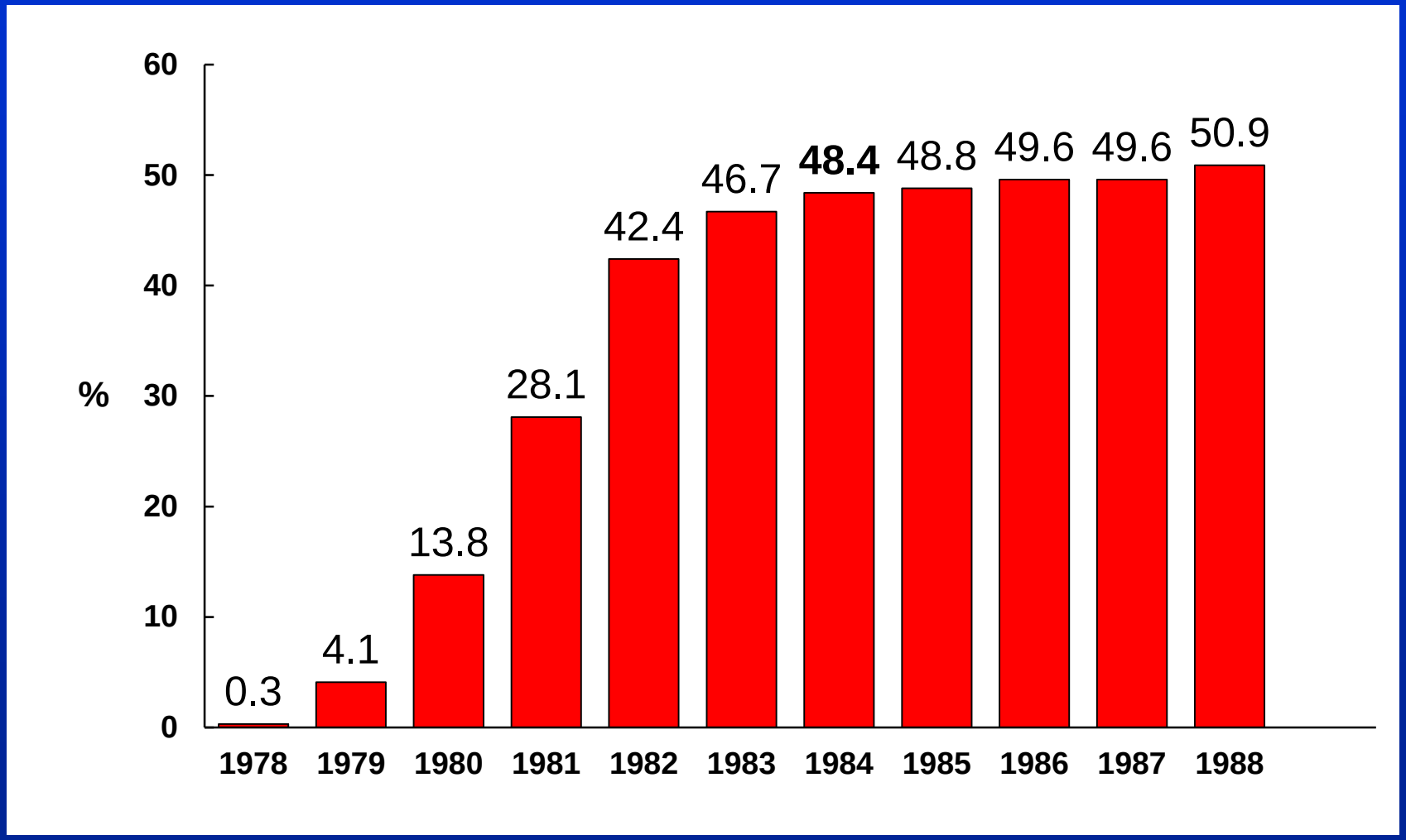
“What is ‘treatment as prevention’ and will it work for gay men?”

Tony Hughes
Research Director
New Zealand AIDS Foundation

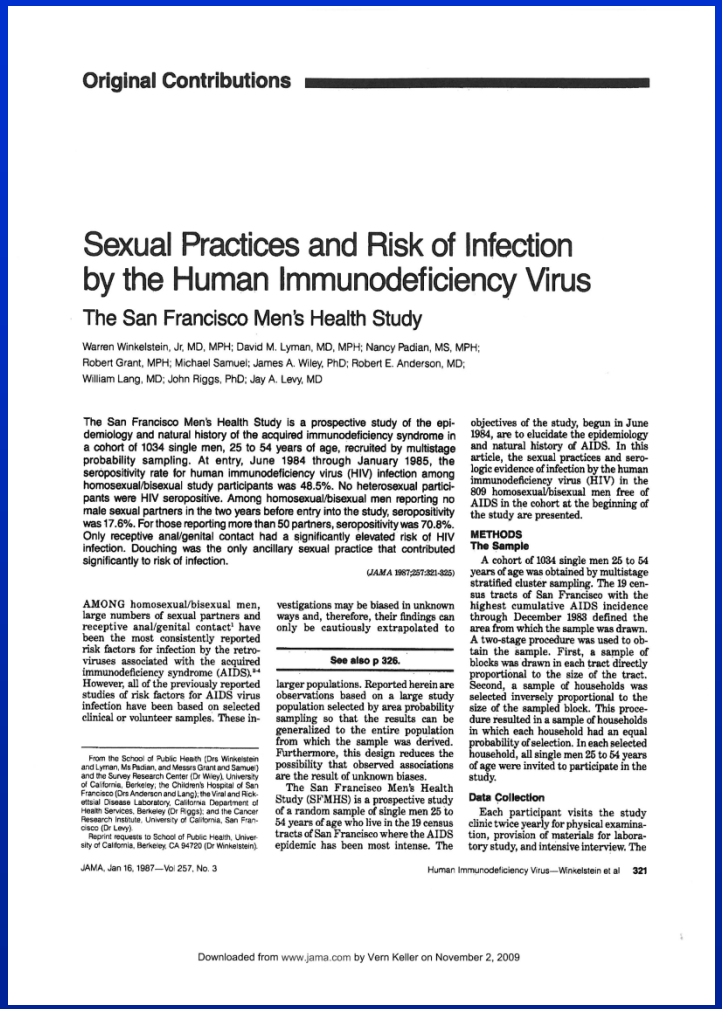
Body Positive Trust Board, Poynton Terrace, Auckland,
6 July 2013

Annual prevalence of HIV infection among 320 Hepatitis B vaccine trial participants, San Francisco, 1978-1988



Hessol, NA. Lifson, AR. O'Malley, PM., et al. "Prevalence, incidence, and progression of Human Immunodeficiency Virus infection in homosexual and bisexual men in hepatitis B vaccine trials, 1978-1988." *Am J Epidemiol* 1989;130: 1167-1175.

Sexual practices and risk of infection by HIV, San Francisco Men's Health Study, 1984-1985



Original Contributions

Sexual Practices and Risk of Infection by the Human Immunodeficiency Virus

The San Francisco Men's Health Study

Warren Winkelstein, Jr, MD, MPH; David M. Lyman, MD, MPH; Nancy Padian, MS, MPH; Robert Grant, MPH; Michael Samuel; James A. Wiley, PhD; Robert E. Anderson, MD; William Lang, MD; John Riggs, PhD; Jay A. Levy, MD

The San Francisco Men's Health Study is a prospective study of the epidemiology and natural history of the acquired immunodeficiency syndrome in a cohort of 1034 single men, 25 to 54 years of age, recruited by multistage probability sampling. At entry, June 1984 through January 1985, the seropositivity rate for human immunodeficiency virus (HIV) infection among homosexual/bisexual study participants was 48.5%. No heterosexual participants were HIV seropositive. Among homosexual/bisexual men reporting no male sexual partners in the two years before entry into the study, seropositivity was 17.6%. For those reporting more than 50 partners, seropositivity was 70.8%. Only receptive anal/genital contact had a significantly elevated risk of HIV infection. Douching was the only ancillary sexual practice that contributed significantly to risk of infection.

(JAMA 1987;257:321-325)

AMONG homosexual/bisexual men, large numbers of sexual partners and receptive anal/genital contact[1] have been the most consistently reported risk factors for infection by the retroviruses associated with the acquired immunodeficiency syndrome (AIDS).[1-4] However, all of the previously reported studies of risk factors for AIDS virus infection have been based on selected clinical or volunteer samples. These investigations may be biased in unknown ways and, therefore, their findings can only be cautiously extrapolated to larger populations. Reported herein are observations based on a large study population selected by area probability sampling so that the results can be generalized to the entire population from which the sample was derived. Furthermore, this design reduces the possibility that observed associations are the result of unknown biases.

See also p 326.

The San Francisco Men's Health Study (SFMHS) is a prospective study of a random sample of single men 25 to 54 years of age who live in the 19 census tracts of San Francisco where the AIDS epidemic has been most intense. The objectives of the study, begun in June 1984, are to elucidate the epidemiology and natural history of AIDS. In this article, the sexual practices and serologic evidence of infection by the human immunodeficiency virus (HIV) in the 809 homosexual/bisexual men free of AIDS in the cohort at the beginning of the study are presented.

METHODS

The Sample

A cohort of 1034 single men 25 to 54 years of age was obtained by multistage stratified cluster sampling. The 19 census tracts of San Francisco with the highest cumulative AIDS incidence through December 1982 defined the area from which the sample was drawn. A two-stage procedure was used to obtain the sample. First, a sample of blocks was drawn in each tract directly proportional to the size of the tract. Second, a sample of households was selected inversely proportional to the size of the sampled block. This procedure resulted in a sample of households in which each household had an equal probability of selection. In each selected household, all single men 25 to 54 years of age were invited to participate in the study.

Data Collection

Each participant visits the study clinic twice yearly for physical examination, provision of materials for laboratory study, and intensive interview. The

From the School of Public Health (Drs Winkelstein and Lyman, Ms Padian, and Messrs Grant and Samuel) and the Survey Research Center (Dr Wiley), University of California, Berkeley; the Children's Hospital of San Francisco (Drs Anderson and Lang); the Viral and Rickettsial Disease Laboratory, California Department of Health Services, Berkeley (Dr Riggs); and the Cancer Research Institute, University of California, San Francisco (Dr Levy).

Reprint requests to School of Public Health, University of California, Berkeley, CA 94720 (Dr Winkelstein).

- "At entry, June 1984 through January 1985, the seropositivity rate for human immunodeficiency virus (HIV) infection among homosexual/bisexual study participants was **48.5%**. No heterosexual participants were HIV seropositive".
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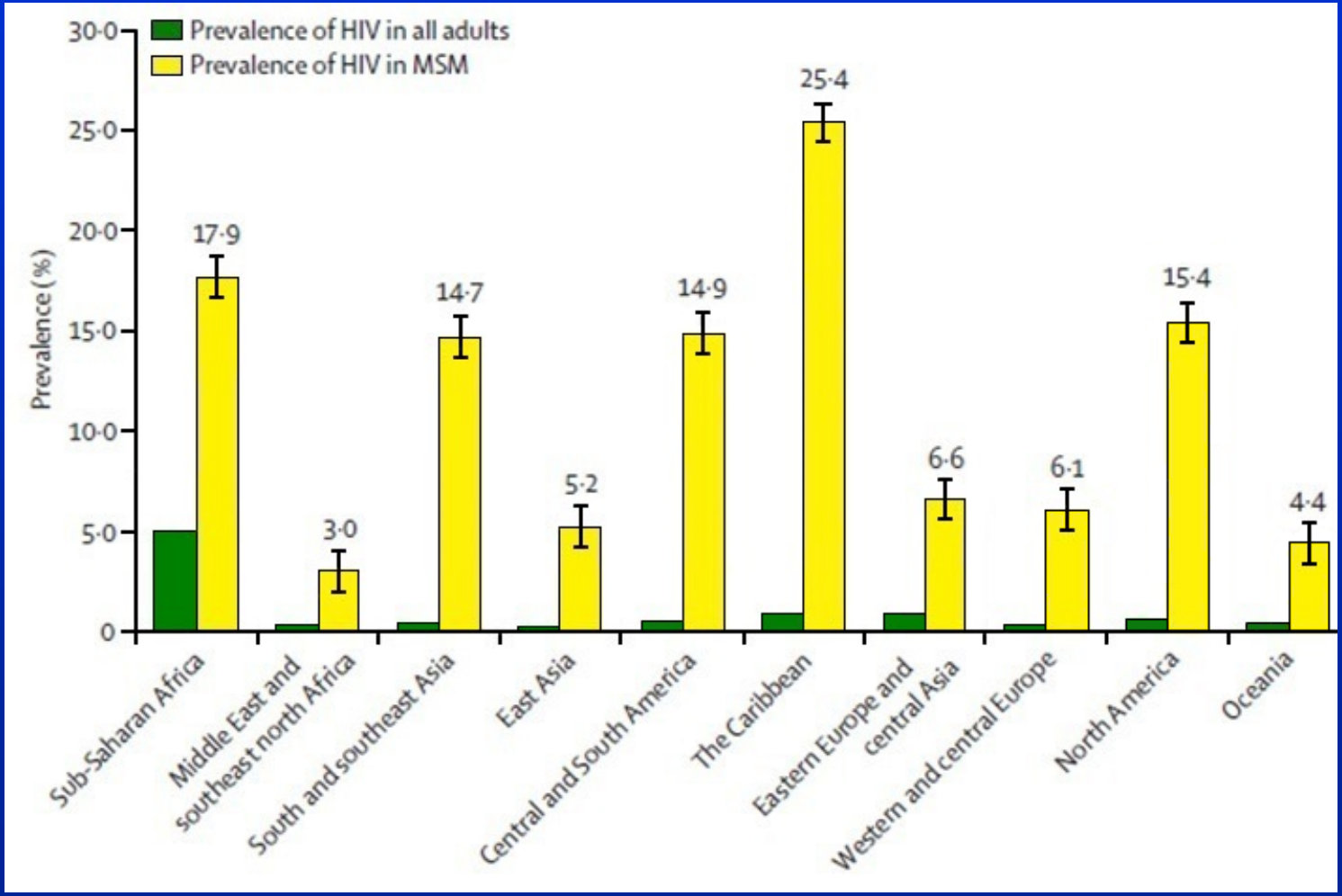
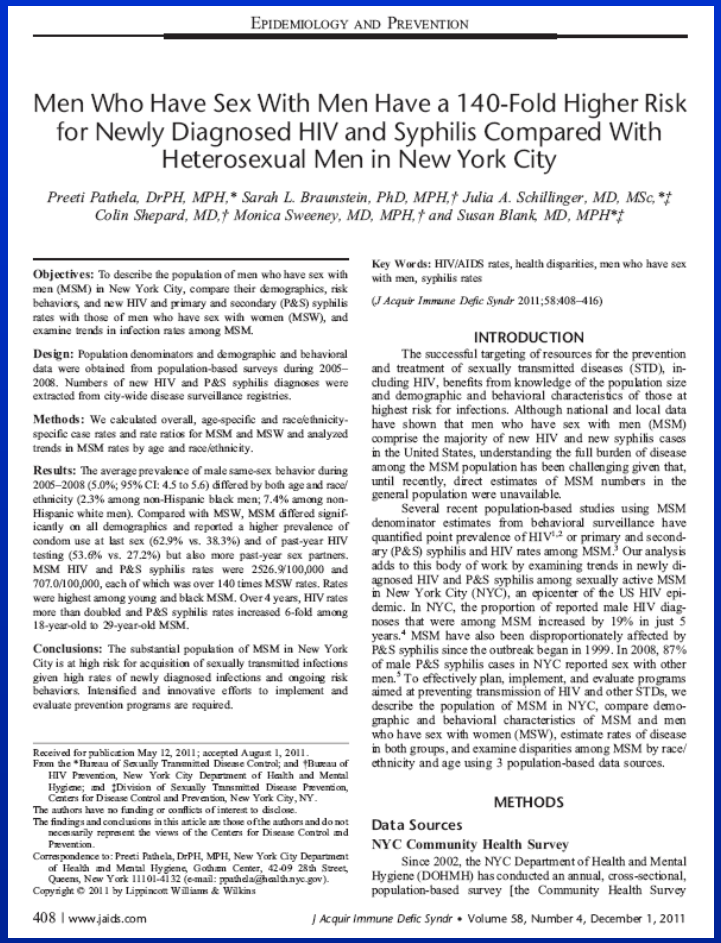
Winkelstein, W. et al. *JAMA* 1987; 257: 321-325.

Global prevalence of HIV in MSM compared with adult prevalence, UNAIDS 2010



Adapted from: Beyrer, C. et al. *Lancet* 2012; 380: 367-377; Thematic issue published online 20 July.

MSM have a 140 fold higher risk for newly diagnosed HIV and syphilis compared with heterosexual men in New York City



EPIDEMIOLOGY AND PREVENTION

Men Who Have Sex With Men Have a 140-Fold Higher Risk for Newly Diagnosed HIV and Syphilis Compared With Heterosexual Men in New York City

Preeti Pathela, DrPH, MPH, Sarah L. Braunstein, PhD, MPH,† Julia A. Schillinger, MD, MSc,*‡ Colin Shepard, MD,† Monica Sweeney, MD, MPH,† and Susan Blank, MD, MPH*‡*

Objectives: To describe the population of men who have sex with men (MSM) in New York City, compare their demographics, risk behaviors, and new HIV and primary and secondary (P&S) syphilis rates with those of men who have sex with women (MSW), and examine trends in infection rates among MSM.

Design: Population denominators and demographic and behavioral data were obtained from population-based surveys during 2005–2008. Numbers of new HIV and P&S syphilis diagnoses were extracted from city-wide disease surveillance registries.

Methods: We calculated overall, age-specific and race/ethnicity-specific case rates and rate ratios for MSM and MSW and analyzed trends in MSM rates by age and race/ethnicity.

Results: The average prevalence of male same-sex behavior during 2005–2008 (5.0%; 95% CI: 4.5 to 5.6) differed by both age and race/ethnicity (2.3% among non-Hispanic black men; 7.4% among non-Hispanic white men). Compared with MSW, MSM differed significantly on all demographics and reported a higher prevalence of condom use at last sex (62.9% vs. 38.3%) and of past-year HIV testing (53.6% vs. 27.2%) but also more past-year sex partners. MSM HIV and P&S syphilis rates were 2526.9/100,000 and 707.0/100,000, each of which was over 140 times MSW rates. Rates were highest among young and black MSM. Over 4 years, HIV rates more than doubled and P&S syphilis rates increased 6-fold among 18-year-old to 29-year-old MSM.

Conclusions: The substantial population of MSM in New York City is at high risk for acquisition of sexually transmitted infections given high rates of newly diagnosed infections and ongoing risk behaviors. Intensified and innovative efforts to implement and evaluate prevention programs are required.

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From the *Bureau of Sexually Transmitted Disease Control; and †Bureau of HIV Prevention, New York City Department of Health and Mental Hygiene; and ‡Division of Sexually Transmitted Disease Prevention, Centers for Disease Control and Prevention, New York City, NY.

The authors have no funding or conflicts of interest to disclose.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Correspondence to: Preeti Pathela, DrPH, MPH, New York City Department of Health and Mental Hygiene, Gotham Center, 42-09 28th Street, Queens, New York 11101-4132 (e-mail: ppathela@health.nyc.gov).

Key Words: HIV/AIDS rates, health disparities, men who have sex with men, syphilis rates

(*J Acquir Immune Defic Syndr* 2011;58:408–416)

INTRODUCTION

The successful targeting of resources for the prevention and treatment of sexually transmitted diseases (STD), including HIV, benefits from knowledge of the population size and demographic and behavioral characteristics of those at highest risk for infections. Although national and local data have shown that men who have sex with men (MSM) comprise the majority of new HIV and new syphilis cases in the United States, understanding the full burden of disease among the MSM population has been challenging given that, until recently, direct estimates of MSM numbers in the general population were unavailable.

Several recent population-based studies using MSM denominator estimates from behavioral surveillance have quantified point prevalence of HIV[1,2] or primary and secondary (P&S) syphilis and HIV rates among MSM.[3] Our analysis adds to this body of work by examining trends in newly diagnosed HIV and P&S syphilis among sexually active MSM in New York City (NYC), an epicenter of the US HIV epidemic. In NYC, the proportion of reported male HIV diagnoses that were among MSM increased by 19% in just 5 years.[4] MSM have also been disproportionately affected by P&S syphilis since the outbreak began in 1999. In 2008, 87% of male P&S syphilis cases in NYC reported sex with other men.[5] To effectively plan, implement, and evaluate programs aimed at preventing transmission of HIV and other STDs, we describe the population of MSM in NYC, compare demographic and behavioral characteristics of MSM and men who have sex with women (MSW), estimate rates of disease in both groups, and examine disparities among MSM by race/ethnicity and age using 3 population-based data sources.

METHODS

Data Sources

NYC Community Health Survey

Since 2002, the NYC Department of Health and Mental Hygiene (DOHMH) has conducted an annual, cross-sectional, population-based survey [the Community Health Survey

- "The average prevalence of male same-sex behaviour for years 2005-2008 (5.0%; 95% CI: 4.5 to 5.6) was highest among men aged 40-49 years (8.0%) and lowest among men aged 18-29 years (3.9%)."
- "During 2005-2008, there were 9571 new HIV cases among MSM and 1249 among MSW, resulting in an MSM HIV case rate that was **140.4 times** as high (95% CI: 132.1 to 148.7) as the rate among MSW (2526.9/100,000 vs 18.0/100,000)."
- "The total number of [primary and secondary] syphilis cases over four years was 2678 among MSM and 334 among MSW, resulting in an MSM syphilis case rate that was **147.3 times** as high (95% CI: 130.5 to 163.2) as the rate among MSW (707.0/100,000 vs 4.8/100,000)."

Pathela, P. et al. *J Acq Imm Def Syn* 2011; 58: 408-416.

Global epidemiology of HIV infection in men who have sex with men

Series

HIV in men who have sex with men 1

Global epidemiology of HIV infection in men who have sex with men

Chris Beyrer, Stefan D Baral, Frits van Griensven, Steven M Goodreau, Suwat Chariyalertsak, Andrea L Wirtz, Ron Brookmeyer

Epidemics of HIV in men who have sex with men (MSM) continue to expand in most countries. We sought to understand the epidemiological drivers of the global epidemic in MSM and why it continues unabated. We did a comprehensive review of available data for HIV prevalence, incidence, risk factors, and the molecular epidemiology of HIV in MSM from 2007 to 2011, and modelled the dynamics of HIV transmission with an agent-based simulation. Our findings show that the high probability of transmission per act through receptive anal intercourse has a central role in explaining the disproportionate disease burden in MSM. HIV can be transmitted through large MSM networks at great speed. Molecular epidemiological data show substantial clustering of HIV infections in MSM networks, and higher rates of dual-variant and multiple-variant HIV infection in MSM than in heterosexual people in the same populations. Prevention strategies that lower biological transmission and acquisition risks, such as approaches based on antiretrovirals, offer promise for controlling the expanding epidemic in MSM, but their potential effectiveness is limited by structural factors that contribute to low health-seeking behaviours in populations of MSM in many parts of the world.

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This is the first in a Series of six papers about HIV in men who have sex with men

Center for Public Health and Human Rights, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (Prof C Beyrer MD, A L Wirtz MHS, SD Baral FRCPC); Institute of Global Health, University of California at San Francisco, CA, USA (F van Griensven PhD); Department of Anthropology, University of Washington, Seattle, WA, USA (SM Goodreau, PhD); Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand (Prof S Chariyalertsak DrPH); Department of Community Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (Prof S Chariyalertsak); and Department of Biostatistics, University of California Los Angeles, CA, USA (Prof R Brookmeyer PhD)
Correspondence to:
Prof Chris Beyrer, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St E 7152, Baltimore, MD 21205, USA
cbeyrer@jhsph.edu

See Online for appendix

Introduction

In 2012, men who have sex with men (MSM) are at substantial risk for HIV infection in virtually every context studied (panel 1).[1,2,4] This risk has been present since the syndrome now known as AIDS was first described in previously healthy homosexual men in Los Angeles (CA, USA) in 1981.[5–7] Despite decades of research and community, medical, and public health efforts, high HIV prevalence and incidence burdens have been reported in MSM throughout the world.[8] In many high-income settings—including Australia, France, the UK, and the USA—overall HIV epidemic trends are in decline except in MSM, where they have been expanding in the era of highly active antiretroviral therapy (HAART) in what have been described as re-emergent epidemics in MSM.[8,9] In the USA, HIV infections in MSM are estimated to be increasing at roughly 8% per year since 2001.[8] And in much of Africa, Asia, and Latin America, the highest rates of HIV infection in any risk group are in these men.[8]

However, our understanding of worldwide epidemiology is far from complete. By the end of 2011, 93 of 196 countries had not reported on HIV prevalence in MSM in the previous 5 years.[10] In several regions, notably the Middle East, north Africa, and sub-Saharan Africa, data for HIV infections in MSM are only emerging.[11,12] Data gaps and challenges to HIV research, surveillance, and epidemiological characterisation in MSM are largely the result of the hidden and stigmatised nature of MSM populations in much of the world, and of ongoing criminalisation of homosexuality and other forms of same-sex behaviour.[13] These structural realities have limited our understanding, and might also have crucial roles in the vulnerability of MSM to HIV.[14,15] We review the global epidemiology and disease burden of HIV infection in MSM; individual-level, couple, and network-level risks for HIV acquisition and transmission; biological aspects of anorectal HIV transmission; and molecular epidemiology advances, with the aim of understanding why MSM continue to bear such disproportionate burdens of HIV. We also developed and report on stochastic agent-based simulation models of HIV transmission to further clarify the drivers of HIV spread in MSM.[16] Finally, we discuss the public health importance of our emerging understanding of the epidemiology of HIV in MSM.

Disease burden of HIV in MSM

We did a comprehensive search for HIV burden and risks in MSM from Jan 1, 2007, to June 30, 2011 (search criteria in the appendix). We retrieved 2105 unique citations, and we identified and reviewed 68 additional surveillance studies in the public domain. We included country progress reports submitted to the UN General Assembly Special Session on HIV/AIDS (UNGASS). We obtained data from 82 peer-reviewed publications on disease burden of HIV in MSM, from 12 of the 68 surveillance reports, and from 38 of 186 country progress reports submitted to UNGASS in 2010.

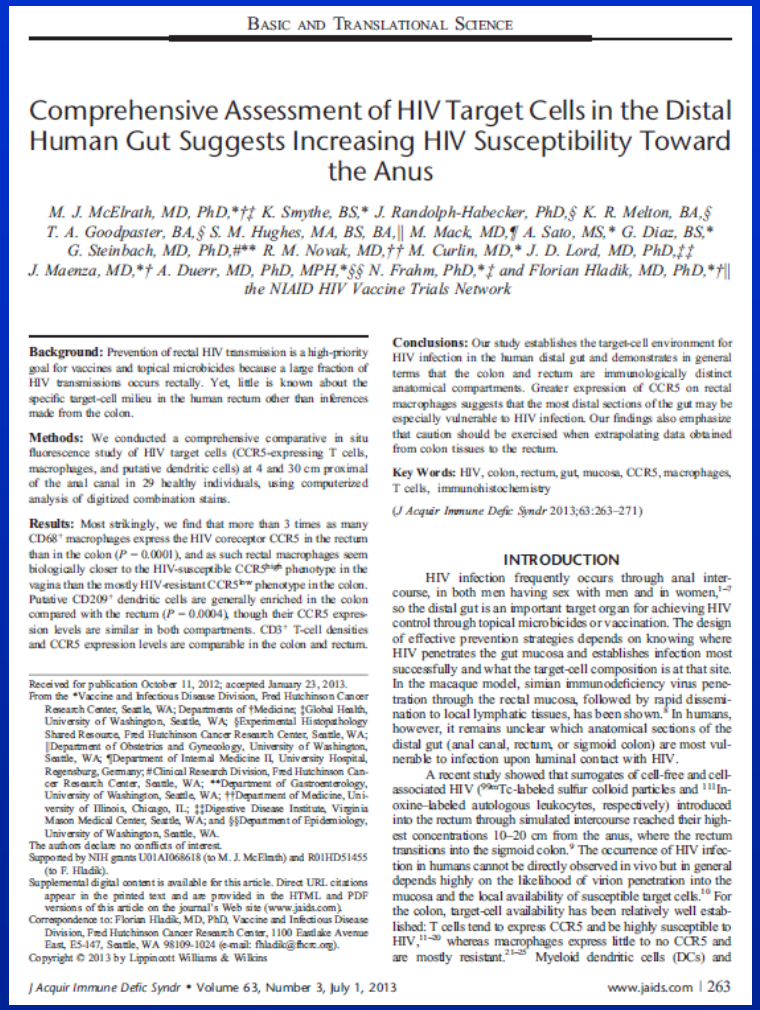
Figure 1 shows aggregate HIV prevalence estimates in MSM by region derived from the comprehensive search (references in the appendix). Pooled HIV prevalence ranged from a low of 3·0% (95% CI 2·4–3·6) in the Middle East and north Africa region to a high of 25·4% (21·4–29·5) in the Caribbean. The CIs for these pooled estimates must be interpreted with caution, since they only account for sampling variation and not the inherent biases of non-representative samples, and so undoubtedly underestimate actual variances. Nevertheless, HIV prevalences were relatively consistent across North, South, and Central America, south and southeast Asia, and sub-Saharan Africa (all within the 14–18%

- "The MSM epidemic is on a different trajectory from the rest of global AIDS."
- "HIV epidemics in men who have sex with men are expanding in countries of all incomes in 2012, and these epidemics are characterised by high HIV burdens, substantial clustering of infections within networks, and high forces of infection."
- "The disproportionate HIV disease burden in MSM is explained largely by the high per-act and per-partner probability of HIV transmission in receptive anal sex."

Beyrer, C. *Lancet* podcast http://www.thelancet.com/series/hiv-in-men-who-have-sex-with-men.

Beyrer, C. et al. *Lancet* 2012; 380: 367-377.

HIV target cells in the rectum are more susceptible to HIV infection



BASIC AND TRANSLATIONAL SCIENCE

Comprehensive Assessment of HIV Target Cells in the Distal Human Gut Suggests Increasing HIV Susceptibility Toward the Anus

M. J. McElrath, MD, PhD,†‡ K. Smythe, BS,* J. Randolph-Habecker, PhD,§ K. R. Melton, BA,§ T. A. Goodpaster, BA,§ S. M. Hughes, MA, BS, BA,‖ M. Mack, MD,¶ A. Sato, MS,* G. Diaz, BS,* G. Steinbach, MD, PhD,#** R. M. Novak, MD,†† M. Curlin, MD,* J. D. Lord, MD, PhD,‡‡ J. Maenza, MD,*† A. Duerr, MD, PhD, MPH,*§§ N. Frahm, PhD,*‡ and Florian Hladik, MD, PhD,*†‖ the NIAID HIV Vaccine Trials Network*

Background: Prevention of rectal HIV transmission is a high-priority goal for vaccines and topical microbicides because a large fraction of HIV transmissions occurs rectally. Yet, little is known about the specific target-cell milieu in the human rectum other than inferences made from the colon.

Methods: We conducted a comprehensive comparative in situ fluorescence study of HIV target cells (CCR5-expressing T cells, macrophages, and putative dendritic cells) at 4 and 30 cm proximal of the anal canal in 29 healthy individuals, using computerized analysis of digitized combination stains.

Results: Most strikingly, we find that more than 3 times as many $CD68^+$ macrophages express the HIV coreceptor CCR5 in the rectum than in the colon ($P = 0.0001$), and as such rectal macrophages seem biologically closer to the HIV-susceptible $CCR5^{high}$ phenotype in the vagina than the mostly HIV-resistant $CCR5^{low}$ phenotype in the colon. Putative $CD209^+$ dendritic cells are generally enriched in the colon compared with the rectum ($P = 0.0004$), though their CCR5 expression levels are similar in both compartments. $CD3^+$ T-cell densities and CCR5 expression levels are comparable in the colon and rectum.

Conclusions: Our study establishes the target-cell environment for HIV infection in the human distal gut and demonstrates in general terms that the colon and rectum are immunologically distinct anatomical compartments. Greater expression of CCR5 on rectal macrophages suggests that the most distal sections of the gut may be especially vulnerable to HIV infection. Our findings also emphasize that caution should be exercised when extrapolating data obtained from colon tissues to the rectum.

Key Words: HIV, colon, rectum, gut, mucosa, CCR5, macrophages, T cells, immunohistochemistry

(*J Acquir Immune Defic Syndr* 2013;63:263–271)

INTRODUCTION

HIV infection frequently occurs through anal intercourse, in both men having sex with men and in women,[1–7] so the distal gut is an important target organ for achieving HIV control through topical microbicides or vaccination. The design of effective prevention strategies depends on knowing where HIV penetrates the gut mucosa and establishes infection most successfully and what the target-cell composition is at that site. In the macaque model, simian immunodeficiency virus penetration through the rectal mucosa, followed by rapid dissemination to local lymphatic tissues, has been shown.[8] In humans, however, it remains unclear which anatomical sections of the distal gut (anal canal, rectum, or sigmoid colon) are most vulnerable to infection upon luminal contact with HIV.

A recent study showed that surrogates of cell-free and cell-associated HIV (^{99m}Tc-labeled sulfur colloid particles and ^{111}In-oxine–labeled autologous leukocytes, respectively) introduced into the rectum through simulated intercourse reached their highest concentrations 10–20 cm from the anus, where the rectum transitions into the sigmoid colon.[9] The occurrence of HIV infection in humans cannot be directly observed in vivo but in general depends highly on the likelihood of virion penetration into the mucosa and the local availability of susceptible target cells.[10] For the colon, target-cell availability has been relatively well established: T cells tend to express CCR5 and be highly susceptible to HIV,[11–20] whereas macrophages express little to no CCR5 and are mostly resistant.[21–25] Myeloid dendritic cells (DCs) and

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From the *Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA; Departments of †Medicine, ‡Global Health, University of Washington, Seattle, WA, §Experimental Histopathology Shared Resource, Fred Hutchinson Cancer Research Center, Seattle, WA; ‖Department of Obstetrics and Gynecology, University of Washington, Seattle, WA; ¶Department of Internal Medicine II, University Hospital, Regensburg, Germany; #Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; **Department of Gastroenterology, University of Washington, Seattle, WA; ††Department of Medicine, University of Illinois, Chicago, IL; ‡‡Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA; and §§Department of Epidemiology, University of Washington, Seattle, WA.

The authors declare no conflicts of interest.

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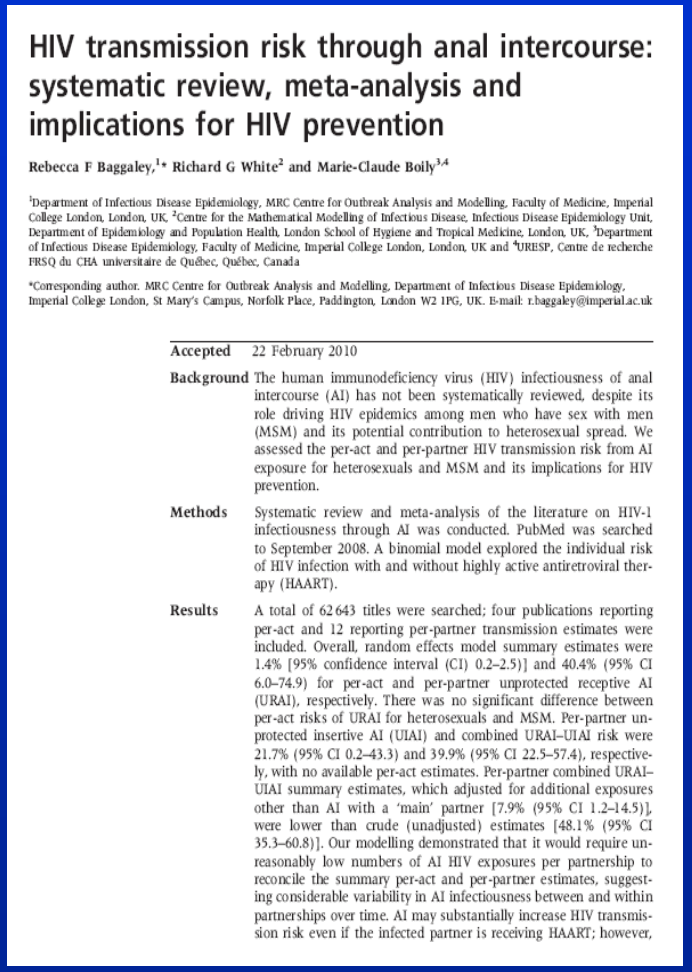
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Florian Hladik, MD, PhD, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, 1100 Eastlake Avenue East, E5-147, Seattle, WA 98109-1024 (e-mail: fhladik@fhcrc.org).

- "Our study establishes the target-cell environment for HIV infection in the human distal gut and demonstrates in general terms that the colon and rectum are immunologically distinct anatomical compartments. Greater expression of CCR5 on rectal macrophages suggests that the most distal sections of the gut may be especially vulnerable to HIV infection."
- "Most strikingly, we find more than 3 times as many $CD68^+$ macrophages express the HIV coreceptor CCR5 in the rectum than in the colon ($P = 0.0001$)."
- "In our analyses, we could not define all $CCR5^+$ cells as macrophages, T cells, or putative DCs… there are multiple possible explanations for our detection of $CCR5^+$ cells that were not DCs, macrophages, or T cells. These cells could potentially contribute to HIV diseases in the gut."
- "The most striking finding of this study was that a markedly higher percentage of macrophages expressed CCR5 in the rectum than in the colon. As a consequence, the rectum harbored about 3 times as many $CCR5^+$ macrophages per square millimeter as the colon, with substantial cell numbers present in the superficial stroma of most rectal biopsies…"

McElrath, M.J. et al. *J Acq Imm Def Syn* 2013; 63: 263-271.

High HIV transmission risk through anal intercourse



HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention

Rebecca F Baggaley,[1]* Richard G White[2] and Marie-Claude Boily[3,4]

[1]Department of Infectious Disease Epidemiology, MRC Centre for Outbreak Analysis and Modelling, Faculty of Medicine, Imperial College London, London, UK, [2]Centre for the Mathematical Modelling of Infectious Disease, Infectious Disease Epidemiology Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK, [3]Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, London, UK and [4]URESP, Centre de recherche FRSQ du CHA universitaire de Québec, Québec, Canada

*Corresponding author. MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, St Mary's Campus, Norfolk Place, Paddington, London W2 1PG, UK. E-mail: r.baggaley@imperial.ac.uk

Accepted 22 February 2010

Background The human immunodeficiency virus (HIV) infectiousness of anal intercourse (AI) has not been systematically reviewed, despite its role driving HIV epidemics among men who have sex with men (MSM) and its potential contribution to heterosexual spread. We assessed the per-act and per-partner HIV transmission risk from AI exposure for heterosexuals and MSM and its implications for HIV prevention.

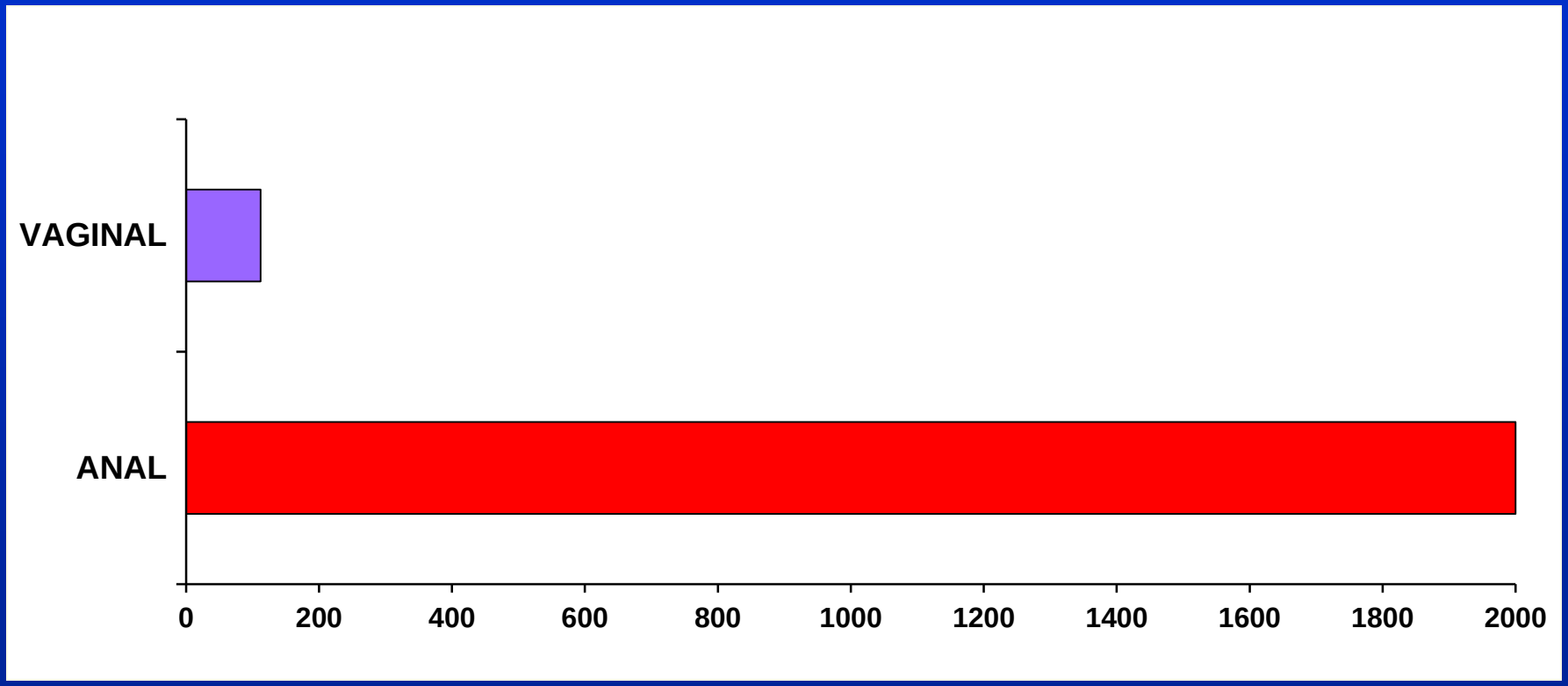
Methods Systematic review and meta-analysis of the literature on HIV-1 infectiousness through AI was conducted. PubMed was searched to September 2008. A binomial model explored the individual risk of HIV infection with and without highly active antiretroviral therapy (HAART).

Results A total of 62 643 titles were searched; four publications reporting per-act and 12 reporting per-partner transmission estimates were included. Overall, random effects model summary estimates were 1.4% [95% confidence interval (CI) 0.2–2.5)] and 40.4% (95% CI 6.0–74.9) for per-act and per-partner unprotected receptive AI (URAI), respectively. There was no significant difference between per-act risks of URAI for heterosexuals and MSM. Per-partner unprotected insertive AI (UIAI) and combined URAI–UIAI risk were 21.7% (95% CI 0.2–43.3) and 39.9% (95% CI 22.5–57.4), respectively, with no available per-act estimates. Per-partner combined URAI–UIAI summary estimates, which adjusted for additional exposures other than AI with a 'main' partner [7.9% (95% CI 1.2–14.5)], were lower than crude (unadjusted) estimates [48.1% (95% CI 35.3–60.8)]. Our modelling demonstrated that it would require unreasonably low numbers of AI HIV exposures per partnership to reconcile the summary per-act and per-partner estimates, suggesting considerable variability in AI infectiousness between and within partnerships over time. AI may substantially increase HIV transmission risk even if the infected partner is receiving HAART; however,

- HIV transmission risk through unprotected receptive anal sex is **18 times higher** than during unprotected receptive vaginal sex in developed countries in this major review.
- The absolute per act transmission risk for unprotected receptive anal intercourse (URAI) is 1.4% (95% CI 0.2→ 2.5).
- The same per act transmission risk for URAI (1.43%; 95% CI 0.48 → 2.85) was recently reported from the Australian HIM cohort study.
- The absolute per act transmission risk for unprotected receptive vaginal intercourse in developed countries is 0.08% (95% CI 0.06 → 0.11) in the review.
- Note that the per partner transmission risk for unprotected receptive anal intercourse is 40.4% (95% CI 6.0→ 74.9).

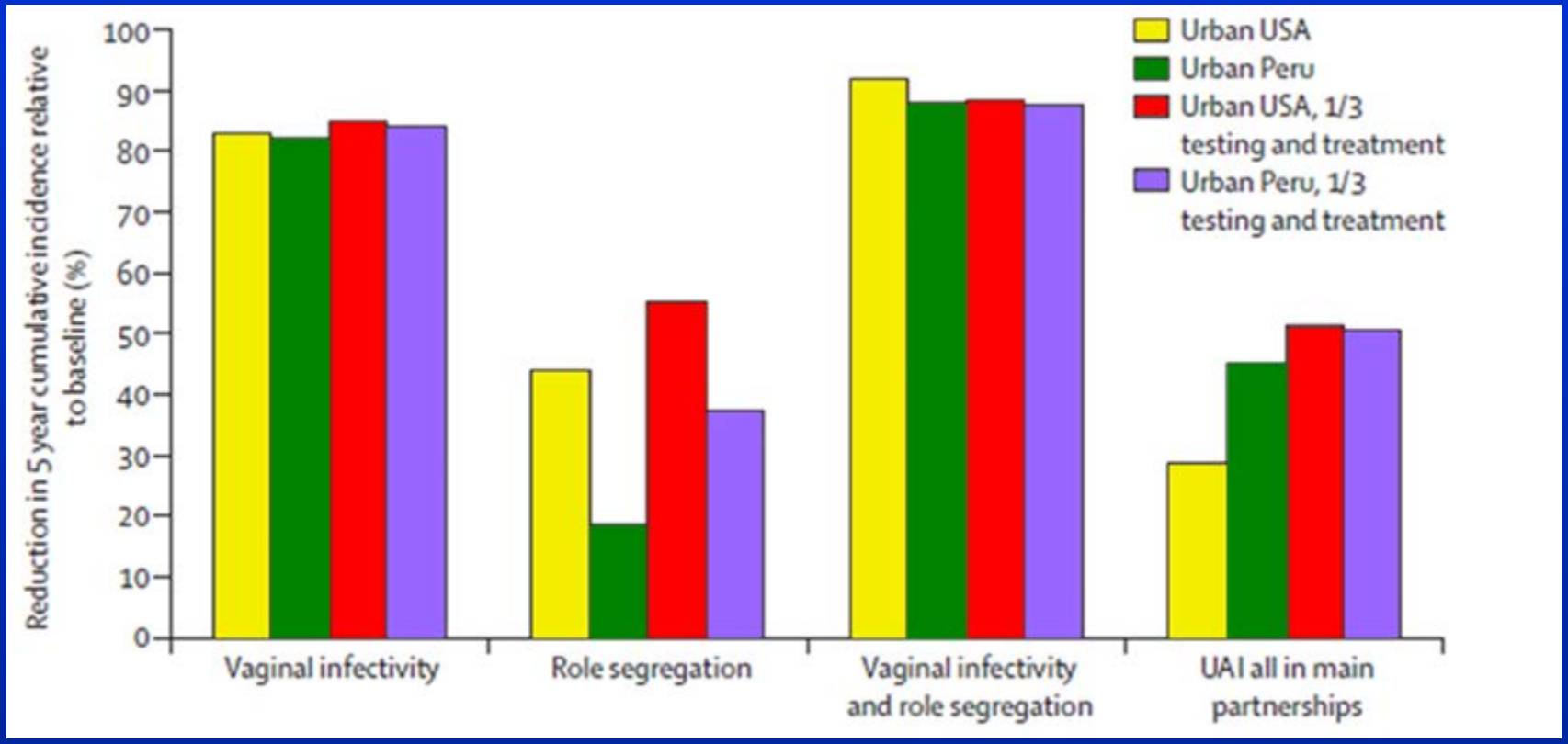
Baggaley, R. F. et al. *Int J Epidemiol* 2010; 39: 1048-1063; Jin, F. et al. *AIDS* 2010; 24: 907-913.

HIV transmission risk for receptive anal and vaginal intercourse without condoms in developed countries



Baggaley, White and Boily (2010); Boily et al (2009); Jin et al (2010).

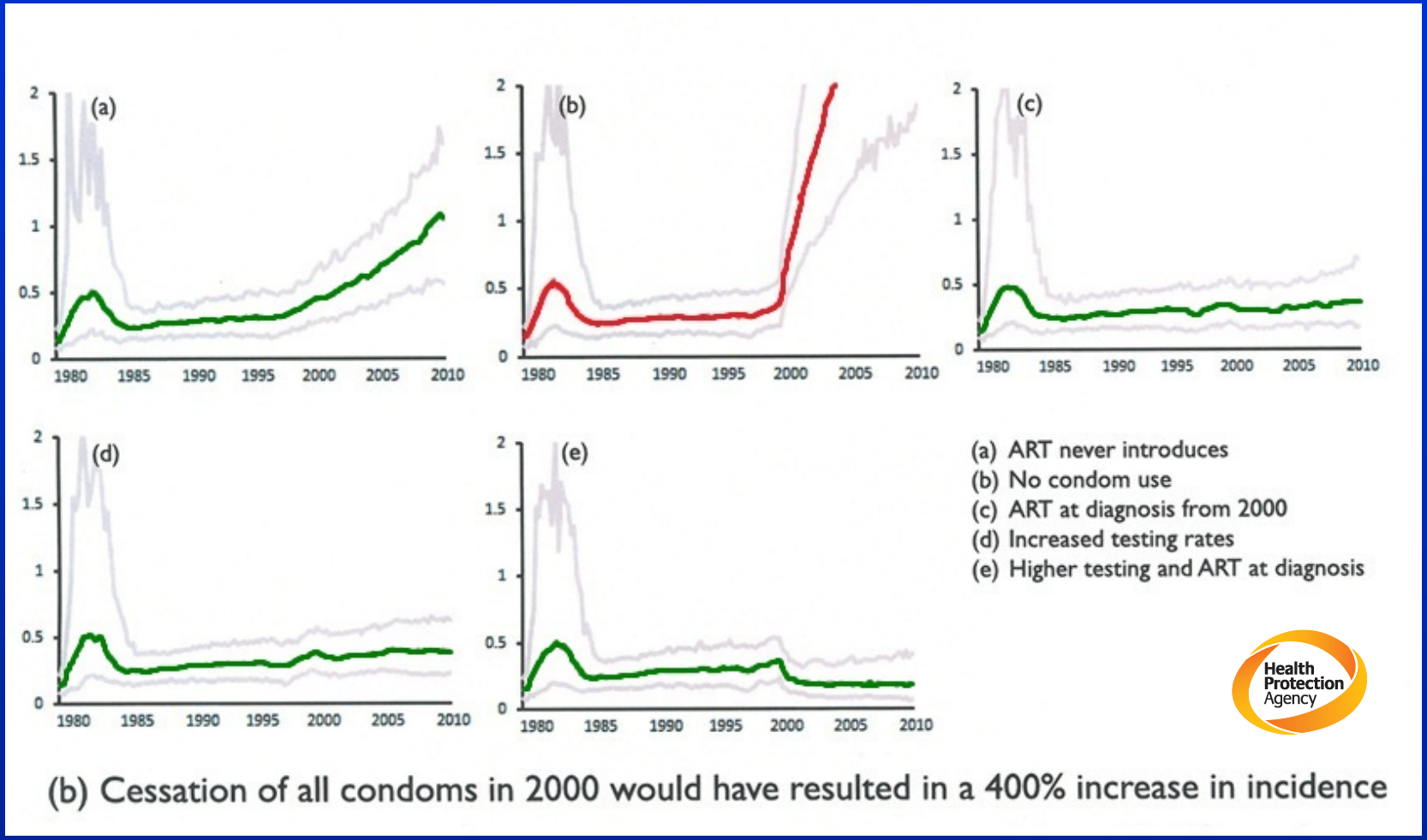
An individual-based computer simulation model for HIV infection in urban MSM in USA and Peru



"The greatest reductions were associated with the scenarios that entailed reducing transmission probabilities to those of vaginal intercourse; in all settings, this quickly reduced incidence by greater than 80%, and in some by as much as 98%. This emphasises that biological factors specific to anal sex have a fundamental effect in driving HIV epidemics in MSM worldwide"

Adapted from: Beyrer, C. et al. *Lancet* 2012; 380: 367-377.

Increased HIV incidence in MSM despite high levels of ART-induced viral suppression: Analysis of the United Kingdom epidemic



Adapted from: Delpech, V. "Health system concerns related to TasP and most at risk populations." Health Protection Agency, UK. Presented at IAPAC. "Controlling the HIV pandemic with antiretrovirals: Treatment as prevention and pre-exposure prophylaxis." Royal Garden Hotel, London, 11-12 June, 2012.

Note: For full data see Phillips, A.N. et al. *PLoS One* 2013; 8: e55312.

"We can think of 'treatment as prevention' in two ways: as a prevention strategy for individuals and as a public health strategy to reduce HIV transmissions in a population. These two types of 'treatment as prevention' are related but also have important differences. Each type raises its own issues and concerns, so it's important to know the difference between the two and not use them interchangeably."

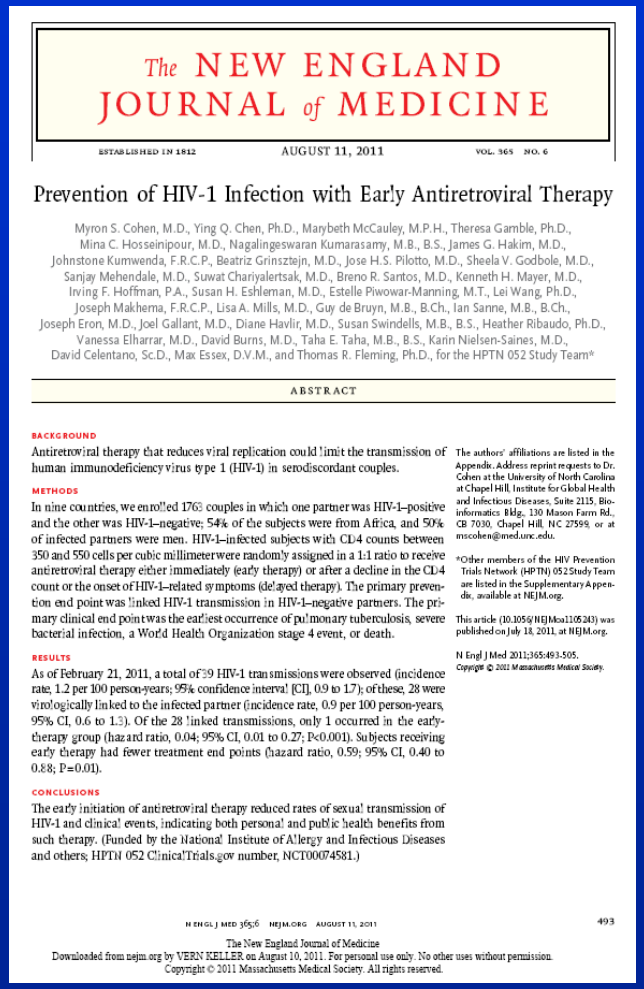
"At the individual level, the term 'treatment as prevention' refers to the use of antiretroviral treatment by a person living with HIV to reduce their personal risk of HIV transmission. Research shows that treatment can reduce HIV replication in the body and lower the amount of virus, or viral load, in the blood and other bodily fluids to undetectable levels. Since viral load is an important factor that determines whether an exposure leads to HIV infection, being on treatment and having undetectable viral load can reduce the risk of HIV transmission."

"As a public health approach, the goal of 'treatment as prevention' is to reduce the number of new transmissions in a population by increasing the proportion of people living with HIV who are on successful antiretroviral treatment. Since we know that treatment can reduce an individual's viral load and risk of HIV transmission, this strategy may be able to reduce the overall viral load circulating in a population and help control the spread of HIV."

James Wilton, CATIE (Canadian AIDS Treatment Information Exchange)

From: "Treatment as prevention: Bob Leahy in conversation with James Wilton." February 27, 2013.

Treating HIV-infected people with antiretrovirals significantly reduces transmission to partners (HPTN 052)



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Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

ABSTRACT

BACKGROUND

Antiretroviral therapy that reduces viral replication could limit the transmission of human immunodeficiency virus type 1 (HIV-1) in serodiscordant couples.

METHODS

In nine countries, we enrolled 1763 couples in which one partner was HIV-1–positive and the other was HIV-1–negative; 54% of the subjects were from Africa, and 50% of infected partners were men. HIV-1–infected subjects with CD4 counts between 350 and 550 cells per cubic millimeter were randomly assigned in a 1:1 ratio to receive antiretroviral therapy either immediately (early therapy) or after a decline in the CD4 count or the onset of HIV-1–related symptoms (delayed therapy). The primary prevention end point was linked HIV-1 transmission in HIV-1–negative partners. The primary clinical end point was the earliest occurrence of pulmonary tuberculosis, severe bacterial infection, a World Health Organization stage 4 event, or death.

RESULTS

As of February 21, 2011, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years; 95% confidence interval [CI], 0.9 to 1.7); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6 to 1.3). Of the 28 linked transmissions, only 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01 to 0.27; P<0.001). Subjects receiving early therapy had fewer treatment end points (hazard ratio, 0.59; 95% CI, 0.40 to 0.88; P=0.01).

CONCLUSIONS

The early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy. (Funded by the National Institute of Allergy and Infectious Diseases and others; HPTN 052 ClinicalTrials.gov number, NCT00074581.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Cohen at the University of North Carolina at Chapel Hill, Institute for Global Health and Infectious Diseases, Suite 2115, Bioinformatics Bldg., 130 Mason Farm Rd., CB 7030, Chapel Hill, NC 27599, or at mscohen@med.unc.edu.

*Other members of the HIV Prevention Trials Network (HPTN) 052 Study Team are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1105243) was published on July 18, 2011, at NEJM.org.

N Engl J Med 2011;365:493-505.

- Study of 1,763 serodiscordant couples, 97% were heterosexual and most were married. Both partners were required to sign an informal consent, suggesting a stable relationship. At enrolment HIV infected partners had CD4+ T cell levels between 350 and 550 cells/mm^3.
- There were two study groups: In the first antiretroviral therapy was started immediately and in the second it was postponed until 250 cells/mm^3, or until AIDS symptoms appeared.
- Condom use was encouraged. Those reporting 100% condom use had a significantly lower likelihood of acquiring HIV than those reporting less frequent condom use.
- Thirty nine new HIV infections were found in the previously uninfected partners. Of those 28 were genetically linked to the enrolled infected partner. The other 11 (ie: 28%) were not linked to that partner.
- Of the 28 partner linked infections, 27 occurred in the group where treatment was delayed, only one occurred in the early treatment group. Twenty three of the linked infections (82%) occurred in couples from sub-Saharan Africa.
- The overall finding is that early initiation of antiretroviral therapy lead to a **96%** reduction in HIV transmission to uninfected partners in this trial.

Cohen, M. S. et al. *N Engl J Med* 2011; 365: 493-505.

Strategic limitations of HPTN 052

- Almost all of the study sample was comprised of serodiscordant heterosexual couples, most were also married and all received counselling on behaviour modification and condom use. This means that direct conclusions cannot be drawn from these results about the likely impact of antiretroviral treatment on HIV prevention in the MSM population.

- Prevention effectiveness outside a tightly controlled clinical trial environment that involves monthly monitoring cannot be reliably assumed. The observed virologic failure rates in HTPN 052 were less than 5%, which is far lower than is generally observed in patients on antiretroviral therapy.

- Because the median duration of follow-up in HPTN 052 at report was only 1.7 years, it is not known if the levels of treatment adherence observed here can be sustained over the long term. The low levels of observed virologic failure suggest that adherence was artificially high and this may reflect a strong motivation to protect uninfected long-term partners.

- The extent to which antiretroviral treatment will be accompanied in practice by reductions in condom use over time is also undetermined, and treatment of HIV infected partners does not – of course – limit the risk of HIV acquisition from other sexual contacts or risk from other STIs.

Panel on Antiretroviral Guidelines for Adults and Adolescents. "Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents." US Department of Health and Human Services 2012. 1-239.

Alcorn, K. Treatment is prevention! HATIP; 180: 29 July 2011.

Does ART prevent HIV transmission among MSM?

OPINION

Does ART prevent HIV transmission among MSM?

Kathryn E. Muessig[a], M. Kumi Smith[b], Kimberly A. Powers[a,b], Ying-Ru Lo[c], David N. Burns[d], Andrew E. Grulich[e], Andrew N. Phillips[f] and Myron S. Cohen[a,b,g]

AIDS 2012, **26**:000–000

Keywords: HIV, sexually transmitted diseases, Highly Active Antiretroviral Therapy, men who have sex with men, MSM, treatment as prevention

One randomized controlled trial [1] and numerous observational studies [2–6] provide strong evidence that antiretroviral therapy (ART) can reduce or prevent the sexual transmission of HIV-1 within serodiscordant heterosexual couples. A key question remains: does ART reduce HIV transmission among men who have sex with men (MSM), where the primary mode of transmission is via condomless anal intercourse? New WHO guidelines for earlier initiation of ART among serodiscordant couples were released in April 2012 [7] and some countries, such as China, have already embraced treatment as prevention (TasP) for heterosexual couples. In the process of reevaluating current ART guidelines, we anticipate that for some countries, the issue of whether to recommend TasP for MSM will be under debate. The evidence supporting TasP for MSM is promising, but major gaps in our knowledge remain. To identify priority areas for research, in this paper we synthesize evidence of (a) the biological plausibility that virally suppressive ART reduces HIV infectiousness via anal intercourse and (b) epidemiologic evidence of whether ART has played a role in attenuating HIV incidence among MSM.

Some biological and epidemiological evidence suggests that ART for preventing transmission via anal intercourse may have more limited efficacy than via vaginal intercourse. Without ART, the probability of HIV transmission is estimated as 1 infection for every 20 to 300 acts of condomless anal intercourse, as compared to 1 in 200 to 1 in 2,000 for penile-vaginal exposure [8–13]. Additionally, a higher median number of HIV variants are transmitted in MSM couples as compared to heterosexual couples [14–16] potentially posing greater challenges for drug resistance [17].

The pharmacology of antiretroviral (ARV) agents also differs between the urogenital tract (vaginal intercourse) and the gastrointestinal (GI) tract (anal intercourse). ARVs can reduce—but not eliminate—the amount of HIV recovered from the genital tract [18–20] and GI tract [21–23]. Higher levels of HIV DNA and RNA have been found in the GI tract (duodenum, ileum, ascending colon, and rectum) as compared to the blood [24,25] and semen [23] irrespective of ART use, although these levels may be positively correlated [21,26,27]. Some ARVs such as tenofovir, tenofovir diphosphate, and maraviroc have been shown to penetrate rectal tissue with greater

[a]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA, [b]Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina, USA, [c]Department of HIV/AIDS, World Health Organization, Geneva, Switzerland, [d]Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA, [e]Kirby Institute (formerly the National Centre in HIV Epidemiology and Clinical Research), University of New South Wales, Sydney, Australia., [f]Department of Infection and Population Health, University College London, London, UK, and [g]Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, North Carolina, USA.

Correspondence to Myron S. Cohen, MD, University of North Carolina at Chapel Hill, CB# 7030, 130 Mason Farm Road, 2115 Bioinformatics Building, Chapel Hill, NC 27599-7030, USA
Tel: +1 919 966 2536; e-mail: mscohen@med.unc.edu
Received: 7 February 2012; revised: 26 April 2012; accepted: 2 May 2012.

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- "Some biological and epidemiological evidence suggests that ART for preventing transmission via anal intercourse may have more limited efficacy than via vaginal intercourse."
- "While the results of HPTN 052 demonstrated the capacity of ARVs to markedly reduce the risk of penile-vaginal transmission… we cannot be certain that this will be the case for anal intercourse given the much higher transmission probability in the absence of ART."
- "The impact of ART on HIV transmission via anal intercourse requires further evaluation… given the inconclusive observational data currently available for MSM and the challenging biological and behavioural risk factors that may present."

Muessig, K.E. et al. *AIDS* 2012; 26: 2267-2273.

Antiviral agents and HIV prevention: Controversies, conflicts and consensus

EDITORIAL REVIEW

Antiviral agents and HIV prevention: controversies, conflicts and consensus

Myron S. Cohen[a,b,c], Kathryn E. Muessig[a], M. Kumi Smith[b], Kimberly Powers[a,b] and Angela D.M. Kashuba[d]

Antiviral agents can be used to prevent HIV transmission before exposure as pre-exposure prophylaxis (PrEP), after exposure as post exposure prophylaxis (PEP), and as treatment of infected people for secondary prevention. Considerable research has shed new light on antiviral agents for PrEP and for prevention of secondary HIV transmission. While promising results have emerged from several PrEP trials, the challenges of poor adherence among HIV negative clients and possible increase in sexual risk behaviors remain of concern. In addition, a broader pipeline of antiviral agents for PrEP that focuses on genital tract pharmacology and safety and resistance issues must be developed. Antiretroviral drugs have also been used to prevent HIV transmission from HIV infected patients to their HIV discordant sexual partners. The HPTN 052 trial demonstrated nearly complete prevention of HIV transmission by early treatment of infection, but the generalizability of the results to other risk groups—including injection drug users and men who have sex with men—has not been determined. Most importantly, the best strategy for use of antiretroviral agents to reduce the spread of HIV at either the individual level or the population level has not been developed, and remains the ultimate goal of this area of investigation.

AIDS 2012, **26**:000–000

Keywords: antiretroviral agents, HIV prevention, pre-exposure prophylaxis, treatment as prevention

Introduction

Antiviral agents can be used to prevent HIV transmission in three ways: before exposure as pre-exposure prophylaxis (PrEP), after exposure as post exposure prophylaxis (PEP), and as treatment of infected people for secondary prevention [1–3]. Post exposure prophylaxis for HIV prevention has been well established but is not well suited to clinical research investigation. However, recent research developments in PrEP and secondary prevention provide a unique opportunity to highlight areas of advancement that have galvanized changes in HIV treatment and prevention, and to highlight topic areas that remain undecided or controversial.

[a]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA, [b]Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina, USA, [c]Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, North Carolina, USA, and [d]School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, USA.
Correspondence to Myron S. Cohen, Mailing address: Institute for Global Health and Infectious Diseases, 2nd Floor, Bioinformatics Building of The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7030.
Tel: +919 966 2536; fax: +919 966 6714; e-mail: mscohen@med.unc.edu
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- "The HPTN 052 trial demonstrated nearly complete prevention of HIV transmission by early treatment of infection, but the generalizability of the results to other risk groups – including injecting drug users and men who have sex with men – has not been determined."
- "Most importantly, the best strategy for use of antiretroviral agents to reduce the spread of HIV at either the individual level or the population level has not been developed, and remains the ultimate goal of this area of investigation."
- "Additionally, combination prevention strategies will need the continued efforts of behavioral interventions to increase condom use, reduce high-risk behaviors, and address suboptimal ARV adherence and risk compensation."

Cohen, M.S. et al. *AIDS* 2012; 26: 1585-1598.

A resurgent HIV-1 epidemic among MSM in the era of potent antiretroviral therapy in the Netherlands

A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy

Daniela Bezemer[a], Frank de Wolf[a,b], Maarten C. Boerlijst[c], Ard van Sighem[a], T. Deirdre Hollingsworth[b], Maria Prins[d,e], Ronald B. Geskus[d,f], Luuk Gras[a], Roel A. Coutinho[g,h] and Christophe Fraser[b]

Objective: Reducing viral load, highly active antiretroviral therapy has the potential to limit onwards transmission of HIV-1 and thus help contain epidemic spread. However, increases in risk behaviour and resurgent epidemics have been widely reported post-highly active antiretroviral therapy. The aim of this study was to quantify the impact that highly active antiretroviral therapy had on the epidemic.

Design: We focus on the HIV-1 epidemic among men who have sex with men in the Netherlands, which has been well documented over the past 20 years within several long-standing national surveillance programs.

Methods: We used a mathematical model including highly active antiretroviral therapy use and estimated the changes in risk behaviour and diagnosis rate needed to explain annual data on HIV and AIDS diagnoses.

Results: We show that the reproduction number $R(t)$, a measure of the state of the epidemic, declined early on from initial values above two and was maintained below one from 1985 to 2000. Since 1996, when highly active antiretroviral therapy became widely used, the risk behaviour rate has increased 66%, resulting in an increase of $R(t)$ to 1.04 in the latest period 2000–2004 (95% confidence interval 0.98–1.09) near or just above the threshold for a self-sustaining epidemic. Hypothetical scenario analysis shows that the epidemiological benefits of highly active antiretroviral therapy and earlier diagnosis on incidence have been entirely offset by increases in the risk behaviour rate.

Conclusion: We provide the first detailed quantitative analysis of the HIV epidemic in a well defined population and find a resurgent epidemic in the era of highly active antiretroviral therapy, most likely predominantly caused by increasing sexual risk behaviour.

AIDS 2008, **22**:1071–1077

Keywords: antiretroviral therapy, homosexual men, infectious diseases, mathematical models, models/projections, sexual behaviour, surveillance

From the [a]HIV Monitoring Foundation, Amsterdam, The Netherlands, the [b]Department of Infectious Disease Epidemiology, Imperial College London, UK, the [c]Institute for Biodiversity and Ecosystem Dynamics, University of Amsterdam, the [d]Health Service Amsterdam, the [e]Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, the [f]Department of Clinical Epidemiology Biostatistics and Bioinformatics, Academic Medical Center, the [g]Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, and the [h]Center for Infectious Disease Control, National Institute of Public Health and the Environment, Bilthoven, The Netherlands.
Correspondence to Christophe Fraser, Department of Infectious Disease Epidemiology, Faculty of Medicine at St Mary's Campus, Imperial College London, London, W2 1PG. UK.
E-mail: cfraser@imperial.ac.uk
Received: 9 May 2007; revised: 7 February 2008; accepted: 15 February 2008.

- "The joint effect of HAART and risk behaviour on HIV incidence has been previously studied using mathematical models and empirical data. Although based on different assumptions, all these studies come to the same conclusion regarding the potential for an increase in risk behaviour to offset the benefits of HAART in reducing transmission."
- Since 1996, when HAART became widely used in the Netherlands, the risk behaviour rate has increased by 66% in MSM.
- "In conclusion, there is an increase in HIV transmission among MSM in the Netherlands, in spite of earlier diagnosis and subsequent effective treatment. The most effective intervention is to bring risk behaviours back to pre-HAART levels."

Bezemer, D. et al. *AIDS* 2008; 22: 1071-1077.

Impact of ART on HIV transmission at population level

First author	Key comments and conclusions on sexual behaviour in MSM
Blower 2000	Significant efforts should be made to prevent risk behaviour increasing because even small increases will overcome the effect of ART on reducing HIV transmission.
Law 2001	Apparently large decreases in infectiousness as a result of treatment can be counterbalanced by much more modest increases in unsafe sex.
Katz 2002	Any decrease in per-contact risk of HIV transmission due to ART use appears to have been counterbalanced or overwhelmed by increases in the number of unsafe sexual episodes.
Velasco-Hernandez 2002	HIV spread is extremely sensitive to changes in risky sex. It is imperative that the usage of ART should be tightly coupled with effective risk-reduction strategies and that levels of risky sex are substantially reduced.
Xiridou 2003	A reduction of 75-99% in infectivity caused by ART will be counterbalanced by increases of 50% (range 30-80%) in risky behaviour with steady partners. Prevention measures should address unsafe behaviour.
Boily 2004	Because ART modifies the natural history of HIV infection it will change the transmission dynamics of the epidemic, and has the potential to increase the aggregate level of risky sexual behaviour in the population over time.

First author	Key comments and conclusions on sexual behaviour in MSM
McCormick 2007	These results indicate that ART must be accompanied by effective HIV risk reduction interventions. Prevention programmes that decrease HIV transmission are crucial to epidemic control.
Wilson 2008	The risk of HIV transmission in male homosexual partnerships is high over repeated exposures. If the claim of non-infectiousness in effectively treated patients is widely accepted, and condom use subsequently declines, there is potential for a substantial increase in HIV incidence.
Hallet 2010	The key message to patients should remain that always using condoms when receiving treatment is the best way to protect partners from the risk of HIV transmission.
Bezemer 2010	This model showed that if nothing changes, twice as many MSM in the Netherlands will be in need of healthcare for HIV infection in the coming decade than at present. The most effective way to prevent this is to decrease risk behaviour.
Long 2010	Even substantial expansion of HIV screening and treatment programmes is not sufficient to reduce the HIV epidemic markedly in the United States without substantial reductions in risk behavior.
Phillips 2013	This analysis suggests that HIV incidence increased as the United Kingdom after ART was introduced as a result of a modest (26%) rise in unprotected anal sex, and that in 2010, 48% of new transmissions came from undiagnosed men with primary HIV infection.

Increased HIV incidence in MSM despite high levels of ART-induced viral suppression in the United Kingdom

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PLOS ONE

Increased HIV Incidence in Men Who Have Sex with Men Despite High Levels of ART-Induced Viral Suppression: Analysis of an Extensively Documented Epidemic

Andrew N. Phillips[1]*, Valentina Cambiano[1], Fumiyo Nakagawa[1], Alison E. Brown[2], Fiona Lampe[1], Alison Rodger[1], Alec Miners[3], Jonathan Elford[4], Graham Hart[1], Anne M. Johnson[1], Jens Lundgren[5], Valerie C. Delpech[2]

1 Research Department of Infection & Population Health, UCL, London, United Kingdom, 2 Health Protection Agency, London, United Kingdom, 3 London School of Hygiene and Tropical Medicine, London, United Kingdom, 4 City University, London, United Kingdom, 5 Copenhagen University Hospital Rigshospitalet, and University of Copenhagen, Copenhagen, Denmark

Abstract

Background: There is interest in expanding ART to prevent HIV transmission, but in the group with the highest levels of ART use, men-who-have-sex-with-men (MSM), numbers of new infections diagnosed each year have not decreased as ARTcoverage has increased for reasons which remain unclear.

Methods: We analysed data on the HIV-epidemic in MSM in the UK from a range of sources using an individual-based simulation model. Model runs using parameter sets found to result in good model fit were used to infer changes in HIV-incidence and risk behaviour.

Results: HIV-incidence has increased (estimated mean incidence 0.30/100 person-years 1990–1997, 0.45/100 py 1998–2010), associated with a modest (26%) rise in condomless sex. We also explored counter-factual scenarios: had ART not been introduced, but the rise in condomless sex had still occurred, then incidence 2006–2010 was 68% higher; a policy of ART initiation in all diagnosed with HIV from 2001 resulted in 32% lower incidence; had levels of HIV testing been higher (68% tested/year instead of 25%) incidence was 25% lower; a combination of higher testing and ART at diagnosis resulted in 62% lower incidence; cessation of all condom use in 2000 resulted in a 424% increase in incidence. In 2010, we estimate that undiagnosed men, the majority in primary infection, accounted for 82% of new infections.

Conclusion: A rise in HIV-incidence has occurred in MSM in the UK despite an only modest increase in levels of condomless sex and high coverage of ART. ART has almost certainly exerted a limiting effect on incidence. Much higher rates of HIV testing combined with initiation of ART at diagnosis would be likely to lead to substantial reductions in HIV incidence. Increased condom use should be promoted to avoid the erosion of the benefits of ART and to prevent other serious sexually transmitted infections.

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* E-mail: andrew.phillips@ucl.ac.uk

Introduction

Epidemics of HIV in men who have sex with men (MSM) started in the late 1970 s and early 1980 s and the numbers of new diagnoses continue to increase in several countries [1–7]. In the UK, for example, over 3000 MSM were diagnosed with HIV in 2010, the highest number since the start of the epidemic [1]. If we are to make informed choices on how to reduce new infections it is important to understand past trends in the epidemic and the factors which shaped them. Changes in self-reported condomless anal sex with persons of unknown or serodiscordant HIV status are clearly one key potential factor. Another potential factor is use of antiretroviral therapy (ART), which reduces transmission risk as well as reversing HIV progression [8–9]. The relative impact of these two factors on the MSM HIV epidemic are uncertain. Ecological analyses have observed correlations between ART use and trends in HIV diagnosis [10–11] (albeit one in the context of a mainly IDU epidemic) but these are difficult to interpret without an underlying model of transmission. There is great interest in the possibility of extending ART use in order to help to reduce HIV incidence [12–14], but a cautionary consideration is that the rise in incidence observed in MSM has occurred during a period in which ART use has expanded and the proportion of people with viral suppression has increased [1,15–16]. Here we aim to use a comprehensive model of HIV transmission, progression and the

- "It seems likely that modest increases in condomless sex in the era of effective ART in the UK have resulted in an increase in HIV incidence in MSM, but that the effects of ART in reducing infectivity have substantially attenuated this effect."
- "A second important message is the fact that promotion of condom use remains a critically important and effective element of prevention polices as it is undoubtedly acting to prevent much more dramatic increases in incidence."
- "The promotion of condom use among negative as well as HIV positive MSM remains vital to ensure the benefits of ART in reducing transmission of HIV are not undermined."

Phillips, A.N. et al. *PLoS One* 2013; 8: e55312.

The effect of expanded antiretroviral treatment strategies on the HIV epidemic among MSM in San Francisco

HIV/AIDS BRIEF REPORT

The Effect of Expanded Antiretroviral Treatment Strategies on the HIV Epidemic Among Men Who Have Sex With Men in San Francisco

Edwin D. Charlebois,[1,2] Moupali Das,[1,3] Travis C. Porco,[4] and Diane V. Havlir[1]

[1]HIV/AIDS Division, Department of Medicine, San Francisco General Hospital, California; [2]Center for AIDS Prevention Studies, Department of Medicine, University of California; [3]San Francisco Department of Public Health, California; [4]Francis I. Proctor Foundation for Research in Ophthalmology, Department of Epidemiology and Biostatistics, University of California, San Francisco, California

(See editorial commentary by DeGruttola and Schooley, on pages 1050–1052.)

Modeling of expanding antiretroviral treatment to all HIV-infected adults already in care in San Francisco predicts reductions in new HIV infection at 5 years of 59% among men who have sex with men. Addition of annual HIV testing for men who have sex with men to universal treatment decreases new infections by 76%.

A model of annual testing and immediate initiation of antiretroviral therapy (ART) in South Africa predicted a dramatic reduction in incidence of HIV infection [1]. In response, critics highlighted the practical applicability of such an approach in South Africa, and the debate about the optimum timing of ART initiation continues. In San Francisco, which has a generalized epidemic among men who have sex with men (MSM; 24% prevalence), challenges exist but are far less significant than those in South Africa. More than 72% of MSM report annual testing, and >85% of MSM are aware of their HIV status. Linkage to primary care is high (88%) even among individuals who receive a diagnosis at a public health clinic [2]. Of most significance, the San Francisco Department of Public Health estimates that 78% of all known HIV-infected persons were receiving care in 2008 [3]. With the public health resources and political will to support wide availability of antiretroviral medications, including Healthy San Francisco, a city-wide public health insurance safety net, high population-level rates of virologic suppression are achievable. In the context of this setting and early 2009 guidelines for starting ART at CD4 cell counts <350, we sought to determine the potential impact on incident HIV infection in the MSM population of offering ART to all patients in care—a strategy that maximizes the individual and public health benefit for those already receiving care without requiring additional investment in outreach and expanded HIV testing.

METHODS

We developed an ordinary differential equation simulation model for HIV testing and treatment among MSM in San Francisco extending previous models [1, 4, 5]. We tested 3 ART expansion strategies: (1) treatment of all individuals currently receiving HIV care with CD4 cell counts <500 cells/mm^3; (2) treatment of all individuals receiving care; and (3) intensified annual HIV testing combined with treatment of all HIV-infected persons (the full test-and-treat strategy). Inputs to the model were based on comprehensive surveillance information on prevalence and incidence of HIV infection, testing rates, and treatment outcomes data available for San Francisco from the local health department and electronic patient databases of the San Francisco General Hospital outpatient HIV treatment clinics that contain information on 95% of individuals known to be HIV infected in San Francisco [6]. We stratified the population of MSM according to risk groups, HIV status, CD4 cell count group, and treatment, as follows. We classified individuals as either uninfected or infected. Infected men, in turn, are classified according to the untreated nadir CD4 cell count into 1 of 4 stages: CD4 cell count >500 cells/mm^3, CD4 cell count of 350–500 cells/mm^3, CD4 cell count of 200–350 cells/mm^3, and CD4 cell count <200 cells/mm^3. Individuals in the model may (1) have unknown serostatus and not be receiving treatment; (2) have known HIV infection but not receiving ART; (3) be receiving ART but not yet achieved suppression; or (4) be receiving long-term antiretroviral therapy. Eighty percent of individuals receiving long-term therapy were assumed to have achieved durable virological suppression. Untreated

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Correspondence: Edwin D. Charlebois, MPH, PhD, Center for AIDS Prevention Studies, University of California, San Francisco, 50 Beale St, 13th Fl, San Francisco, CA 94105 (edwin.charlebois@ucsf.edu).

Clinical Infectious Diseases 2011;52(8):1046–1049

1058-4838/2011/5208-0014$14.00
DOI: 10.1093/cid/cir385

- "The model does not predict elimination of the HIV epidemic among MSM in San Francisco (reduction of prevalence and incidence of HIV infection to negligible or zero levels). However, at 20 years, and test-and-treat strategy predicts reduction in prevalence of HIV infection among MSM in San Francisco from 26.2% to 12.8%…"
- "Retention in care and expanded financial, clinical, social, and structural adherence and support measures for treatment including specific support for psychiatric and substance use co-morbid conditions, and addressing homelessness and marginal housing all need to be components of the strategy in a city such as San Francisco."
- "Also of concern is the potential for changes in behavior among MSM leading to increased transmission risk, thereby offsetting any potential gains and [generating] the spectre of resistant strains of HIV."

Charlebois, E.D. et al. *Clin Infect Dis* 2011; 52: 1046-1049.

A mathematical model of comprehensive test and treat services and HIV incidence among MSM in the United States

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PLoS one

A Mathematical Model of Comprehensive Test-and-Treat Services and HIV Incidence among Men Who Have Sex with Men in the United States

Stephen W. Sorensen[1], Stephanie L. Sansom[1]*, John T. Brooks[1], Gary Marks[1], Elizabeth M. Begier[2], Kate Buchacz[1], Elizabeth A. DiNenno[1], Jonathan H. Mermin[1], Peter H. Kilmarx[1]

1 Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, 2 New York City Department of Health and Mental Hygiene, New York, New York, United States of America

Abstract

Background: Early diagnosis and treatment of HIV infection and suppression of viral load are potentially powerful interventions for reducing HIV incidence. A test-and-treat strategy may have long-term effects on the epidemic among urban men who have sex with men (MSM) in the United States and may achieve the 5-year goals of the 2010 National AIDS Strategy that include: 1) lowering to 25% the annual number of new infections, 2) reducing by 30% the HIV transmission rate, 3) increasing to 90% the proportion of persons living with HIV infection who know their HIV status, 4) increasing to 85% the proportion of newly diagnosed patients linked to clinical care, and 5) increasing by 20% the proportion of HIV-infected MSM with an undetectable HIV RNA viral load.

Methods and Findings: We constructed a dynamic compartmental model among MSM in an urban population (based on New York City) that projects new HIV infections over time. We compared the cumulative number of HIV infections in 20 years, assuming current annual testing rate and treatment practices, with new infections after improvements in the annual HIV testing rate, notification of test results, linkage to care, initiation of antiretroviral therapy (ART) and viral load suppression. We also assessed whether five of the national HIV prevention goals could be met by the year 2015. Over a 20-year period, improvements in test-and-treat practice decreased the cumulative number of new infections by a predicted 39.3% to 69.1% in the urban population based on New York City. Institution of intermediate improvements in services would be predicted to meet at least four of the five goals of the National HIV/AIDS Strategy by the 2015 target.

Conclusions: Improving the five components of a test-and-treat strategy could substantially reduce HIV incidence among urban MSM, and meet most of the five goals of the National HIV/AIDS Strategy.

Citation: Sorensen SW, Sansom SL, Brooks JT, Marks G, Begier EM, et al. (2012) A Mathematical Model of Comprehensive Test-and-Treat Services and HIV Incidence among Men Who Have Sex with Men in the United States. PLoS ONE 7(2): e29098. doi:10.1371/journal.pone.0029098

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Competing Interests: The authors have declared that no competing interests exist.

* E-mail: sos9@cdc.gov

Introduction

Men who have sex with men (MSM) represent about 2% of the U.S. population [1] but accounted for 57% of new HIV diagnoses in 2009. In addition, MSM with a history of injection drug use accounted for another 3% of new diagnoses [2]. Not only are MSM the population most severely affected by HIV, they are the only risk group in which new HIV infections have been increasing steadily since the early 1990s [3]. A 2008 surveillance project employing venue-based sampling found that one in five (19%) MSM in 21 major U.S. cities were infected with HIV [4]. In addition, nearly half (44%) were unaware of their infection and 55% had not been tested for HIV infection in the previous 12 months.

Several modeling studies have shown that a test-and-treat approach to HIV infection, whereby at-risk individuals are tested frequently and linked to early treatment if diagnosed, could reduce HIV epidemics [5]. One dynamic transmission model of males and females suggested that a strategy of universal screening with immediate initiation of effective antiretroviral therapy could virtually eliminate the HIV epidemic in South Africa within 50 years [6]. Results from a similar dynamic transmission model of MSM and injection drug users indicated that expanding access to antiretroviral treatment, including earlier initiation of antiretroviral therapy (ART) (*i.e.*, at a CD4 count of 350 versus 200 cells/mm^3) could substantially reduce the HIV epidemic in British Columbia, Canada [7]. A dynamic model based on San Francisco MSM also showed improvement from earlier initiation of ART therapy [8].

However, an individual simulation model of test-and-treat for males and females in Washington, D.C., showed a modest impact on HIV transmission over the next 5 years [9]. A dynamic transmission model that explored the implications for low- and high-risk U.S. populations of males and females also showed more modest levels of improvement in HIV incidence over time [10].

- "Our strategy required implementing multiple interventions to ensure widespread and frequent testing of the at-risk populations and greater and more comprehensive provision of treatment."
- "While improving each intervention individually had some effect, the most significant impact resulted from improving all simultaneously."
- "Among individual interventions, the most effective was increasing the annual testing rate. Diagnosing previously undiagnosed HIV-infection was associated with a substantial reduction in risk behaviour and enabled infected individuals to enter care with possibility of achieving viral load suppression."
- " The results of our sensitivity analyses indicated that a reduction in condom use to 50% from 75% among all urban infected MSM negated the benefits of the intervention. This finding underscores that safer sex practices such as condom use must be maintained in the MSM community."

Sorensen, S.W. et al. *PLoS One* 2012; 7: e29098.

Natural experiments highlight the limits of antiretroviral treatment as HIV prevention

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PLOS MEDICINE

Review

HIV Treatment as Prevention: Natural Experiments Highlight Limits of Antiretroviral Treatment as HIV Prevention

David P. Wilson*

The Kirby Institute, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia

Abstract: There is growing enthusiasm for increasing coverage of antiretroviral treatment among HIV-infected people for the purposes of preventing ongoing transmission. Treatment as prevention will face a number of barriers when implemented in real world populations, which will likely lead to the effectiveness of this strategy being lower than proposed by optimistic modelling scenarios or ideal clinical trial settings. Some settings, as part of their prevention and treatment strategies, have already attained rates of HIV testing and use of antiretroviral therapy—with high levels of viral suppression—that many countries would aspire to as targets for a treatment-as-prevention strategy. This review examines a number of these "natural experiments", namely, British Columbia, San Francisco, France, and Australia, to provide commentary on whether treatment as prevention has worked in real world populations. This review suggests that the population-level impact of this strategy is likely to be considerably less than as inferred from ideal conditions.

Introduction

HIV prevention decision-makers across the world are considering the expansion of antiretroviral therapy (ART) for HIV-infected people in order to reduce their infectiousness and thus prevent onward transmission. This approach, called treatment as prevention, is a paradigm shift from using ART for the sole purpose of improving the health and longevity of patients with HIV. We are now in an era where the secondary benefit of ART is being considered as potentially the primary public health approach to controlling HIV epidemics.

Several findings suggest that treatment might be effective as prevention: the HPTN 052 study demonstrated that ART reduces sexual transmission between discordant couples in a trial setting [1]; various ecological studies from community settings have shown an association between ART programs and reduced markers of incidence [2–5]; associations have been demonstrated between reduced viral load and lower infectiousness [6–8]; and some theoretical models even suggest that under idealised conditions, elimination might be possible [9,10]. However, these findings do not imply that widespread scale-up of ART programs under real world conditions will reduce HIV incidence at a population level to the degree that some people are expecting (i.e., towards elimination). Cluster-randomised trials are currently underway in Africa to investigate the impact of high coverage of ART at the population level. In the meantime, models are projecting potential epidemic trajectories associated with treatment-as-prevention strategies under less ideal conditions [11], and various national and international organisations are already discussing operational issues about how to implement treatment as prevention [12].

We do not need to wait for trials of increased ART coverage to be completed, or speculate through the use of mathematical models, to have some understanding of the likely population-level impact of this strategy. Treatment as prevention has essentially been implemented in some settings already for a considerable time. Planned treatment-as-prevention approaches involve frequent universal testing and initiation of ART early post-diagnosis, but increasing treatment coverage at any stage of infection—and reaching high degrees of viral suppression across a population of people living with HIV—is de facto treatment as prevention. Some settings have achieved these objectives as part of their independent prevention and treatment responses: these settings can be considered as natural experiments for treatment as prevention at the population level.

Natural Experiment Case Studies

British Columbia, Canada

A study by Montaner et al. [3] has been widely promoted as demonstrating treatment as prevention in a community setting, namely, among people who inject drugs (PWID) in British Columbia, Canada. In British Columbia, there is universal access to free rapid HIV testing (though it is not known what proportion of PWID get tested for HIV each year). Guidelines for ART in British Columbia indicate that any HIV-positive patient may commence treatment, regardless of CD4 count, and ART is recommended for all symptomatic patients with established disease, and for asymptomatic individuals with CD4 cell count ≤500 cells/μl [13]. Estimates for ART coverage are difficult to quantify precisely, but coverage is considered to be relatively high and has certainly increased over time.

Citation: Wilson DP (2012) HIV Treatment as Prevention: Natural Experiments Highlight Limits of Antiretroviral Treatment as HIV Prevention. PLoS Med 9(7): e1001231. doi:10.1371/journal.pmed.1001231

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Competing Interests: The author has declared that no competing interests exist.

Abbreviations: ART, antiretroviral therapy; MSM, men who have sex with men; PWID, people who inject drugs

* E-mail: dwilson@unsw.edu.au

Provenance: Submitted as part of a sponsored Collection; externally reviewed.

- "While trial results are obtained under optimised conditions, where regular counselling and condoms are provided and where there are relatively low rates of sexually transmitted infections, this is often not the situation in the real world."
- "Justifiably, there is large enthusiasm for treatment as prevention. But current planning is based on expected outcomes informed by clinical trials and models - with supporting evidence from ecological and observational studies - that may be overly optimistic."
- "Natural experiments suggest that there are limitations to the overall benefit that can be achieved with this strategy. Before large portions of HIV/AIDS budgets are shifted to treatment as prevention in place of traditional prevention approaches, these limitations need to be given appropriate consideration."

Wilson, D. *PloS Med* 2012; 9: e1001231.

Key drivers of HIV spread in the MSM population

(a) Very high HIV acquisition risk from unprotected receptive anal intercourse.

(b) Extreme infectiousness in the acute/early HIV infection stage.

(c) Strong effect of high HIV prevalence levels on rates of HIV spread.

(d) Significant role of sexual network structure – frequent multi-partnering, short gaps between partners, concurrent relationships and group sex.

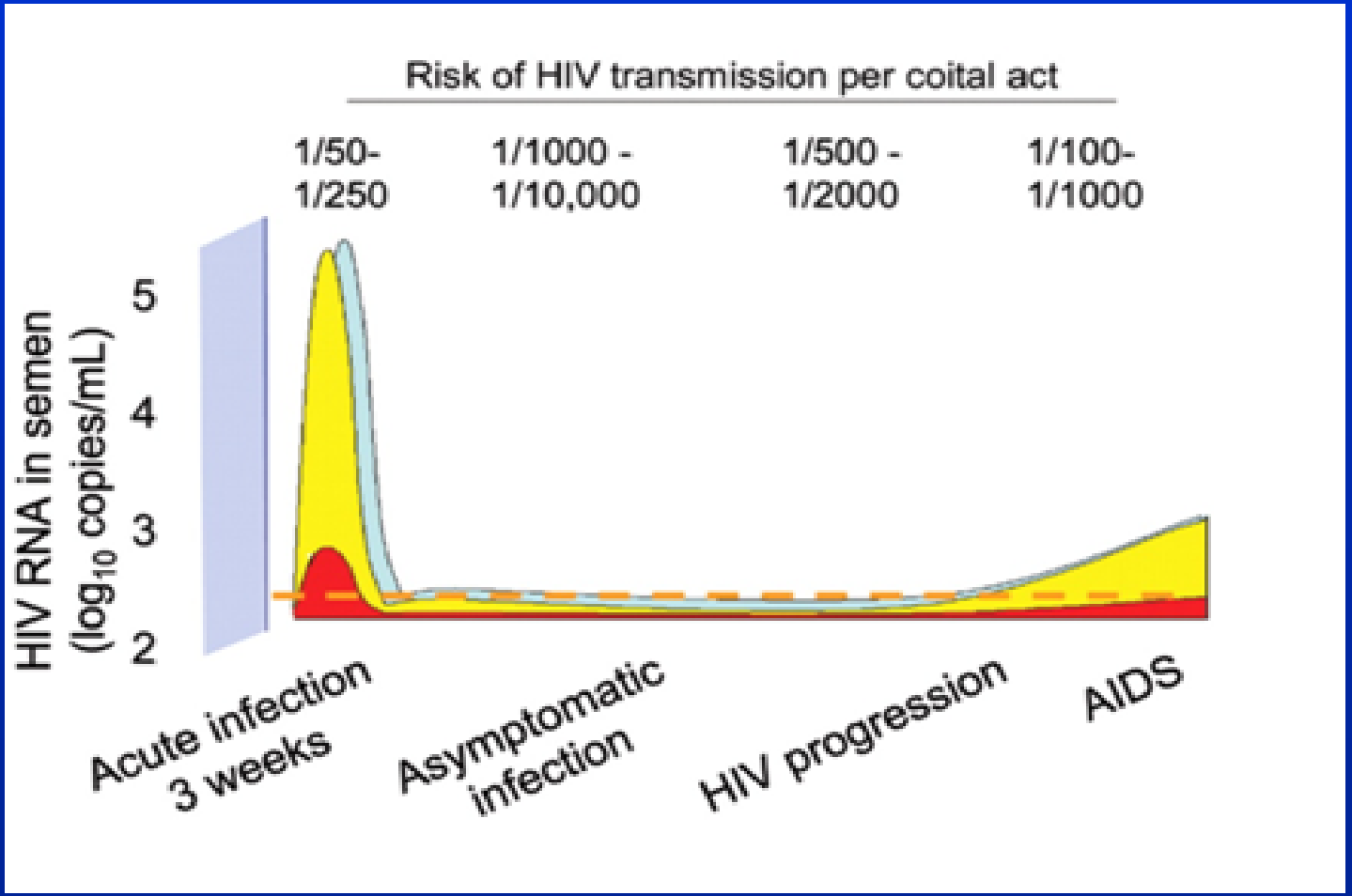
(e) Influence of the internet in sharply increasing partner availability and choice since 2000.

(f) Importance of a small group of superspreaders in accelerating HIV and STI transmission.

(g) Presence of a diffused subset of individuals with undiagnosed HIV infection.

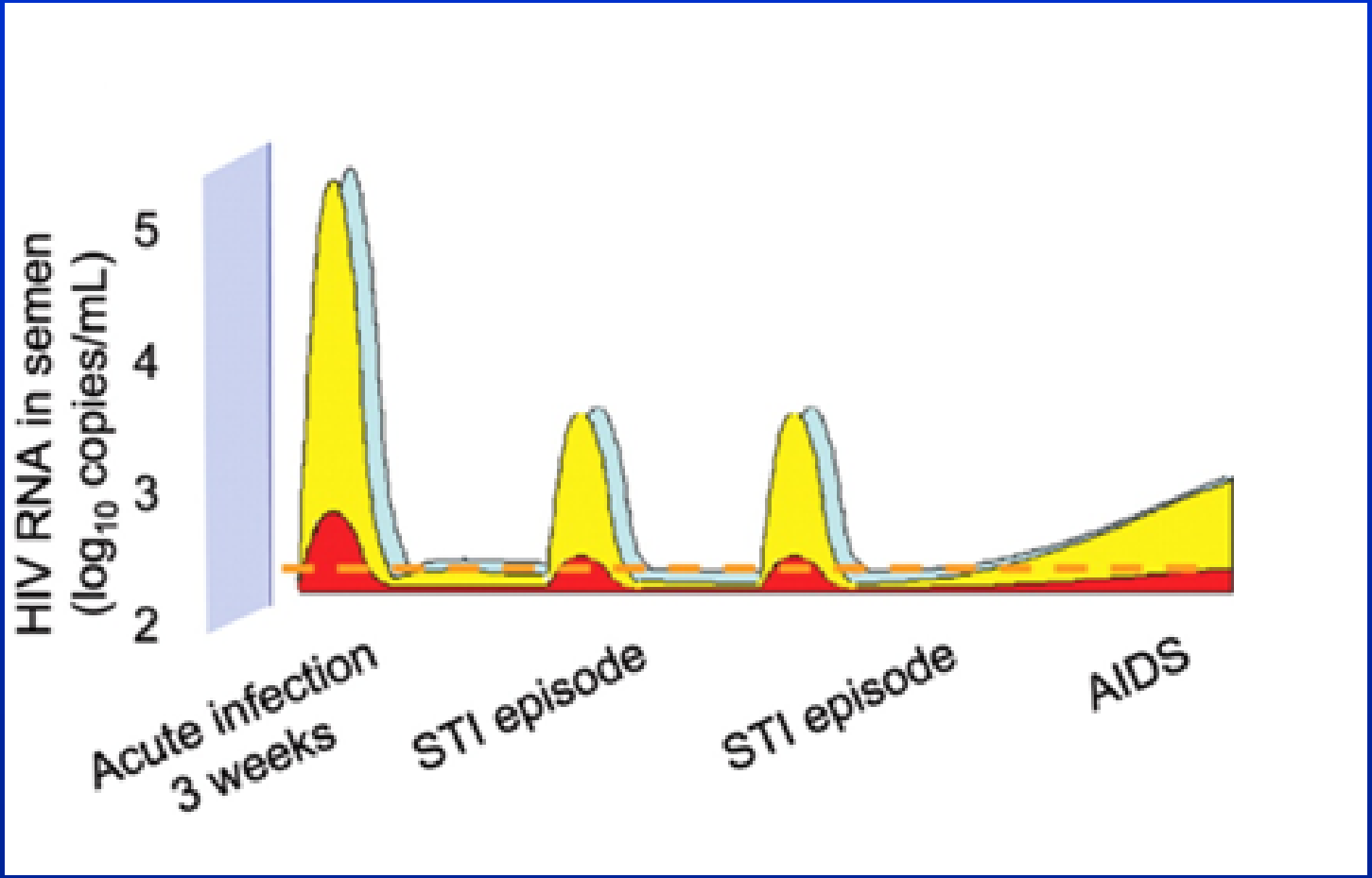
(h) Heightened risk of HIV acquisition and transmission in presence of STI co-infections.

Individual level: Sharply increased transmission risk in primary HIV infection



Cohen, M .S. Pilcher , C.D. *J Infect Dis* 2005; 191: 1391-1393.

Increased HIV transmission risk in the presence of STIs



Cohen, M.S. Pilcher , C.D. *J Infect Dis* 2005; 191: 1391-1393.

Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected MSM

Highly active antiretroviral therapy does not completely suppress HIV in semen of sexually active HIV-infected men who have sex with men

Joseph A. Politch[a], Kenneth H. Mayer[b,d], Seth L. Welles[c], William X. O'brien[b], Chong Xu[a], Frederick P. Bowman[a] and Deborah J. Anderson[a]

Objective: Although HAART can suppress genital shedding and sexual transmission of HIV, men who have sex with men (MSM) have experienced a resurgent HIV epidemic in the HAART era. Many HIV-infected MSM continue to engage in unsafe sex, and sexually transmitted infections (STIs) or other factors may promote genital HIV shedding and transmission in this population despite HAART. In this study, we determined the prevalence of seminal HIV shedding in HIV-infected MSM on stable HAART, and its relationship with a number of clinical, behavioral and biological variables.

Design: Sexually active HIV-infected men using HAART were recruited from an MSM health clinic to provide semen and blood samples.

Methods: HIV levels were assessed in paired semen and blood samples by PCR. Clinical and behavioral data were obtained from medical records and questionnaires. HSV-2 serostatus, seminal HSV-2 DNA, and markers of genital inflammation were measured using standard laboratory methods.

Results: Overall, HIV-1 was detected in 18/101 (18%) blood and 30/101 (30%) semen samples. Of 83 men with undetectable HIV in blood plasma, 25% had HIV in semen with copy numbers ranging from 80 – 2,560. Multivariate analysis identified STI/urethritis ($p = 0.003$), TNF-α ($p = 0.0003$), and unprotected insertive anal sex with an HIV-infected partner ($p = 0.007$) as independent predictors of seminal HIV detection.

Conclusions: STIs and genital inflammation can partially override the suppressive effect of HAART on seminal HIV shedding in sexually active HIV-infected MSM. Low seminal HIV titers could potentially pose a transmission risk in MSM, who are highly susceptible to HIV infection.

AIDS 2012, **26**:000–000

Keywords: antiretroviral therapy, HIV-1, MSM, Semen, sexually transmitted infections

Introduction

Approximately 33.3 million people worldwide are living with HIV/AIDS, and 1.8 million deaths and 2.6 million new infections occur annually [1]. Unprotected intercourse is the most common route through which HIV-1 is transmitted, and semen of HIV-infected men is an important source of infectious HIV [2]. Whereas the HIV/AIDS epidemic in Sub-Saharan Africa is generalized with approximately equal percentages of infections occurring in men and women, the epidemic in the US and many other developed countries is concentrated in men who have sex with men (MSM) [3]. Recent reports suggest that MSM populations in lower and middle

[a]Division of Reproductive Biology, Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston, MA, [b]The Fenway Institute, Fenway Community Health, Boston, MA, [c]Department of Epidemiology and Biostatistics, Drexel University School of Public Health, Philadelphia, PA, and [d]Departments of Medicine and Community Health, Warren Alpert Medical School of Brown University, Providence, RI

Correspondence to Deborah J. Anderson, Ph.D, Division of Reproductive Biology, Department of Obstetrics and Gynecology, Boston University School of Medicine, 670 Albany Street, Room 516, Boston, MA 02118
Tel: +617 414 8482; fax: +617 414 8481; e-mail: Deborah.Anderson@BMC.org
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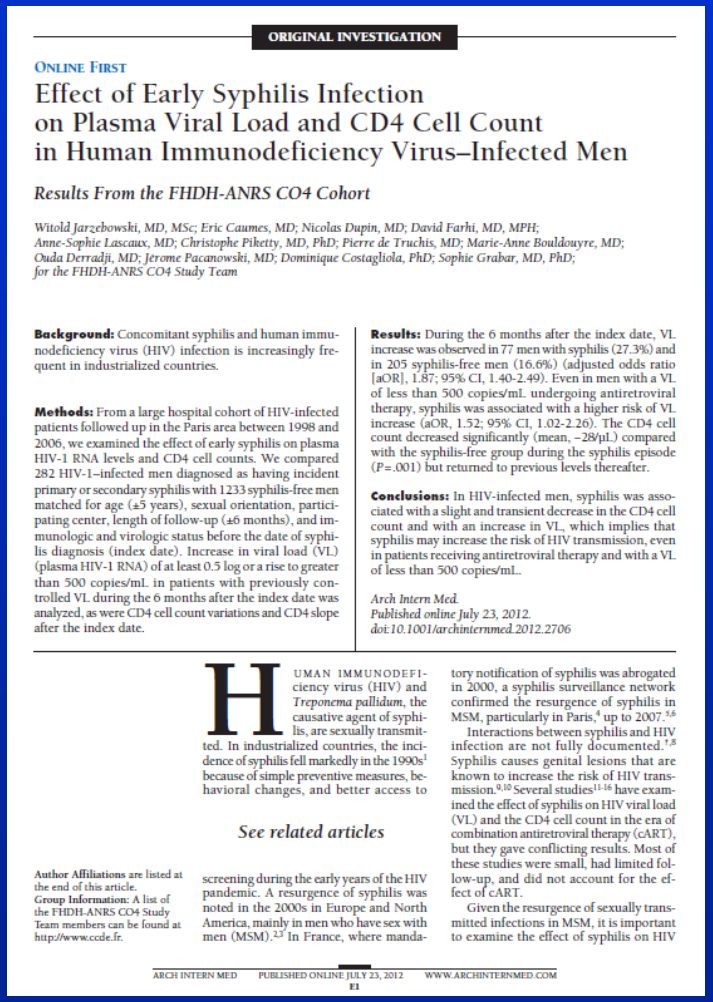
DOI:10.1097/QAD.0b013e328353b11b

- "STIs and genital inflammation can partially override the suppressive effect of HAART on seminal HIV shedding in sexually active HIV-infected MSM. Low seminal HIV titers could potentially pose a transmission risk in MSM, who are highly susceptible to HIV infection."
- "Until more information on transmission risk for MSM is available, it would be prudent to advise sexually active HIV-infected MSM to use condoms and other risk-reduction strategies throughout all stages of HIV disease regardless of HIV treatment status, and to promote the aggressive diagnosis and treatment of STIs."

Politch, J.A. et al. *AIDS* 2012; 26: 1535-1543.

Effect of early syphilis infection on plasma viral load in HIV-infected men



ORIGINAL INVESTIGATION

ONLINE FIRST

Effect of Early Syphilis Infection on Plasma Viral Load and CD4 Cell Count in Human Immunodeficiency Virus–Infected Men

Results From the FHDH-ANRS CO4 Cohort

Witold Jarzebowski, MD, MSc; Eric Caumes, MD; Nicolas Dupin, MD; David Farhi, MD, MPH; Anne-Sophie Lascaux, MD; Christophe Piketty, MD, PhD; Pierre de Truchis, MD; Marie-Anne Bouldouyre, MD; Ouda Derradji, MD; Jerome Pacanowski, MD; Dominique Costagliola, PhD; Sophie Grabar, MD, PhD; for the FHDH-ANRS CO4 Study Team

Background: Concomitant syphilis and human immunodeficiency virus (HIV) infection is increasingly frequent in industrialized countries.

Methods: From a large hospital cohort of HIV-infected patients followed up in the Paris area between 1998 and 2006, we examined the effect of early syphilis on plasma HIV-1 RNA levels and CD4 cell counts. We compared 282 HIV-1–infected men diagnosed as having incident primary or secondary syphilis with 1233 syphilis-free men matched for age (±5 years), sexual orientation, participating center, length of follow-up (±6 months), and immunologic and virologic status before the date of syphilis diagnosis (index date). Increase in viral load (VL) (plasma HIV-1 RNA) of at least 0.5 log or a rise to greater than 500 copies/mL in patients with previously controlled VL during the 6 months after the index date was analyzed, as were CD4 cell count variations and CD4 slope after the index date.

Results: During the 6 months after the index date, VL increase was observed in 77 men with syphilis (27.3%) and in 205 syphilis-free men (16.6%) (adjusted odds ratio [aOR], 1.87; 95% CI, 1.40-2.49). Even in men with a VL of less than 500 copies/mL undergoing antiretroviral therapy, syphilis was associated with a higher risk of VL increase (aOR, 1.52; 95% CI, 1.02-2.26). The CD4 cell count decreased significantly (mean, −28/μL) compared with the syphilis-free group during the syphilis episode ($P=.001$) but returned to previous levels thereafter.

Conclusions: In HIV-infected men, syphilis was associated with a slight and transient decrease in the CD4 cell count and with an increase in VL, which implies that syphilis may increase the risk of HIV transmission, even in patients receiving antiretroviral therapy and with a VL of less than 500 copies/mL.

Arch Intern Med
Published online July 23, 2012.
doi:10.1001/archinternmed.2012.2706

HUMAN IMMUNODEFICIENCY virus (HIV) and *Treponema pallidum*, the causative agent of syphilis, are sexually transmitted. In industrialized countries, the incidence of syphilis fell markedly in the 1990s[1] because of simple preventive measures, behavioral changes, and better access to screening during the early years of the HIV pandemic. A resurgence of syphilis was noted in the 2000s in Europe and North America, mainly in men who have sex with men (MSM).[2,3] In France, where mandatory notification of syphilis was abrogated in 2000, a syphilis surveillance network confirmed the resurgence of syphilis in MSM, particularly in Paris,[4] up to 2007.[5,6]

Interactions between syphilis and HIV infection are not fully documented.[7,8] Syphilis causes genital lesions that are known to increase the risk of HIV transmission.[9,10] Several studies[11-16] have examined the effect of syphilis on HIV viral load (VL) and the CD4 cell count in the era of combination antiretroviral therapy (cART), but they gave conflicting results. Most of these studies were small, had limited follow-up, and did not account for the effect of cART.

Given the resurgence of sexually transmitted infections in MSM, it is important to examine the effect of syphilis on HIV

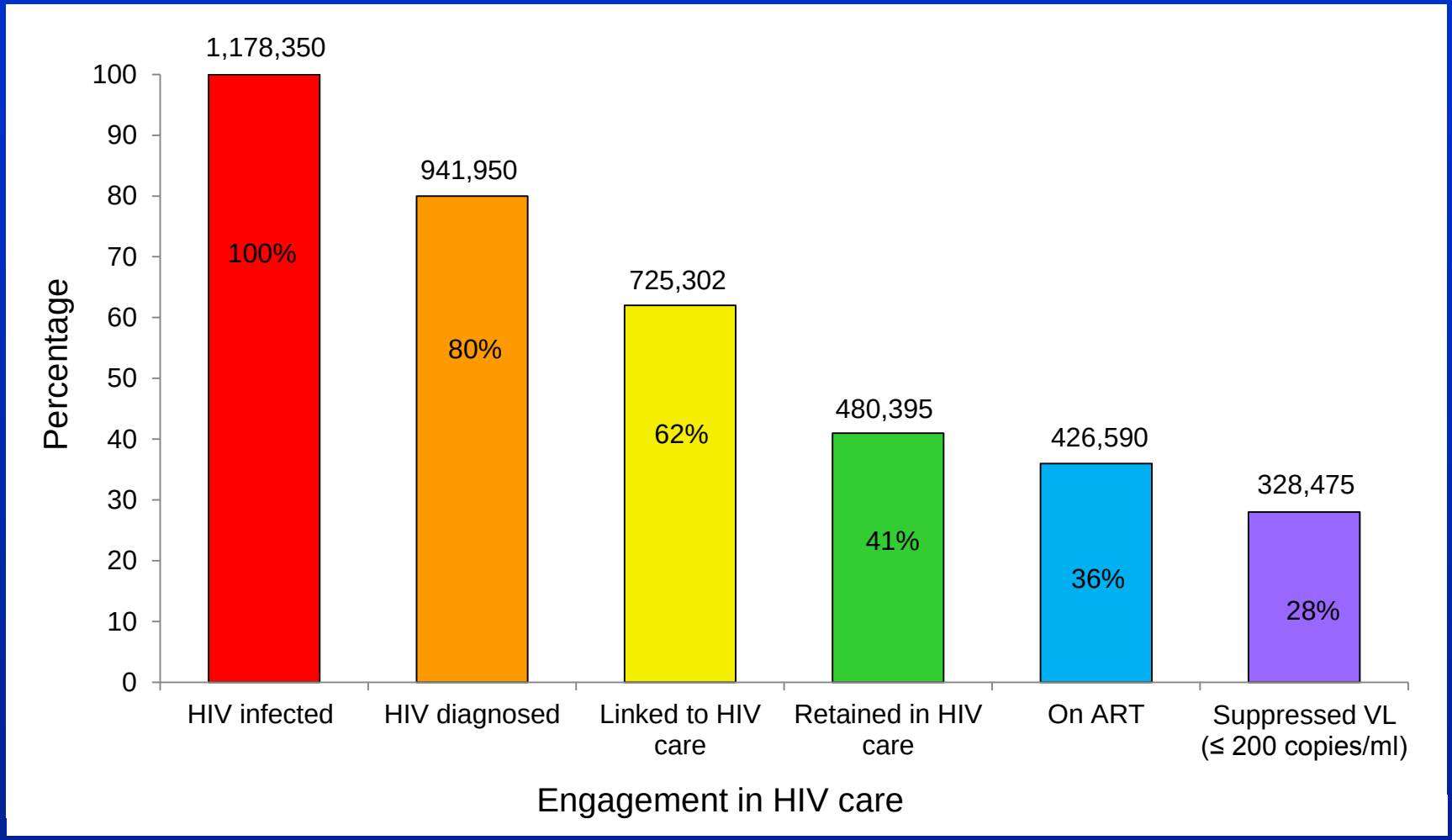
See related articles

Author Affiliations are listed at the end of this article.
Group Information: A list of the FHDH-ANRS CO4 Study Team members can be found at http://www.ccde.fr.

- "In HIV-infected men, syphilis was associated with… an increase in viral load, which implies that syphilis may increase the risk of HIV transmission, even in patients receiving antiretroviral therapy and with a viral load of less than 500 copies/ml."
- "The present study population consisted mainly of MSM infected by syphilis... This population is not covered by the Swiss guideline regarding HIV transmission during effective ART, which concerns couples in stable relationships and who have no other sexually transmitted infections."
- "The present results indicate that populations with high-risk sexual behavior, in which syphilis reinfection is relatively common, must be warned of the risk of HIV transmission and be advised to use condoms."

Jarzebowski, W. et al. *Arch Intern Med* 2012; 172: 1237-1243.

Population level: Potential impact of treatment on HIV prevention in the United States in 2008



"Vital signs: HIV prevention through care and treatment - United States." *MMWR Morb Mortal Wkly Rep* 2011; 60:1618-1623.

Note: This means that out of **1.2 million** people living with HIV in the United States in 2008, **850,000** individuals did not have suppressed viral load (ie: **72%**).

Understanding the complexities of the antiretroviral treatment cascade

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PLoS MEDICINE

Review

HIV Treatment as Prevention: Natural Experiments Highlight Limits of Antiretroviral Treatment as HIV Prevention

David P. Wilson*

The Kirby Institute, Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia

Abstract: There is growing enthusiasm for increasing coverage of antiretroviral treatment among HIV-infected people for the purposes of preventing ongoing transmission. Treatment as prevention will face a number of barriers when implemented in real world populations, which will likely lead to the effectiveness of this strategy being lower than proposed by optimistic modelling scenarios or ideal clinical trial settings. Some settings, as part of their prevention and treatment strategies, have already attained rates of HIV testing and use of antiretroviral therapy—with high levels of viral suppression—that many countries would aspire to as targets for a treatment-as-prevention strategy. This review examines a number of these "natural experiments", namely, British Columbia, San Francisco, France, and Australia, to provide commentary on whether treatment as prevention has worked in real world populations. This review suggests that the population-level impact of this strategy is likely to be considerably less than as inferred from ideal conditions.

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A study by Montaner et al. [3] has been widely promoted as demonstrating treatment as prevention in a community setting, namely, among people who inject drugs (PWID) in British Columbia, Canada. In British Columbia, there is universal access to free rapid HIV testing (though it is not known what proportion of PWID get tested for HIV each year). Guidelines for ART in British Columbia indicate that any HIV-positive patient may commence treatment, regardless of CD4 count, and ART is recommended for all symptomatic patients with established disease, and for asymptomatic individuals with CD4 cell count ≤500 cells/μl [13]. Estimates for ART coverage are difficult to quantify precisely, but coverage is considered to be relatively high and has certainly increased over time.

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Abbreviations: ART, antiretroviral therapy; MSM, men who have sex with men; PWID, people who inject drugs

* E-mail: dwilson@unsw.edu.au

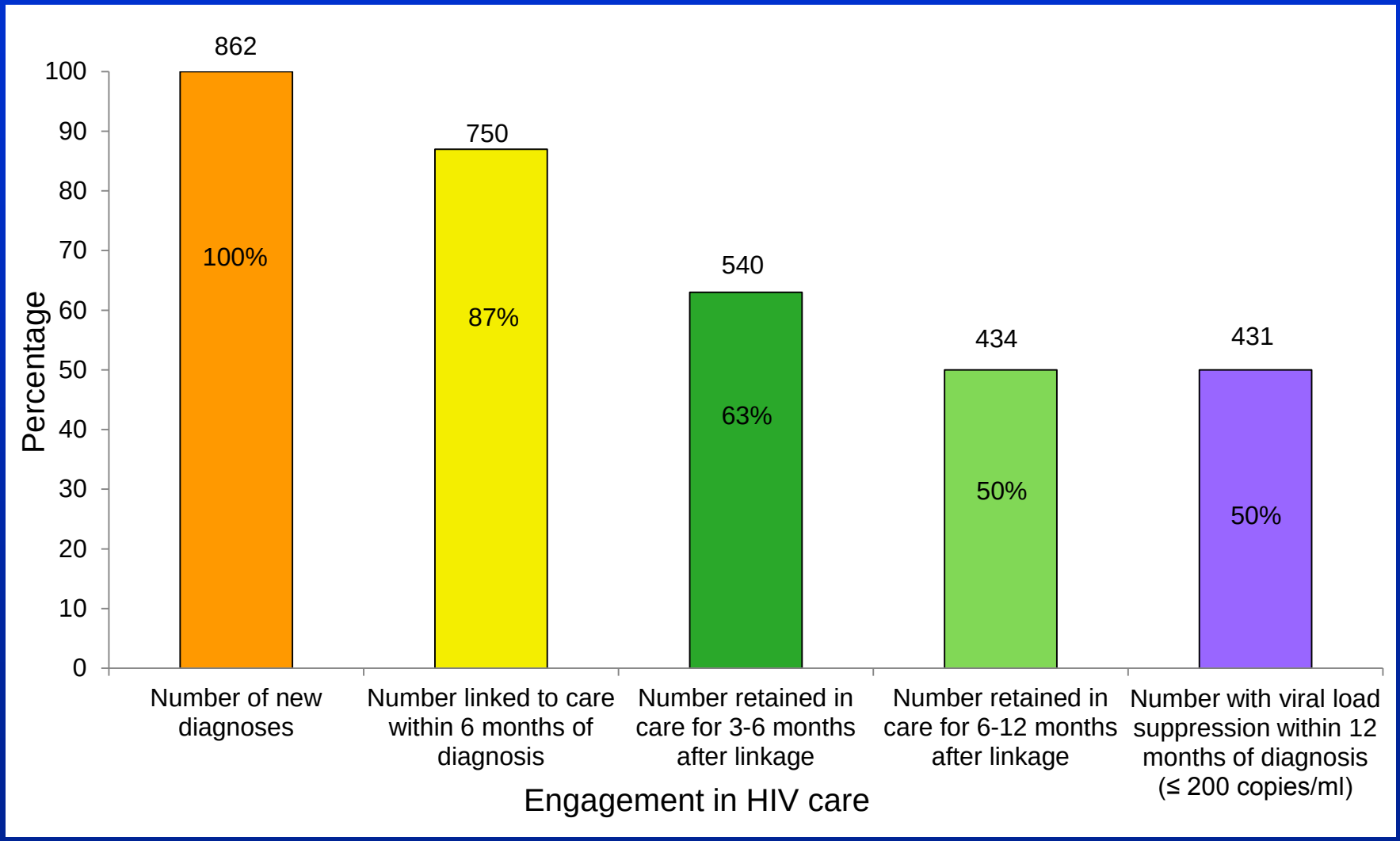
Provenance: Submitted as part of a sponsored Collection; externally reviewed.

- "The efficacy of treatment in reducing transmission has been demonstrated for heterosexual transmission in the HPTN 052 trial, with supporting evidence from other types of studies. However, this does not imply that increased ART coverage will result in substantial declines in incidence in real world populations."
- "One way to consider the problem is that there is a series of barriers to overcome for treatment to be effective in reducing infectiousness."
- "It is not uncommon for people to drop out at any of these barriers. Idealised conditions for a treatment-as-prevention strategy may involve setting targets of 90% of all people at each barrier progressing to the next stage. However, as pointed out by Gardner et al. (2011), this would result in a maximum of just 66% of HIV-infected people in the population having suppressed virus."

Wilson, D. *PloS Med* 2012; 9: e1001231

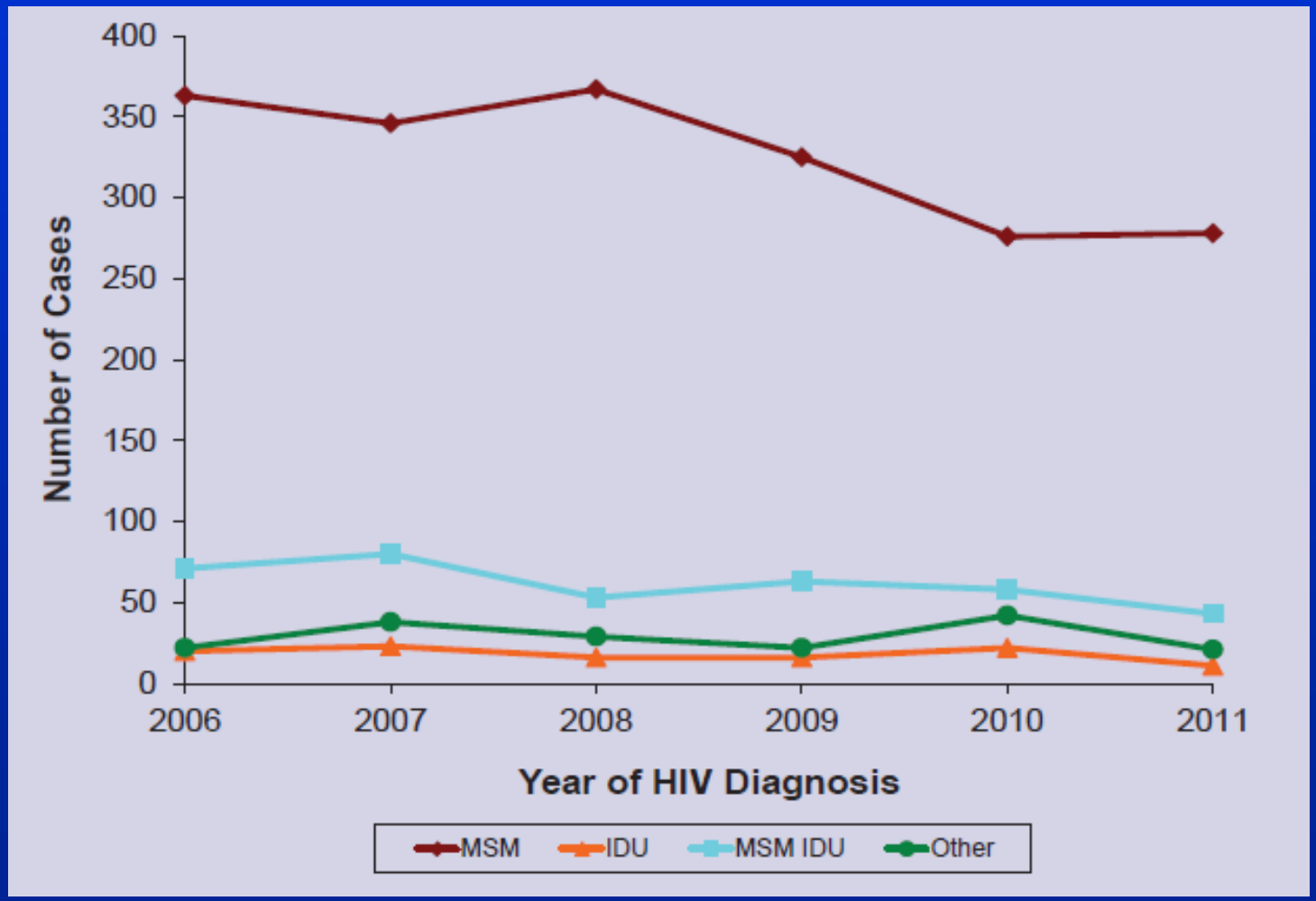
Also: Gardner, E.M. et al. *Clin Infect Dis* 2011; 52: 793-800.

Spectrum of engagement in care among persons diagnosed with HIV, San Francisco, 2009-2010



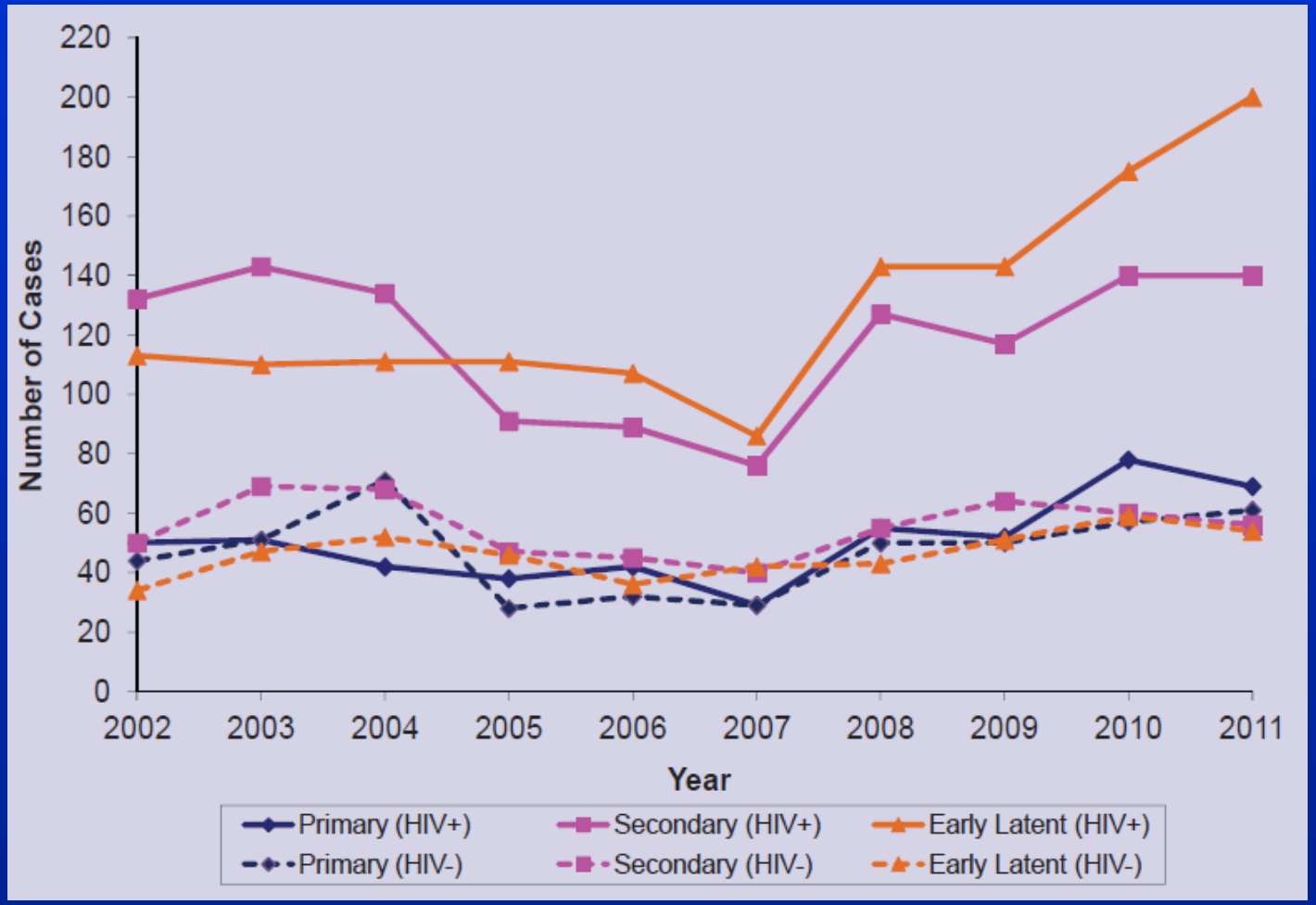
San Francisco Department of Public Health. "HIV/AIDS epidemiology annual report." 2011.

Number of male cases diagnosed with HIV infection by exposure category, San Francisco, 2006-2011



San Francisco Department of Public Health. "HIV/AIDS epidemiology annual report." 2011.

Early syphilis among MSM by HIV serostatus, San Francisco, 2002-2011



San Francisco Department of Public Health. "HIV/AIDS epidemiology annual report." 2011.

Epidemiologic characteristics of an ongoing syphilis epidemic among MSM in San Francisco

ORIGINAL STUDY

Epidemiologic Characteristics of an Ongoing Syphilis Epidemic Among Men Who Have Sex With Men, San Francisco

Kyle T. Bernstein, PhD, ScM,† Sally C. Stephens, MPH,* Frank V. Strona, MPH,‡ Robert P. Kohn, MPH,* and Susan S. Philip, MD, MPH**

Background: Since 2001, San Francisco has experienced a sustained syphilis epidemic that has been nearly exclusively limited to men who have sex with men. We examined the characteristics associated with changes in the syphilis epidemic in San Francisco.

Methods: All primary and secondary (P&S) syphilis cases reported to the San Francisco Department of Public Health between 2001 and 2011 were examined using joinpoint analysis to identify periods within the broader epidemic. Characteristics of the index cases were compared across the periods using χ^2 statistics and *t* tests.

Results: Three distinct periods were identified, an acute increase, decline, and then period of resurgence. In the most recent period of resurgence, compared with earlier periods, patients with P&S syphilis were more likely to have a prior syphilis infection, were older, were more likely to meet partners online, and were more likely to have a partner from outside San Francisco.

Conclusions: In an analysis of 11 years of P&S syphilis data, several factors were associated with declines or resurgences. Innovative prevention measures are needed to reduce syphilis morbidity among men who have sex with men.

BACKGROUND

Between 1999 and 2010, the number of primary and secondary (P&S) syphilis cases reported annually to the San Francisco Department of Public Health rose from 29 to 373, an increase of 1186%.[1] A concurrent increase in reported cases was seen in southern California,[2,3] and shortly thereafter, similar trends became apparent nationally.[4,5] Before 1999, syphilis transmission was largely associated with exchanges of sex for drugs or money and crack cocaine use.[6] The rise in syphilis that began in the late 1990s was associated with increased transmission among men who have sex with men (MSM), many of whom were HIV infected and also met their sex partners online.[7] As the MSM syphilis epidemic spread across the United States, new and innovative prevention and intervention efforts were needed.

Over the past decade, San Francisco has developed and implemented a number of interventions across many domains in an effort to reduce syphilis morbidity among the city's MSM population. These efforts include the development of Internet partner notification protocols,[8] inSPOT (anonymous online partner notification),[9] online syphilis testing (www.stdtest.org),[10] and several social marketing campaigns.[11,12] Despite these novel programs and declines in syphilis seen between 2003 and 2007 (Fig. 1), reported P&S syphilis began to once again increase later in 2007 and continued to rise through 2011.

In their seminal work on sexually transmitted disease (STD) epidemiology, Wasserheit and Aral[13] describe how approaches to prevention may differ in distinct epidemic phases. Others have explored the ways in which transmission dynamics may change over the course of these phases, primarily for HIV.[14,15] An examination of epidemic phases was explored in Baltimore by Cunnigham and colleagues; however, the epidemic examined was almost exclusively among heterosexuals.[16] Here we build on the existing foundation of examining epidemic phases and explored the epidemiologic characteristics of P&S syphilis in San Francisco from 2001 to 2011 in an attempt to elucidate what may have precipitated the decline and subsequent resurgence.

METHODS

Epidemiologic Data

All reactive serologic tests for syphilis and clinical diagnoses of syphilis are required to be reported to the local health authority as per California Public Health law. We examined all reported P&S syphilis cases among San Francisco residents from 2001 through 2011. Cases of P&S syphilis reported within 30 days of a prior report for the same individual are considered duplicate case reports, and only the first report was included in the analysis. If cases were reported with an intervening interval greater than 30 days, these were considered separate episodes of P&S syphilis. Although we cannot rule out the possibility of a treatment failure, it is unlikely because all cases were treated with Centers for Disease Control and Prevention–recommended treatment regimens.[17] Persons infected with P&S syphilis multiple times during the 11 years of data were included multiple times.

Suspected or confirmed cases of P&S syphilis reported to the San Francisco Department of Health were investigated by trained field staff. These investigations included an interview with the index patient, assurance of appropriate treatment, and

From the *San Francisco Department of Public Health, San Francisco, CA; †Division of Epidemiology, School of Public Health, University of California, Berkeley, CA; ‡Centers for Disease Control and Prevention, Atlanta, GA

We thank Rilene Ng, Nicole Olson, and Michael Samuel, California Department of Public Health, for providing data and analysis of Bay Area primary and secondary syphilis case reports; Mark Pandori, San Francisco Public Health Laboratory, for providing data on VDRL testing; and Jen Hecht from the STOP AIDS Project for providing data on syphilis testing among men who have sex with men.

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Conflict of interest: None to report

Correspondence: Kyle Bernstein, PhD, ScM, STD Prevention and Control Services, San Francisco Department of Public Health, 1360 Mission St, Suite 401, San Francisco, CA 94103. E-mail: kyle.bernstein@sfdph.org.

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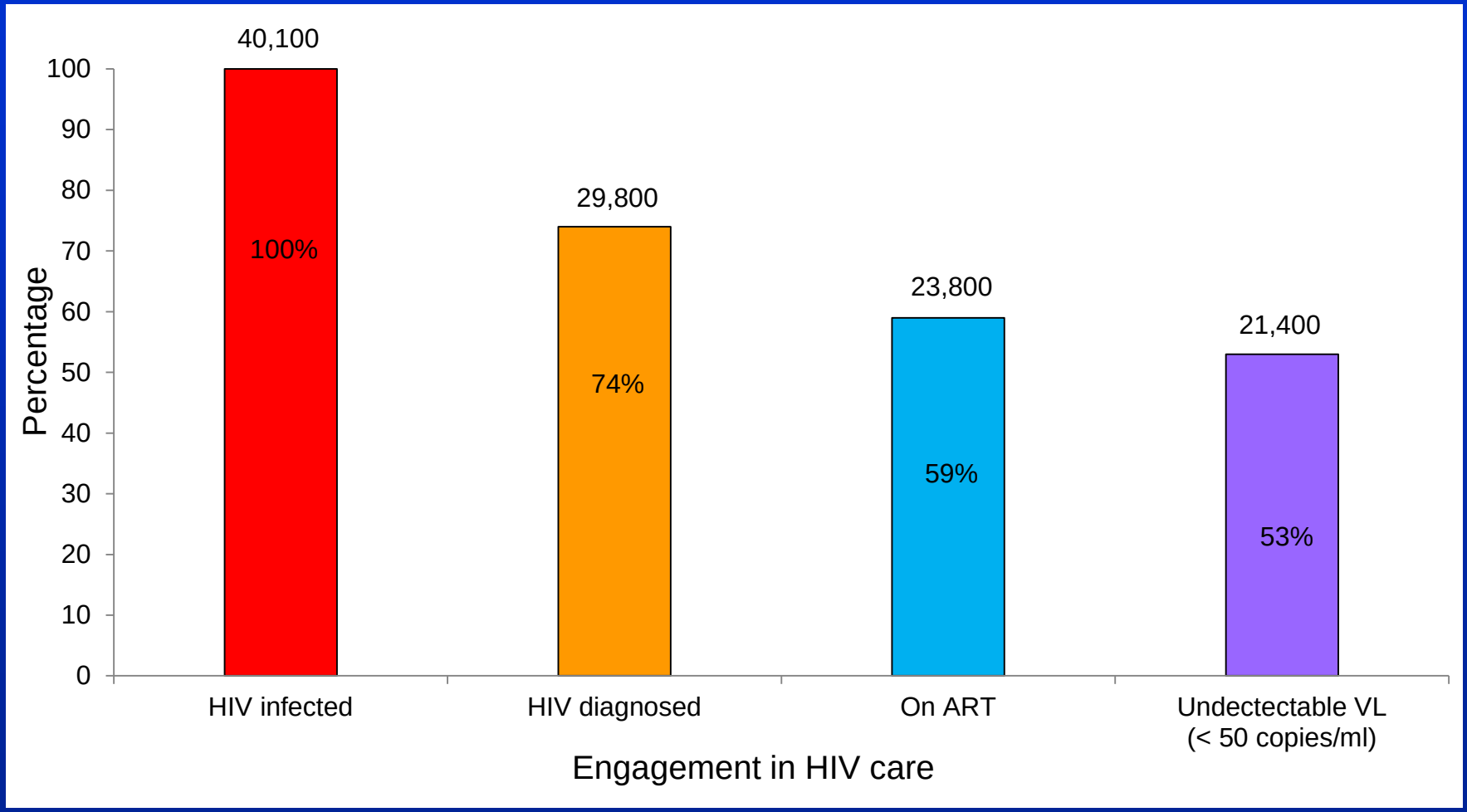
- "Throughout the 11 years of analytic data, the overall characteristics of the populations affected by syphilis have been strikingly consistent - older, mostly white, and MSM, of which approximately 60% are HIV infected."
- "The proportion of patients with syphilis with a prior syphilis infection increased significantly from 6.6% [between 2001 and 2002] to 24.9% [between 2007 and 2011]. These data suggest that a small but important core group of men with multiple episodes of syphilis may be sustaining on-going syphilis transmission."
- "Efforts that target the small core of repeatedly infected patients with syphilis may have an impact on the overall trajectory of syphilis. Furthermore, the role of HIV positive serosorting in maintaining endemic STDs also requires further exploration. Unfortunately, data on serosorting practices among the general population of MSM in San Francisco are sparse."

Bernstein, K. T. *Sex Trans Dis* 2013; 40: 11-17.

MSM living with HIV by diagnosis, treatment and viral load status in the United Kingdom, 2010

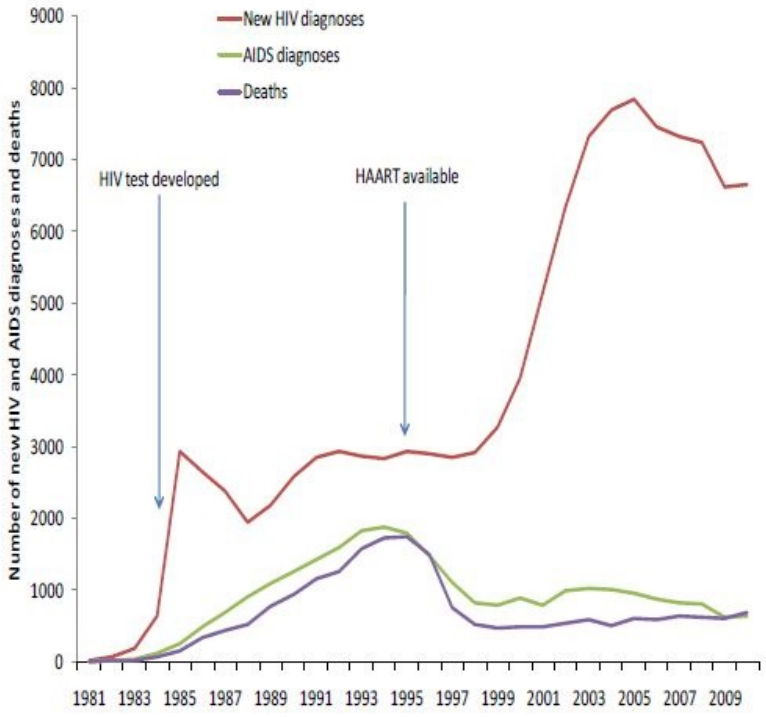


Delpech, V. "Health system concerns related to TasP and most at risk populations."
Presented at: International Association of Physicians in AIDS Care, Royal Gardens Hotel, London, June 2012.

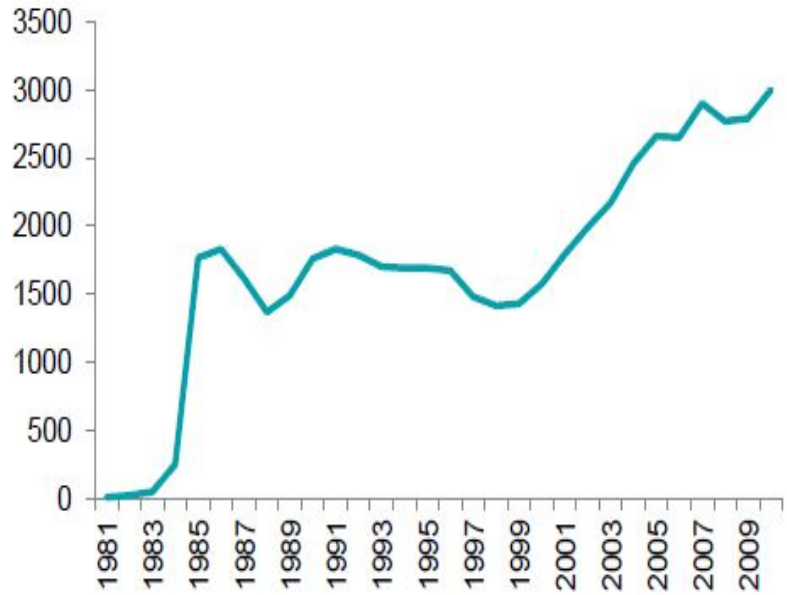
Note: Numbers were adjusted by missing information and rounded to the nearest 100.

HIV epidemic in the United Kingdom

HIV and AIDS diagnoses and deaths



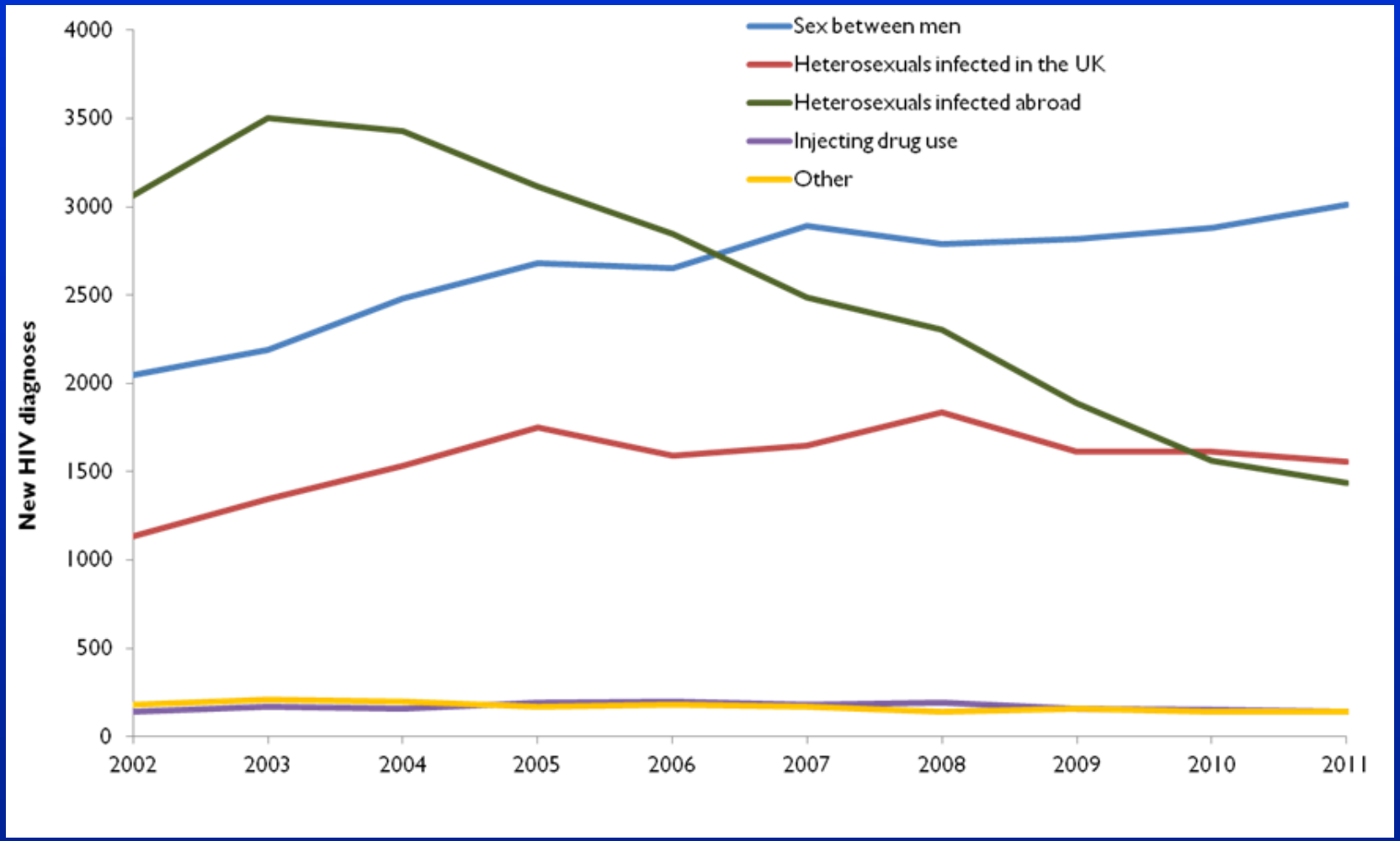
HIV diagnoses in MSM



Adapted from: Delpech, V. "Health system concerns related to TasP and most at risk populations." Health Protection Agency, UK.

Presented at: IAPAC. "Controlling the HIV pandemic with antiretrovirals: Treatment as prevention and pre-exposure prophylaxis." Royal Garden Hotel, London, 11-12 June, 2012.

New HIV diagnoses by exposure group: United Kingdom, 2002 - 2011



HIV and STI Department, Health Protection Agency, Colindale.

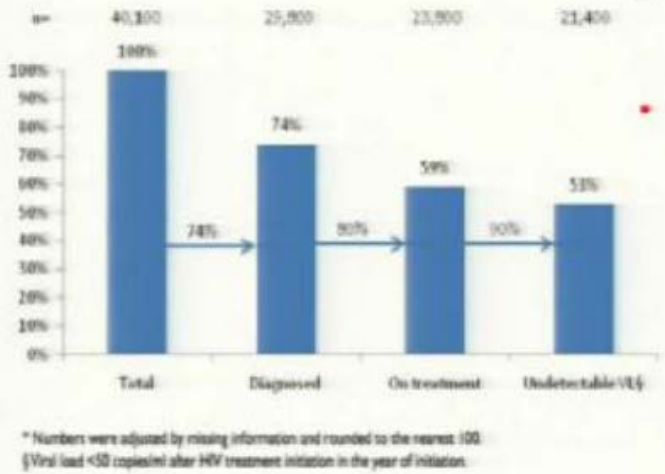
"HIV in the United Kingdom: 2012 Overview."

Beyrer, C. "The global MSM HIV epidemic: Time to act."

Presented at: The 20th Conference on Retroviruses and Opportunistic Infections (CROI 2013), Atlanta, USA, 3-6 March 2013.

TasP not associated with reductions in HIV incidence among MSM in UK

MSM living with HIV by diagnosis, treatment and viral load status: UK, 2010



* Numbers were adjusted by missing information and rounded to the nearest 100
§Viral load <50 copies/ml after HIV treatment initiation in the year of initiation

(Delpech, IAPAC, 2012)

- 40 000 HIV+ UK MSM
  - 26% undiagnosed
  - 80% of diagnosed MSM on ART (84% with CD4>350)
- Access to & retention in care >95% from 2001-2010
- **BUT** HIV incidence still climbing because
  - Risk behavior and increasing STIs
  - Low annual testing (only 15 – 25%) among MSM ages 15-59
  - Undiagnosed → 60%-80% transmissions
    - 62% of undiagnosed infective (VL >1500 copies/ml)
    - 34-60% transmissions due to primary HIV infection in first few months of infection

Beyrer, C. "The global MSM HIV epidemic: Time to act."

Presented at: The 20th Conference on Retroviruses and Opportunistic Infections (CROI 2013), Atlanta, USA, 3-6 March 2013.

Treatment as prevention (TasP)
Can treatment reduce the transmission of HIV: Experience from the UK

Dr Valerie Delpech
Health Protection Agency, London
(Public Health England)

Delpech, V. "Treatment as prevention (TasP). Can treatment reduce the transmission of HIV: Experience from the UK."

Presented at: The third webinar in our series addressing a range of topics in HIV prevention research, hosted jointly by NAM and AVAC (AIDS Vaccine Advocacy Coalition) "Treatment as prevention: Evidence from Europe and beyond," 28 March 2013.

Failure of TasP among MSM in the UK?

- Despite substantial progress of 'test and treat' prevention policies over the past decade in the UK, there is no evidence of a reduction in the incidence of HIV infection in MSM

Reasons

- Declines in safer sex with the introduction of ART
- Continued high rates of undiagnosed
- Low testing rates
- ?High rates of STIs

Delpech, V. "Treatment as prevention (TasP). Can treatment reduce the transmission of HIV: Experience from the UK."

Presented at: The third webinar in our series addressing a range of topics in HIV prevention research, hosted jointly by NAM and AVAC (AIDS Vaccine Advocacy Coalition) "Treatment as prevention: Evidence from Europe and beyond." 28 March 2013.

HIV in MSM in England and Wales: Back to the drawing board?

"Despite substantial investment in HIV prevention, including increased access to HIV testing and treatment, around 2500 men are infected every year and there is no statistical evidence that this rate is decreasing over time. These findings contradict the significant trend towards earlier diagnosis, as shown by the decline in mean time to diagnosis from 4 years to 3.2 years…"

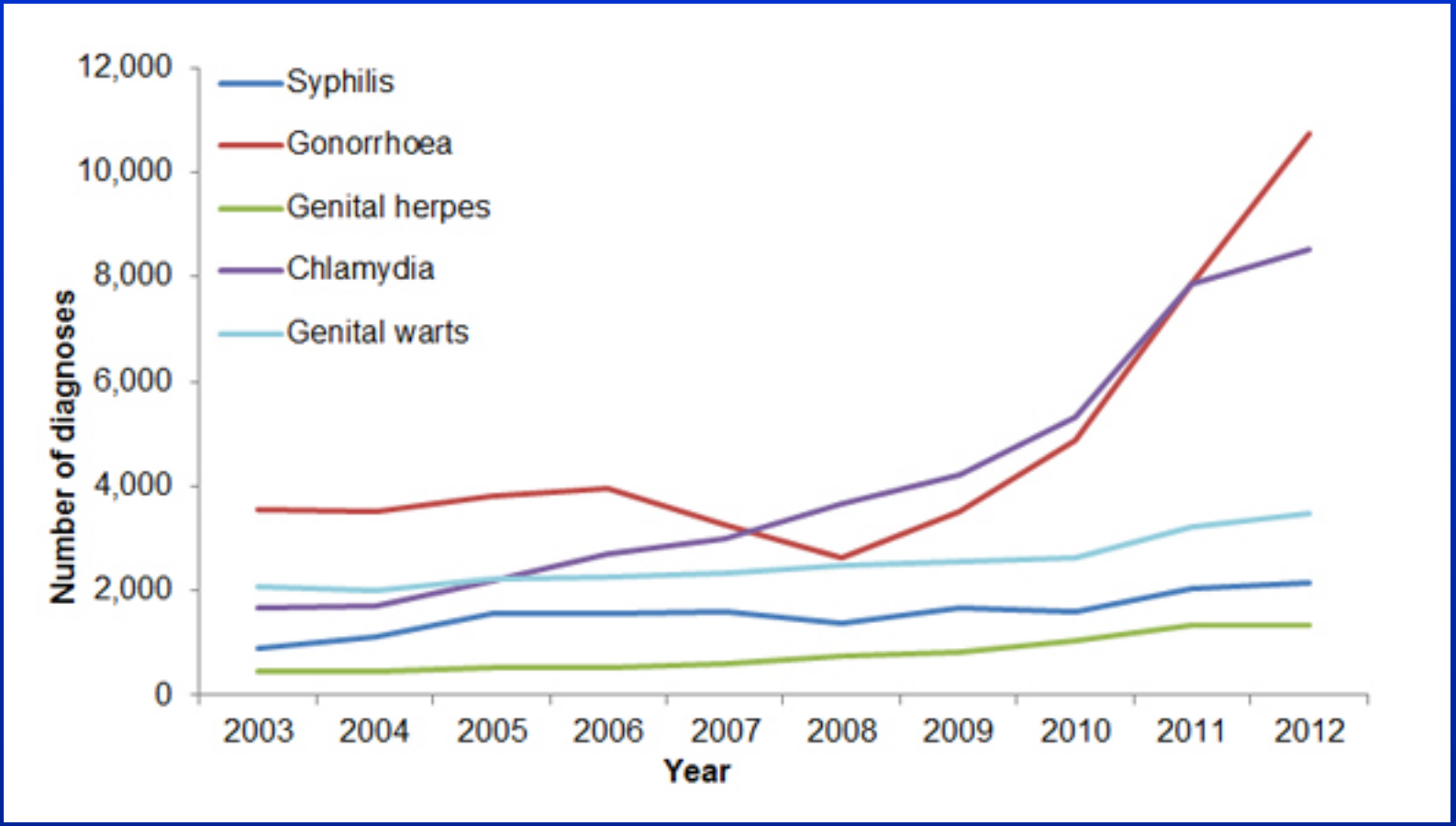
"Additionally [between 2001 and 2010] testing for HIV in sexual health clinics increased from around 16,000 to around 59,300 people, diagnoses increased to around 2,500 in 2010, an estimated 78% of men who have sex with men living with HIV knew their status, the number of men living with HIV rose to 27,900 and the proportion of men in care who received ART rose to 80%."

"Although Birrell and colleagues mainly discuss the evidence regarding HIV testing and treatment, the analysis also clearly shows that increased testing and earlier treatment is no quick and easy solution. Given the complexity of the epidemic, a comprehensive response including the full range of societal and public health interventions will be necessary to reduce incidence."

Dr Reuben Granich,
Joint United Nations Programme on HIV/AIDS (UNAIDS)
Geneva, Switzerland .

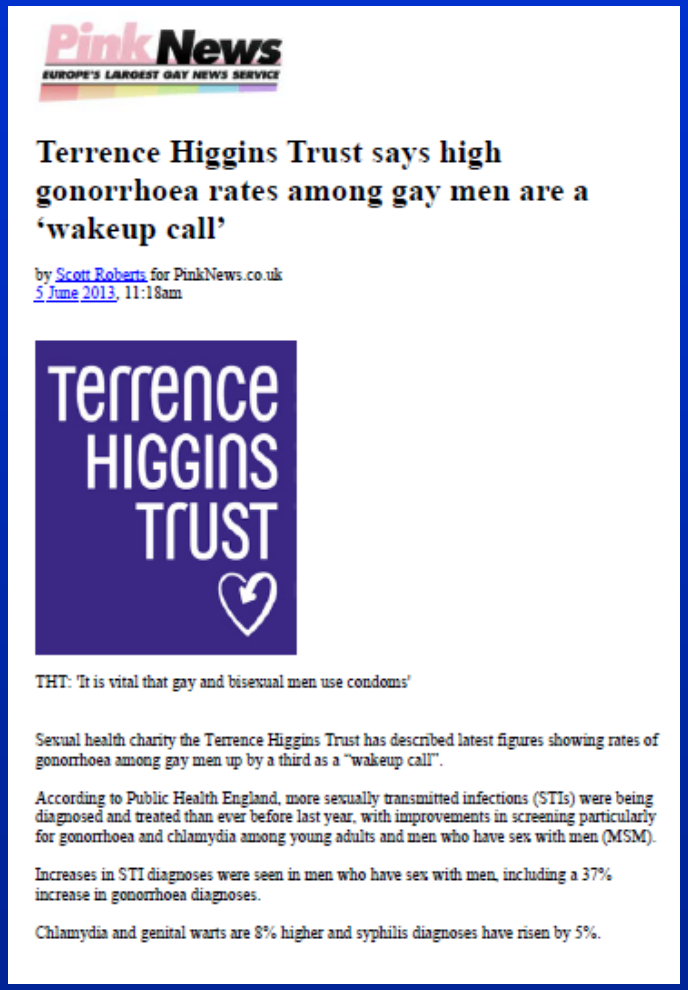
Granich, R. *Lancet Infect Dis* 2013: 13; 279-280.

Number of new diagnoses of selected STIs in MSM, Genitourinary Clinics in England, 2003-2012



Health Protection Agency. "Sexually transmitted infections and chlamydia screening in England, 2012."

STI rates are rising to alarming levels in gay men in England



PinkNews
EUROPE'S LARGEST GAY NEWS SERVICE

Terrence Higgins Trust says high gonorrhoea rates among gay men are a 'wakeup call'

by Scott Roberts for PinkNews.co.uk
5 June 2013, 11:18am

Terrence HIGGINS TRUST

THT: 'It is vital that gay and bisexual men use condoms'

Sexual health charity the Terrence Higgins Trust has described latest figures showing rates of gonorrhoea among gay men up by a third as a "wakeup call".

According to Public Health England, more sexually transmitted infections (STIs) were being diagnosed and treated than ever before last year, with improvements in screening particularly for gonorrhoea and chlamydia among young adults and men who have sex with men (MSM).

Increases in STI diagnoses were seen in men who have sex with men, including a 37% increase in gonorrhoea diagnoses.

Chlamydia and genital warts are 8% higher and syphilis diagnoses have risen by 5%.

- Lisa Power, Policy Director at the Terrence Higgins Trust said: "The rising numbers of almost every STI among gay men should act as a wakeup call to us all. Unlike heterosexuals, where most infections are in young people aged 15-24, gay men are most likely to get STIs in their late 20s and 30s and high levels continue in their 50s. This is due to different patterns of sexual behaviour, and more frequent partner change."

- "We need to remind ourselves that treatment as prevention works to reduce transmission of HIV, but it doesn't do anything to prevent other STIs – and sexually transmitted infections like gonorrhoea and chlamydia actually increase the risk of HIV transmission, even when someone is on treatment. As such, condoms remain a key ingredient not just in protecting against STIs, but also in controlling the spread of HIV."

- "Gonorrhoea in particular has increased by a third in the last year in gay men and has tripled since 2009. In the context of new reports of drug-resistant strains of the infection, it is vital that gay men use condoms and go for regular sexual health check-ups to control the outbreak."

Roberts, S. *Pink News,* 5 June 2013.

Protective effect of condoms for HIV and STI prevention

Sexually Transmitted Infection	Protective effect of condoms
HIV	High
Gonorrhoea	High (unless pharyngeal)
Chlamydia	High
Hepatitis B	High
Syphilis	High (if lesions covered by condom)
Epididymitis	High (where sexually transmitted)
Chancroid	Probably high
Lymphogranuloma venereum	Probably high
Mycoplasma genitalium	Probably high
Trichomoniasis	Probably high
Herpes	Moderate (depends on lesion site)
Warts	Moderate
Hepatitis C	Unknown
Donovanosis	Probably low
Hepatitis A	Very low (transmission is faecal-oral)

Australasian Society for HIV Medicine. "Australasian contract tracing manual." 2010; 4th edition. Endorsed: Royal Australasian College of Physicians

Primary prevention is essential to control HIV and STI transmission in the MSM population

"At present, the priority given to prevention at national and local levels is woefully inadequate. This is demonstrated by the disparity in spending between HIV treatment and prevention. £2.9m will be spent on national prevention programmes in 2011/12. This spending has been static since 2009/10, and is less than half a percent of the £762m spent on treatment and care in England in that year."

"This failure to invest persists despite evidence of the savings that prevention work could yield. The Health Protection Agency indicated that each infection prevented would save between £280,000 and £360,000 in direct lifetime treatment costs. This means that if the estimated 3,000 UK-acquired HIV cases diagnosed in 2010 had been prevented, more than £1.2bn in lifetime costs, would have been avoided."

Lord Norman Fowler, House of Lords.
Select Committee on HIV and AIDS in the United Kingdom:
"No vaccine, no cure: HIV and AIDS in the United Kingdom."
Official Report, HL Paper 188, pp 1- 145, September 2011.

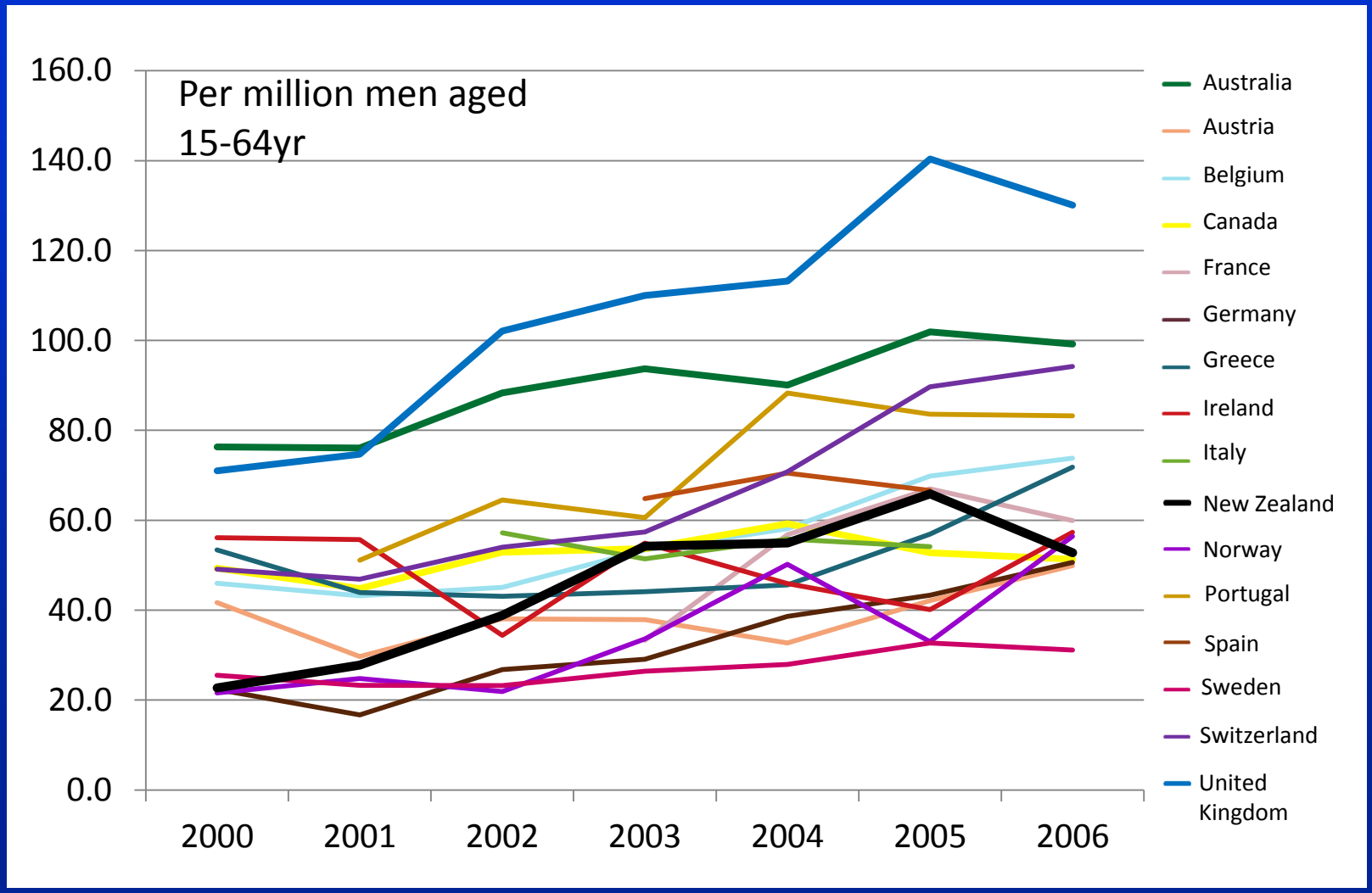
“Have we come to depend so much on the panacea of the antimicrobial that we have forgotten the lessons of Semmelweis, Pasteur and Lister? Prevention of infection must be as important as treatment, and this will require effort on a global scale.”

“It may yet be the simplest preventive measures that have the greatest effect for the least cost.”

Susan Maddocks, Deputy Editor,
“Antimicrobial resistance: Global problems need global solutions.”
Medical Journal of Australia,
18 March 2013

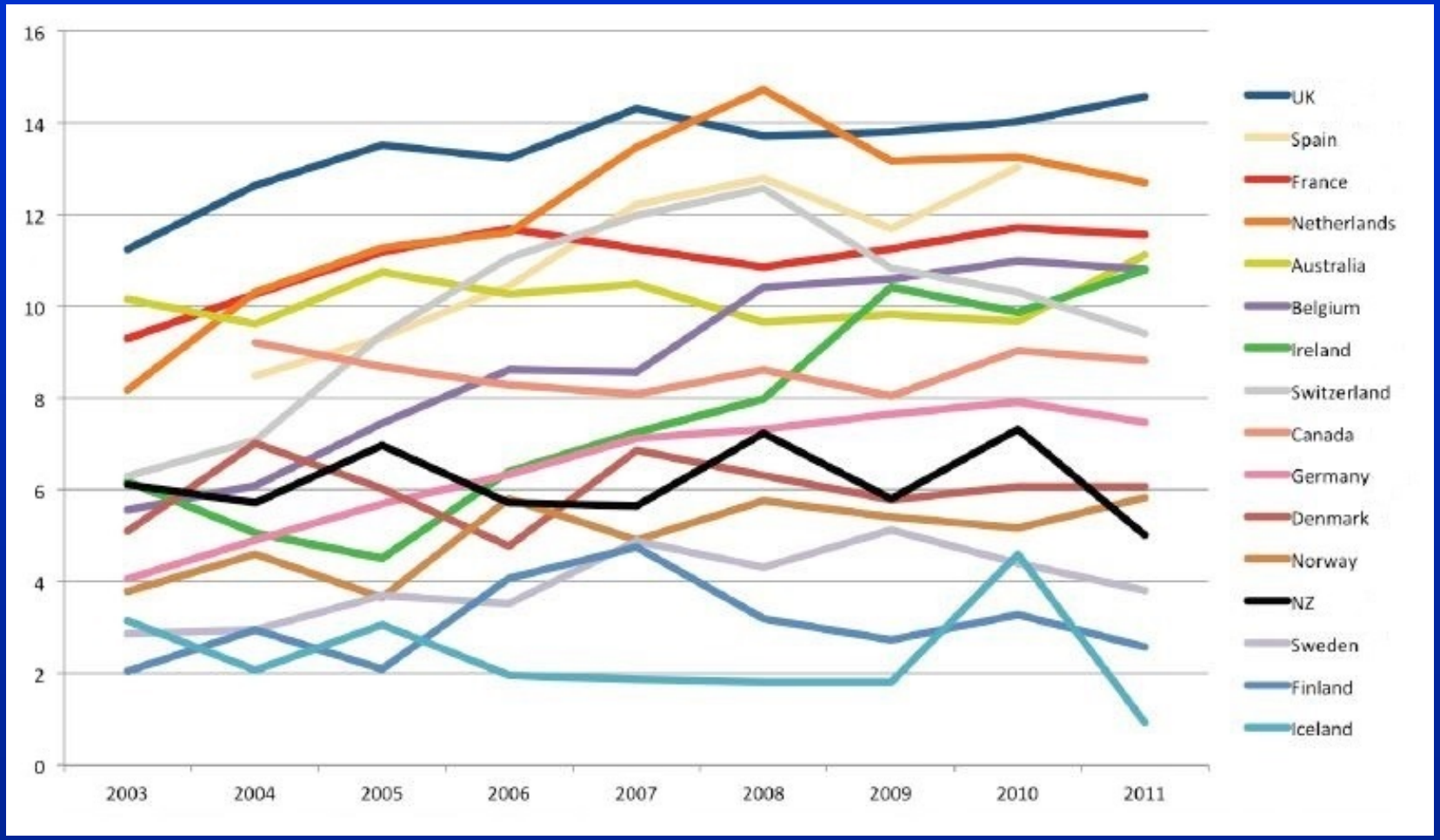
Universal primary prevention response to HIV and other sexually transmitted infections in MSM

HIV diagnosis rate among MSM in Western European countries plus Australia, Canada and New Zealand



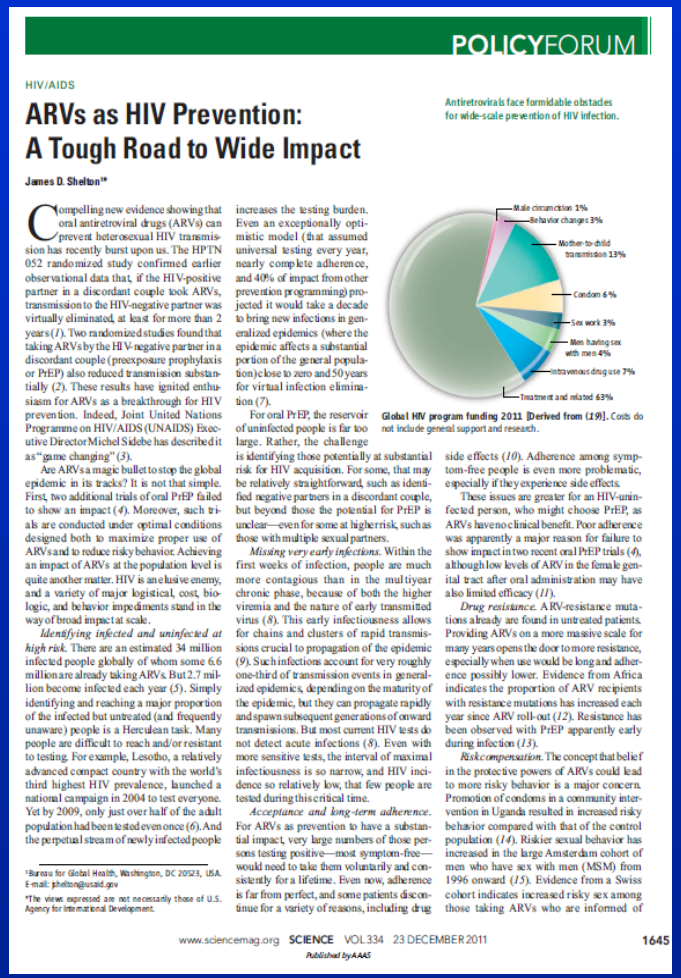
Adapted from: Dickson, N.P. "HIV/AIDS epidemic update." Presented at: 'HIV clinical update meeting.' Auckland City Hospital, 20 Feb 2009.

New HIV diagnoses among MSM, per 100,000 men aged 15-64, 2003-2011



Adapted from: Dickson, N. "Update on HIV epidemiology." Presentation: Auckland City Hospital, Friday 12 April 2013.

ARVs as HIV prevention: A tough road to wide impact



POLICYFORUM

HIV/AIDS

ARVs as HIV Prevention: A Tough Road to Wide Impact

Antiretrovirals face formidable obstacles for wide-scale prevention of HIV infection.

James D. Shelton*†

Compelling new evidence showing that oral antiretroviral drugs (ARVs) can prevent heterosexual HIV transmission has recently burst upon us. The HPTN 052 randomized study confirmed earlier observational data that, if the HIV-positive partner in a discordant couple took ARVs, transmission to the HIV-negative partner was virtually eliminated, at least for more than 2 years (*1*). Two randomized studies found that taking ARVs by the HIV-negative partner in a discordant couple (preexposure prophylaxis or PrEP) also reduced transmission substantially (*2*). These results have ignited enthusiasm for ARVs as a breakthrough for HIV prevention. Indeed, Joint United Nations Programme on HIV/AIDS (UNAIDS) Executive Director Michel Sidebe has described it as "game changing" (*3*).

Are ARVs a magic bullet to stop the global epidemic in its tracks? It is not that simple. First, two additional trials of oral PrEP failed to show an impact (*4*). Moreover, such trials are conducted under optimal conditions designed both to maximize proper use of ARVs and to reduce risky behavior. Achieving an impact of ARVs at the population level is quite another matter. HIV is an elusive enemy, and a variety of major logistical, cost, biologic, and behavior impediments stand in the way of broad impact at scale.

Identifying infected and uninfected at high risk. There are an estimated 34 million infected people globally of whom some 6.6 million are already taking ARVs. But 2.7 million become infected each year (*5*). Simply identifying and reaching a major proportion of the infected but untreated (and frequently unaware) people is a Herculean task. Many people are difficult to reach and/or resistant to testing. For example, Lesotho, a relatively advanced compact country with the world's third highest HIV prevalence, launched a national campaign in 2004 to test everyone. Yet by 2009, only just over half of the adult population had been tested even once (*6*). And the perpetual stream of newly infected people increases the testing burden. Even an exceptionally optimistic model (that assumed universal testing every year, nearly complete adherence, and 40% of impact from other prevention programming) projected it would take a decade to bring new infections in generalized epidemics (where the epidemic affects a substantial portion of the general population) close to zero and 50 years for virtual infection elimination (*7*).

For oral PrEP, the reservoir of uninfected people is far too large. Rather, the challenge is identifying those potentially at substantial risk for HIV acquisition. For some, that may be relatively straightforward, such as identified negative partners in a discordant couple, but beyond those the potential for PrEP is unclear—even for some at higher risk, such as those with multiple sexual partners.

Missing very early infections. Within the first weeks of infection, people are much more contagious than in the multiyear chronic phase, because of both the higher viremia and the nature of early transmitted virus (*8*). This early infectiousness allows for chains and clusters of rapid transmissions crucial to propagation of the epidemic (*9*). Such infections account for very roughly one-third of transmission events in generalized epidemics, depending on the maturity of the epidemic, but they can propagate rapidly and spawn subsequent generations of onward transmissions. But most current HIV tests do not detect acute infections (*8*). Even with more sensitive tests, the interval of maximal infectiousness is so narrow, and HIV incidence so relatively low, that few people are tested during this critical time.

Acceptance and long-term adherence. For ARVs as prevention to have a substantial impact, very large numbers of those persons testing positive—most symptom-free—would need to take them voluntarily and consistently for a lifetime. Even now, adherence is far from perfect, and some patients discontinue for a variety of reasons, including drug side effects (*10*). Adherence among symptom-free people is even more problematic, especially if they experience side effects.

These issues are greater for an HIV-uninfected person, who might choose PrEP, as ARVs have no clinical benefit. Poor adherence was apparently a major reason for failure to show impact in two recent oral PrEP trials (*4*), although low levels of ARV in the female genital tract after oral administration may have also limited efficacy (*11*).

Drug resistance. ARV-resistance mutations already are found in untreated patients. Providing ARVs on a more massive scale for many years opens the door to more resistance, especially when use would be long and adherence possibly lower. Evidence from Africa indicates the proportion of ARV recipients with resistance mutations has increased each year since ARV roll-out (*12*). Resistance has been observed with PrEP apparently early during infection (*13*).

Risk compensation. The concept that belief in the protective powers of ARVs could lead to more risky behavior is a major concern. Promotion of condoms in a community intervention in Uganda resulted in increased risky behavior compared with that of the control population (*14*). Riskier sexual behavior has increased in the large Amsterdam cohort of men who have sex with men (MSM) from 1996 onward (*15*). Evidence from a Swiss cohort indicates increased risky sex among those taking ARVs who are informed of

Global HIV program funding 2011 [Derived from (19)]. Costs do not include general support and research.

*Bureau for Global Health, Washington, DC 20523, USA. E-mail: jshelton@usaid.gov
†The views expressed are not necessarily those of U.S. Agency for International Development.

Published by AAAS

- "For ARVs as prevention to have a substantial impact, very large numbers of those persons testing positive - most symptom-free - would need to take them voluntarily and consistently for a lifetime."
- "At the same time, we need to strengthen behavioral risk reduction and adherence for these high-priority individuals to avoid compromising ARVs prevention benefit."
- "Primary prevention suffers from striking underfunding, especially the core prevention approaches - behavior change, male circumcision, and condoms."
- "Accordingly, ARVs as prevention must not jeopardise already precariously low funding for complementary prevention interventions, particularly the behavioral ones."
- "ARVs are no 'magic bullet'. But ARVs best potential is to contribute to the existing combination arsenal, which, well applied, can have a major impact in stemming the global HIV pandemic."

Shelton, J.D. *Science* 2011; 334: 1645-1646.

Conclusion

(1) Actively promote universal condom use for anal sex to prevent HIV and STI spread in the MSM population.

(2) Encourage regular testing for HIV and STIs in the MSM population.

(3) Facilitate early HIV and STI treatment in the MSM population.

(4) Implement vaccination for STIs wherever possible in the MSM population.

Acknowledgements

Vern Keller, Library and Information Service, New Zealand AIDS Foundation, Auckland for obtaining the scientific papers used in this presentation and assistance with slide preparation.

Dr Peter Saxton, AIDS Epidemiology Group (Auckland) and Associate Professor Nigel Dickson and Sue McAllister, AIDS Epidemiology Group (Dunedin), Department of Preventive and Social Medicine, University of Otago.

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