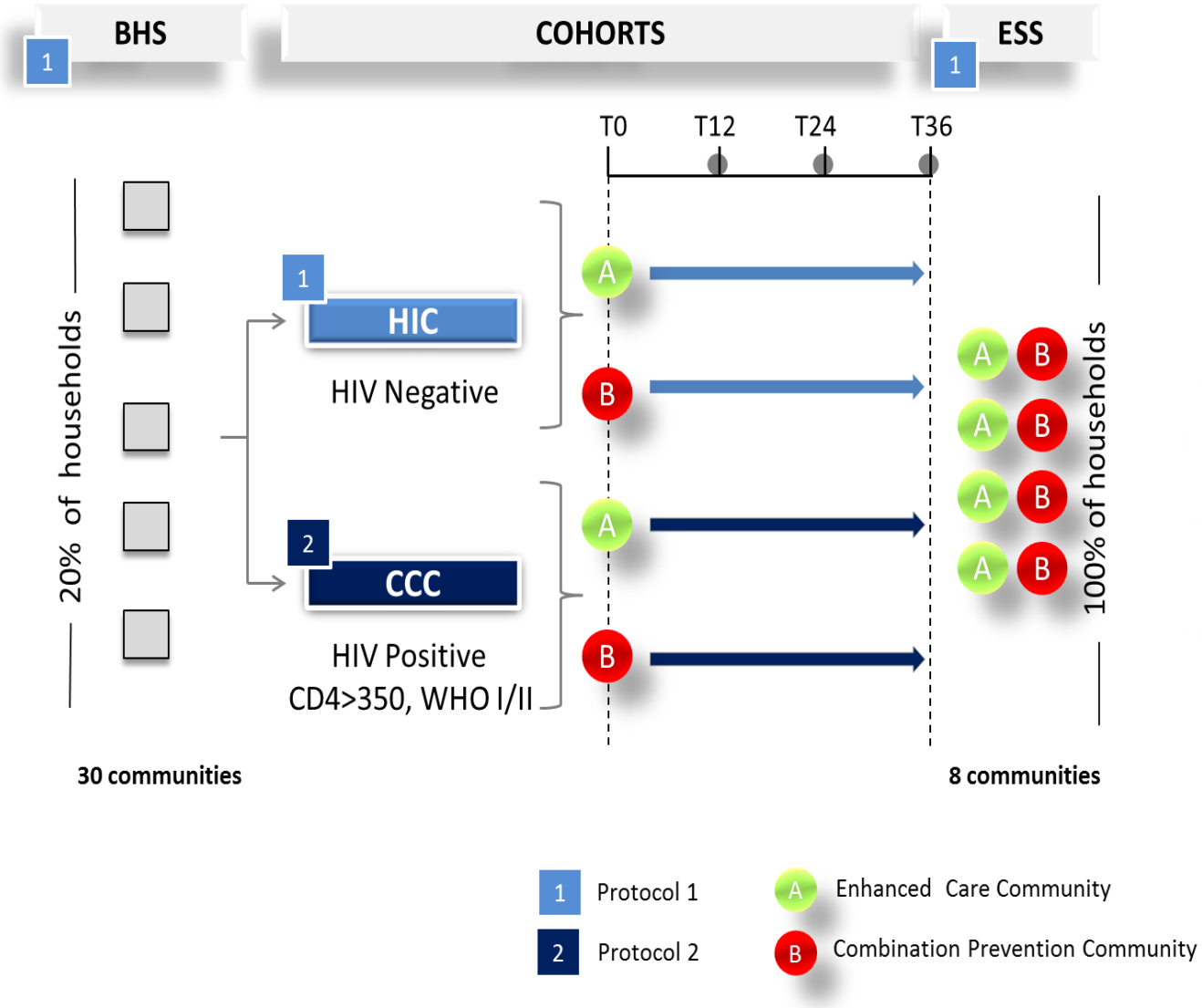


- Baseline census
- Repeated CHC's obtaining individual-level linked data
- Ascertainment of non-returnees (10% sample)

Community Health
HIV incidence
Community viral load
AIDS
Maternal/child health
TB incidence
Malaria incidence

Community Productivity
Workforce participation
Child labor prevalence
Agricultural output
Household income
Educational attainment
Healthcare utilization

Botswana Combination Prevention



TasP (ANRS 12249)

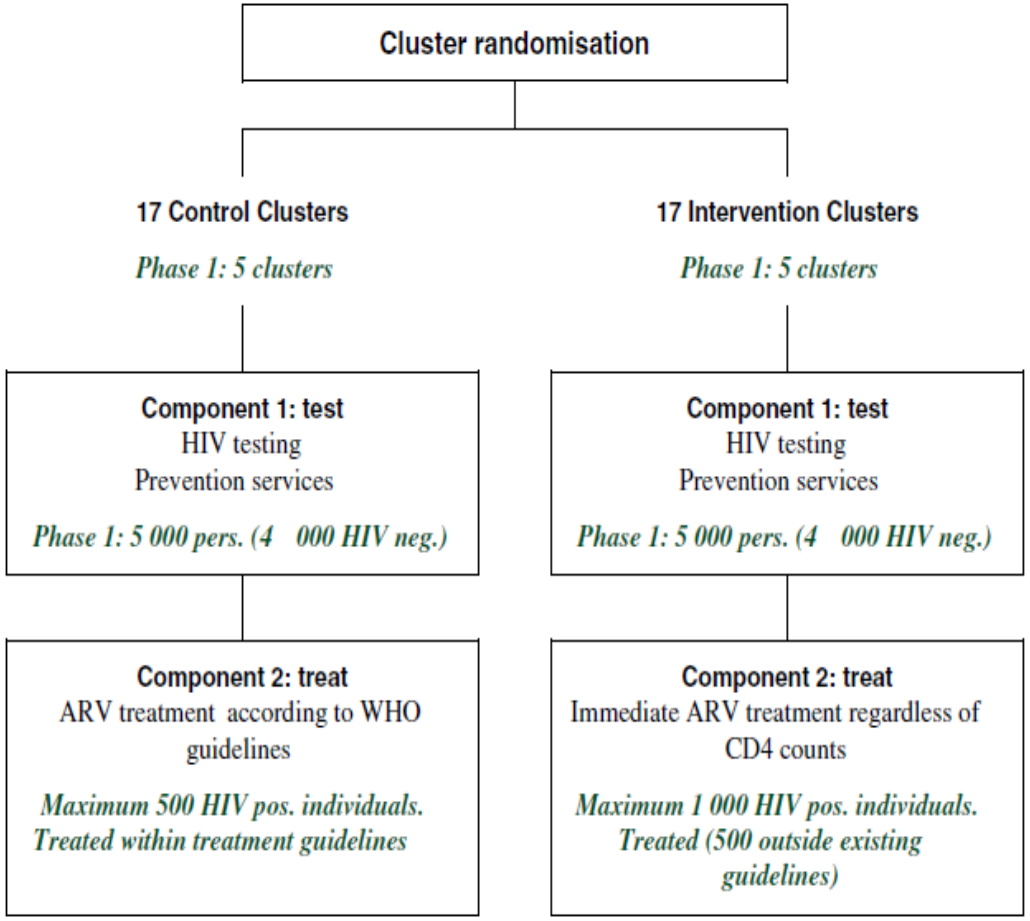


Figure 1 Description of the different components of the ANRS 12249 TasP trial.

Summary

- There is high level of individual level evidence that ART is highly effective to prevent HIV transmission amongst heterosexual serodifferent couples.
- Ongoing trial (PARTNER) will explore the level of evidence amongst MSM couples.
- It is unknown whether ART as prevention in high prevalence settings (e.g. SSA) can actually deliver a significant reduction 4 trials are ongoing to address this:
  - TasP (KZN S Africa)
  - HPTN071 PopART (S Africa & Zambia)
  - SEARCH (Kenya)
  - BCCP (Botswana)