Antiretrovirals for the Prevention of HIV infection: where are we in 2011?

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Prevention goes Biological

Behavioral interventions

- Until recently HIV prevention was based primarily on behavioral interventions.
- However, there is no RCT that has shown that any behavioral intervention can reduce HIV incidence although many have shown reductions in self-reported risk behavior on in surrogate markers like STIs.

Biomedical HIV Prevention

- Vaccines – Thai RV144
- Microbicides – Caprisa 004
- Antiretrovirals for prevention:
  - PrEP – iPrEX, FEM-PrEP; Partners PrEP & TDF-2 (VOICE?)
  - HPTN 052
  - Test and Treat – HPTN 065

Antiretrovirals for prevention

1. Before exposure: PrEP
2. Treatment of infection

Viral Load and HIV Transmission

- In individuals, suppressing HIV viral load reduces perinatal transmission

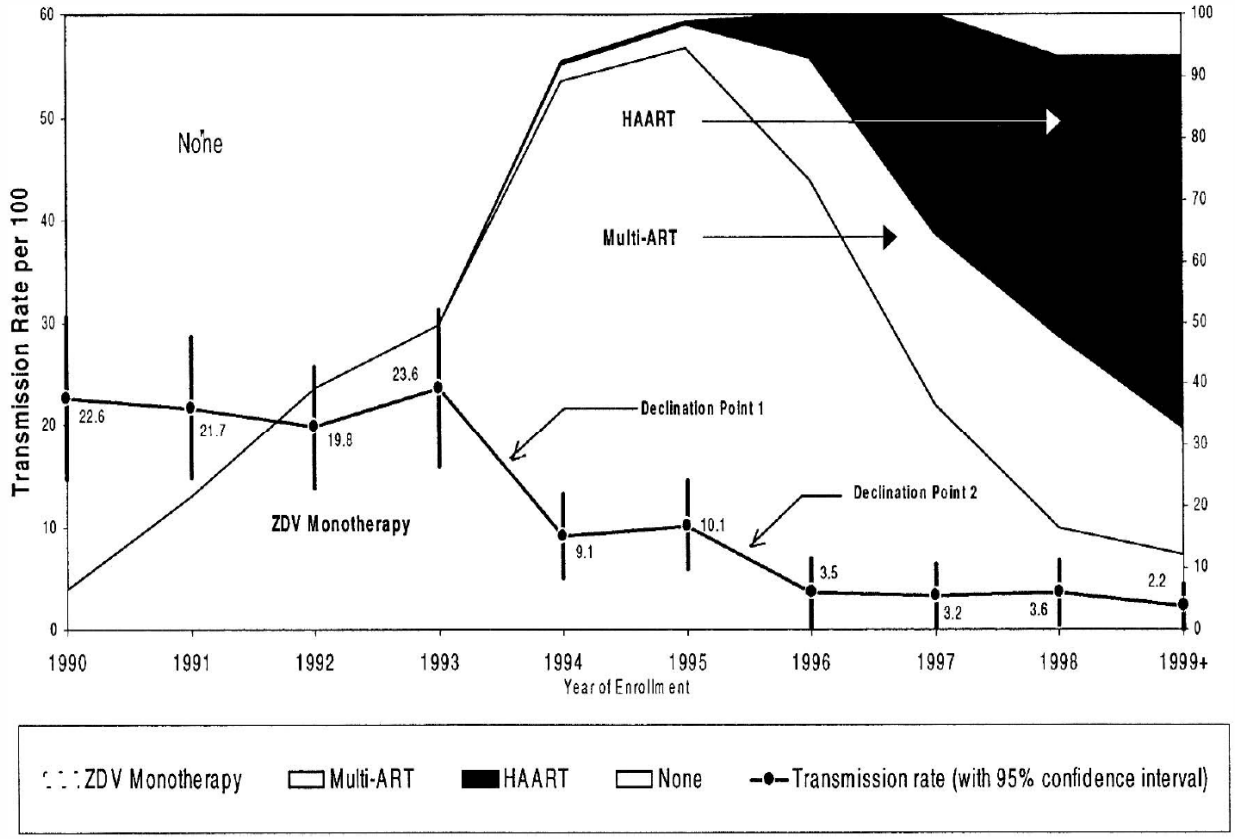


FIG. 1. Trends in mother-to-infant transmission rate and maternal antiretroviral therapy: 1990–1999+ (Women and Infants Transmission Study Group). Rates per 100 (95% confidence interval).

iPrEx

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 30, 2010 VOL. 363 NO. 27

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S.,

Conclusions:

- 44% reduction in the incidence of HIV
- If pill use $\geq$90%, 73% reduction in incidence of HIV
- Risk compensation was not observed in either treatment group.

Challenges for PrEP

- Intervention may be less effective in real world vs. clinical trial setting
- Potential for behavioral impact (disinhibition)
- Risk of resistance development in HIV+ individuals
- Risk of hepatic flares in HBV-infected individuals
- High cost relative to other prevention interventions; potential reimbursement barriers?
- Challenge of delivering appropriate education to healthcare providers and target populations; who will be prescribing it?
- Need to ensure no impact of ease of access to medication for HIV+ individuals

ART for Prevention: Discordant Couples

- Evaluate effect of ART on HIV transmission among HIV serodiscordant, heterosexual couples (2993)

- ARV only if clinically indicated, negative partner tested q3 mo.
  - Not on ARV: 171 linked infections (3.4/100 CY)
  - On ARV: 4 linked infections (0.7/100 CY)
  - Sexual risk behavior lower in those on ARV (19% vs 25%; $p < 0.05$)

  - Both ART and change in behavior independently reduced HIV transmission

Sullivan P, et al. CROI 2009; Abst# 52bLb

ART for Prevention: Discordant Couples

ART in HIV+ve partner	Linked Transmission	Person-years of follow up	HIV sero-incidence
Post ART initiation	1	256	0.39 (95% CI: 0.09-2.18)
No ART	102	4851	2.23 (95% CI: 1.84-2.70)

Donnell et al CROI 2010, session 40 # 136 & Lancet May 2010

Extending ART for prevention: clinical trial evaluation of strategy

HPTN HIV Prevention Trials Network

HPTN 052

A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 in Serodiscordant Couples

What is HPTN 052?

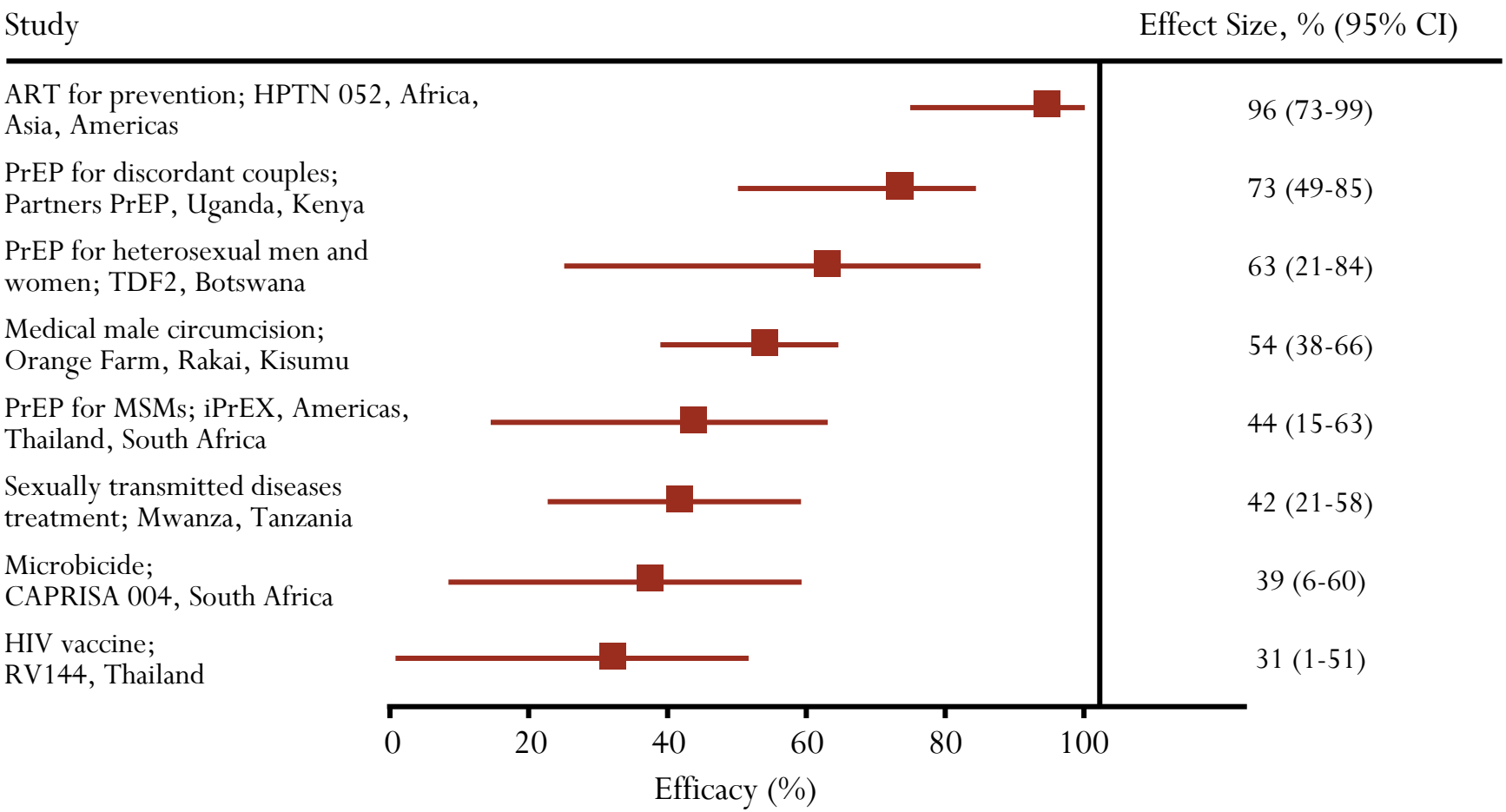
HPTN 052 is a Phase III, two-arm, multi-site, randomized trial to determine the effectiveness of two treatment strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples.

Based on data collected in Africa and Thailand, there is a correlation between HIV viral load (blood levels) and HIV transmission. Specifically, the higher the viral load in the blood, the more likely the chance for transmission. Antiretroviral therapy (ART) reduces the viral load in the blood, as well as in genital secretions (for both men and women), and the drugs can be detected in semen and vaginal and cervical secretions. All of this information strongly suggests that ART may make HIV-infected people less contagious. HPTN 052 compares the HIV–infection rates of two groups of HIV-serodiscordant couples. The index case of the first group starts taking ART as soon as the couple is enrolled in the study, while the index case of the second group starts taking ART when he or she has two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm^3, or when he or she develops an AIDS-defining illness. Both groups will receive HIV primary care and couples counseling sessions to teach them how to reduce their risk of transmission.

HPTN 052

- DSMB interim analysis
- 1763 HIV serodiscordant couples (97% heterosexual)
- CD4 counts 350 – 550 cells/uL
- Randomized to ART or defer ART until CD4 < 250 cells/uL
- At the time of DSMB review: 39 cases of HIV infection with 28 confirmed as genetically linked
  - 27 among couples not on ART
  - 1 among couples on ART
- Thus 96% reduction in transmission with ART!

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials



Abdool Karim SS, et al. Lancet. 2011;[Epub ahead of print].

Extending ART for prevention: mathematical modeling impact

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

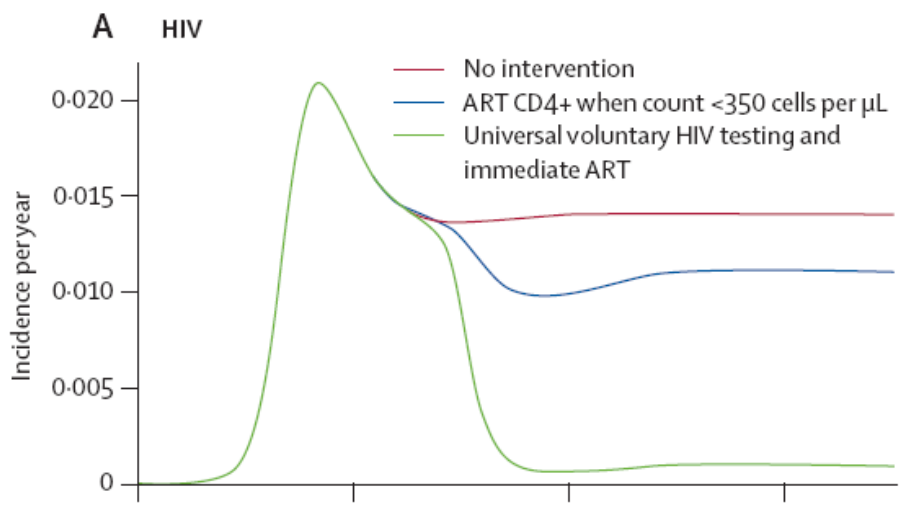
Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams

Summary

Background Roughly 3 million people worldwide were receiving antiretroviral therapy (ART) at the end of 2007, but an estimated 6·7 million were still in need of treatment and a further 2·7 million became infected with HIV in 2007. Prevention efforts might reduce HIV incidence but are unlikely to eliminate this disease. We investigated a theoretical strategy of uni litions under which the HIV

Methods We u c model) and long-term dyn our test-case community (a after they are diagnosed HI nd assumed that all HIV tr

Findings The s which most adults living w in 5 years. It could reduce I thin 10 years of full implem We estimate that in 2032, th ion; however, after this time tical strategy would decreas



Testing and Transmission

Expand testing to as many as possible :

- People who know their status less likely to engage in high risk behavior
- Those found to be HIV infected can then be treated reducing their HIV viral load

Testing and Transmission

- Couples Counseling and Testing is now more important than ever
- Discordant couples: Unprotected sex is high
- In Thailand, 74 % of incident infections in married discordant couples.
- In US, 68% of HIV among MSM: unprotected sex with main partners
- In Kenya, 84% don't know status: Of those infected with HIV, 75% had unprotected sex with partner of unknown or negative status
- Unsafe sex higher in those not knowing status

Burnell, CROI 2010, Mwangi et al , CROI 2010

Can antiretrovirals decrease transmission at a population level?

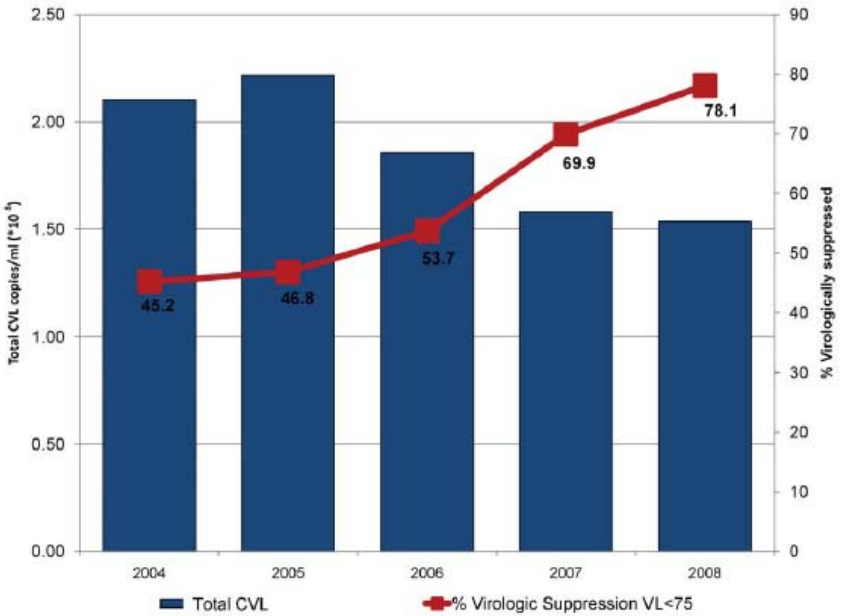
MSM: Increased ART options and coverage, increasing status awareness associated with decreased community VL and new infections- San Francisco from 2004 to 2008

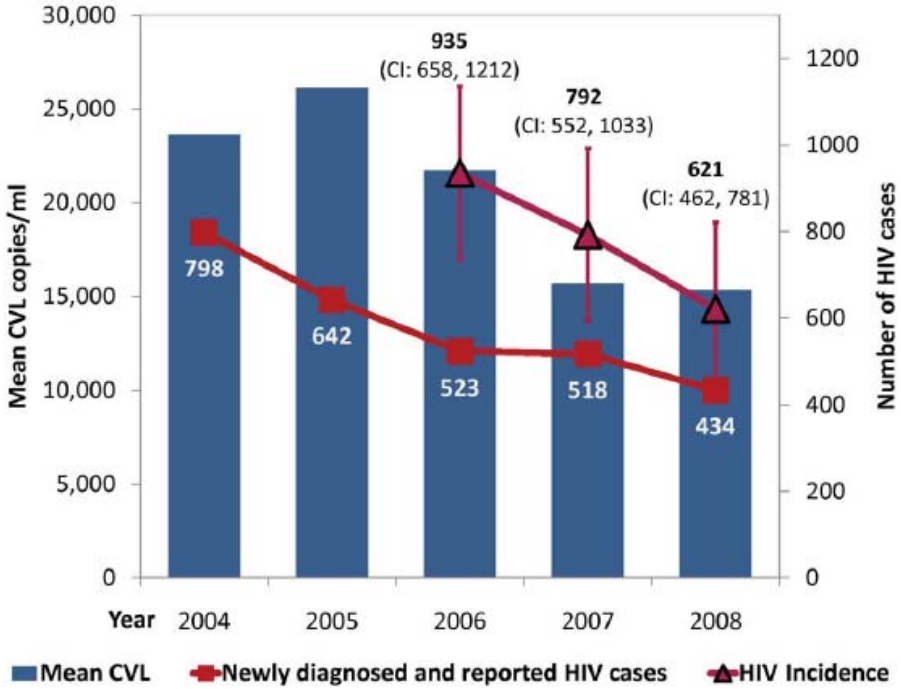
Das-Douglas et al, CROI 2010, Session 10 # 33

Decreases in Community Viral Load Are Accompanied by Reductions in New HIV Infections in San Francisco

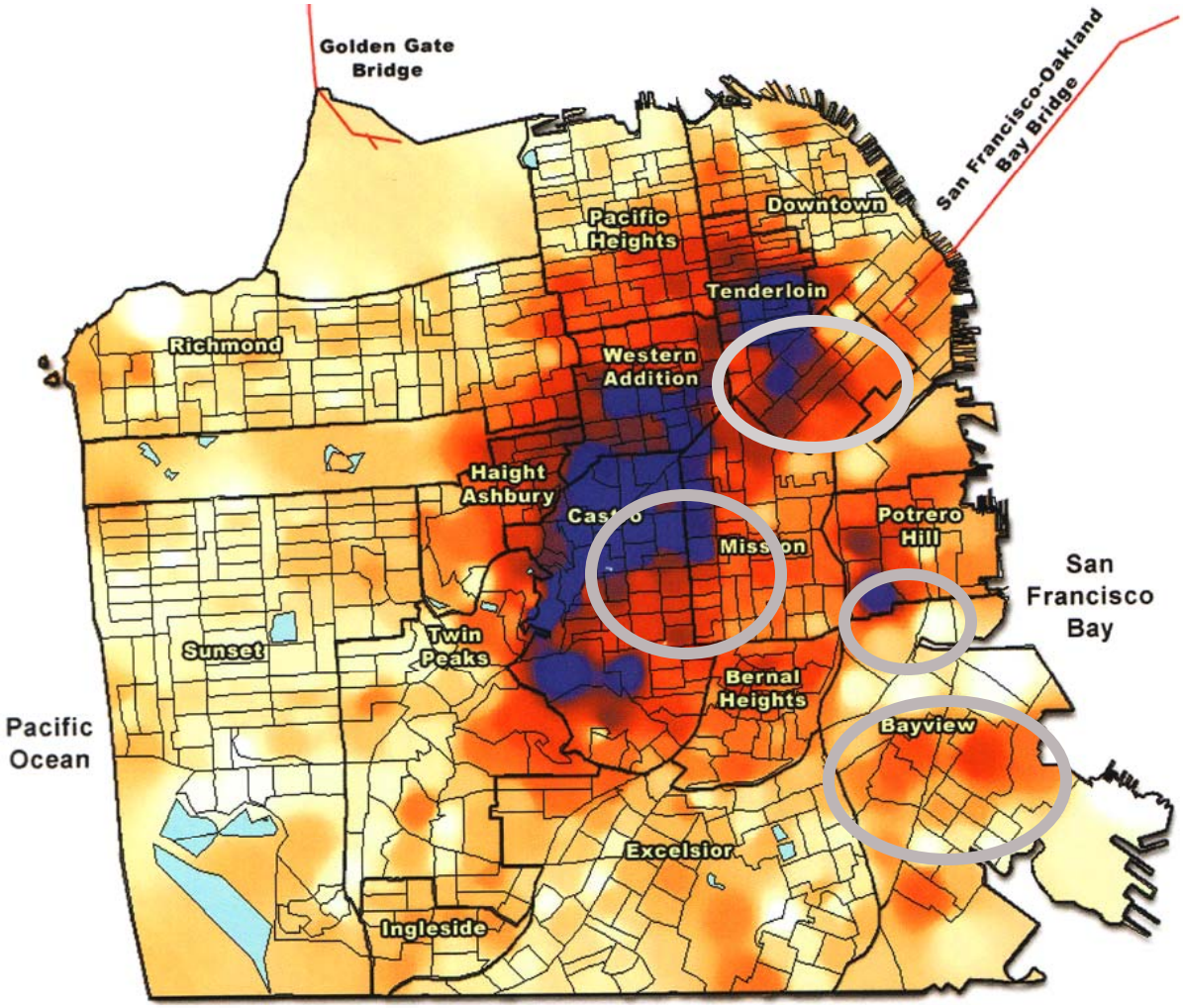
Moupali Das[1,2]*, Priscilla Lee Chu[1], Glenn-Milo Santos[1], Susan Scheer[1], Eric Vittinghoff[2], Willi McFarland[1,2], Grant N. Colfax[1,2]

1 San Francisco Department of Public Health, San Francisco, California, United States of America, **2** University of California San Francisco, San Francisco, California, United States of America



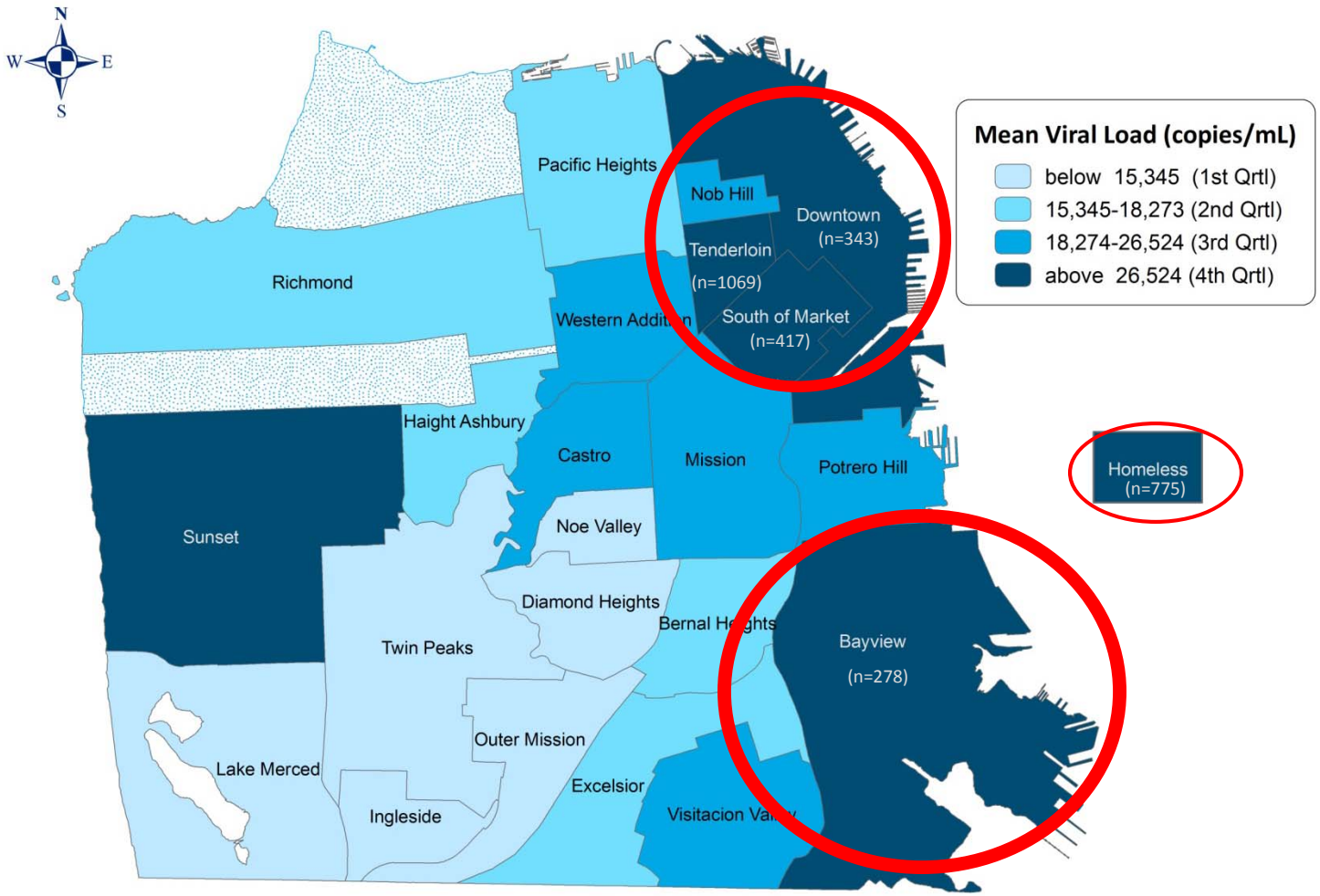


Spatial distribution of AIDS in San Francisco



2000
N=22,830

Spatial Distribution of Mean CVL by Neighborhood, 2005-2008



Homeless persons had the highest mean viral load (38,974 copies/mL.)

Can antiretrovirals decrease transmission at a population level?

Expanded HAART coverage associated with decrease in New HIV diagnosis, particularly in IDU in British Columbia.

Number of individuals on HAART increased from 2500 to 5000 from 2004 to 2009

50% decrease in new HIV diagnosis in IDU

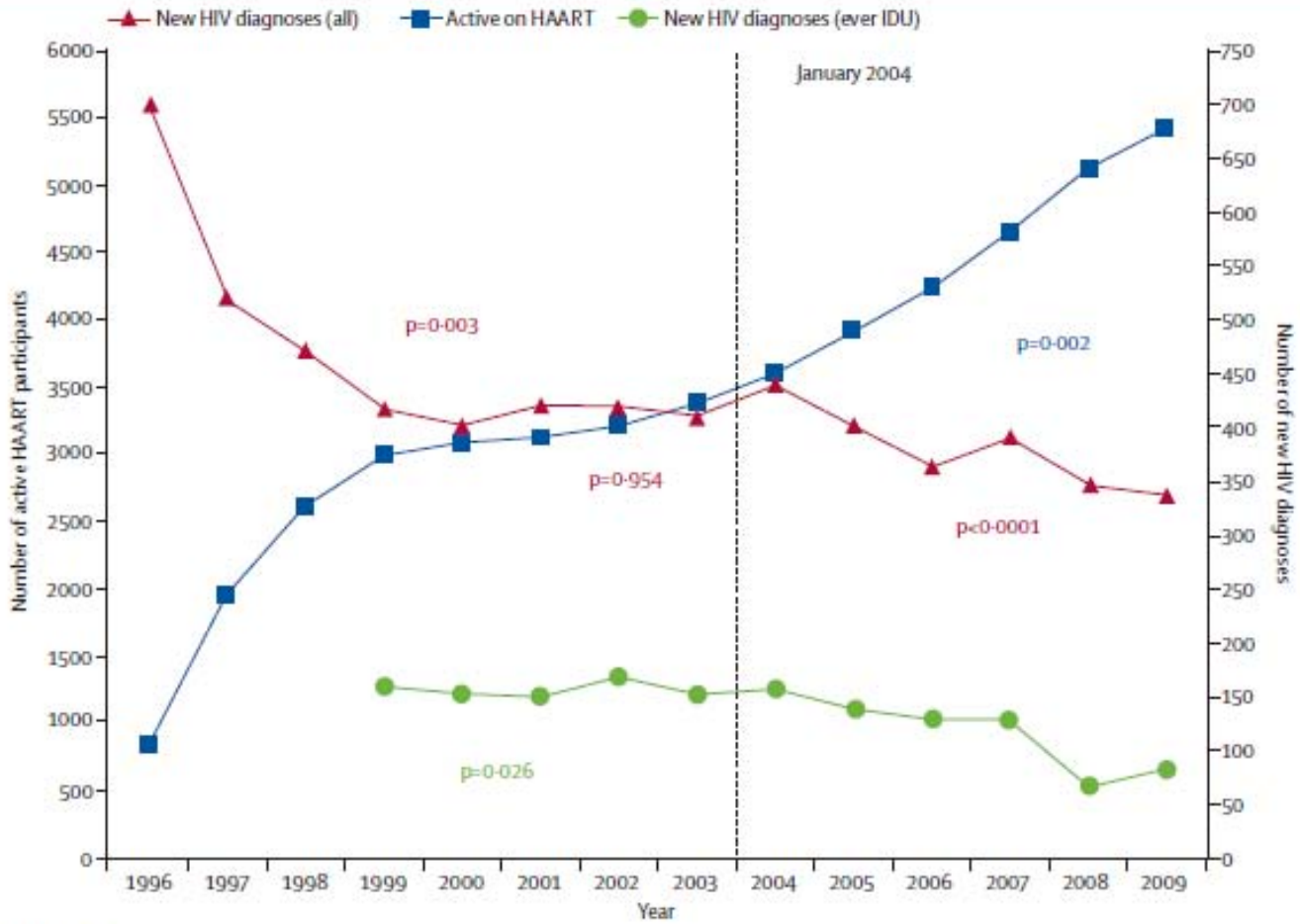
Proportion of HIV infected IDU with VL >1500 copies/mL decreased from 50% to 20%

Montaner et al, CROI 2010, Session 24 # 88LB

Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study

Julio S G Montaner, Viviane D Lima, Rolando Barrios, Benita Yip, Evan Wood, Thomas Kerr, Kate Shannon, P Richard Harrigan, Robert S Hogg, Patricia Daly, Perry Kendall

www.thelancet.com Published online July 18, 2010 DOI:10.1016/S0140-6736(10)60936-1

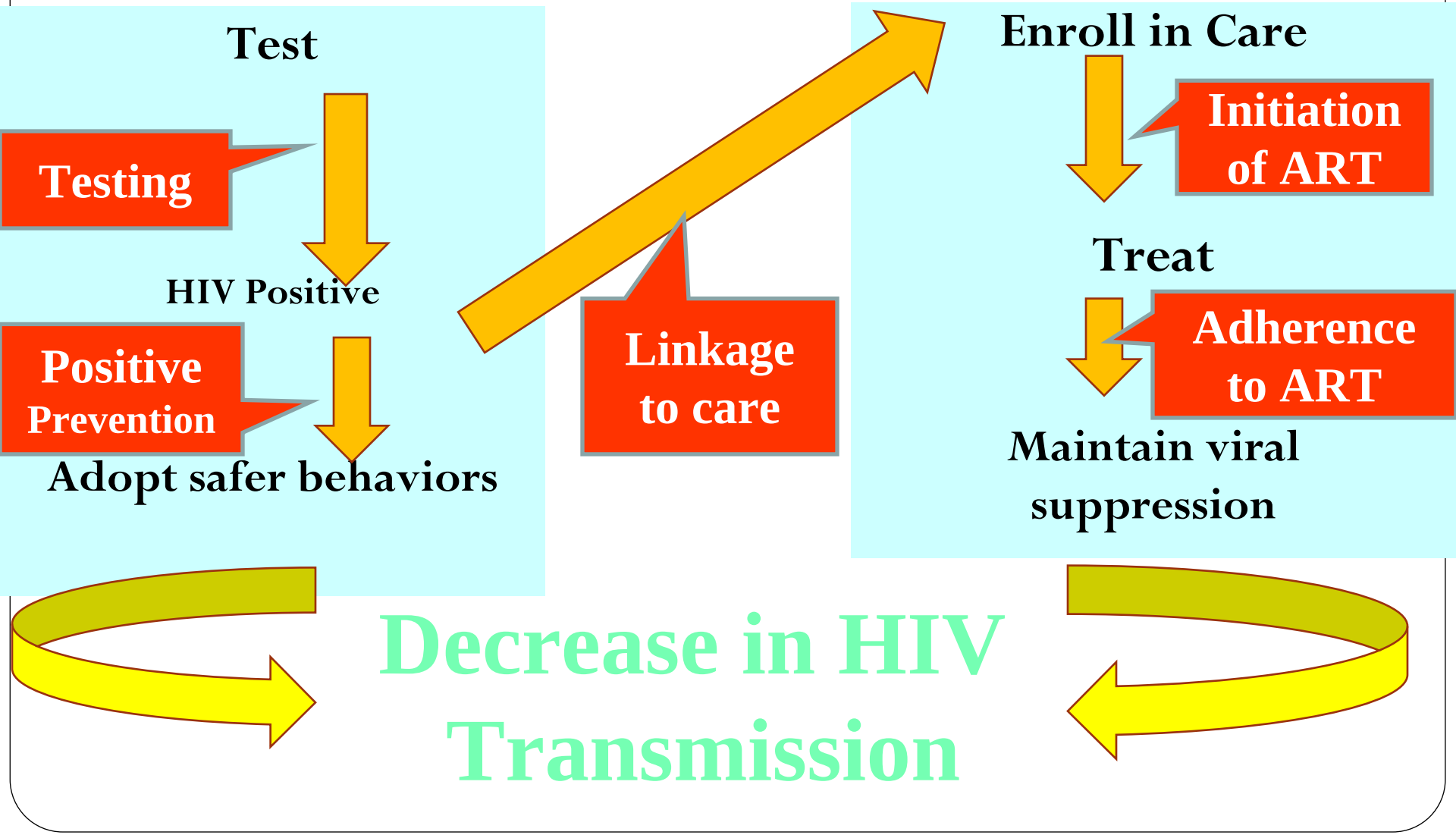


Number at risk	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Active on HAART	837	1960	2597	2994	3079	3120	3211	3356	3585	3913	4255	4654	5123	5413
New HIV diagnoses (all)	702	519	471	416	400	420	418	408	441	400	361	391	346	338
New HIV diagnoses (ever IDU)	NA	NA	NA	159	152	149	168	149	156	137	128	128	65	80
HIV tests done in BC (per 1000)	138	140	137	135	135	135	145	142	154	161	172	176	182	NA

Figure 1: **Number of active HAART participants and number of new HIV diagnoses per year in British Columbia, Canada, 1996–2009**
p values are for trend and were obtained from the generalised additive model. Injecting drug user (IDU) refers to individuals who have ever injected illicit drugs. HAART=highly active antiretroviral therapy. BC=British Columbia. NA=not available.

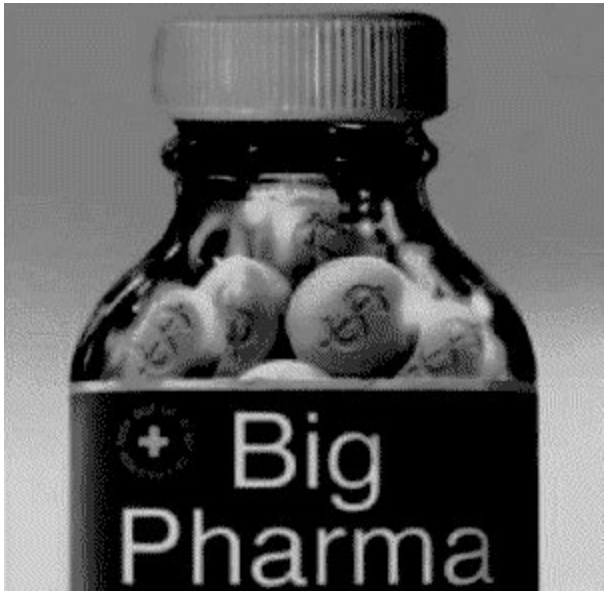
www.thelancet.com Published online July 18, 2010 DOI:10.1016/S0140-6736(10)60936-1

HPTN 065 (TLC Plus): Testing, Linkage to Care, Plus Treatment



POZ

"Medical Ethics and the Rights of People with HIV Under Assault" by Sean Strub



"Going too far to battle AIDS
Drug experiment on blacks looms in Washington" by Terry Michael Washington Post March 17 2010

Controversies

JAMA®

1998

Treat HIV-1 Infection Like Other Infections—Treat It

Bruce D. Walker, MD; Nesli Basgoz, MD

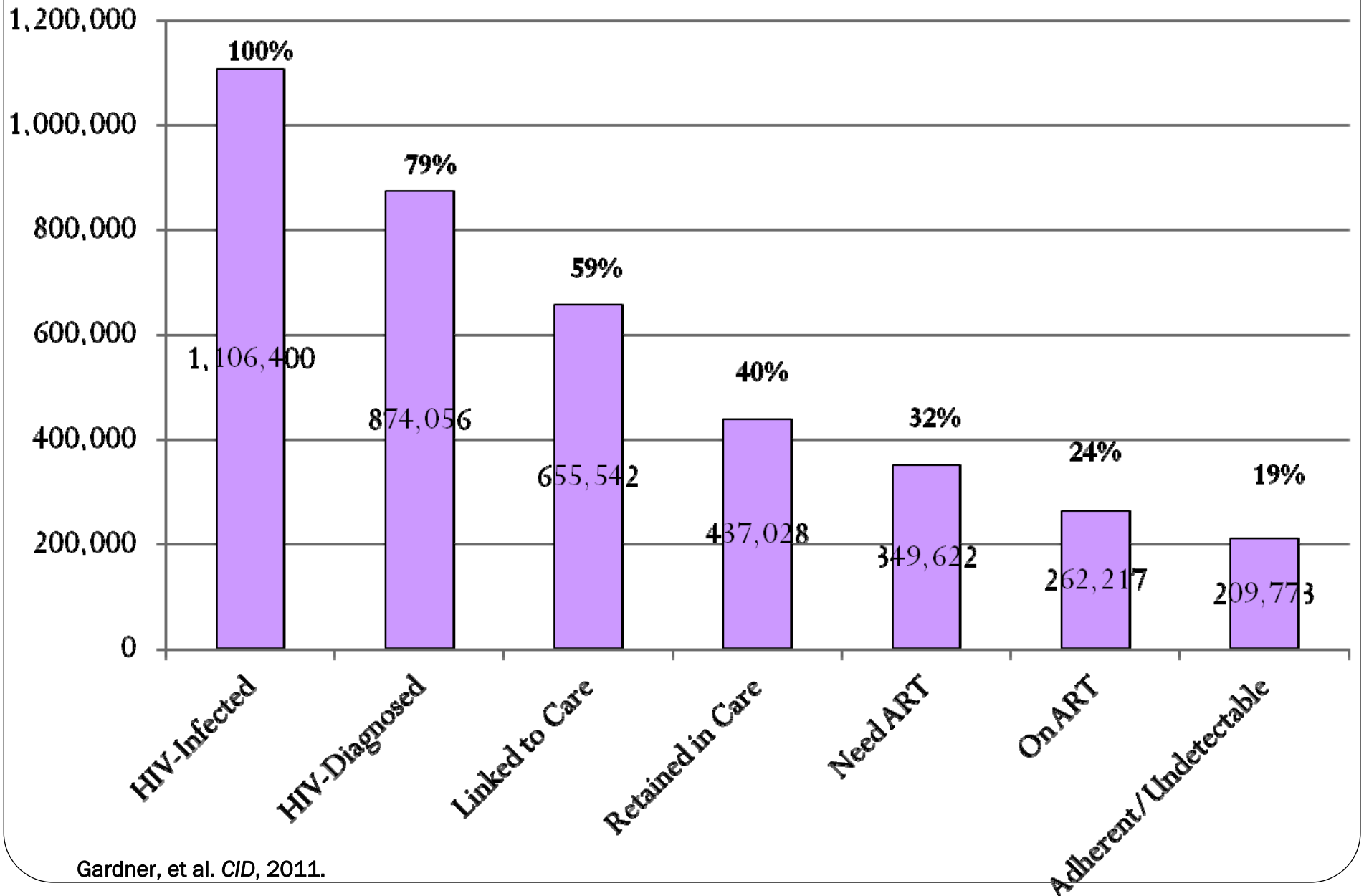
The spectrum of engagement in care

Not in HIV Care ⟷ Engaged in HIV Care

Unaware of HIV infection	Aware of HIV infection (not in care)	Receiving some medical care but not HIV care	Entered HIV care but lost to follow-up	Cyclical or intermittent user of HIV care	Fully engaged in HIV care

Eldred, *AIDS Patient Care and STD* 2007; 21 (suppl1)

Major Gaps in the Implementation Cascade



Gardner, et al. *CID*, 2011.

Not just TnT: Comprehensive Multi-level Highly Active HIV Prevention

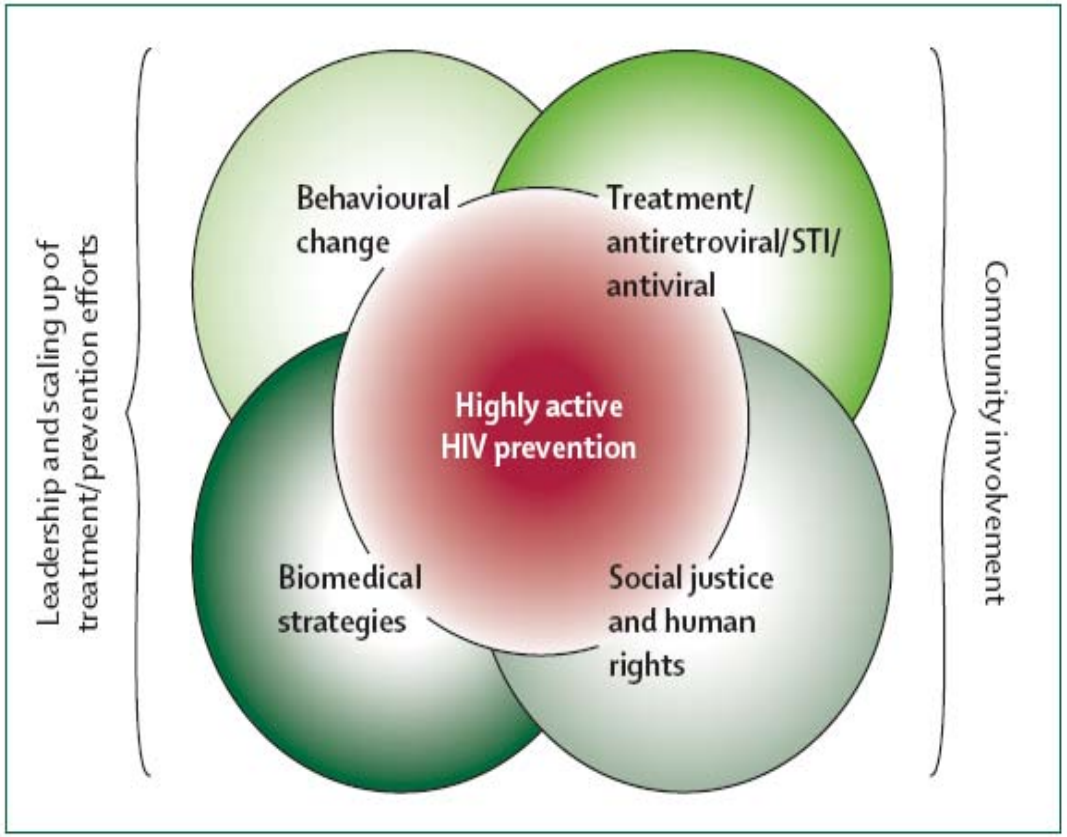


Figure 1: **Highly active HIV prevention**
This term was coined by Prof K Holmes, University of Washington School of Medicine, Seattle, WA, USA.[5] STI=sexually transmitted infections.

Coates, *Lancet*, 2008

Treatment is Prevention

Science AAAS

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women
Quarraisha Abdool Karim, *et al.*
Science **329**, 1168 (2010);
DOI: 10.1126/science.1193748

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 30, 2010 VOL. 363 NO. 27

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

The NEW ENGLAND JOURNAL of MEDICINE

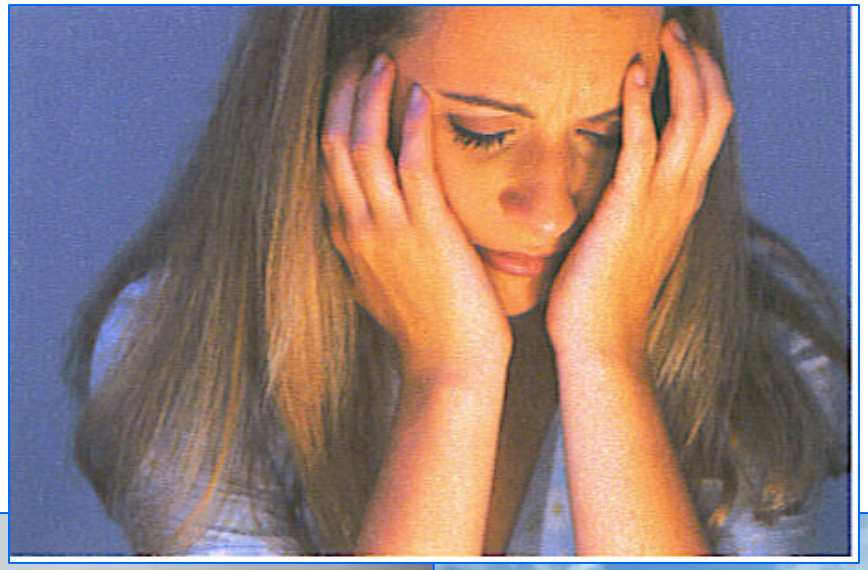
ESTABLISHED IN 1812 AUGUST 11, 2011 VOL. 365 NO. 6

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

But not all prevention is treatment…

Substance Use Treatment is Prevention

Mental Health Treatment is Prevention



Housing is Prevention

Food Security is Prevention

Conclusions:

- HPTN 052 is a "game changer" study and offers tremendous opportunities to really impact the HIV epidemic in the US and abroad.
- With 96% reduction in risk of transmitting HIV and 40% reduction in risk of clinical events there are advantages to early therapy to both the individual and society.
- The epidemic in the US has changed dramatically, most new infections are now among young African-American MSM's.
  - How do we find them?; get them HIV tested and linked to care and prevention services?
- iPrEx results are encouraging and PrEP for high risk MSM need to be tested and found before they are infected so they can be offered PrEP.

Policy implications:

- Need to scale up HIV testing including couples testing.
- Diagnosing HIV infection at a higher CD4 count should be a priority (current median CD4 at diagnosis in the US is 317 cells/ul).
- Case management at the time of diagnosis to ensure linkage to care is paramount.
- DHHS treatment guidelines should reflect the study findings and CD4 guided for "when to start" should be less important.
- Availability of antiretroviral therapy for those who need it should not be a problem (ADAP waiting lists should end).
- Engagement and retention into care must be priorities in all HIV clinical settings.
- Mental health and substance abuse treatment should be part of comprehensive HIV care.

“The arc of the moral universe in long but it bends toward justice.”

Martin Luther King, 1929-1968