

Sexually transmitted infection, BBV and global health

BSc Global Health
21st October, 2012

Leading Causes of Death Due to Infectious Diseases, 2002

Lower respiratory infections	3.9 million
HIV/AIDS	2.8 million
Diarrhoeal diseases	1.8 million
Tuberculosis	1.6 million
Malaria	1.2 million
Measles	0.6 million

Source: World Health Report, 2004 WHO

	Number of deaths (millions)	% of all deaths	% of all DALYs*
All infectious and parasitic diseases	9.5	16.2	19.8
Lower respiratory infections	4.2	7.1	6.2
Diarrhoeal diseases	2.2	3.7	4.8
→ HIV/AIDS	2.0	3.5	3.8
Tuberculosis	1.5	2.5	2.2
Malaria	0.9	1.5	2.2
Childhood infections** (inc measles)	0.9	1.4	2.0
Measles	0.4	0.7	1.0
→ Hepatitis B & C	0.2	0.3	0.2
Neglected tropical diseases***	0.2	0.3	1.3
→ STIs excluding HIV	0.1	0.2	0.7

Source: Global Burden Disease 2004 Update, 2008. www.who.int/healthinfo/global_burden_disease/

* Disability Adjusted Life Year; ** Childhood infections includes pertussis, polio, diphtheria, measles, tetanus; *** NTDs defined later

We'll come back to HIV....



Hepatitis B and C

High prevalence of viral infection globally

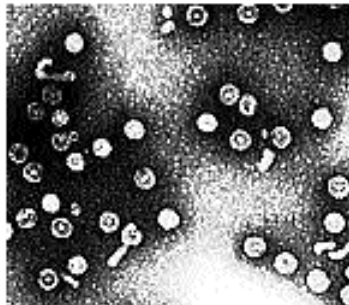
Some similarities of transmission

Both contribute to substantial global morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma

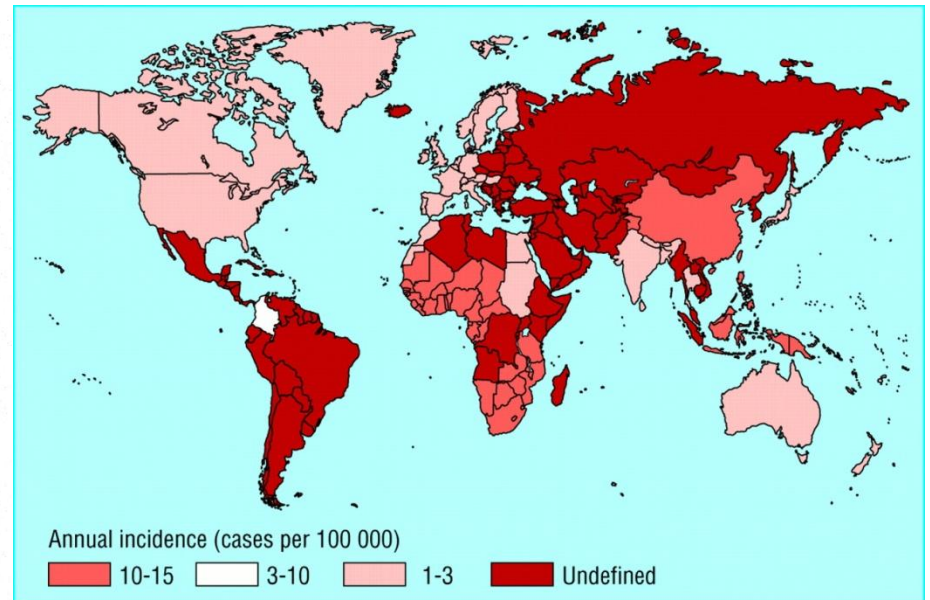
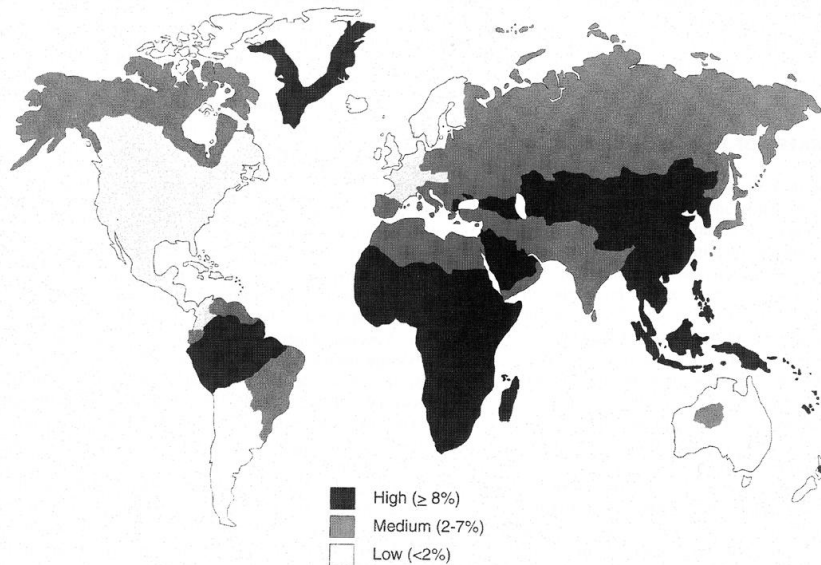
HBV vaccination widely implemented, HCV no effective vaccine on horizon

HBV Epidemiology

32 nM virus



350 Million chronically infected
1 Million deaths per year



HBsAg prevalence in adult males in Africa

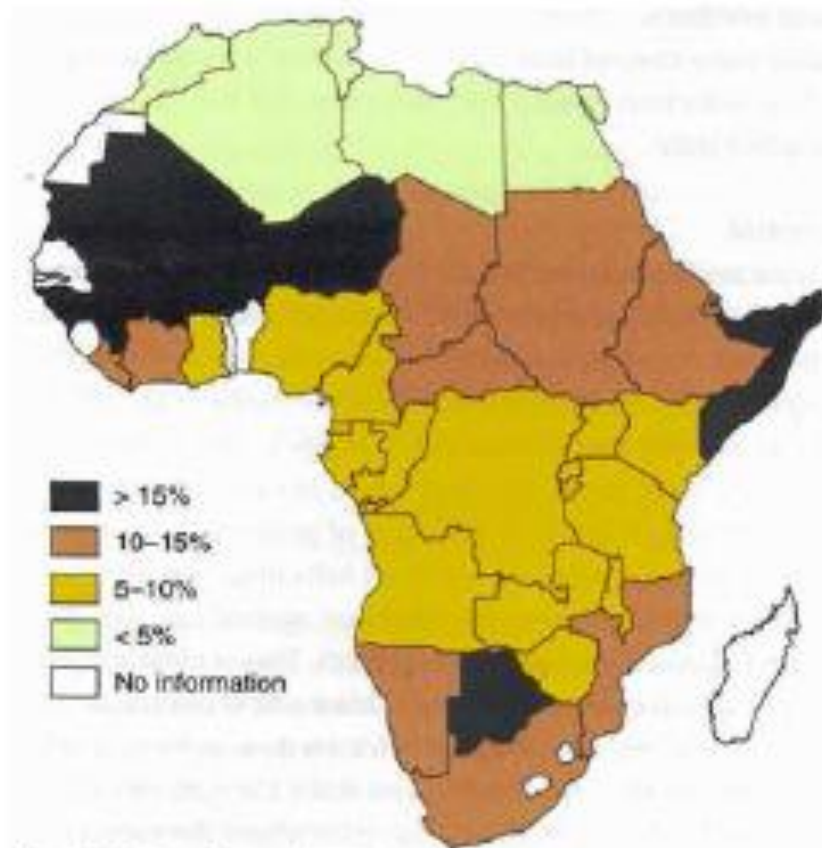


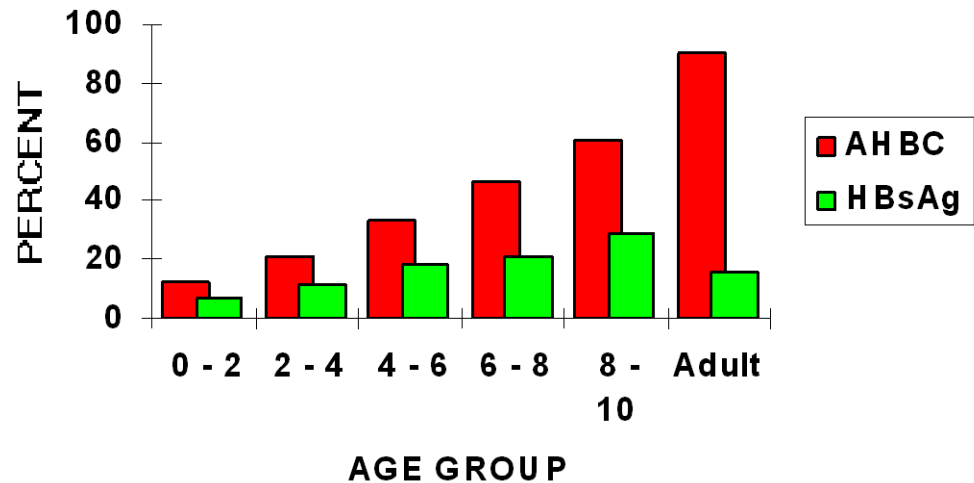
Fig. 67.1. Prevalence of HB_sAg in adult males.

Modes of Transmission HBV



90% Chronicity

Rise in HBV Exposure and HBsAg Carriage with Age



20% Chronicity

Sexual transmission - < 5% chronicity

Hepatitis C

RNA flavivirus transmitted by MTCT, infected needles, blood transfusion, more rarely sexually transmitted

No effective vaccination

Tests widely available and well validated, including point of care

Treatment available and rapidly becoming more effective but logistically difficult, at least until can get rid of interferon

What are the other major STIs?

Major Sexually Transmitted diseases

Bacterial:

Acute Disease

Severe disease

Treponema pallidum

1° , 2° & latent syphilis

Gumma; Neurosyphilis;
Cardiovascular syphilis

Neisseria gonorrhoeae

Inflammation

Infertility;
Ectopic pregnancy

Chlamydia trachomatis D-K L1-3

Inflammation

Infertility;
Ectopic pregnancy
Strictures,

Lymphogranuloma venereum

Haemophilus ducreyi

Genital Ulcer Disease

Major Sexually Transmitted diseases

Virus

Human immunodeficiency virus
(HIV-1)

Acute Disease

Febrile illness

Major disease

AIDS

Human Papilloma Virus
(HPV)

Genital warts
(6/11)

Cervical
cancer (16/18
etc)

Herpes Simplex Virus types 1
and 2 (HSV-1, HSV-2)

Genital ulcers

Neonatal
herpes

Protozoa

Trichomonas vaginalis

Inflammation

Global burden - incidence

- 340 million new cases of curable STI globally (1999).
 - In the UK over 700,000 new diagnoses in GUM clinics each year, including
 - >100,000 cases of chlamydia
 - 79,000 new diagnoses of genital warts (HPV)
 - 20,000 cases of gonorrhoea.
 - There were an estimated 23.6 million new HSV-2 infections globally (2003).
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Prevalence

- prevalence > reported incidence as many are asymptomatic, undiagnosed
 - For curable, bacterial STI, estimated prevalence ranges
 - 2% (for 15-49 year olds) in Western Europe
 - 12% in Sub-Saharan Africa
 - The number of adults living with HSV-2 infection worldwide is estimated to be 536 million (2003).
 - In the UK, the prevalence of genital chlamydia is 10% in 16 – 24 year olds
-

Burden

- Mortality:
 - Estimated 0.1 million deaths annually from STI other than HIV
 - Morbidity
 - primarily measured in terms of reproductive morbidity.
 - 5.1 million YLDs (Years lost due to disability) in women (2002)
 - 1.9m in men
-

Major Sexually Transmitted diseases

Gonorrhoea

Chlamydia

HSV-1/2

HPV

Syphilis

Ano-genital herpes

- Rising incidence in UK
 - Fever, Dysuria, Malaise
 - Inguinal lymphadenopathy
 - Pain++
 - ♂ Vesicular rash penis, peri-anal, anal
 - ♀ Vulva, vagina and cervix
 - Perineum, upper thigh, buttocks
 - Herpes meningitis 4-8% of primary genital herpes
 - Sacral radiculomyelitis – urinary retention
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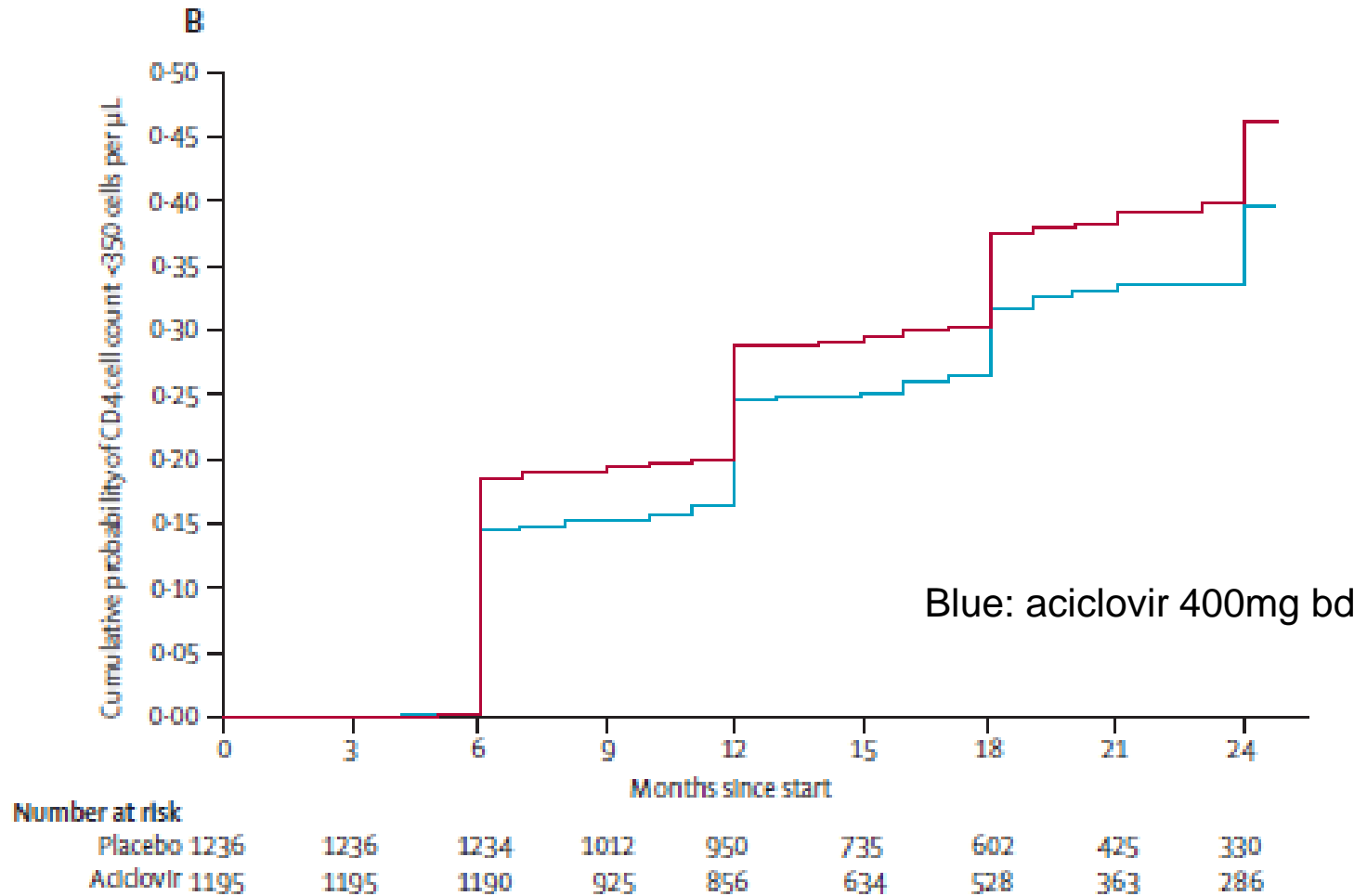
HSV and HIV-1

- HSV prevalence high in areas worst affected by HIV-1 (70-90%)
 - HSV suppressive therapy can reduce HIV viral load (and hence could reduce transmission and/or progression)
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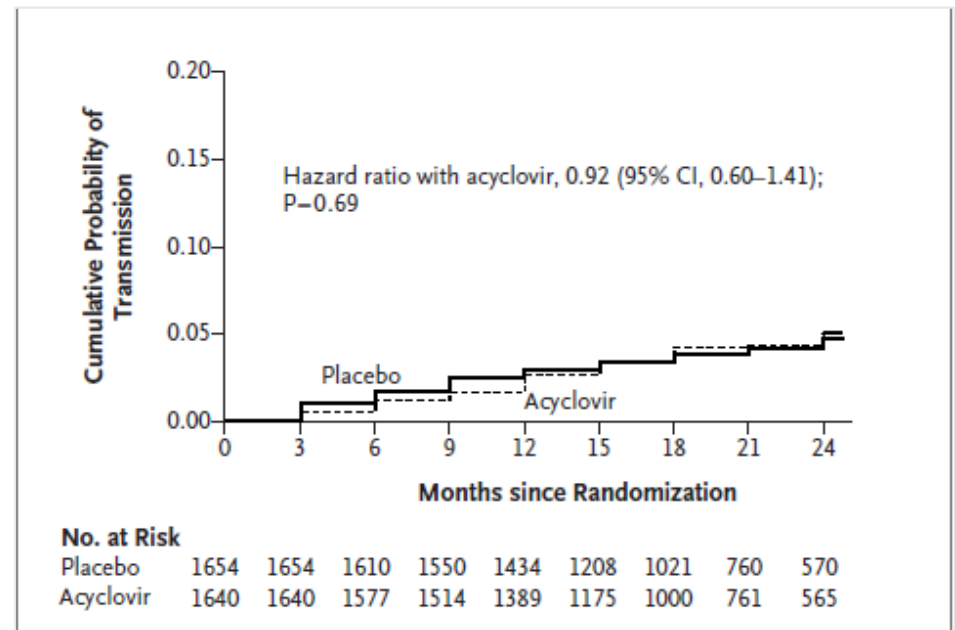
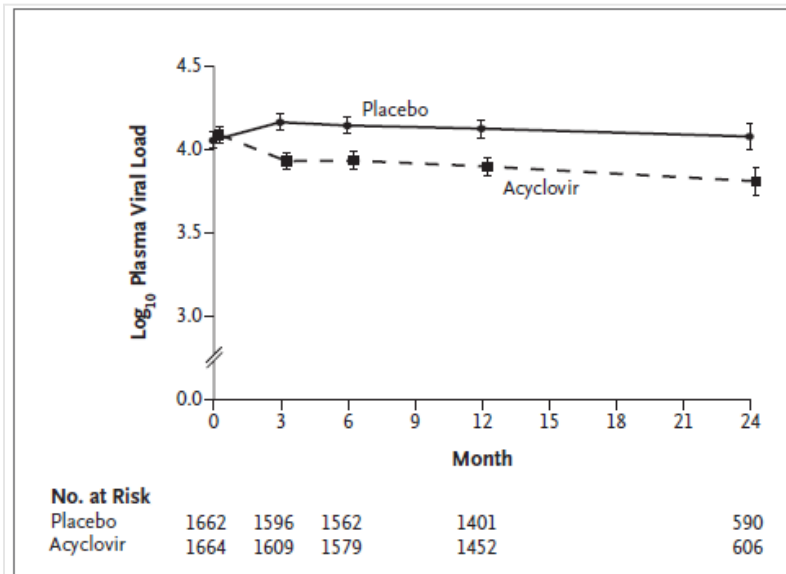
HSV suppression reduces HIV-1 viral load

	Baseline		Treatment				
	Placebo	VACV	Placebo	VACV			
Plasma HIV-1 RNA							
Mean quantity — \log_{10} copies/ml	4.65	4.33	4.76	3.93	-0.86	-0.45	<0.001
					(-1.18 to -0.54)	(-0.62 to -0.29)	
95% CI	4.53 to 4.77	4.17 to 4.49	4.64 to 4.89	3.76 to 4.10			

HSV suppression reduces risk of disease progression



But although HIV-1 suppression is replicated, does not reduce transmission



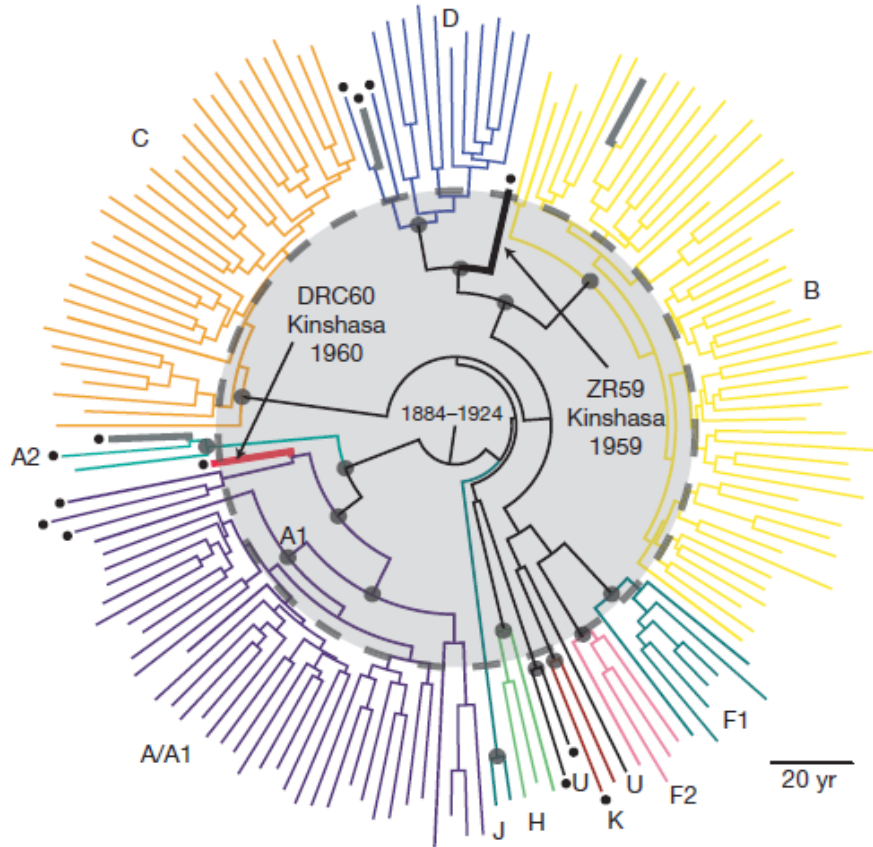
Back to HIV....



HIV/AIDS

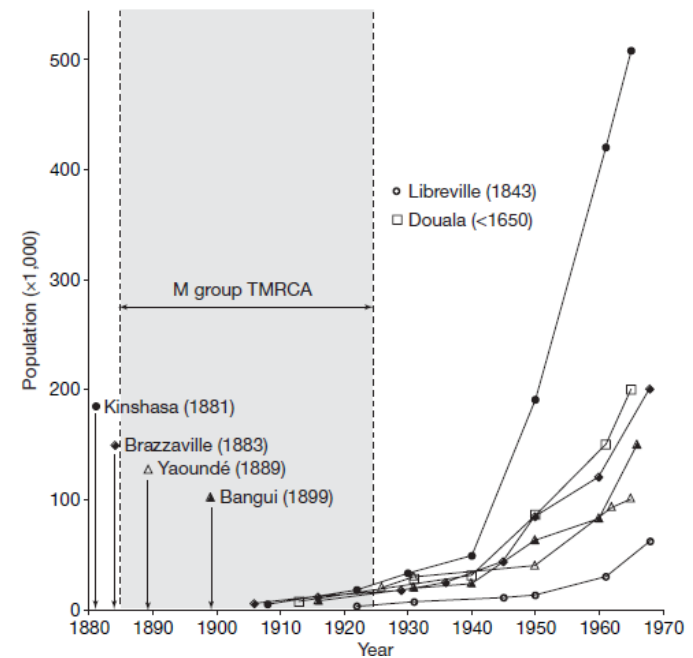
- Acquired immune deficiency syndrome
- Caused by human immunodeficiency virus (HIV-1) a retrovirus
- First recognised in 1981
- Modes of transmission
 - Blood (transfusion of blood products, needlestick injury/ unsafe injecting)
 - Sexual contact
 - Mother to child (at birth and through breast milk)

Key moments in the history of HIV/AIDS



Earliest isolate from 1959

Phylogenetic analysis strongly suggests transfer to man very unlikely to be after 1930



HIV/AIDS global burden

- Prevalence

- 34 million people living with HIV
- 5% of adults in sub-Saharan Africa (but much higher in some population groups)
- 0.8% globally

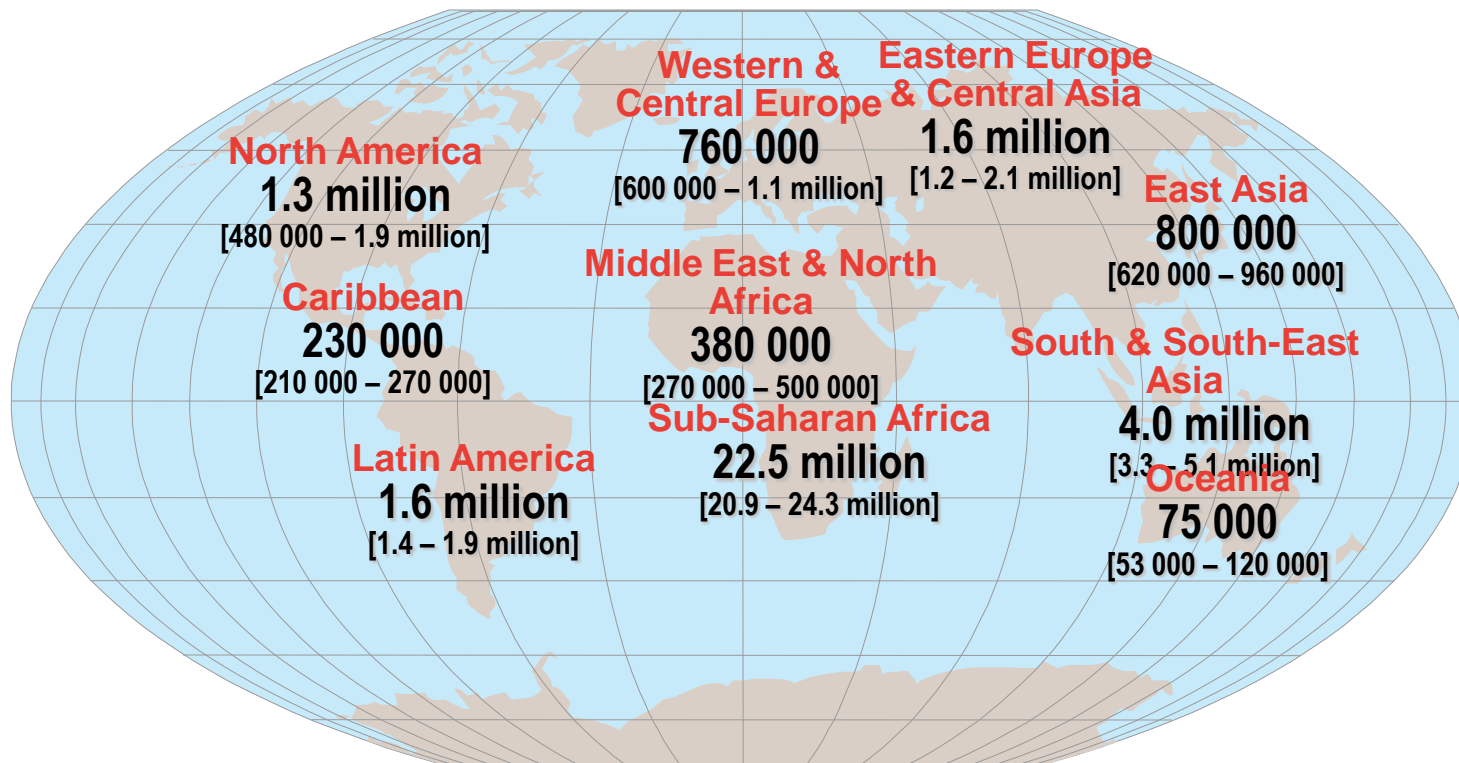
- Incidence

- 2.7 million new cases in 2010

- Mortality

- 1.8 million in 2010

Global distribution: people living with HIV, 2010



Total: 34 (31.6 – 35.2) million

	2001	2005	2008	2009	2010
People living with HIV	28.6 million [26.7-30.9 million]	31.0 million [29.2-32.7 million]	32.3 million [30.4-33.8 million]	32.9 million [31.0-34.4 million]	34 million [31.6-35.2 million]
New HIV infections	3.15 million [2.96-3.33 million]	2.81 million [2.63-2.97 million]	2.74 million [2.52-2.93million]	2.72 million [2.48-2.93 million]	2.67 million [2.46-2.90 million]
AIDS-related deaths	1.85 million [1.67-2.16 million]	2.22 million [2.07-2.48 million]	2.04 million [1.87-2.21 million]	1.89 million [1.72-2.05 million]	1.76 million [1.59-1.91 million]
New infections in children	550 000 [490 000-620 000]	540 000 [480 000-600 000]	460 000 [400 000-510 000]	430 000 [370 000-490 000]	390 000 [340 000-450 000]

The global challenge

- 2.6 million new infections in 2009
 - 1–1.5 million patients started on ART each year
 - Unless new infections can be steeply reduced there will be an ever-increasing number of patients requiring treatment
 - Universal treatment as prevention is expensive, but so are all the other options
-

Control of HIV/AIDS

- Primary prevention
 - Change sexual behaviour, including condom promotion
 - Clean blood supply
 - Prevent mother to child transmission
 - Safe drug use
 - Vaccines, microbicides and PREP
- Secondary prevention
 - Testing and intervention to those infected
- Treatment with ARVs

Challenges for HIV control

- Social determinants
 - Sexual behaviour
 - Drug use
- Resources (financial and human)
 - For primary prevention
 - Treatment
 - Care

Key moments: The beginning of the drug era

First drug for HIV treatment licensed in 1987

Zidovudine (AZT, retrovir) an NRTI

Originally developed as anti-tumour agent in 1960s and in 1970s found to have anti retroviral activity (a murine leukaemia virus)

Activity of AZT against HIV shown in 1985 (25 months before Licensing)

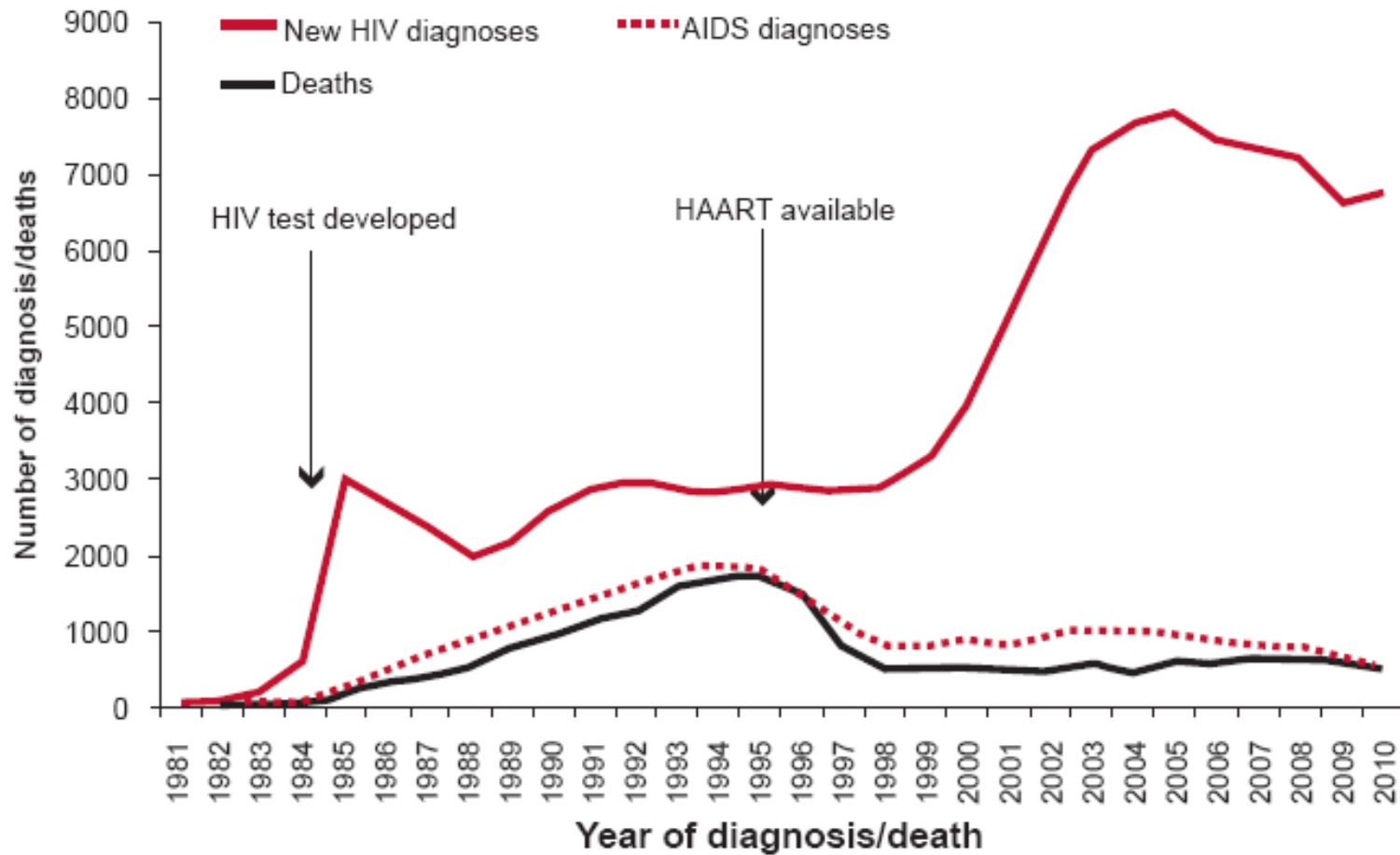
Trends in HIV mortality

Table 1. ART dramatically decreased mortality

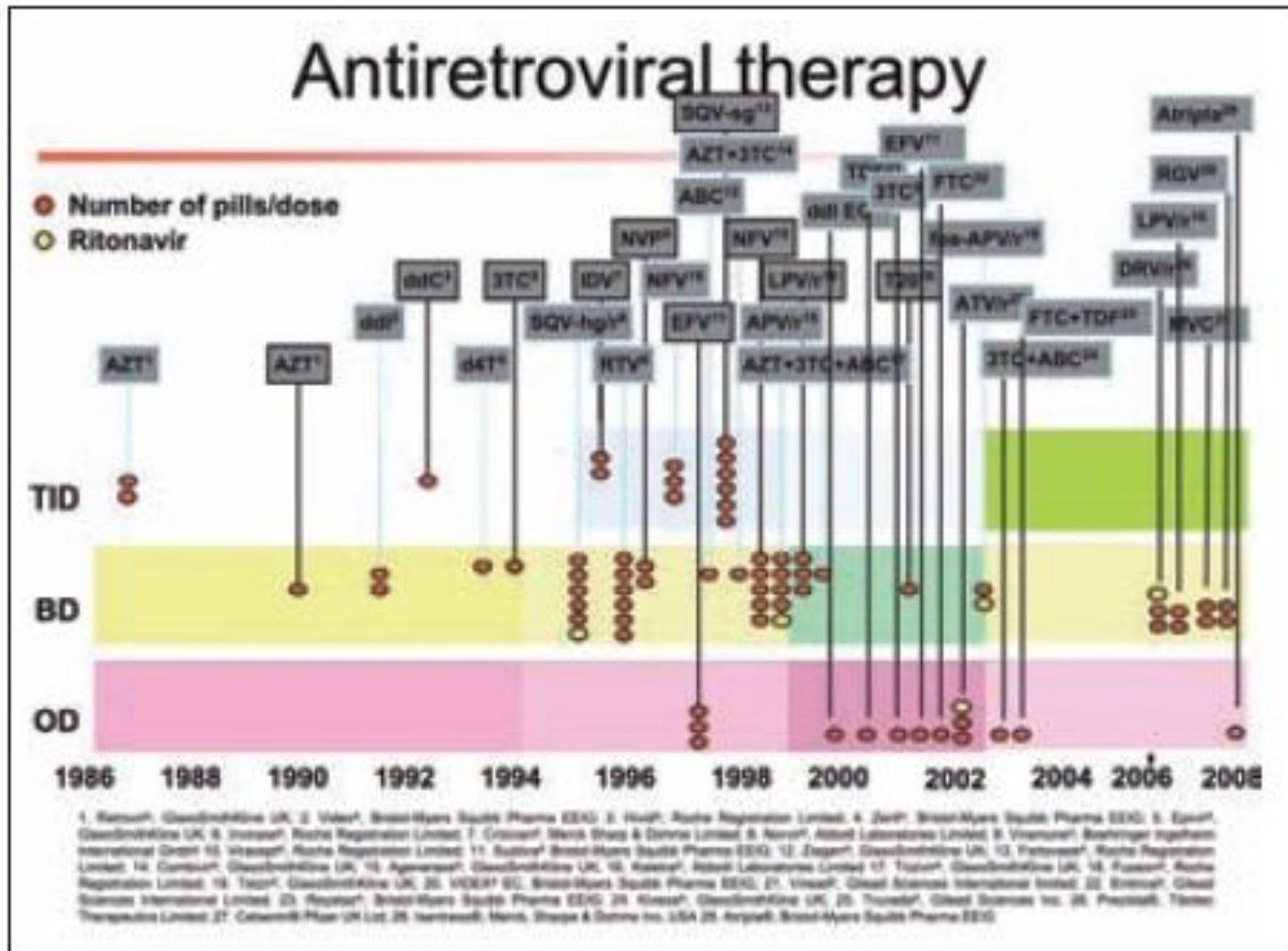
Year	Study	Design		Decrease in mortality (%)
1997	Delta ⁵	RCT	ZDV versus dual ART	30–50
1997	ACTG 175 ⁷	RCT	ZDV versus dual ART	30–50
1997	ACTG 320 ⁸	RCT	dual versus HAART	70–80
1997	SHCS ¹	OS	no HAART versus HAART	70–80
1998	HOPS ⁹	OS	no HAART versus HAART	70–80
2003	EUROSIDA ¹⁰	OS	1996–97 HAART versus 1998–2002 HAART	86
2005	SHCS ¹¹	OS	no HAART versus HAART	86
2007	Danish cohort ¹²	OS	HIV versus non-HIV	~10–38 years of life prolongation after start of ART normal life expectancy (?)

RCT, randomized controlled trial; OS, observational study; ZDV, zidovudine; HAART, highly active antiretroviral therapy.

The impact of HAART in the UK



The beginning of the drug era



Trends to single pill therapy

More effective therapy with options for those failing treatment

Less toxic medication

Much reduced pill burden , once daily dosing

Better management of complications

Trends to single pill therapy



Trends in single pill therapy

Currently

Atripla - Tenofovir / FTC / Efavirenz

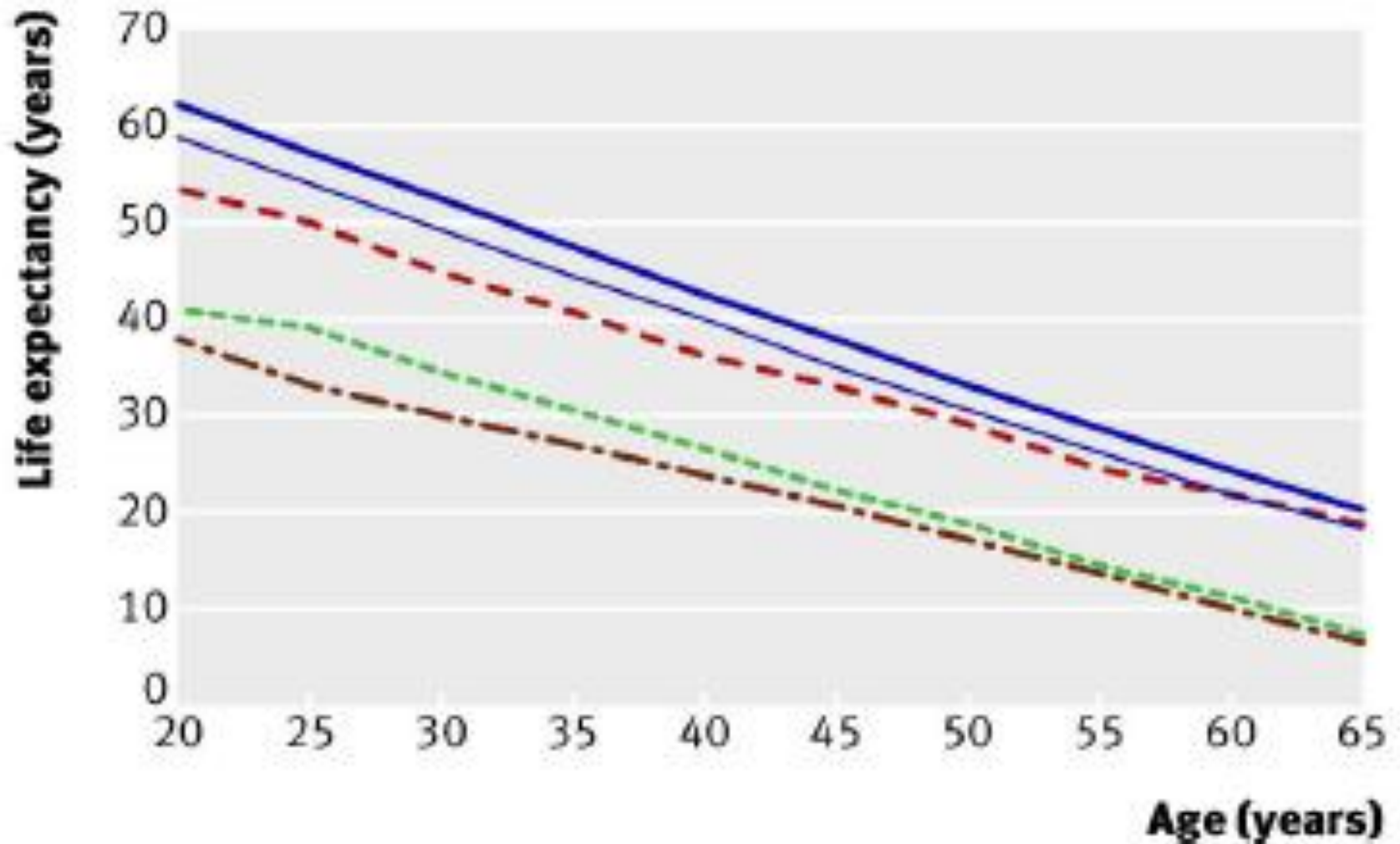
Eviplera - Tenofovir/ FTC / Rilpivrine

Coming soon

Quad - Tenofovir/ FTC / Elivitegrevir

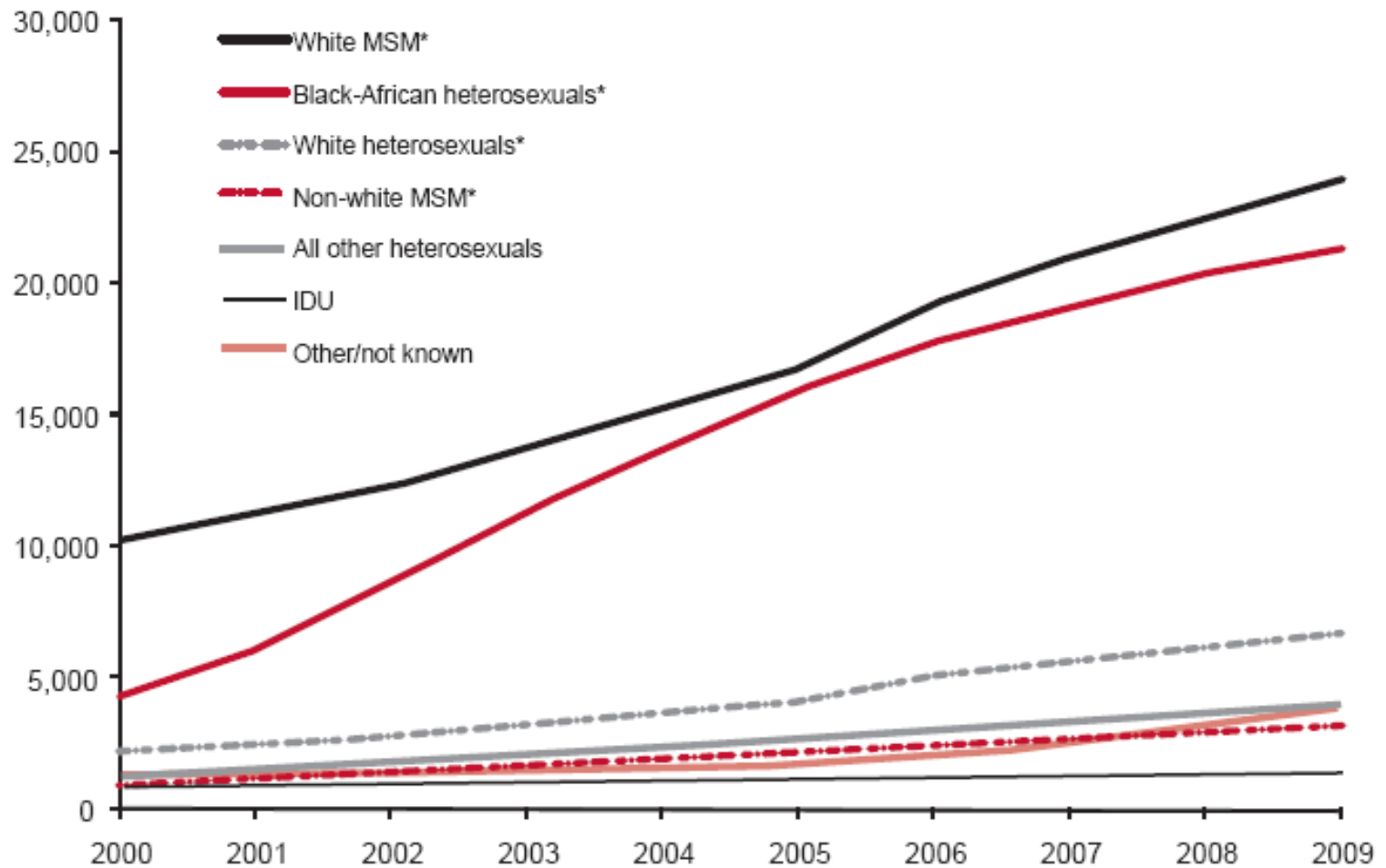
GSK - Abacavir/ 3TC / Dolutegrevir

Trends in Life expectancy (UK) Post HAART



Source: May et al (2011)

Diagnosed, HIV infected individuals in UK



* Excludes individuals with ethnicity not reported: 1,416 in 2000 and 934 in 2009

Sustainability globally

But still 9000 new infections a day in 2009 (UNAIDS)

And “There’s no money left” (Liam Byrne 2010)

Combination prevention?

- No magic bullets. Targets the prevention needs of different populations based upon epidemiological and demographic data
 - Includes existing prevention (condoms, male circumcision, behaviour change) as well as maximising new prevention opportunities of ART
-

Opportunities for biomedical interventions

← YEARS →

← HOURS →

← 72 HOURS →

← YEARS →

Prior to exposure

Exposure
(pre-coital/coital)

Exposure
(post-injury/-coital)

After infection

- Male circumcision
- PMTCT
- Harm reduction for IDU
- Oral PrEP (daily TDF or TDF/FTC)
- Topical PrEP (gels or intra-vaginal rings (microbicides))
- Preventive HIV vaccine

- Oral intermittent PrEP
- Coitally dependent topical PrEP (microbicides)

- Oral post exposure prophylaxis (PEP)

- ART \leq 350
- ART \leq 500
- “Incremental” TasP (SD couples, pregnant women, key populations, TB)
- “Test and Treat”

HPTN 052: HIV transmissions

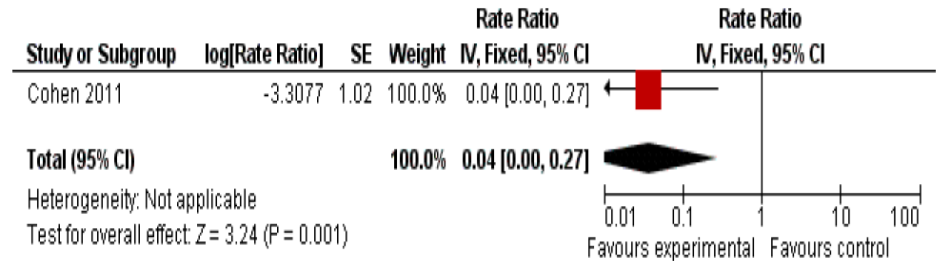
Total HIV-1 Transmission Events: 39

Linked
Transmissions: 28

Immediate
Arm: 1

Delayed
Arm: 27

$p < 0.001$



Forest plot of comparison: 1 Delayed vs Immediate ART (RCTs), outcome: 1.1 Linked Incident HIV Infection.

96% reduction in
HIV transmission

What is PrEP?

- Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by uninfected people to avoid HIV acquisition
 - Trials have typically evaluated either oral TDF/FTC or TDF alone; studies of other drugs
 - Topical TDF has also been tried as vaginal microbicide
 - Four trials have completed; one was stopped

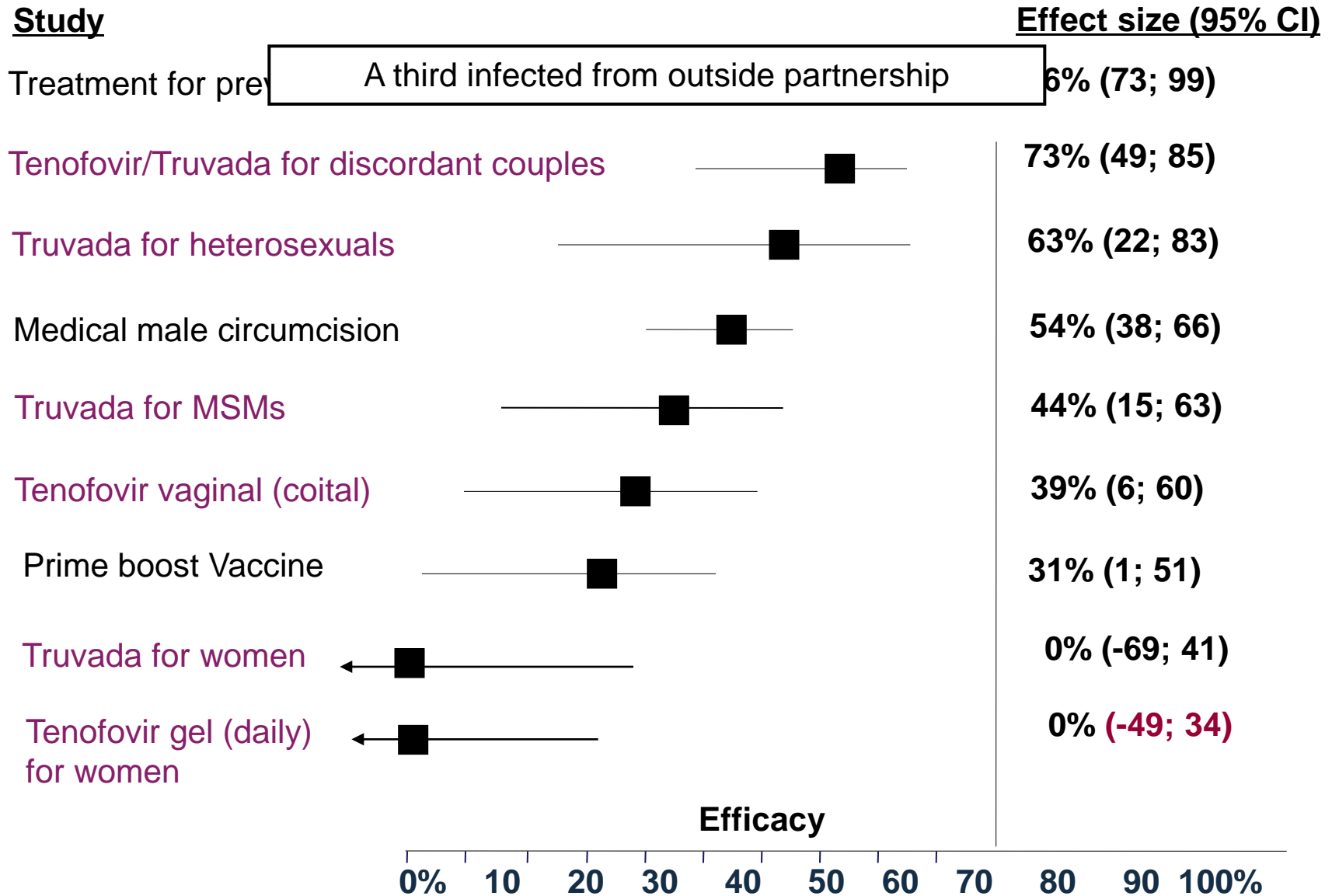
The options for PrEP

- Oral Truvada
 - Drug 4x higher in rectal tissue than plasma
 - Drug in rectal tissue higher than cervico-vaginal
 - Takes 14-21d before trough level settles
 - Topical tenofovir (vaginal or rectal gel)
 - Drug 10-100x higher in genital tissue than after oral dosing
 - Absorption influenced by female hormones in macaques
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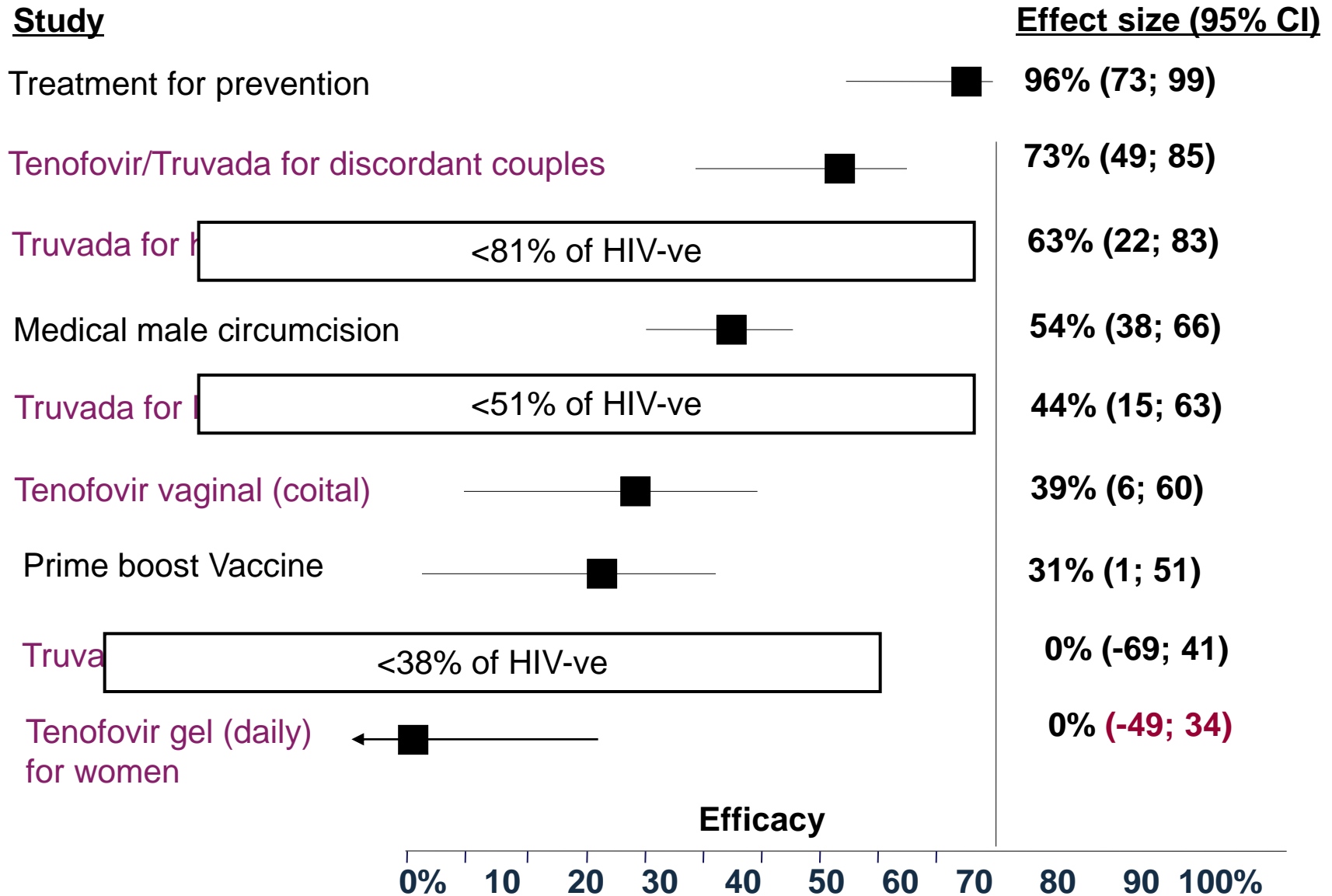
Demonstrated efficacy of PrEP in serodiscordant couples and men who have sex with men

Study	Population	N	Intention to treat ^b		
iPrEx	MSM	2499	44% (15-63%)		
Partners PrEP	Heterosexual HIV discordant couples	4758 couples	<u>All</u> 75% (55-87%)	<u>Men</u> 84% (54-95%)	<u>Women</u> 66% (28-84%)
TDF2	Heterosexual men and women		<u>All</u> 62% (21-83%)	<u>Men</u> 80% (25-97%)	<u>Women</u> 49% (-21-81%)
Fem-PrEP	Heterosexual women	2056	NS		

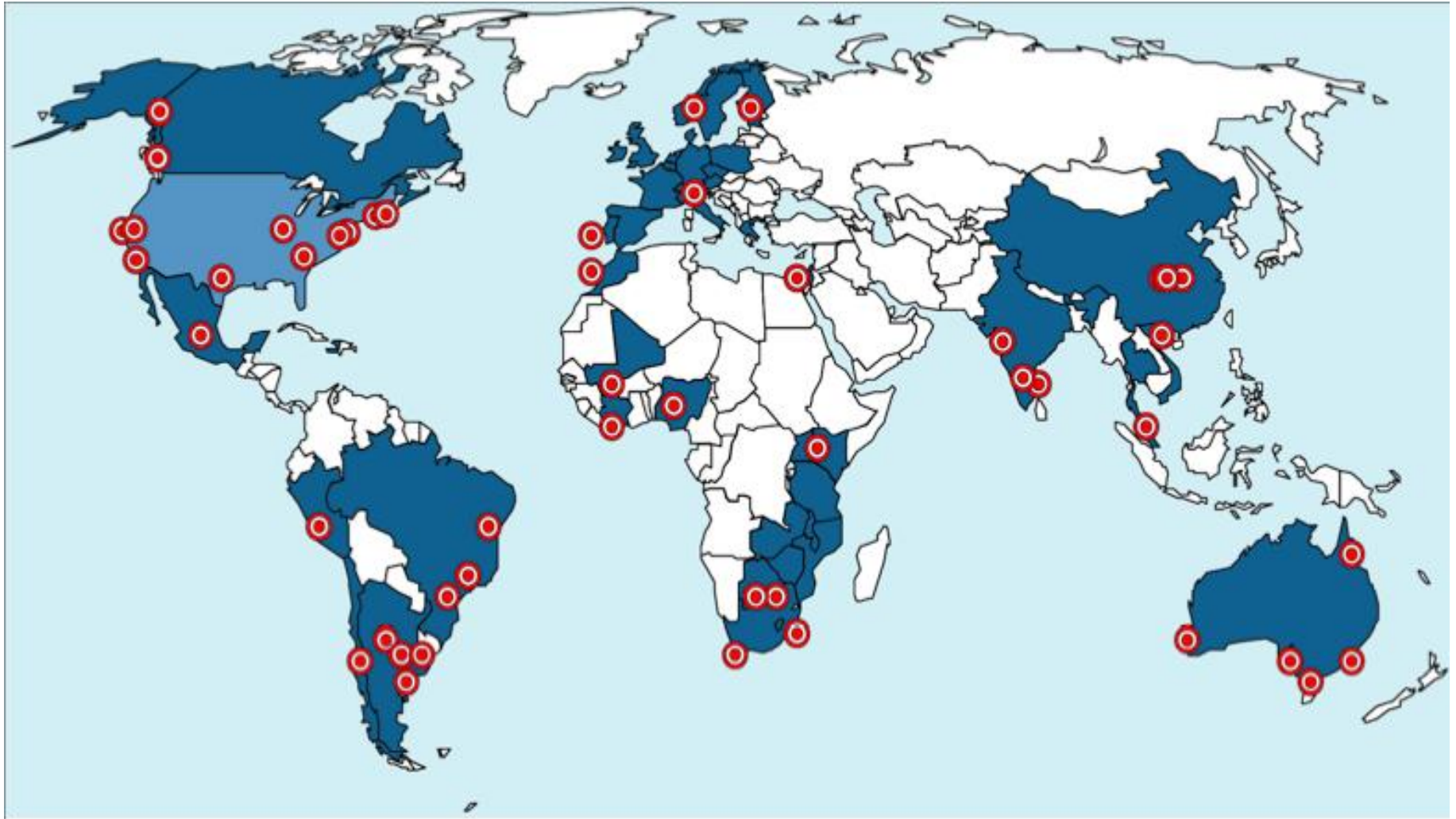
Biomedical Interventions for HIV



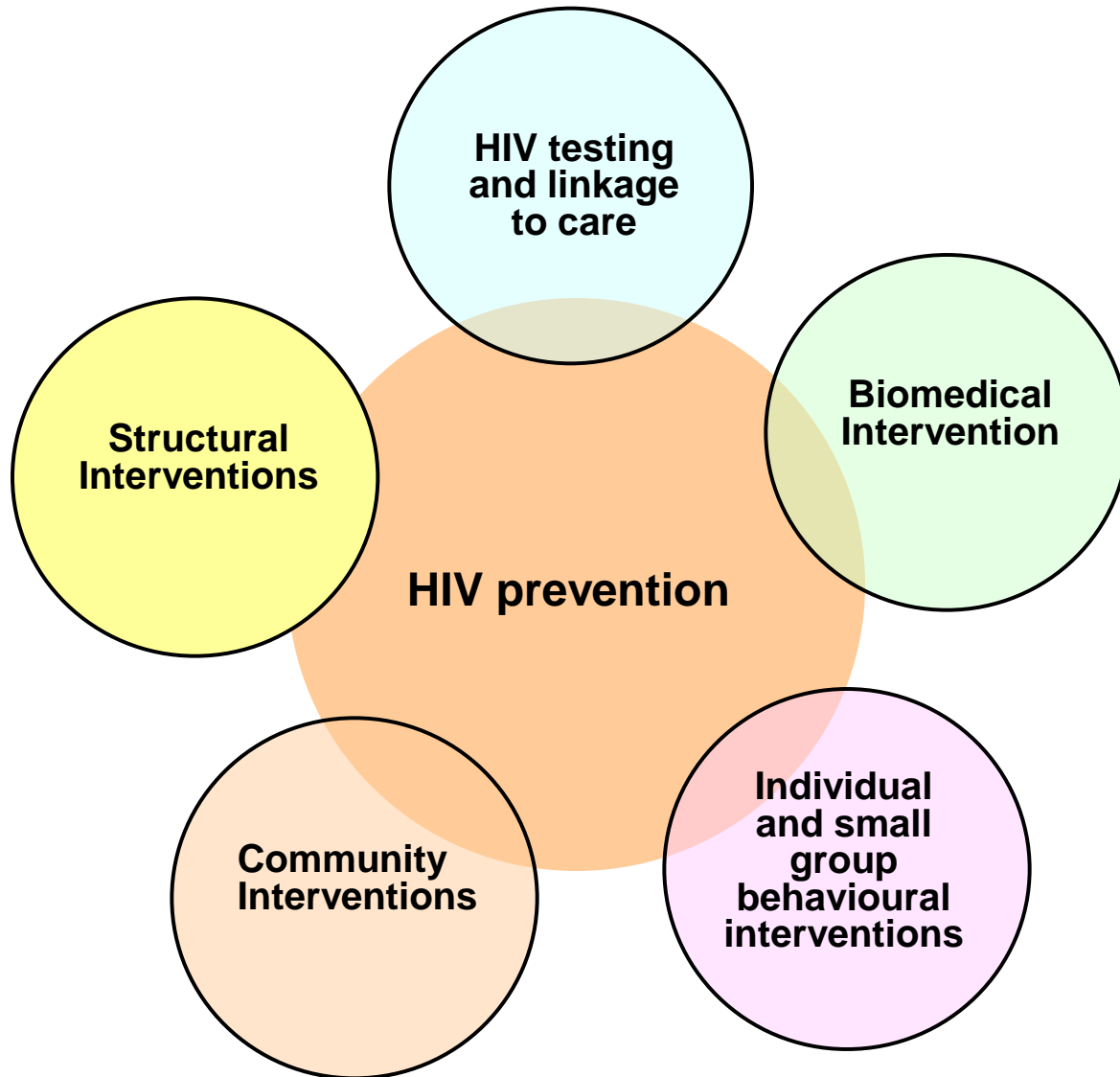
Adherence according to drug levels



More evidence on the way: 2011 ART for prevention studies



Combination prevention involves multiple disciplines and approaches



Thank you