

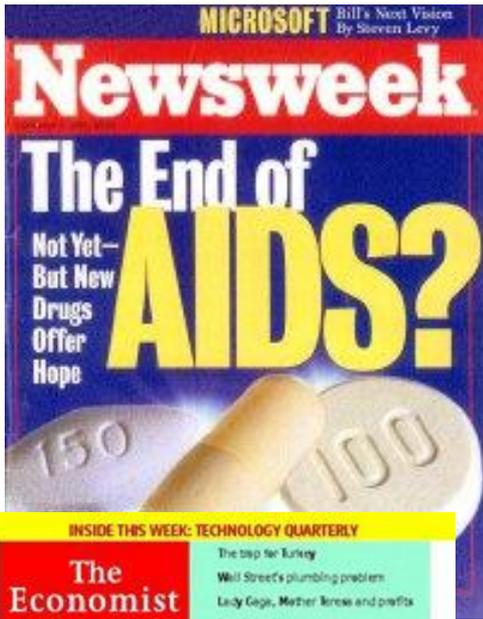
Frontiers in the Research of HIV (& STDs)

Khalil Ghanem, MD, PhD
Associate Professor of Medicine
Johns Hopkins University School of Medicine
Director, STD/HIV/TB Clinical Services
Baltimore City Health Department

Disclosures

- None

The Hope





The NEW ENGLAND JOURNAL of MEDICINE

Perspective
AUGUST 23, 2012

The Beginning of the End of AIDS?
Diane Havlir, M.D., and Chris Beyrer, M.D., M.P.H.



The Current Reality

Global summary of the AIDS epidemic | 2011

Number of people living with HIV

Total	34.2 million [31.8 million–35.9 million]
Adults	30.7 million [28.6 million–32.2 million]
Children (<15 years)	3.4 million [3.1 million–3.9 million]

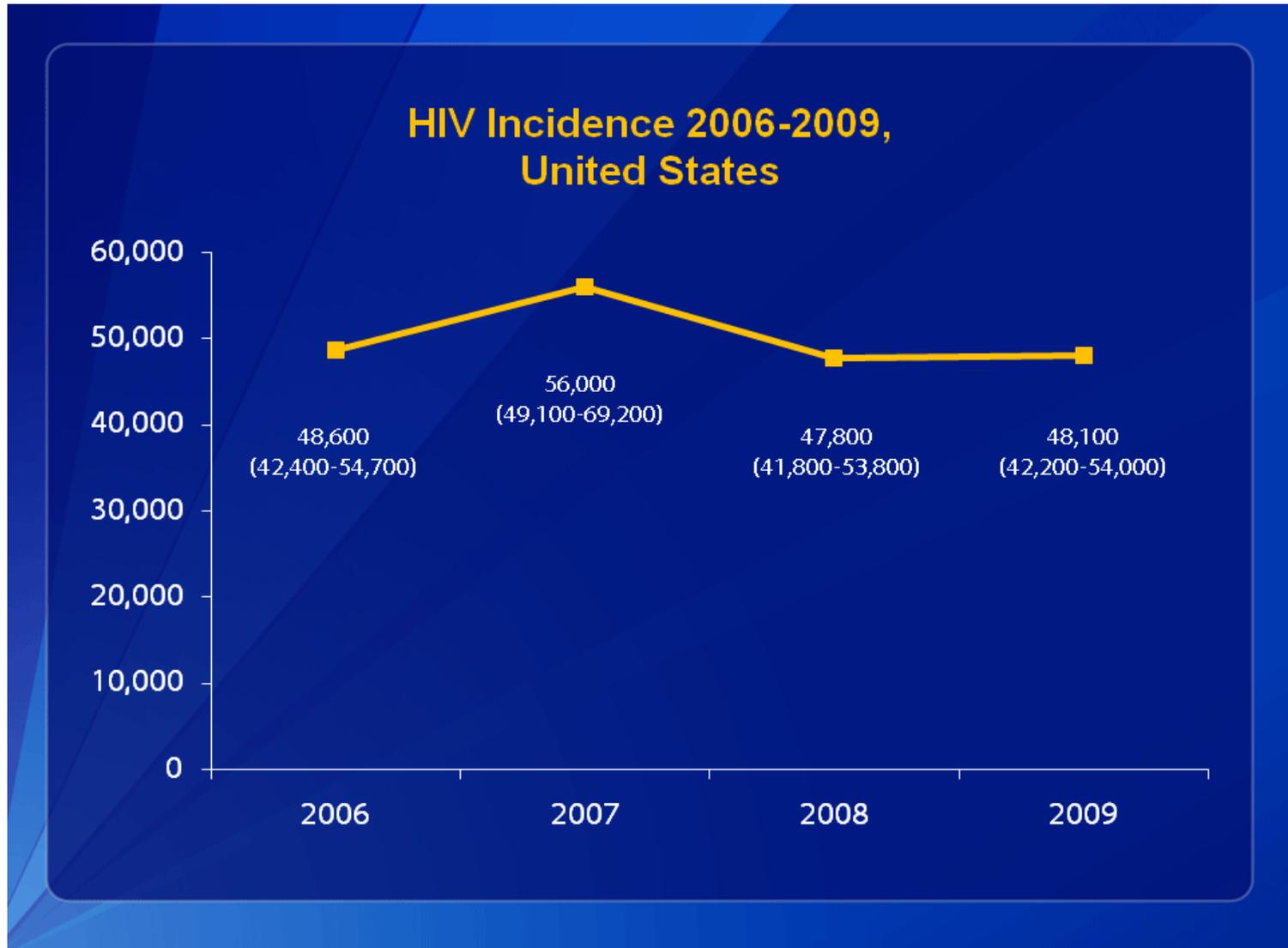
People newly infected with HIV in 2011

Total	2.5 million [2.2 million–2.8 million]
Adults	2.2 million [2.0 million–2.4 million]
Children (<15 years)	330 000 [280 000–380 000]

AIDS deaths in 2011

Total	1.7 million [1.6 million–2.0 million]
Adults	1.5 million [1.3 million–1.7 million]
Children (<15 years)	230 000 [200 000–270 000]

The Reality in the US



Overall Goal of this Talk

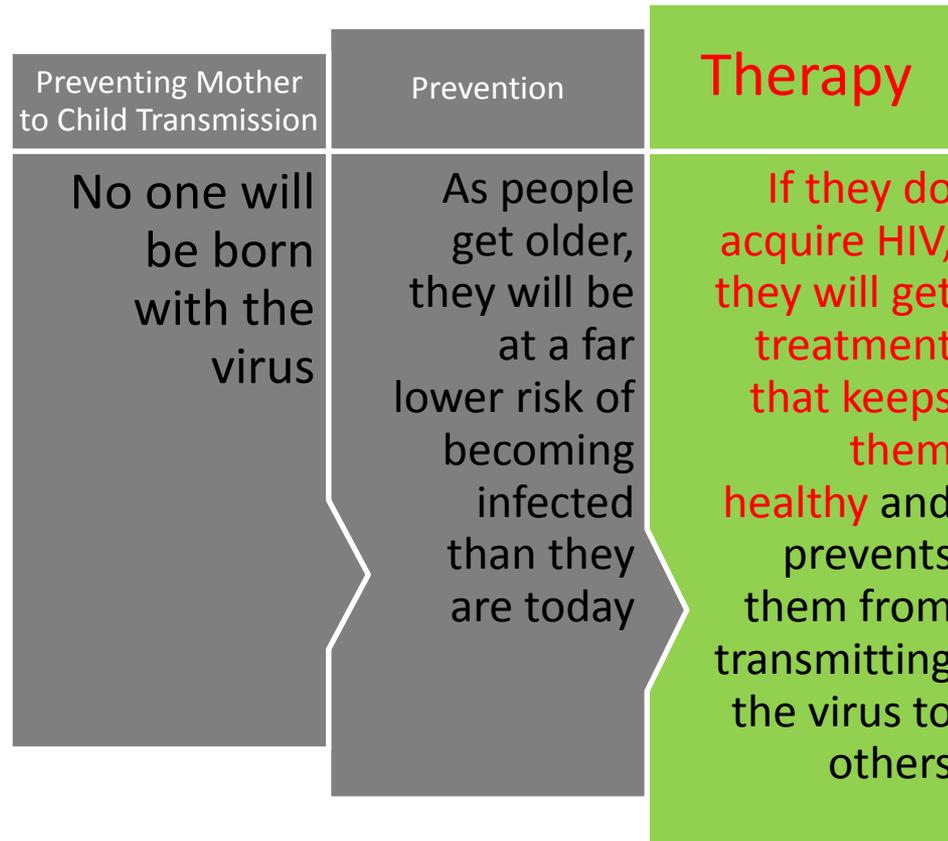
- An AIDS-Free Generation: Is it Feasible?
 - What does the latest research tell us?
 - How do we focus our future efforts on achieving that goal?

The End of AIDS

VS.

The End of HIV

How do we Achieve an AIDS-Free Generation?



HIV Therapy

- 6 classes of drugs
- Multiple generations within most classes
- Fewer side effects
- Fewer pills

SINGLE-TABLET REGIMEN



Atripla
efavirenz / emtricitabine / tenofovir, or EFV / FTC / TDF

STANDARD DOSE: One tablet (600 mg efavirenz / 200 mg emtricitabine / 300 mg tenofovir), once daily. Take on an empty stomach, or may be taken with a light, low-fat snack.

The “Quad”
elvitegravir / cobicistat / emtricitabine / tenofovir, or EVG / COBI / FTC / TDF

STANDARD DOSE: One tablet (150 mg elvitegravir / 150 mg cobicistat / 200 mg emtricitabine / 300 mg tenofovir) once daily has been selected in Phase 3 studies. Take with food. (Not yet approved at press time; photo unavailable.)



Complera
rilpivirine / emtricitabine / tenofovir, or RPV / FTC / TDF

STANDARD DOSE: One tablet (25 mg rilpivirine / 200 mg emtricitabine / 300 mg tenofovir) once daily. Take with food (with a meal of at least 400 calories).

cobicistat
(formerly GS-9350, or COBI)

PK ENHANCER

STANDARD DOSE: Not yet established. 150 mg used in research. Cobicistat is not an HIV drug, but is used to increase (boost) the levels of elvitegravir (an investigational integrase inhibitor, see elvitegravir) and HIV protease inhibitors. (Not yet approved at press time; photo unavailable.)

What Has Therapy Gotten Us?

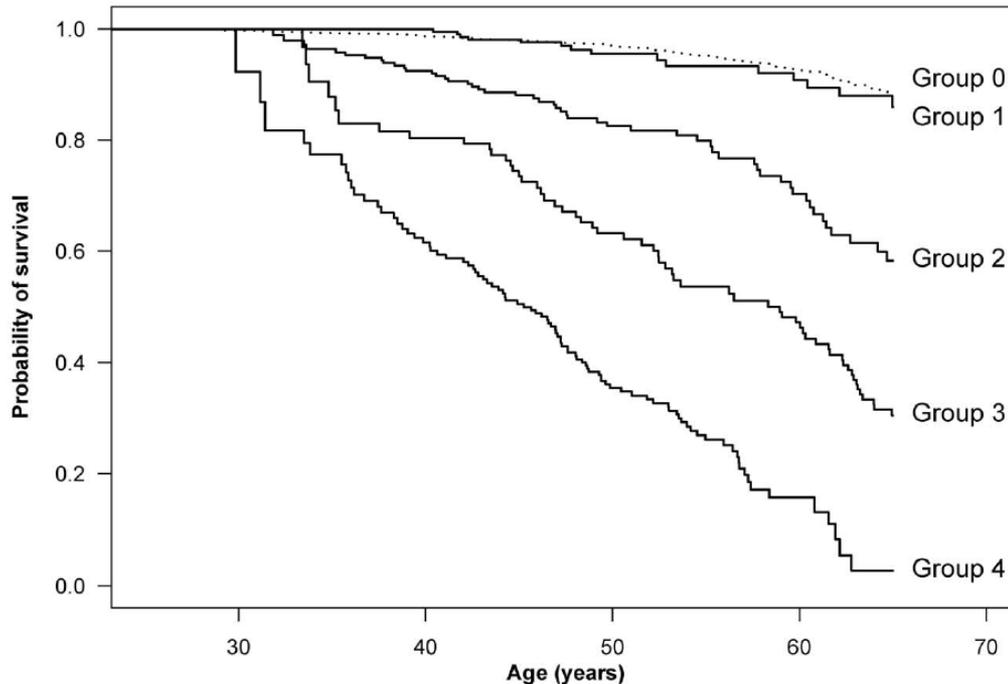


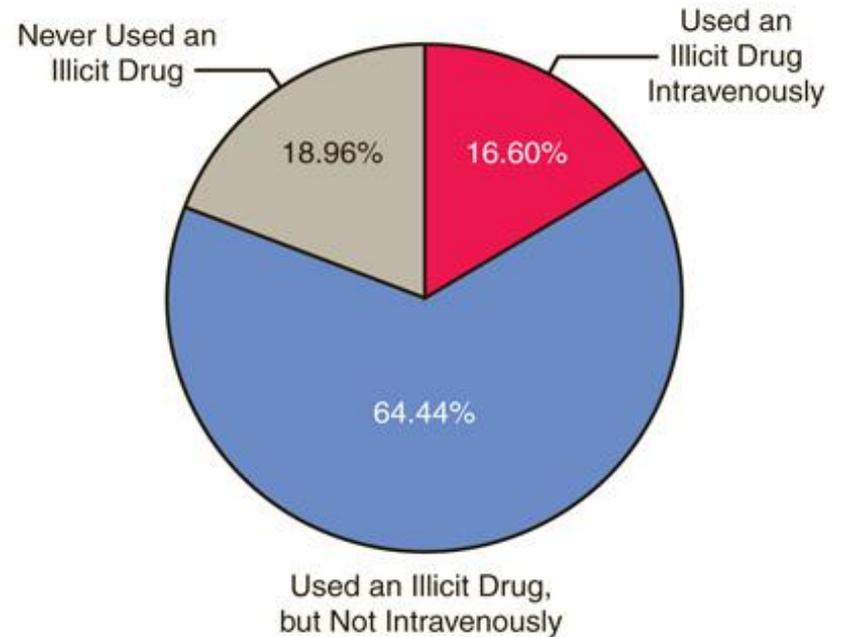
Figure 1. Cumulative survival for HIV-infected patients starting HAART and persons from the general population. Time was calculated from 1 year after start of HAART. The study population was categorized as: Group 0: Population comparison cohort (dotted line, N = 9,068). Group 1: HIV-infected patients without HIV risk factors, comorbidity or alcohol/drug abuse (N = 871). Group 2: HIV-infected patients with HIV risk factors, but no comorbidity or alcohol/drug abuse (N = 704). Group 3: HIV-infected patients with comorbidity, but no alcohol/drug abuse (N = 379). Group 4: HIV-infected patients with alcohol/drug abuse (N = 313). *HIV risk factors:* detectable viral load (>49 copies/ml) and/or CD4 below 200 cells/ul at the last measurement prior to the index date and/or AIDS- defining disease as of the index date. *Comorbidity:* diagnosed with comorbidity as defined in the Charlson Comorbidity Index before index date. *Abuse:* diagnosed with drug or alcohol abuse before index date or reporting drug abuse as route of HIV transmission.

Probability of survival in persons with HIV who do not have risk factors* is almost identical to the probability of survival in persons who do not have HIV

* Risk factors-such as lack of response to antiretroviral therapy, presence of a significant comorbidity, the abuse of alcohol and drugs

Substance Use and HIV

- **Nearly one quarter of persons with HIV/AIDS were in need of treatment for alcohol use or illicit drug use in the past year**



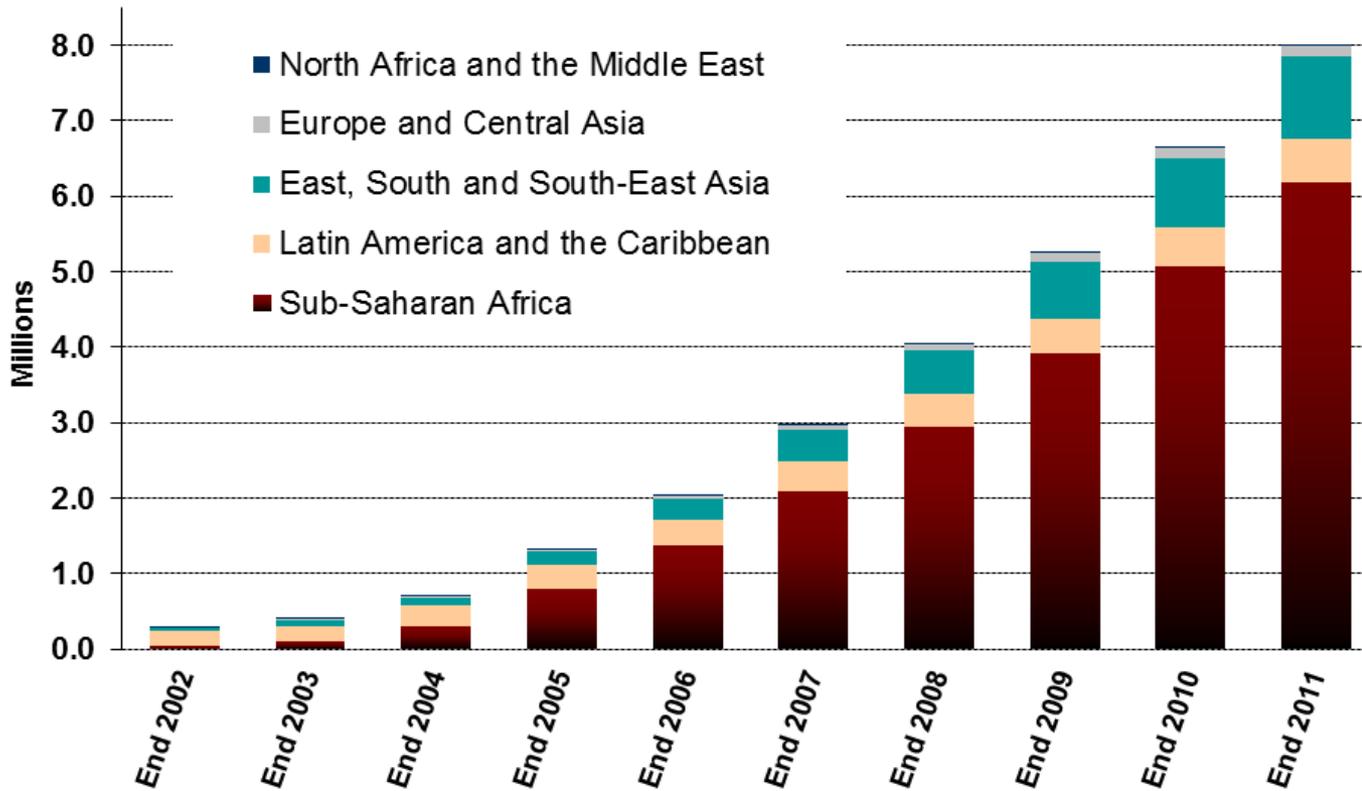
Source: 2005 to 2009 SAMHSA National Surveys on Drug Use and Health (NSDUHs).

HIV Therapy

- HIV therapy is only effective if:
 - Patients have access to the drugs
 - Patients are adherent to the medications
- **What does the latest research tell us about access and adherence?**

Access to HIV Therapy Worldwide

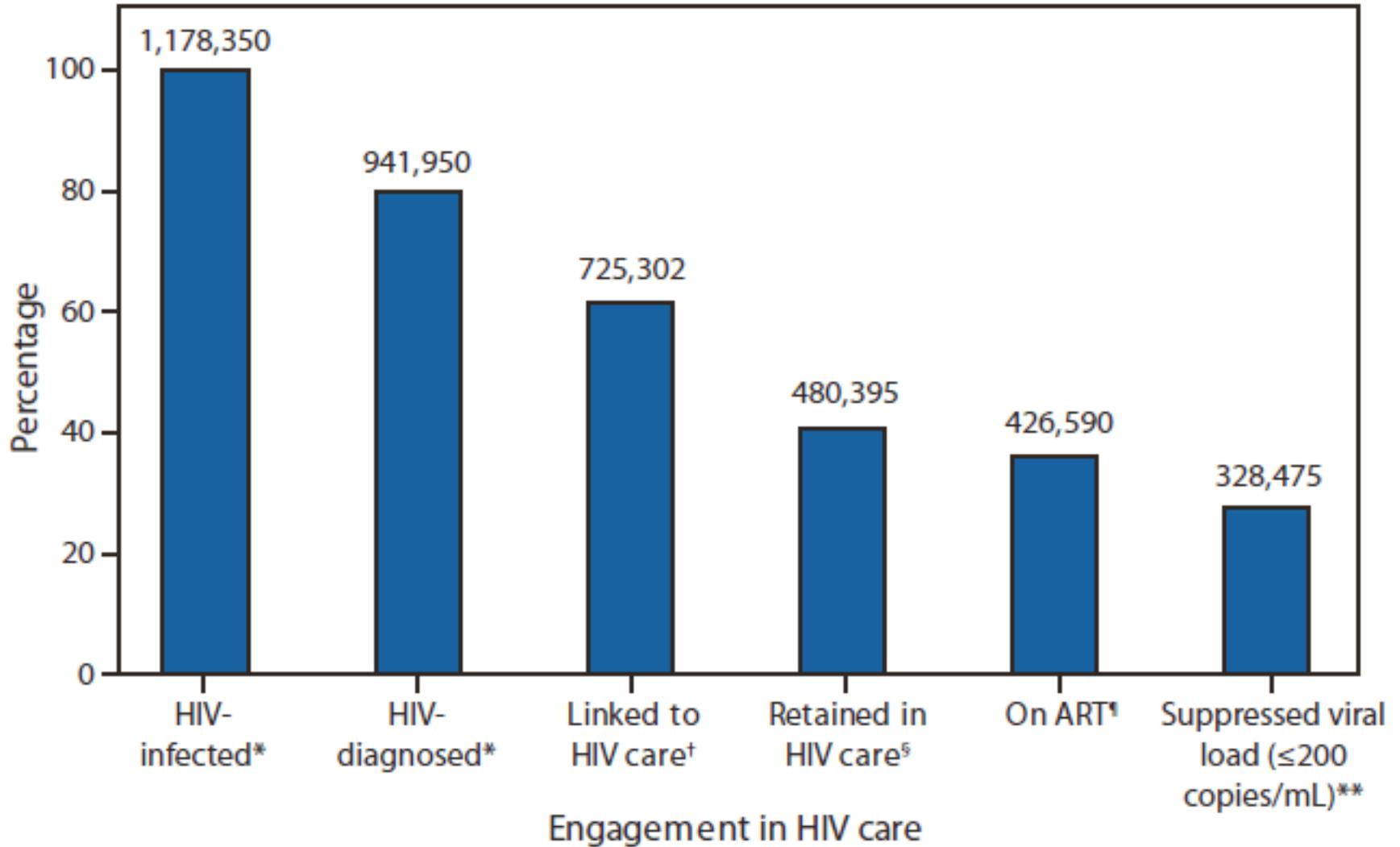
Number of people receiving ART in low- and middle-income countries, by region, 2002–2011



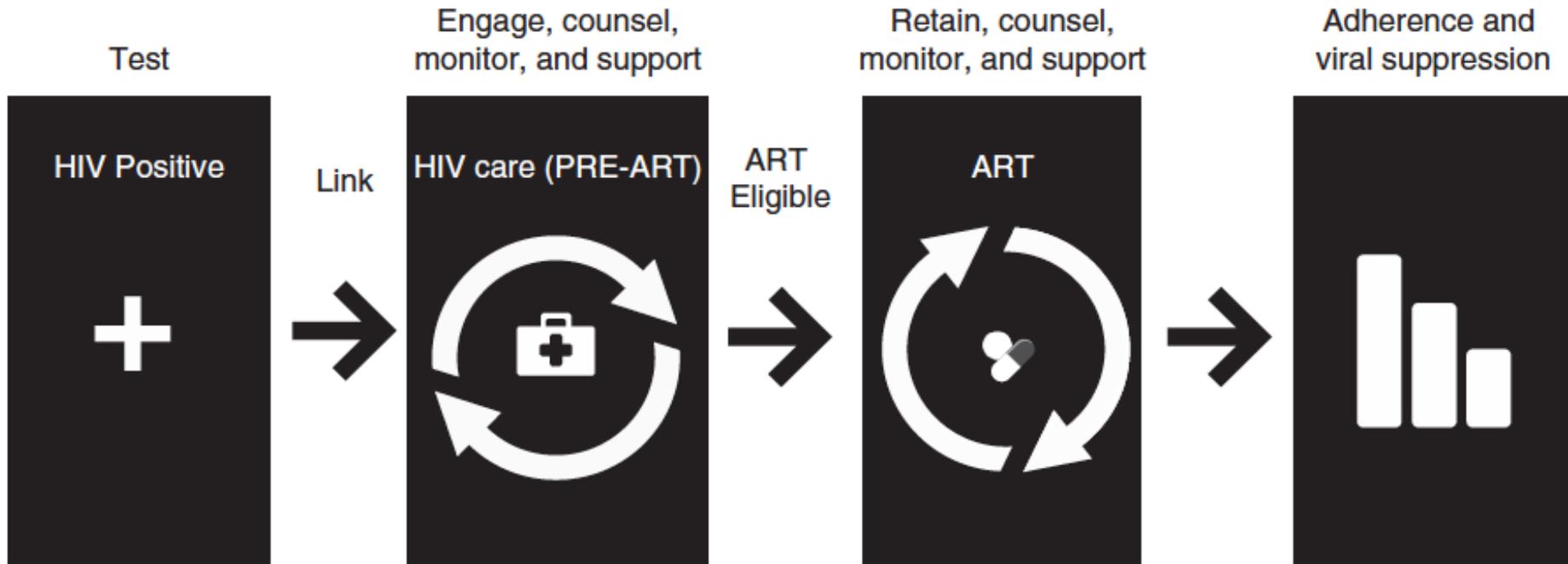
**BUT 14.2 million people
needed ART**



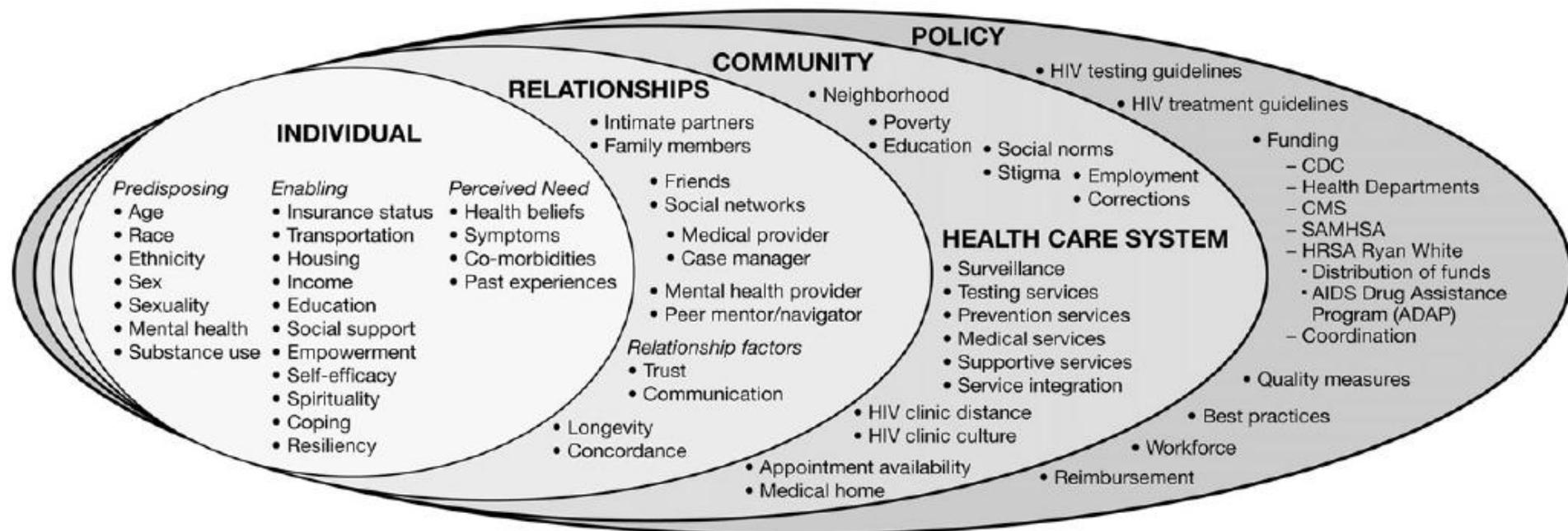
HIV Therapy U.S.



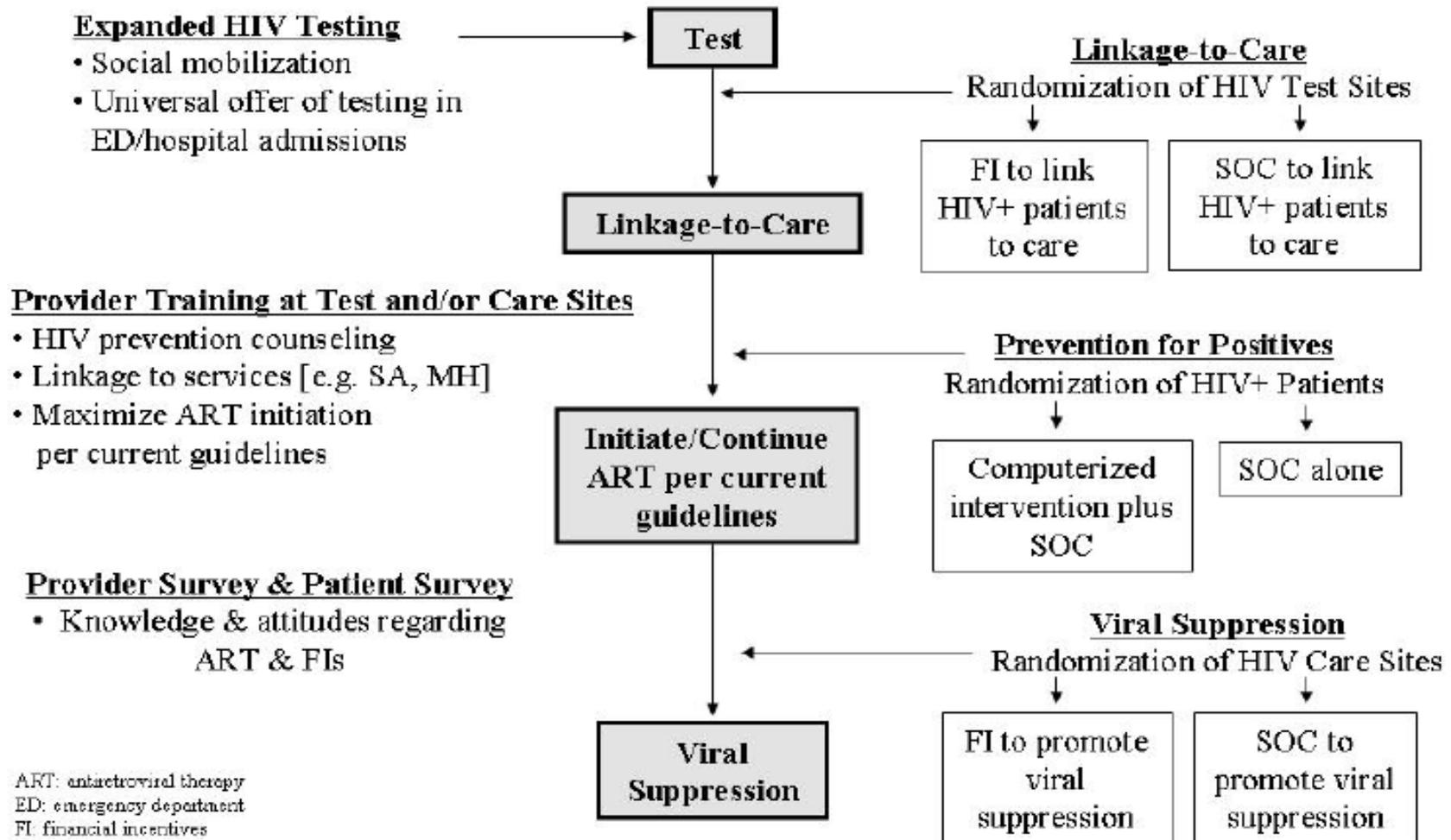
The HIV Care Continuum



The complex interplay of individual, relationship, community, health care system, and policy factors that influence the processes of engagement in care

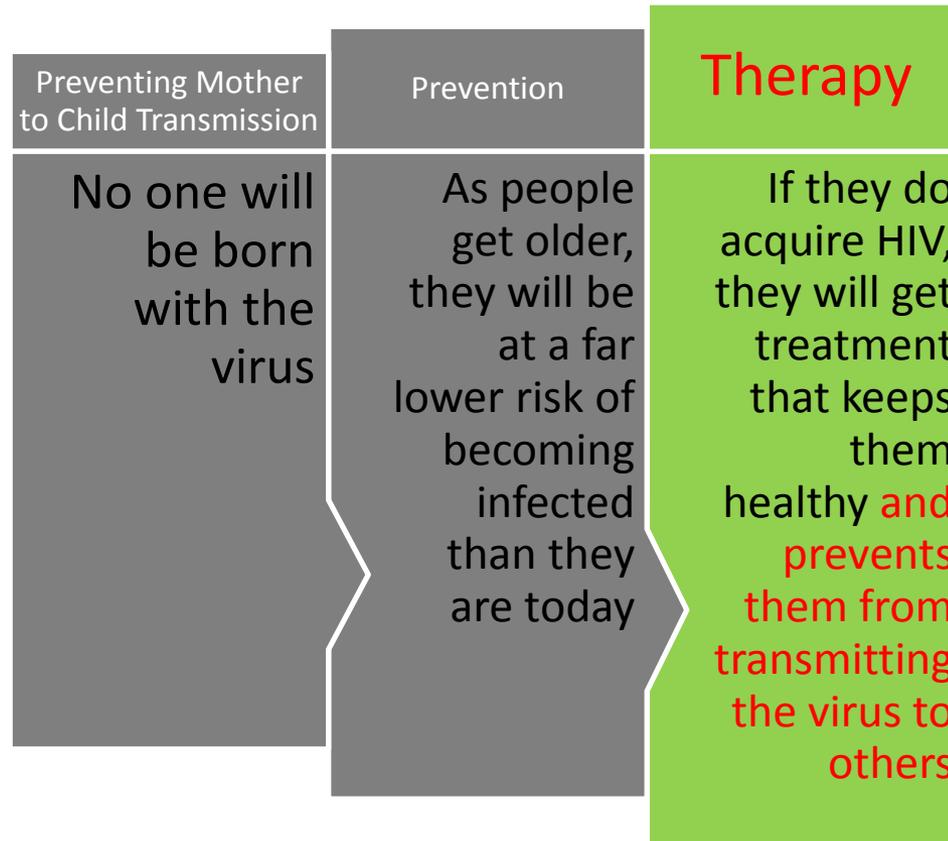


Future Research: HPTN 065TLC-Plus: A Study to Evaluate the Feasibility of an Enhanced Test, Link to Care, Plus Treat Approach for HIV Prevention in the United States

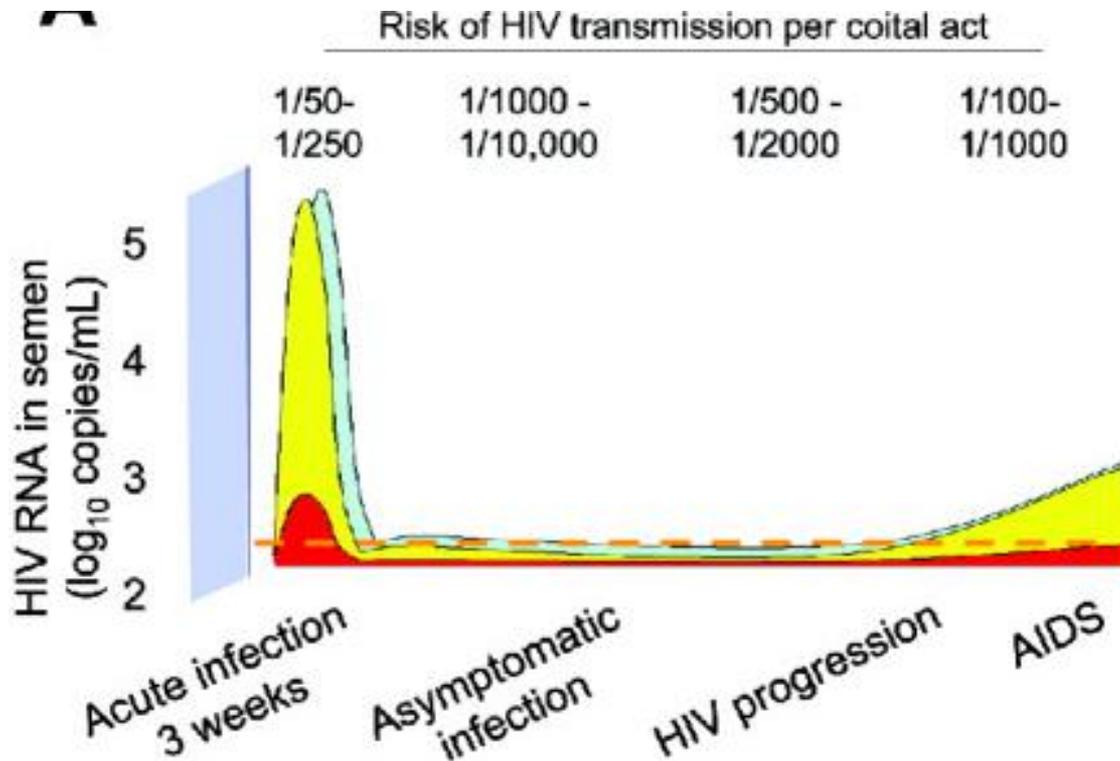


ART: antiretroviral therapy
 ED: emergency department
 FI: financial incentives
 MH: mental health
 SA: substance abuse
 SOC: standard of care

How do we Achieve an AIDS-Free Generation?



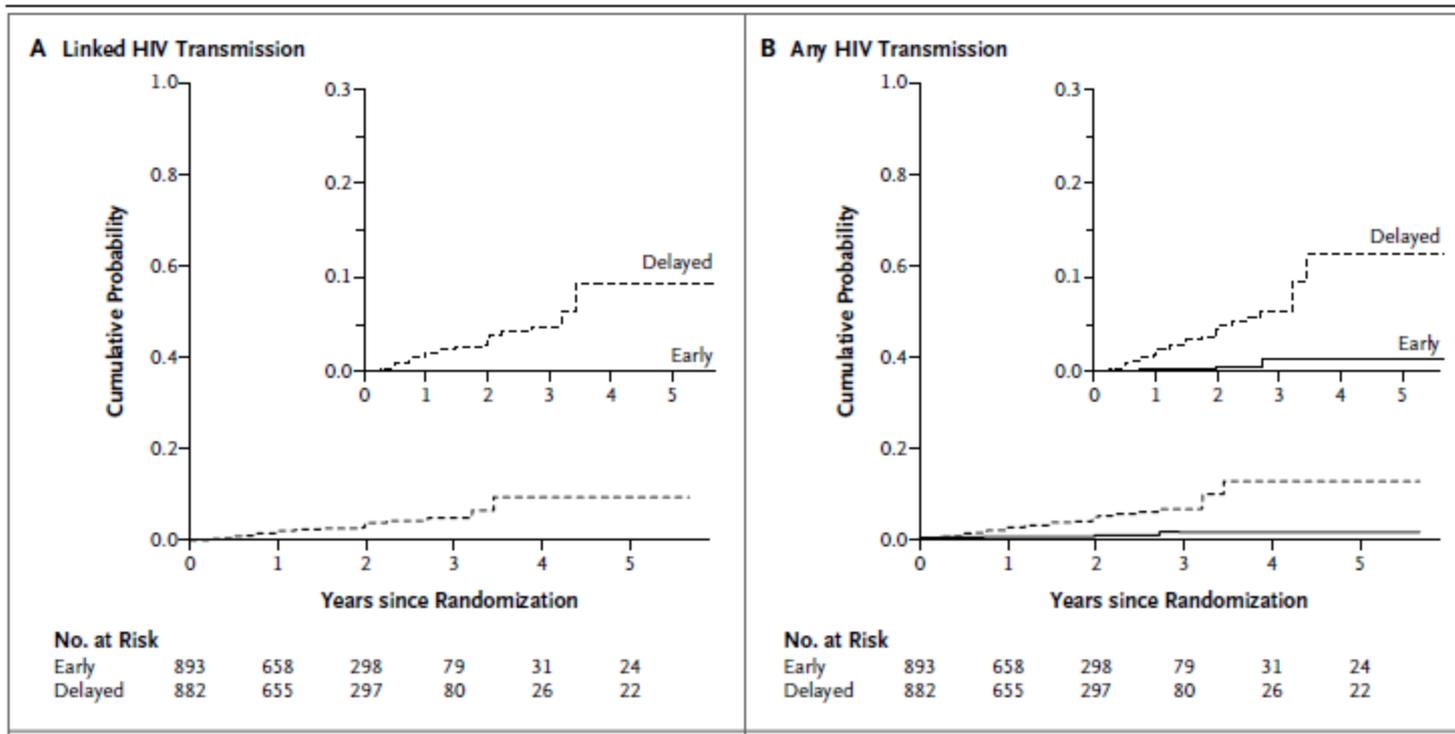
Sexual Transmission of HIV



Cohen MS, et al. J Infect Dis. 2005 May 1;191(9):1391-3.

Treatment as Prevention

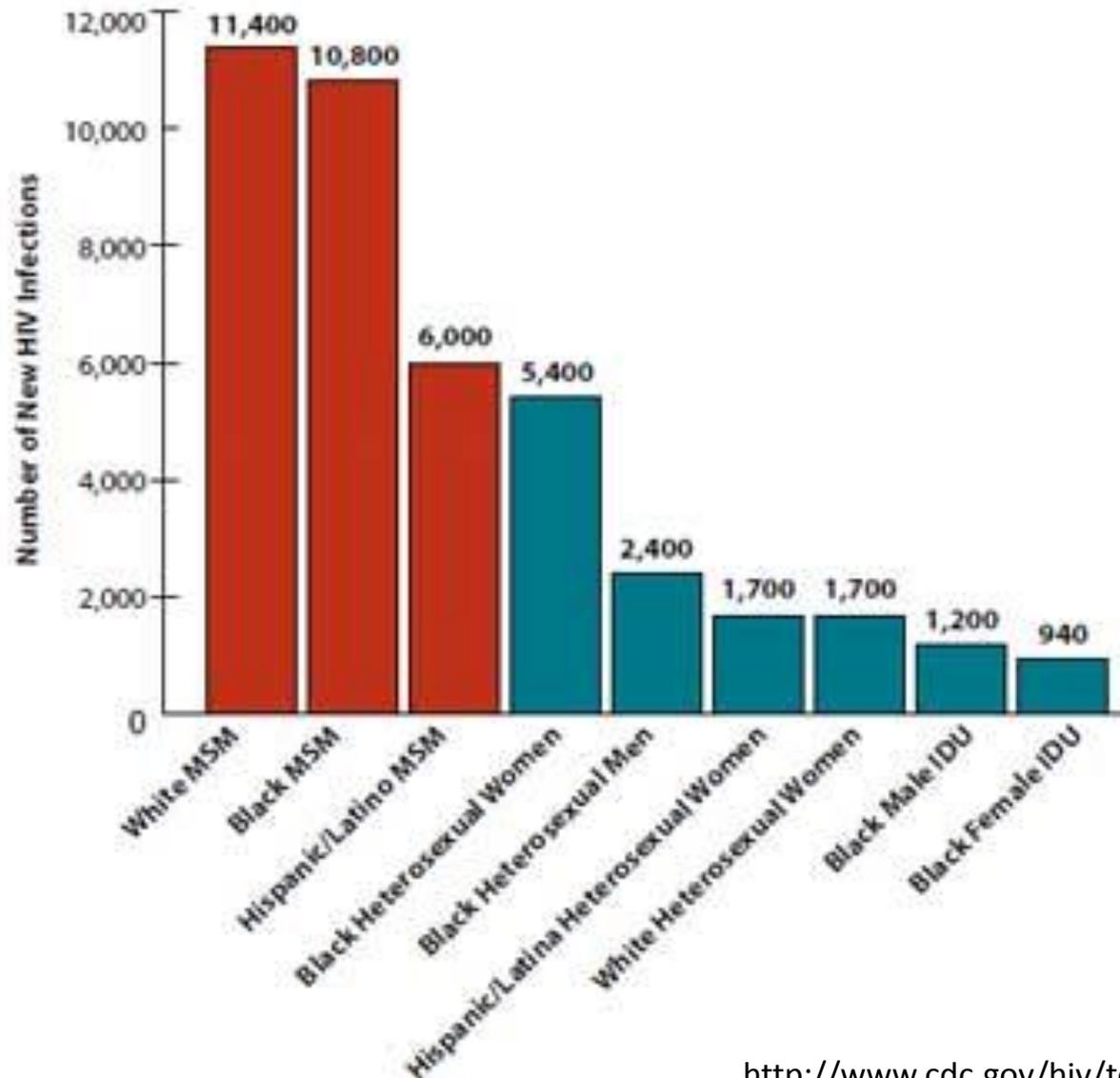
PEP in heterosexual discordant couples



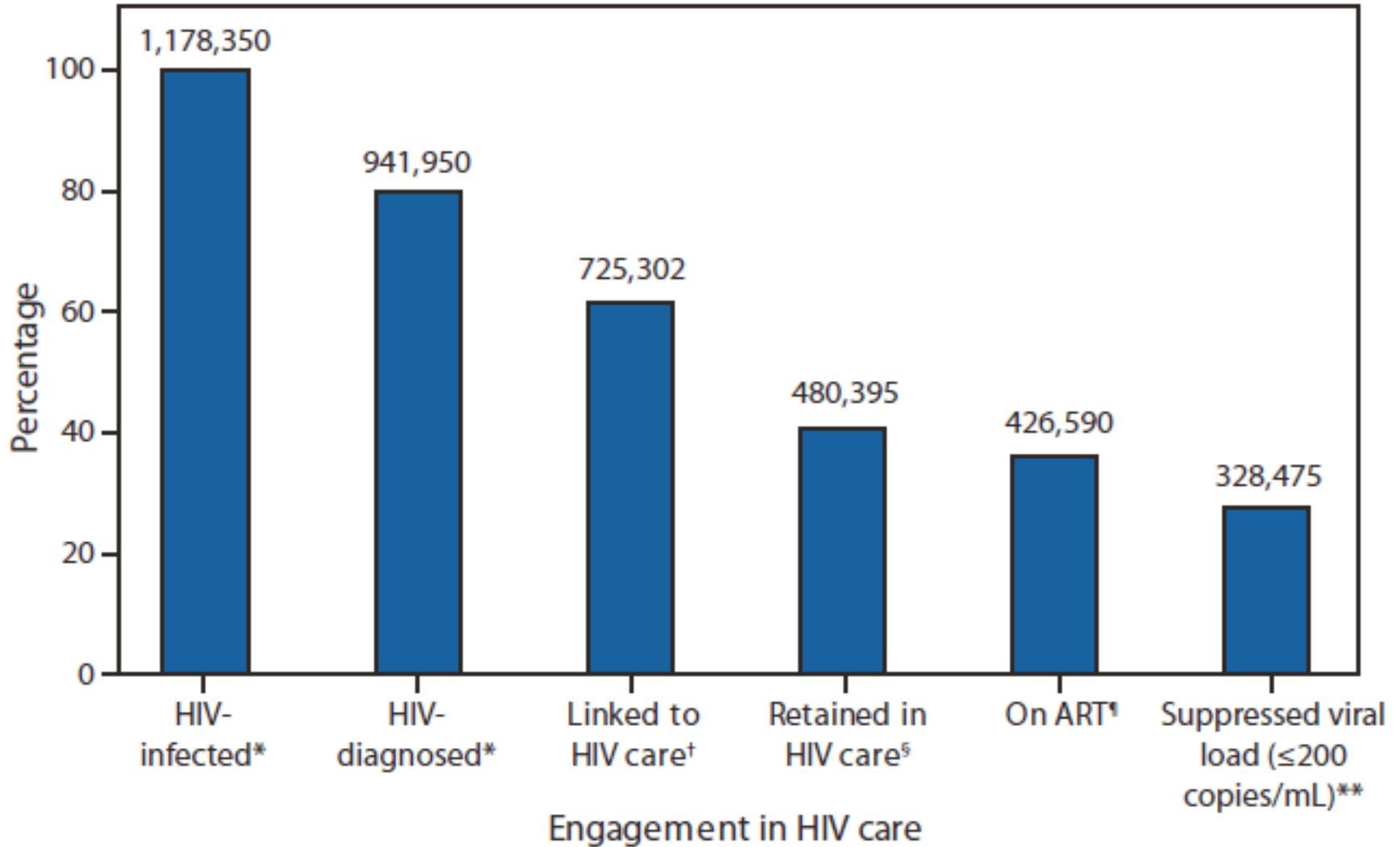
Multivariate analysis

Early therapy vs. delayed therapy 0.04 (0.01–0.28) 0.11 (0.04–0.33) 0.59 (0.40–0.89) 0.28 (0.18–0.45)

New HIV Infections in US

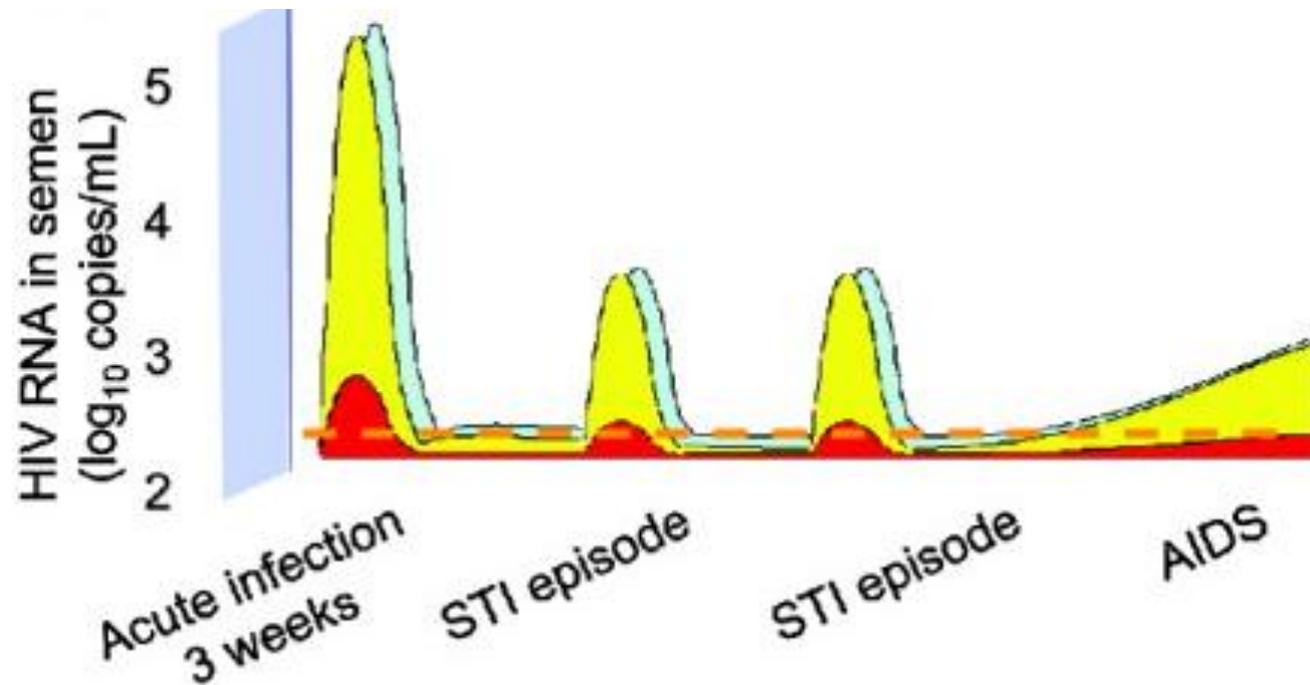


HIV Therapy U.S.

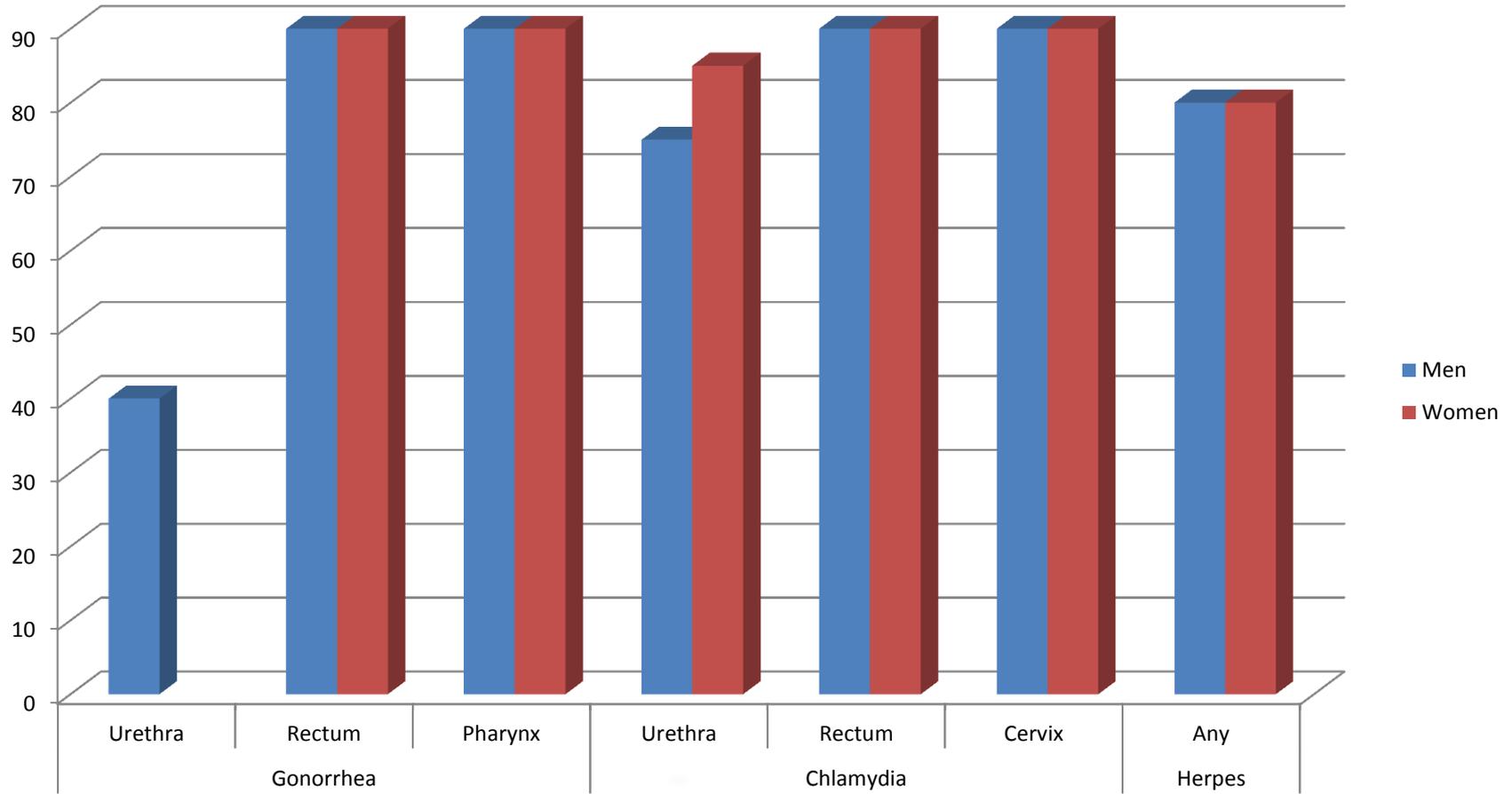


HIV & STDs

Remember: HIV RNA levels in the blood tend to CORRELATE with HIV RNA levels in genital secretions, but NOT ALWAYS



The Percent of Asymptomatic STDs



Prevalence of Extragenital Sexual Behaviors

ORAL SEX

Oral Sex	Males		Females	
	Active Oral	Passive Oral	Active Oral	Passive Oral
Lifetime	77%	79%	68%	73%
Last sex	27%	28%	19%	28%

Michael RT, et al. Sex in America: A Definitive Survey. Little, Brown and Co. UK. 1994

ANAL SEX

- Young MSM: 50%
- Young heterosexual men and women: 14-49%

Ekstrand M, et al. AIDS 1999; 13 (12): 1525-33
Halperin D, et al. AIDS Patient Care STDs 1999; 13(12); 717-30

Screening for STDs in HIV+ Persons

- **Syphilis:** at least annually for all sexually active HIV-infected persons, with more frequent screening (every 3–6 months) in those with multiple partners, a history of unprotected intercourse, a history of sex in conjunction with illicit drug use, methamphetamine use, or sexual partners who participate in such activities
- **Chlamydia:** (1) all sexually active women $\leq 25y$ and (2) all men and women $>25y$ at increased risk (new or multiple partners; previous CT history; area of high prevalence; CSW, drug use, inconsistent condom use)
 - Repeat testing of all CT+ women and men is recommended 3-6 months after treatment
- **Gonorrhea:** Annual screening for gonorrhea is recommended for all sexually active MSM, and targeted screening is recommended for high-risk women (e.g., women with previous gonorrhea infection, other STDs, new or multiple sex partners, and inconsistent condom use; CSW and drug use; area of high prevalence)
 - Repeat testing of GC+ patients recommended 3 months after treatment
- **Trichomonas:** All HIV+ women should be screened for trichomoniasis on a yearly basis
 - Repeat testing of all trichomonas+ women recommended 3 months after treatment

Extragenital Gonorrhea and Chlamydia Infections

- Studies suggest that up to 65% of cases of gonorrhea and 50% of cases of chlamydia among MSM may be missed if genital-only testing were performed.

Sex Transm Dis. 2008;35(10):845

Clin Infect Dis. 2005;41(1):67

- In women, 10% of CT and 31% of GC infections would have been missed if extragenital testing were not done

Sex Transm Dis. 2011;38(9):783

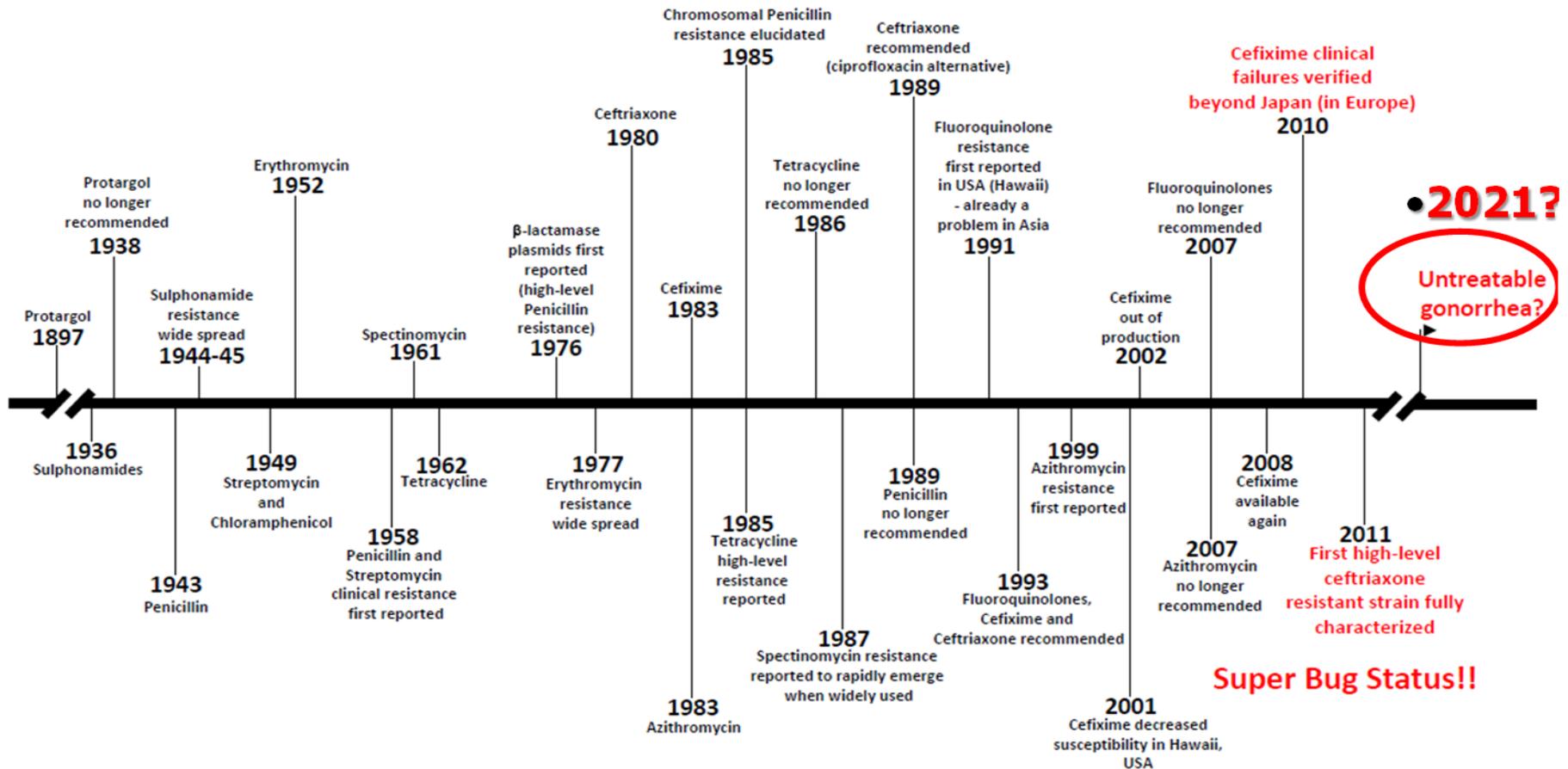
- The majority of rectal and pharyngeal GC & CT infections are ASYMPTOMATIC
- Rectal and pharyngeal infections are of public health significance

Clin Infect Dis. 2009;49(12):1793

Extragenital STI Diagnostics

- All persons should be tested for rectal and pharyngeal gonorrhea if they report pharyngeal or rectal exposures
- Sensitivity of culture <50% to detect rectal and pharyngeal GC vs. >90% sensitivity for Nucleic Acid Amplification Tests (NAATs) *Sex Transm Infect.* 2009 Jun;85(3):182-6
- The CDC recommends that NAATs be used to detect these extragenital infections *MMWR Recomm Rep.* 2011 ;60(1):18
- If NAATs for extragenital testing of GC are not feasible in your setting, use culture to detect these infections. It is an acceptable alternative

History of Gonorrhea treatment and resistance – only 1-2 decades needed for international spread



Updated CDC Treatment Recommendations for Gonorrhea

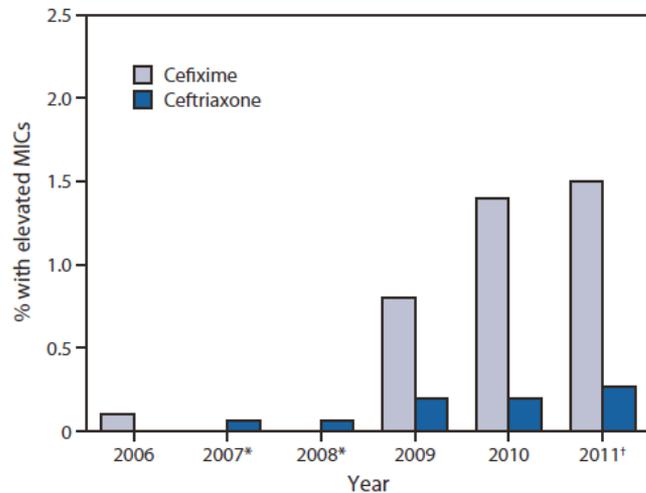
- **First-Line (preferred)**

- Ceftriaxone 250 mg IM X1 + Azithromycin **1g** PO X 1 **or** Doxycycline 100mg PO BID X 7 days
- Azithromycin is preferred over doxycycline but both are acceptable
- Use dual therapy even if *C. trachomatis* is ruled out!

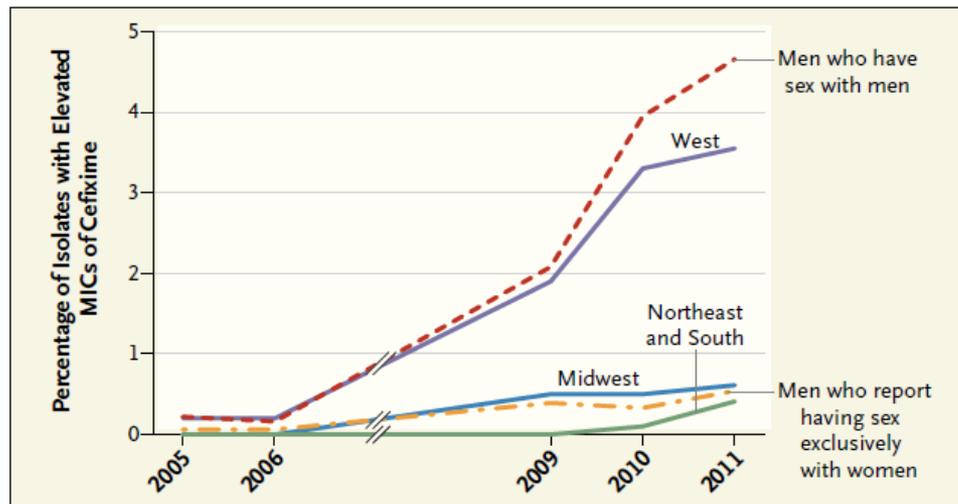
- **Alternate**

- Cefixime 400mg PO X1 + Azithromycin **1g** PO X1 **or** Doxycycline 100mg PO BID X 7 days
- Azithromycin **2g** PO X 1 (single therapy single dose)
 - Azithromycin 2g PO X1 is the only regimen currently available to treat a patient who has an allergy to cephalosporins

Cephalosporin MICs in the US:2000-2011



Although the MIC breakpoints for resistance to cephalosporin have not been defined, the CLSI defines susceptibility to cefixime and ceftriaxone as MICs of 0.25 µg per milliliter or below, and 0.125 µg per milliliter or below, respectively



Percentage of Isolates in Which Minimal Inhibitory Concentrations (MICs) of Cefixime Were 0.25 µg per Milliliter or Higher, 2005–2011.

Susceptibility to cefixime was not tested in 2007 or 2008. From the Gonococcal Isolate Surveillance Project.

Reduced Susceptibility to Cephalosporins Worldwide

Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010

M Unemo (magnus.unemo@orebroll.se)¹, D Golparian¹, G Syversen², D F Vestrheim^{3,4}, H Moi^{3,5}

Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010

M Unemo (magnus.unemo@orebroll.se)¹, D Golparian¹, A Hestner²

1. Swedish Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden

2. Department of Dermatology and Venereology, Kärnjukhuset, Skövde, Sweden

Research articles

MULTIDRUG-RESISTANT *NEISSERIA GONORRHOEAE* WITH REDUCED CEFOTAXIME SUSCEPTIBILITY IS INCREASINGLY COMMON IN MEN WHO HAVE SEX WITH MEN, AMSTERDAM, THE NETHERLANDS

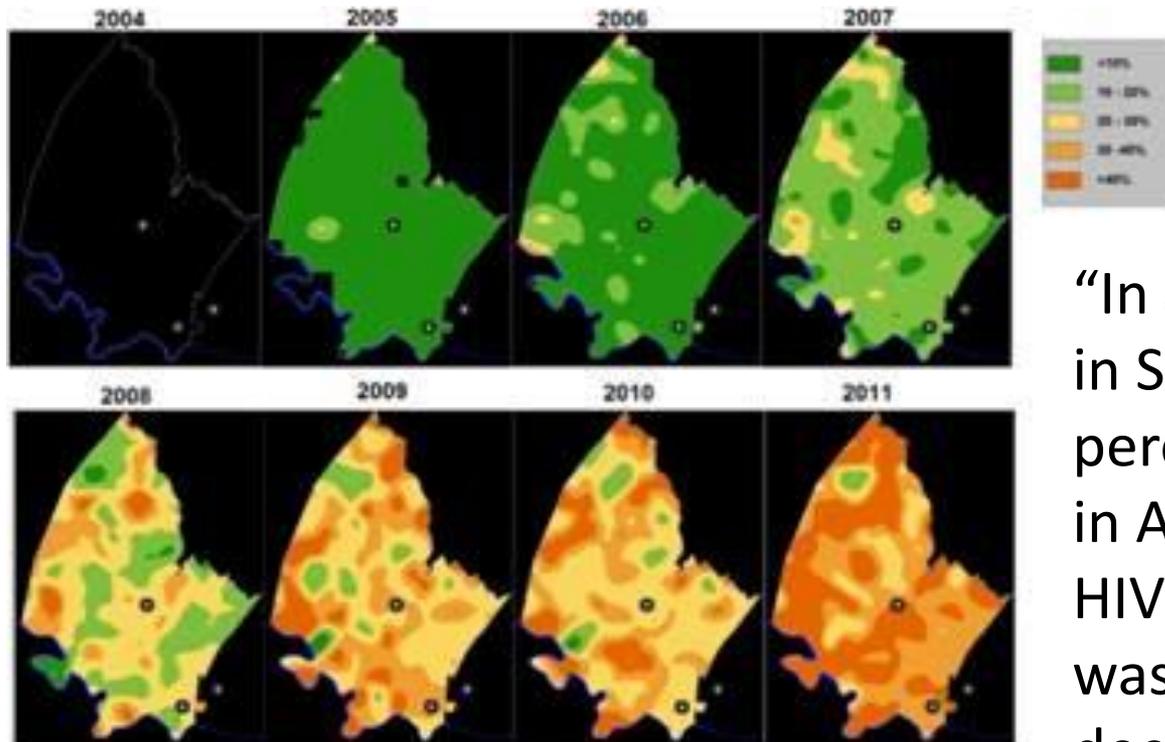


High-Level Cefixime- and Ceftriaxone-Resistant *Neisseria gonorrhoeae* in France: Novel *penA* Mosaic Allele in a Successful International Clone Causes Treatment Failure

Magnus Unemo,^a Daniel Golparian,^a Robert Nicholas,^b Makoto Ohnishi,^c Anne Gallay,^d and Patrice Sednaoui^b

**SO WHERE DOES THAT LEAVE
'TREATMENT AS PREVENTION' ?**

Treatment as Prevention: Community-Level Impact



“In a hyperendemic region in South Africa, every percentage point increase in ART coverage among all HIV⁺ adults in a community, was associated with a 1.7% decline in the hazard of HIV acquisition faced by an HIV⁻ adult living in the same community.”

The Concept of “Community Viral Load”

- In San Francisco, decreases in community viral load were accompanied by reductions in new HIV infections

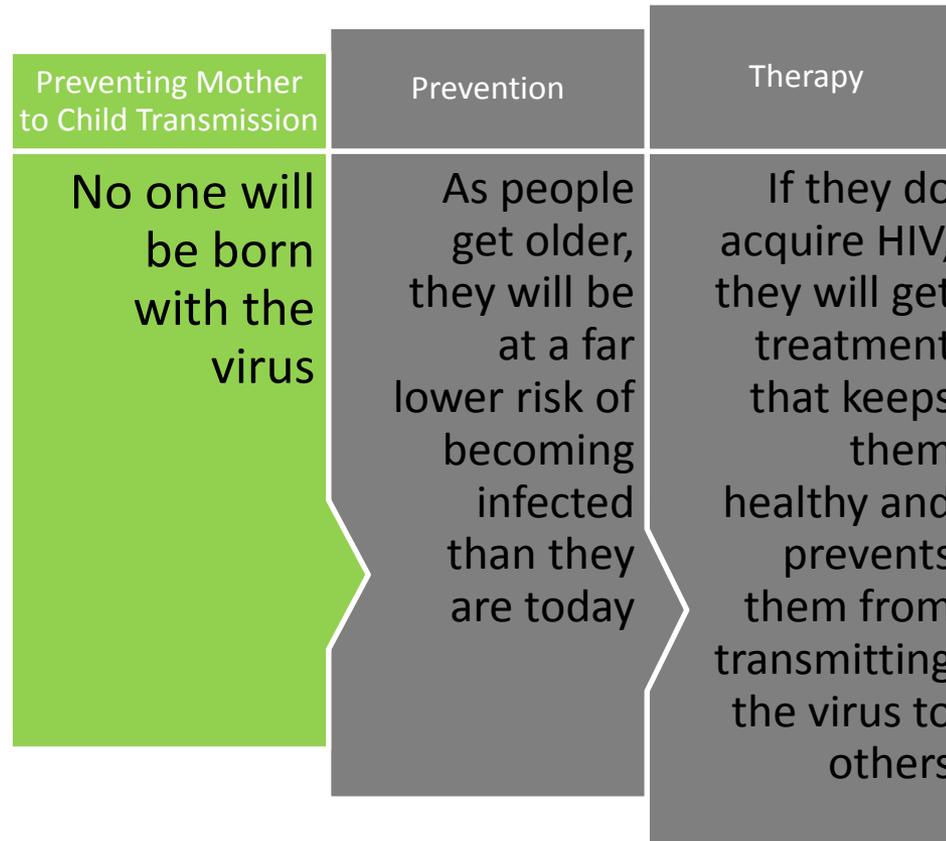
Das et al. PLOS One 5(6):e11068

- What are the challenges of this approach?

PH Reporting of CD4 Counts and Viral Loads

- 34 states mandate reporting of CD4 counts and HIV viral loads (including TX)

An AIDS-Free Generation



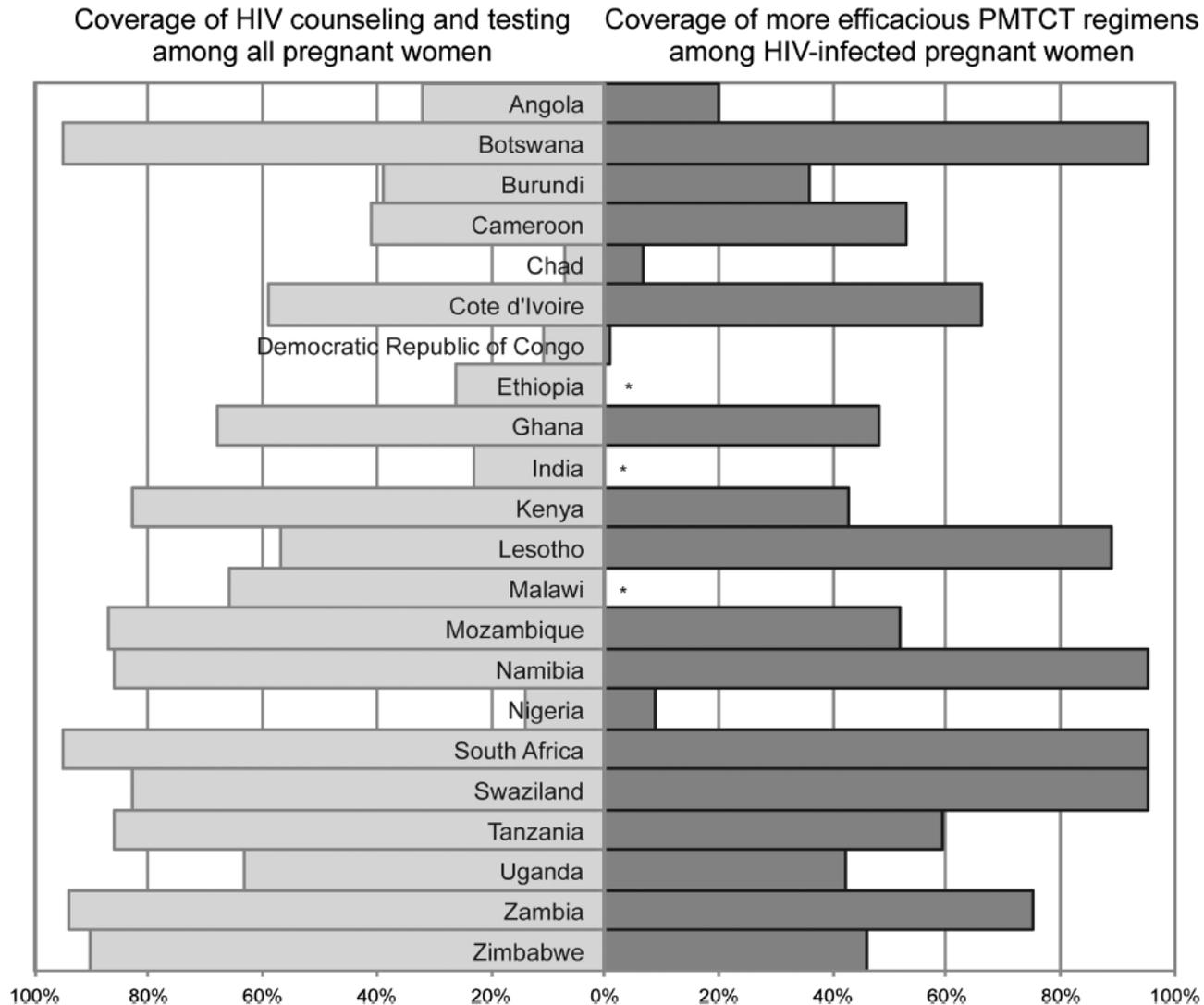
MTCT in the U.S.

- About 100–200 infants in the United States are infected with HIV annually. Many of these infections involve women who were not tested early enough in pregnancy or who did not receive prevention services
- Of the perinatally infected persons living with HIV/AIDS at the end of 2005, an estimated 66% were black (not Hispanic or Latino), and an estimated 20% were Hispanic/Latino

Preventing Mother to Child HIV Transmission

- Prevention of HIV infection among women of childbearing age
- Prevention of unintended pregnancies among those living with HIV
- Prevention of HIV transmission from infected mothers to their infants
- Treatment, care, and support for infected mothers and children
- Global Plan Toward Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive
- Co-led by UNAIDS and PEPFAR, this initiative seeks to reduce new pediatric infections by 90% and halve HIV-related maternal mortality by 2015

PMTCT in 22 High-Priority Countries

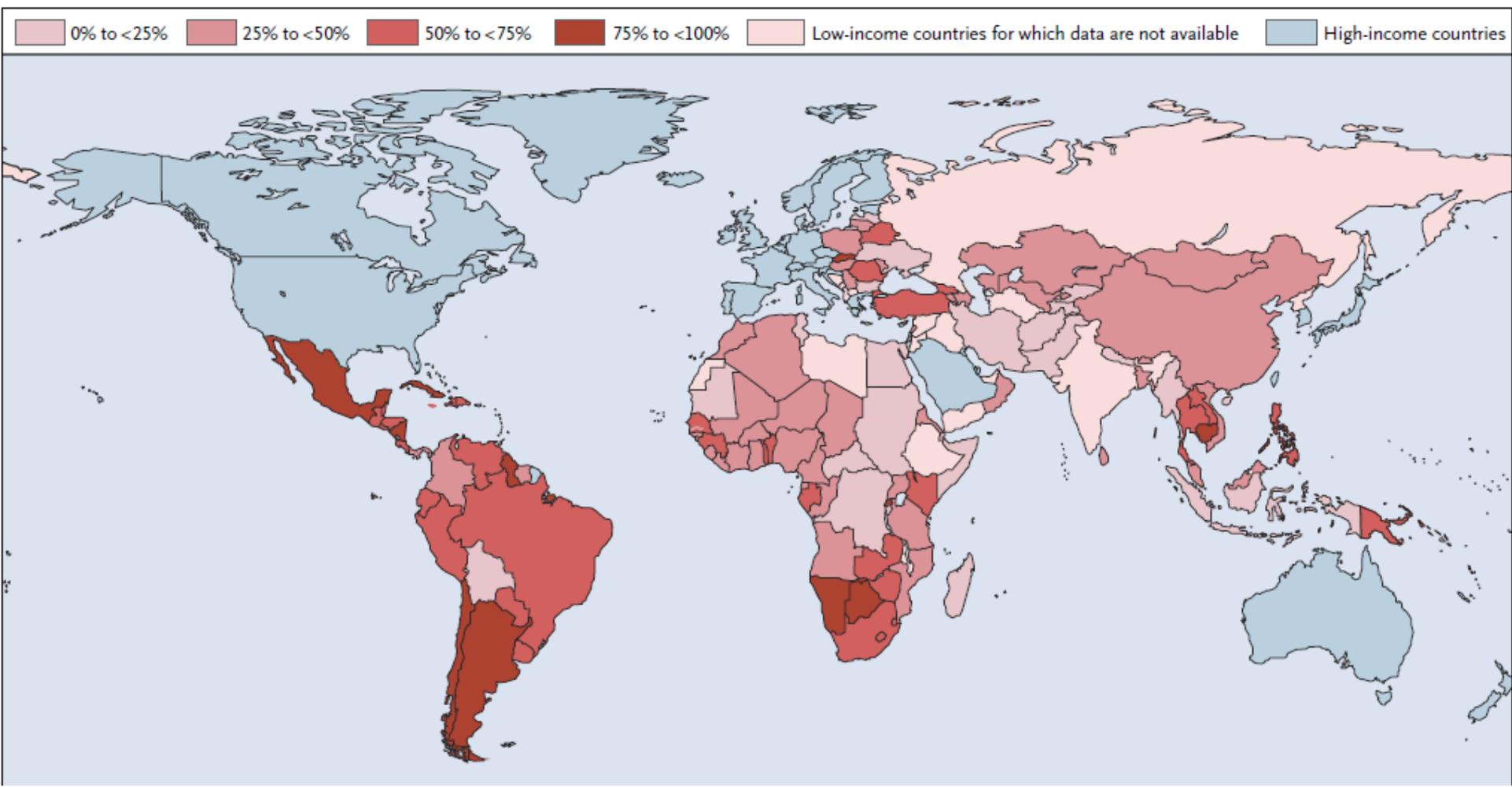


Estimated number of women living with HIV receiving the most effective antiretroviral regimens for preventing mother-to-child transmission and coverages with most effective regimens and with single dose nevirapine, low- and middle-income countries, by geographical region, 2010

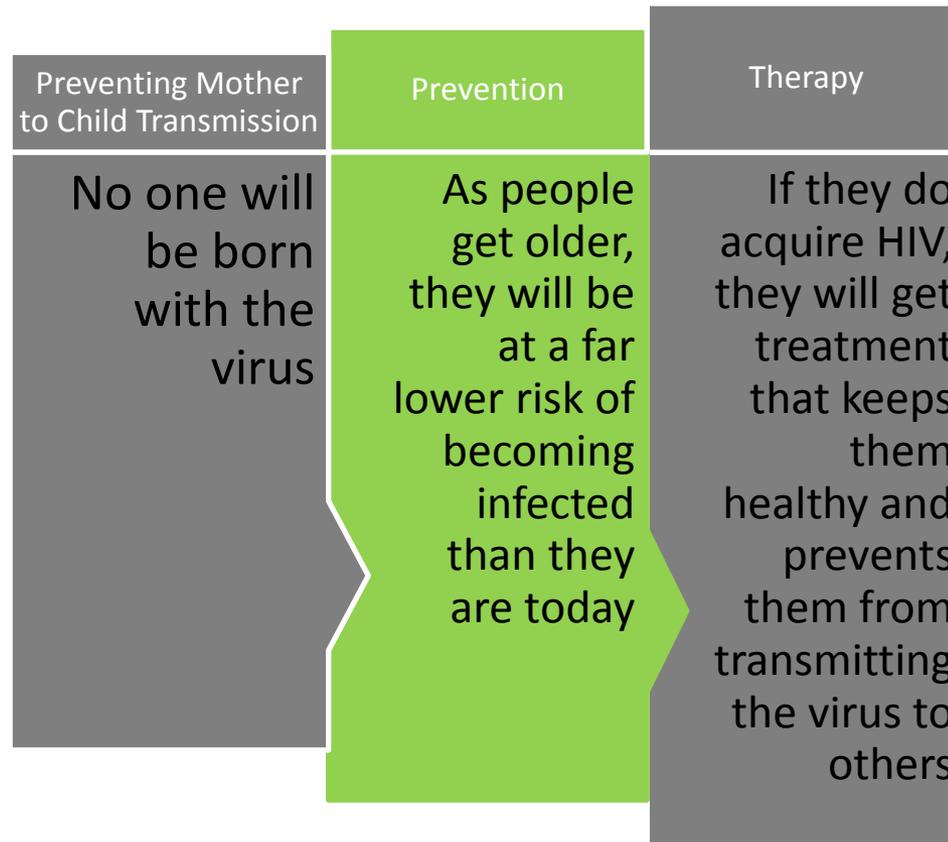
Preliminary update 2011: 57% of the estimated 1.5 million pregnant women living with HIV were receiving most effective regimens

Geographical region	Number of pregnant women living with HIV receiving the most effective antiretroviral regimens (excluding single-dose nevirapine) for preventing mother-to-child transmission	Estimated number of pregnant women living with HIV who need antiretroviral medicine for preventing mother-to-child transmission	Estimated coverage with the most effective regimens, as recommended by WHO	Estimated coverage with single-dose nevirapine only (regimen no longer recommended by WHO)
Sub-Saharan Africa	674 000	1 360 000 [1 200 000-1 500 000]	50% [45-56%]	10%
Eastern and southern Africa	600 700	940 000 [840 000-1 000 000]	64% [57-71%]	13%
Western and central Africa	73 300	410 000 [360 000-470 000]	18% [15-20%]	3%
Latin America and the Caribbean	15 000	25 600 [17 000-33 000]	59% [46-90%]	2%
Latin America	11 700	18 300 [11 000-25 000]	64% [47->95%]	2%
Caribbean	3 300	7 300 [5 900-9 000]	46% [37-57%]	3%
East, South and South-East Asia	12 200	73 800 [53 000-95 000]	16% [13-23%]	16%
Europe and Central Asia	14 700	18 600 [15 000-22 000]	79% [65-94%]	9%
North Africa and the Middle East	600	14 200 [9 900-19 000]	4% [3-6%]	3%
All low- and middle-income countries	716 500	1 490 000 [1 300 000-1 600 000]	48% [44-54%]	11%

Note: Some numbers do not add up because of rounding.



How do we Achieve an AIDS-Free Generation?



Definitions

Prevention: Measures taken to prevent diseases, (or injuries) rather than curing them or treating their symptoms

Biomedical intervention: a biological intervention that modifies a person's risk of acquiring a disease or condition in the future

Jeanne Marrazzo

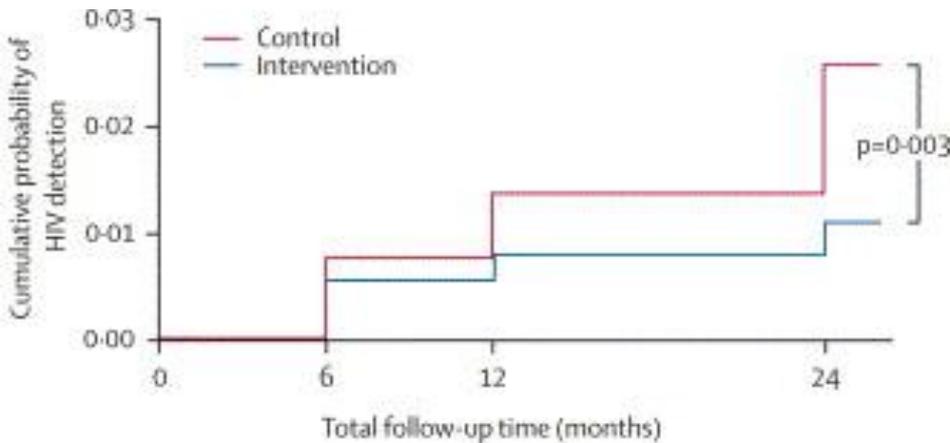
HIV Prevention

- Condoms

What makes a man use a condom?

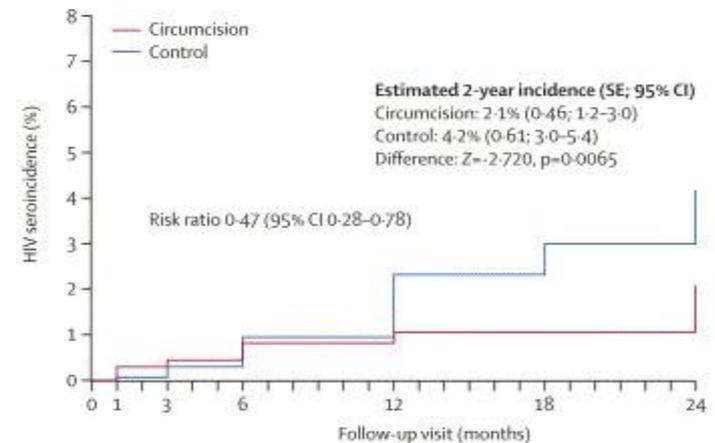
HIV Prevention: Circumcision

RCTs in Africa demonstrated that circumcision afforded a protection rate from acquisition of HIV ranging from 48%-60% in men



Cases of HIV/total participants

Intervention	0/2474	14/2387	5/2274	3/964
Control	0/2522	19/2430	14/2279	12/980



Circumcision (n=1391)

Number at risk	1367	1351	1323	1287	1029	764
Number HIV positive	4	2	5	3	0	8 (22 total)
Control (n=1393)	1380	1368	1350	1302	1035	740
Number HIV positive	1	3	9	18	7	9 (47 total)

Where are we with circumcision?

- WHO and UNAIDS recommend voluntary male circumcision particularly in settings with high prevalence of HIV and low prevalence of circumcision
- In the U.S., prevalence of HIV is relatively low, rates of circumcision are relatively high, and most infections occur in MSM
- AAP found that benefits of male circumcision outweigh the risks, but the benefits are not great enough to recommend universal male circumcision in the U.S.

PrEP: Pre-Exposure Prophylaxis

Study (location)	Population	n	PrEP agent	Status
CAPRISA 004 (South Africa)	Women	889	Tenofovir vaginal gel (coitally associated use)	39% reduction in HIV incidence
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, United States)	Men who have sex with men; transgender women	2,499	FTC/TDF	44% reduction in HIV incidence
FEM-PrEP (Kenya, South Africa, Tanzania)	Higher-risk women	2,120	FTC/TDF	Trial stopped early for lack of efficacy
TDF2 Study (Botswana)	Young heterosexual men and women	1,200	FTC/TDF	62% reduction in HIV incidence
Partners PrEP Study (Kenya, Uganda)	Heterosexual HIV-serodiscordant couples	4,758	TDF, FTC/TDF	67% reduction in HIV incidence for TDF 75% reduction in HIV incidence for FTC/TDF
VOICE (South Africa, Uganda, Zimbabwe)	Women	5,021	TDF, FTC/TDF, vaginal tenofovir gel (daily use)	Oral TDF and vaginal tenofovir gel arms stopped early for lack of efficacy, FTC/TDF arm results expected early 2013
Bangkok Tenofovir Study (Thailand)	Injection drug users	2,400	TDF	Ongoing, results expected late 2012
FACTS 001 (South Africa)	Women	2,600	Vaginal tenofovir gel (coitally associated use)	Initiated October 2011

Any Way to Enhance Adherence for PrEP?



Andrew Loxely

Phase III study that seeks to determine whether a vaginal ring containing the antiretroviral drug dapivirine is a safe and effective method for protecting against the sexual transmission of HIV when used by women for a month at a time.

The study, which was launched in August 2012, will enroll approximately 3,476 women at several sites in Africa and take approximately two years to conduct, with results anticipated late 2014 or early 2015.

Post-Exposure HIV Prophylaxis (PEP)

Exposure type	Status of source patient	PEP recommended	
		EACS	CDC
Blood			
More severe (intravascular device, deep puncture, visible blood on device, or large-bore hollow needle)	HIV ⁺	Yes (3 drugs)	Yes (3 drugs)
	Unknown but HIV risk factors	Yes (3 drugs)	To be considered (2 drugs)
	HIV ⁻	No	No
Less severe (superficial injury, solid needle, im. or sc. needle)	HIV ⁺	Yes (3 drugs)	Yes (2 or 3 drugs)
	Unknown but HIV risk factors	No	To be considered (2 drugs)
	HIV ⁻	No	No
Nonintact skin or mucous membrane >15 min	HIV ⁺	Yes (3 drugs)	Yes (2 or 3 drugs)
	Unknown but HIV risk factors	No	To be considered in case of large volume exposure (2 drugs)
	HIV ⁻	No	No
Sexual			
Anal or vaginal sex	HIV ⁺	Yes (3 drugs)	Yes
	Unknown but HIV risk factors	Yes (3 drugs)	Case-by-case determination
	HIV ⁻	No	No
Receptive oral sex with ejaculation	HIV ⁺	Yes (3 drugs)	Yes
	Unknown but HIV risk factors	No	Case-by-case determination
	HIV ⁻	No	No
Intravenous drug use			
Exchange of syringe, needle, preparation material, or any other material	HIV ⁺	Yes (3 drugs)	?

Type of exposure [†]	Risk per 1000 exposures to an infected source
Needle-sharing injection-drug use	6.7
Receptive anal intercourse	5
Percutaneous needle exposure	3
Receptive vaginal intercourse	1
Mucous membrane exposure	0.9
Insertive anal intercourse	0.65
Insertive vaginal intercourse	0.5
Receptive oral intercourse	0.1
Insertive oral intercourse	0.05

AIDS-Free Generation

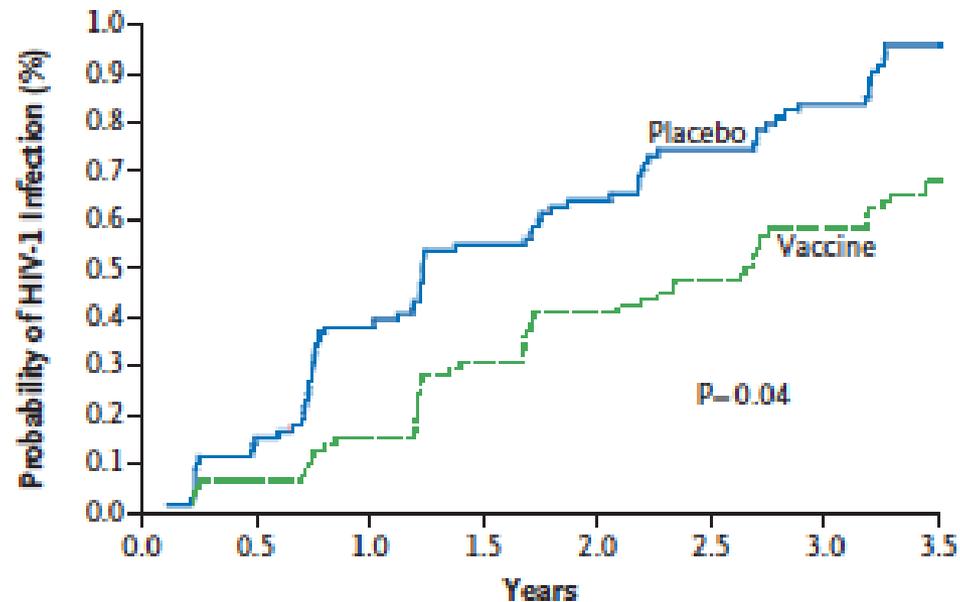
- PrEP
 - PEP
 - ART as prevention
-
- Are we going to be able to treat ourselves out of this epidemic?

The End of AIDS

VS.

The End of HIV

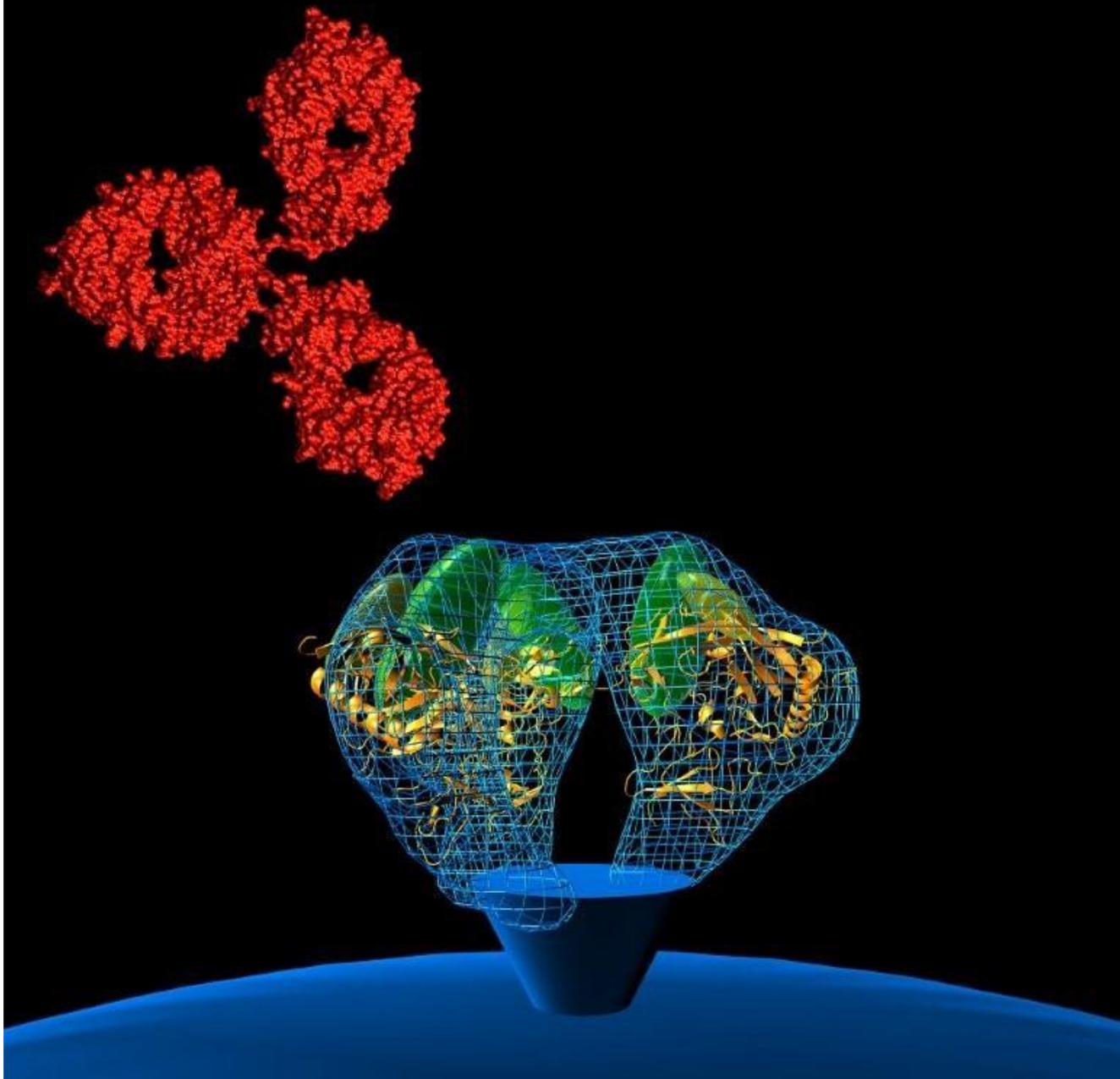
What About a Vaccine?



No. at Risk					
Placebo	8198	7775	7643	7441	7325
Vaccine	8197	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		30	50	65	74
Vaccine		12	32	45	51

Vaccine Update

- Subjects whose blood contained an antibody that recognizes a portion of a HIV's outer envelope called the V2 loop were 43 percent less likely to become infected with HIV than subjects whose immune systems did not make these antibodies
- Participants who churned out another kind of antibody, called IgA, that recognizes different parts of the HIV envelope were 54 percent more likely to become infected than people who did not make these antibodies



Two newly discovered broadly neutralizing antibodies, called PG9 and PG16, are the first to have been identified in more than a decade.

Approaches to Curing HIV

- Sterilizing Cure Model: The Berlin Patient
- Functional Cure Model: The Elite Controllers
- Multipronged Approaches
 - Purging the viral reservoir
 - Improve host immune responses
 - Gene therapy (to make uninfected host cells resistant to therapy)

Steps that Could Lead to a Cure

Determine the cellular and viral mechanisms that maintain HIV persistence. This includes defining the role of mechanisms that contribute to the establishment and maintenance of latent infection, as well as defining the role of viral replication and or homeostatic proliferation.

Determine the tissue and cellular sources of persistent HIV in long term ART-treated individuals.

Determine the origins of immune activation and inflammation in the presence of ART and their consequences for HIV persistence.

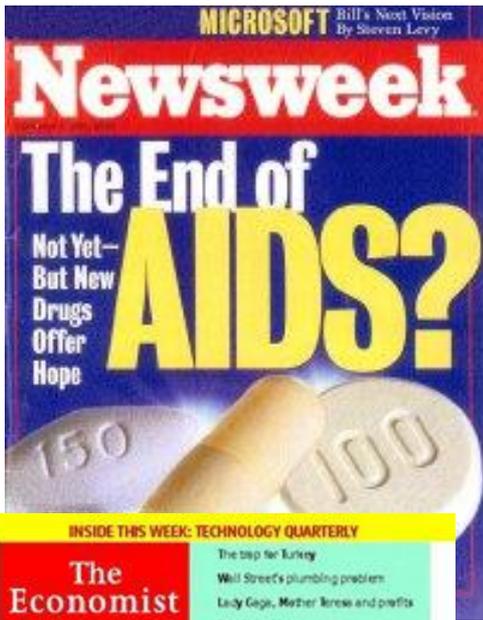
Determine host and immune mechanisms that control infection but allow viral persistence.

Study, compare, and validate assays to measure persistent infection.

Develop and test therapeutic agents or immunological strategies to safely eliminate latent infection in individuals on ART. This includes strategies aimed at clearing latency.

Develop and test strategies to enhance the capacity of the host response to control active viral replication.

The Hope



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Perspective
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The Beginning of the End of AIDS?
Diane Havlir, M.D., and Chris Beyrer, M.D., M.P.H.

