‘Treatment as prevention’ to reduce HIV transmission in the MSM population: Will it work?

Tony Hughes
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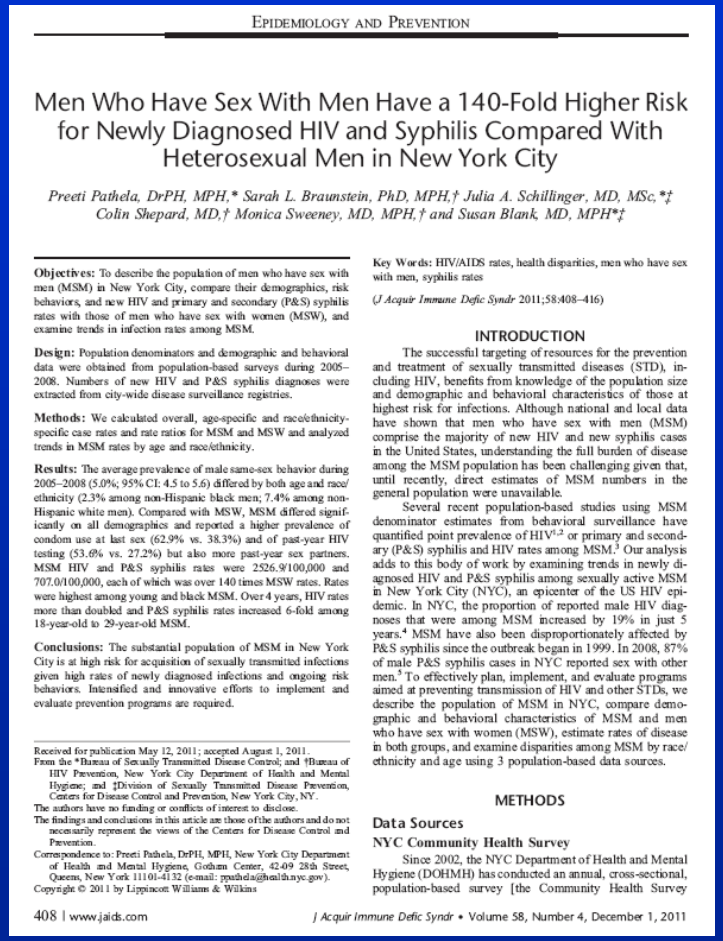
New Zealand Sexual Health Society 34th Annual Conference,
Palmerston North, 30 August - 1 September 2012

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.

Received for publication May 12, 2011; accepted August 1, 2011.

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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.

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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

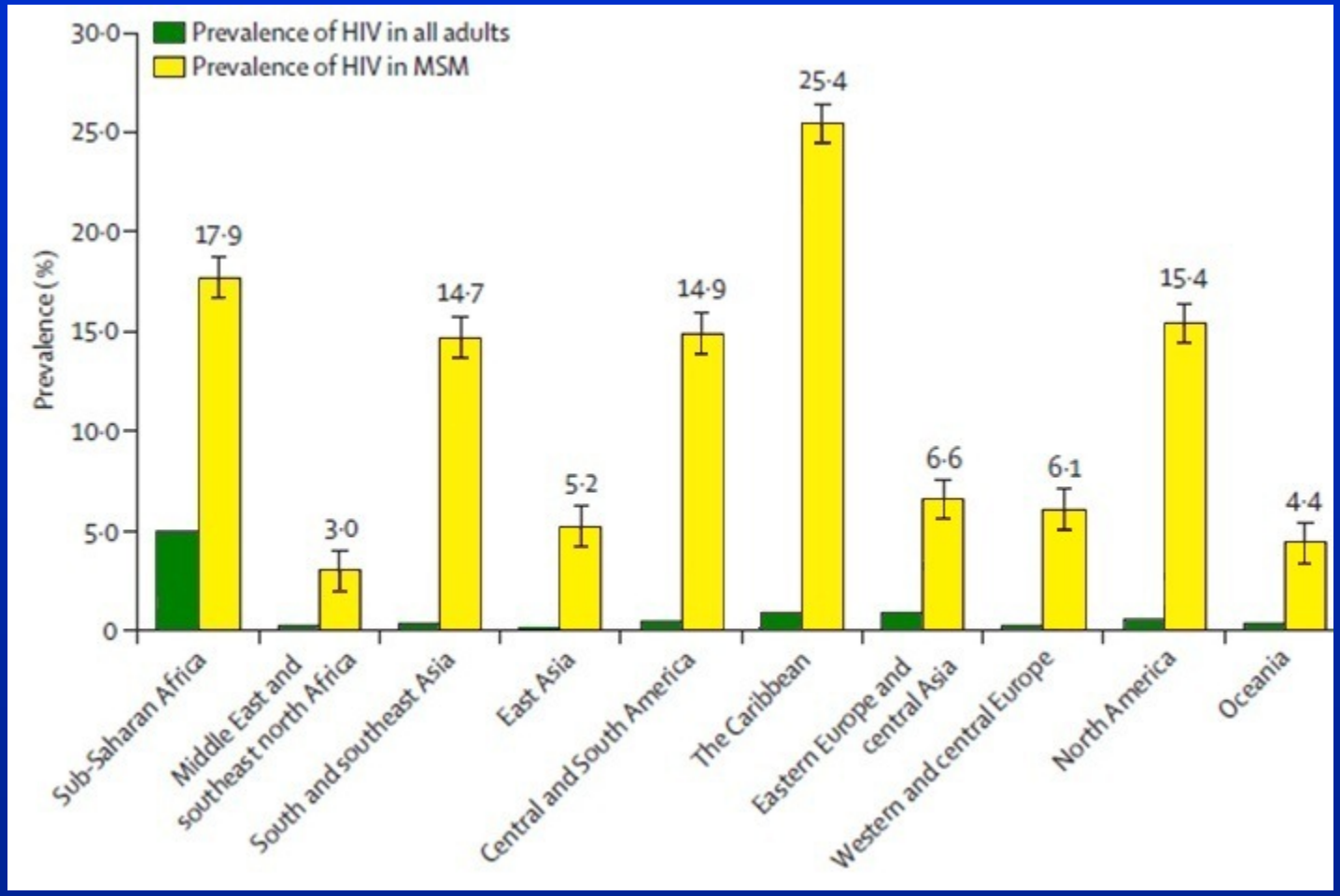
NYC Community Health Survey

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)."

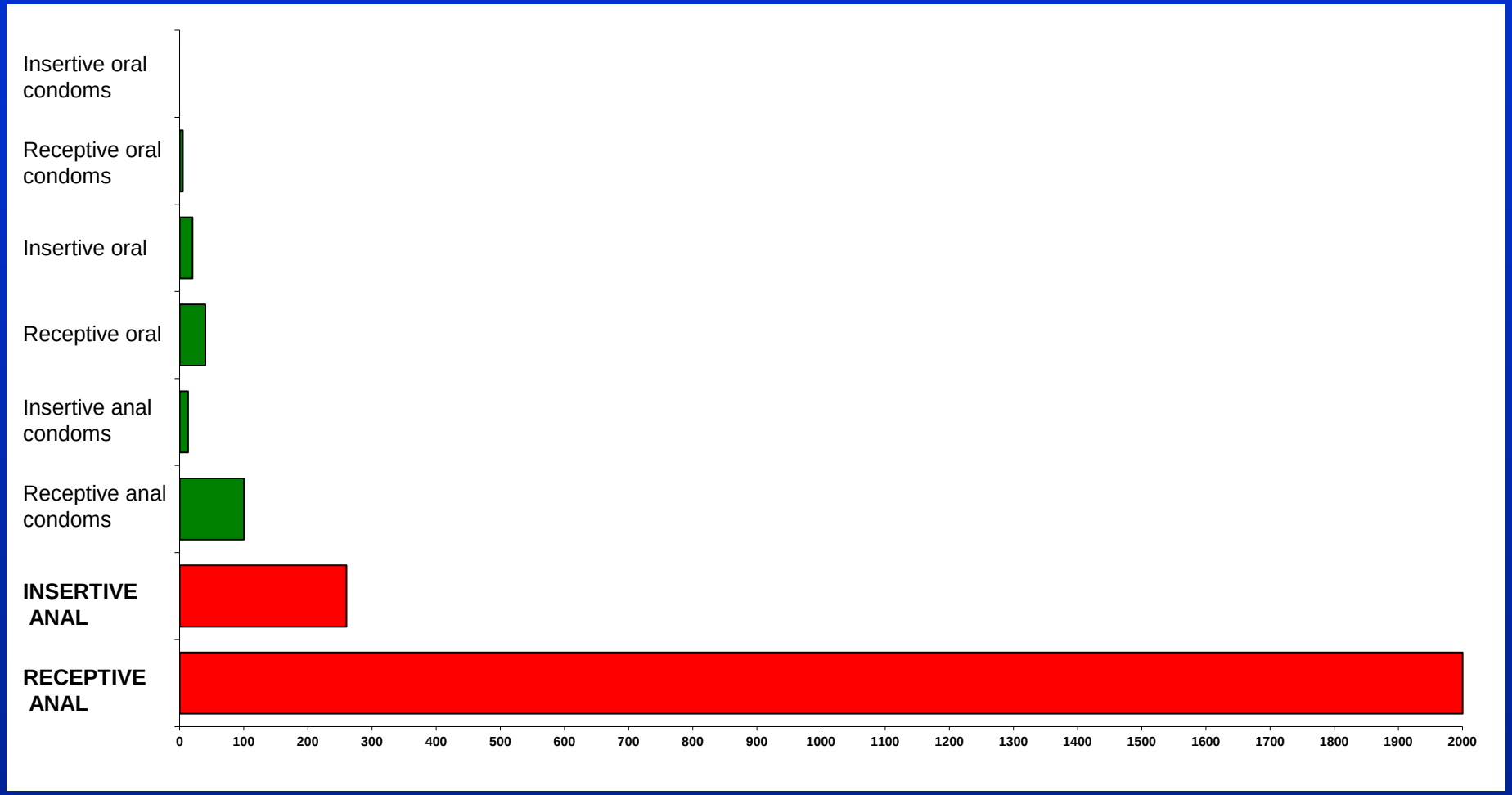
Pathela, P. et al. *J Acq Imm Def Syn* 2011; 58: 408-416.

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



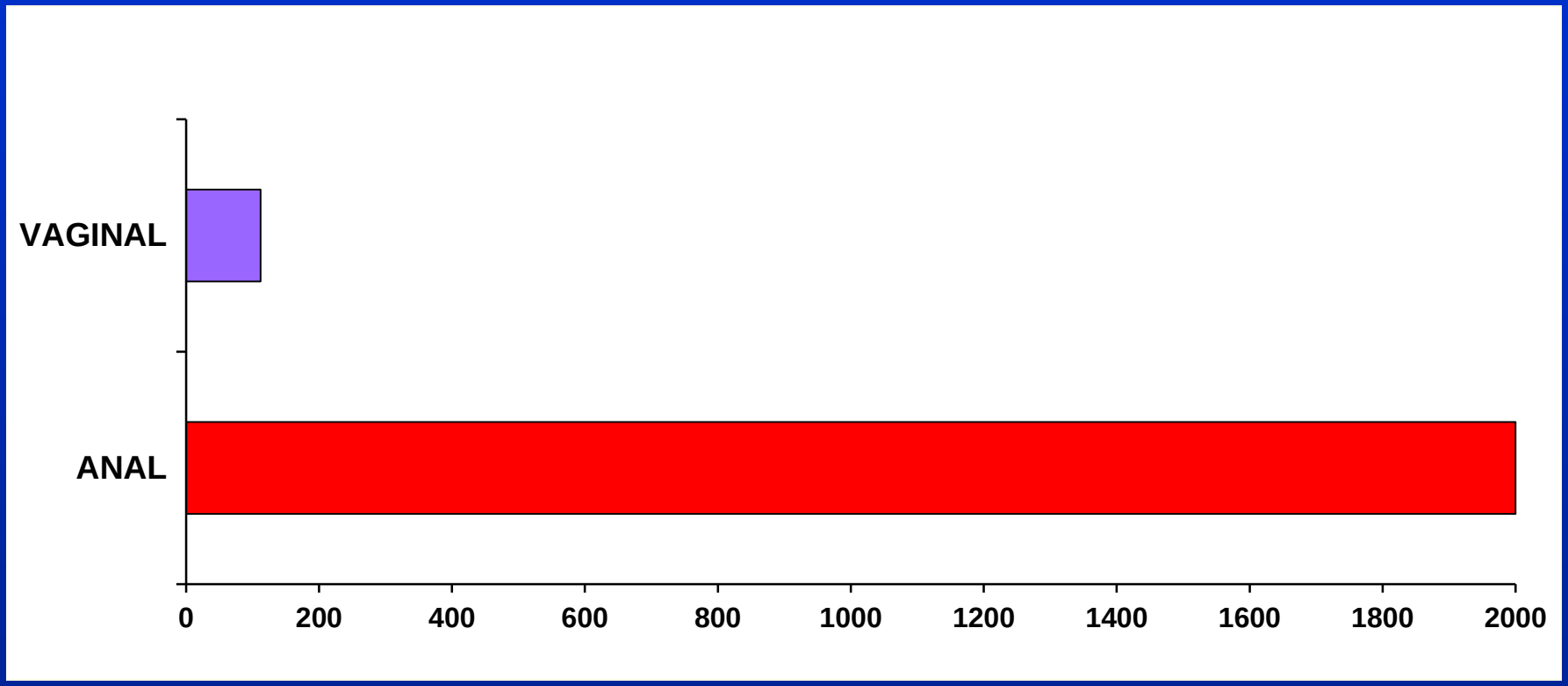
Adapted from: Beyrer, C. et al. *Lancet* 2012; 380: 367-77.

HIV risk for different male-to-male sexual activities relative to receptive anal sex without condoms



Baggaley, White and B oily (2010); Boily et al (2009); Jin et al (2010); Vargese et al (2002); Pinkerton and Abramson (1997); Smith et al (2005); European Study Group on Heterosexual Transmission of HIV (1992).

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).

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.

Lancet 2012; 380: 367–77

Published Online
July 20, 2012
http://dx.doi.org/10.1016/S0140-6736(12)60821-6

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

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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] 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.[3–7] 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.[9,10] 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.[11] In several regions, notably the Middle East, north Africa, and sub-Saharan Africa, data for HIV infections in MSM are only emerging.[12,13] 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.[11] 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

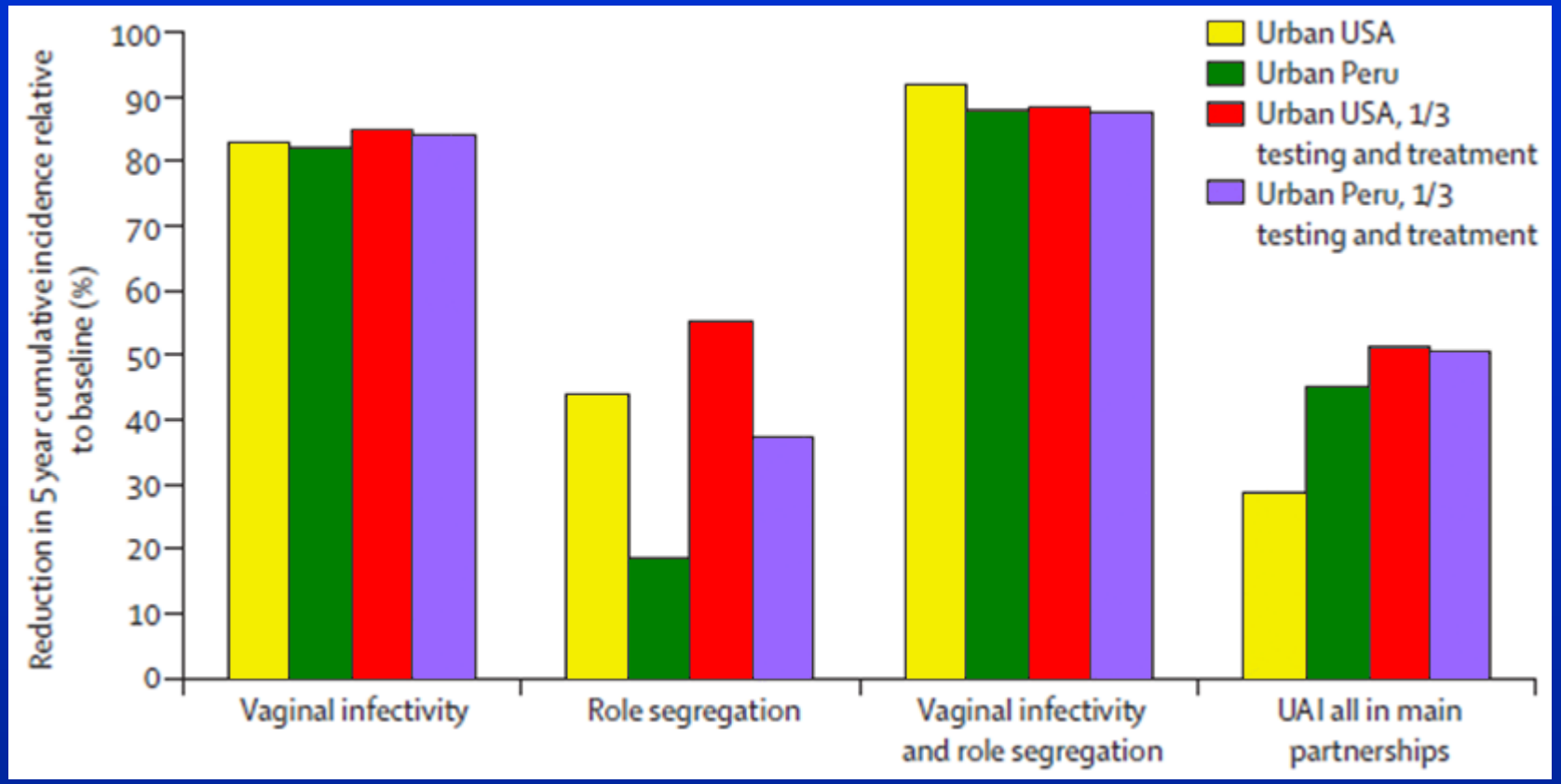
We did a comprehensive search for HIV burden and risks in MSM from Jan 1, 2007, to June 30, 2011 (search criteria in the appendix). We retrieved 2105 unique citations, and we identified and reviewed 68 additional surveillance studies in the public domain. We included country progress reports submitted 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%

- "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 multi-variant HIV infection in MSM than in heterosexual people in the same populations."

Beyrer, C. et al. *Lancet* 2012; 380: 367-77.

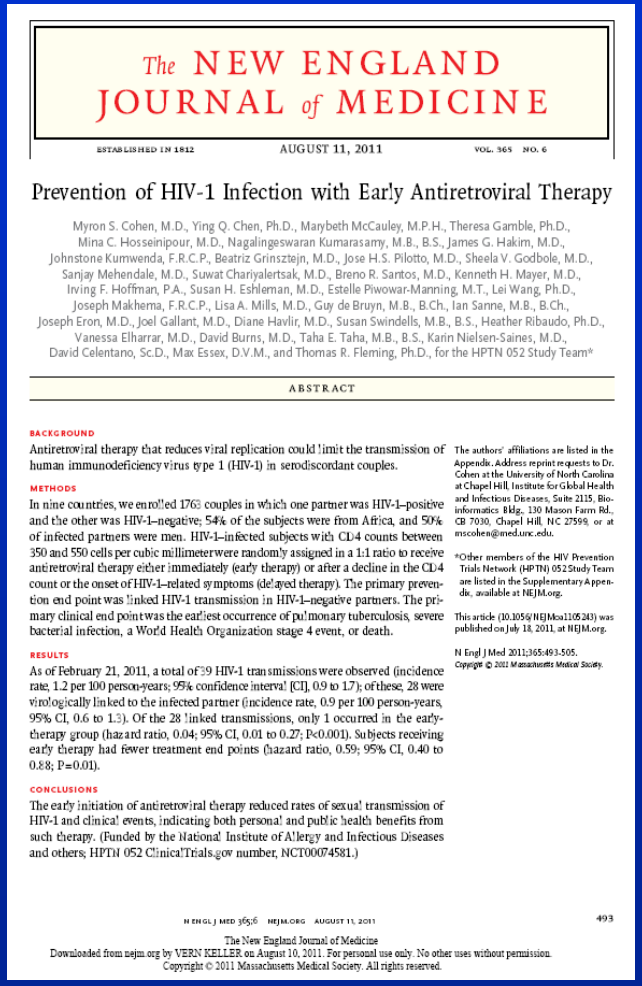
Modelling results for HIV infection in urban MSM in USA and Peru



"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: 367-77.

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



The NEW ENGLAND JOURNAL of MEDICINE

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

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

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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.)

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*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. 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 an infected partner. The other 11 were not clearly partner linked.
- 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.

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

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Received: 7 February 2012; revised: 26 April 2012; accepted: 2 May 2012.

DOI:10.1097/QAD.0b013e328355713d

- "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. [Epub ahead of print]

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.

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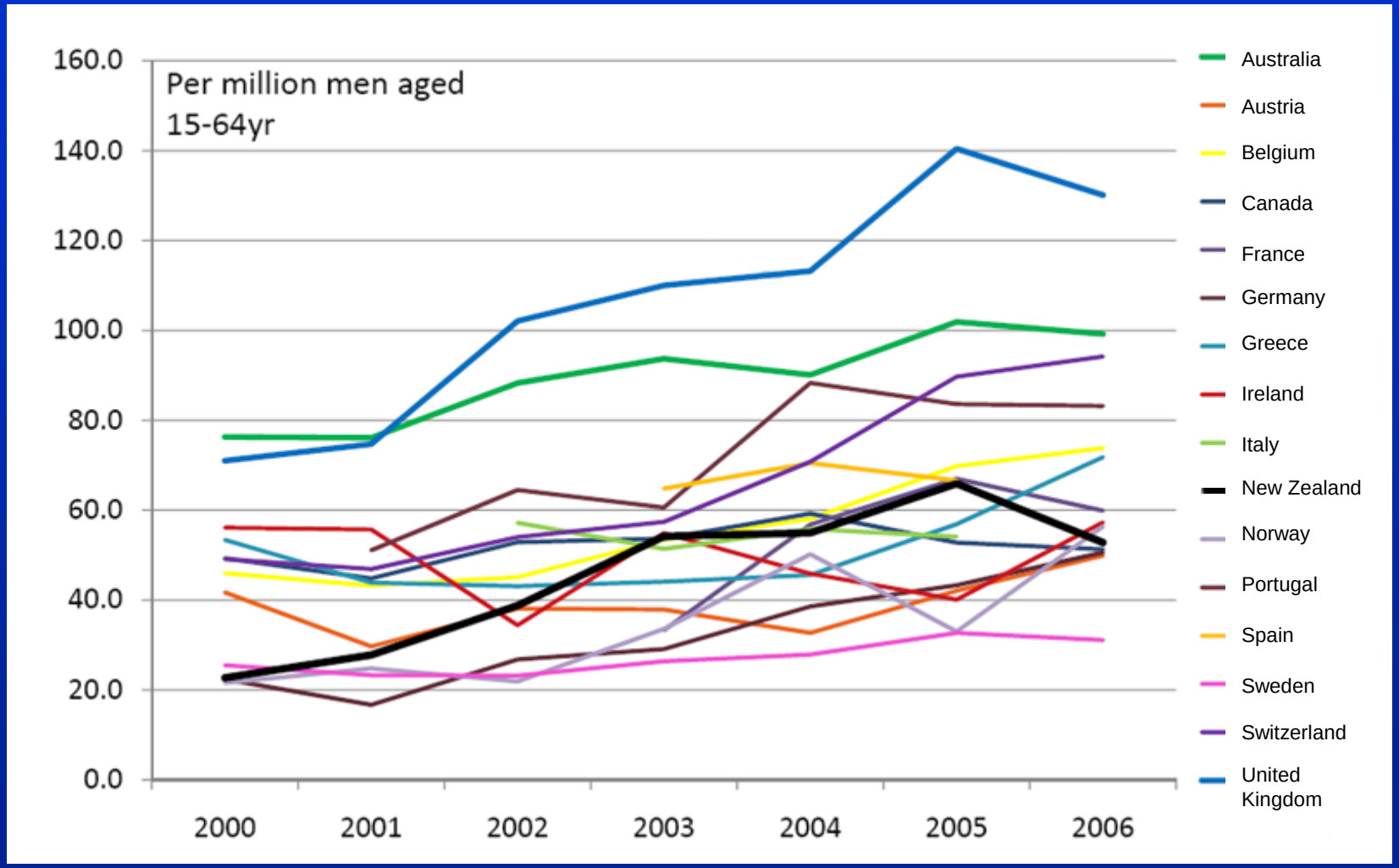
Received: 13 February 2012; revised: 13 March 2012; accepted: 29 March 2012.

DOI:10.1097/QAD.0b013e3283543e83

- "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."

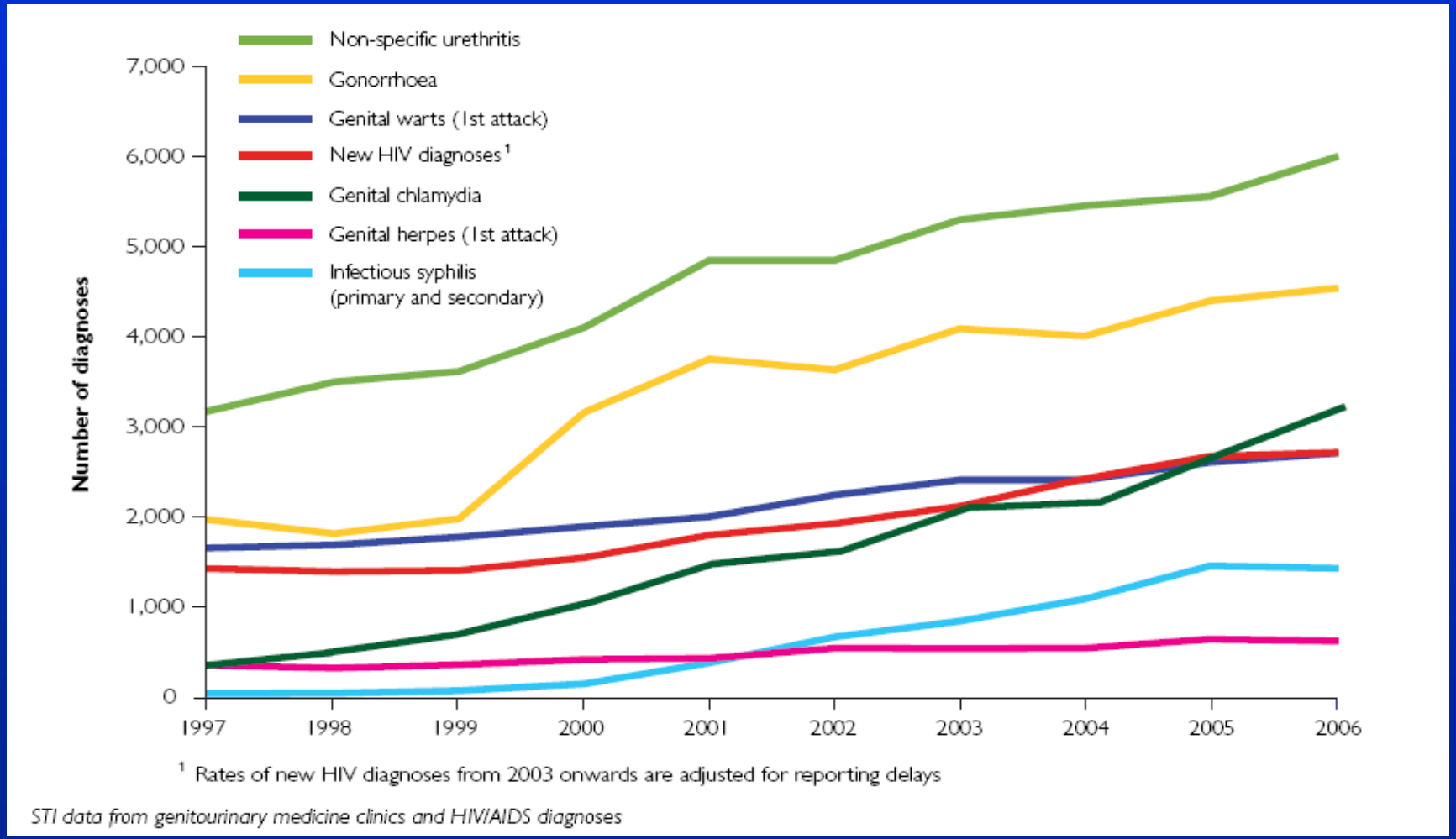
Cohen, M.S. et al. *AIDS* 2012; 26: 1585-98.

HIV diagnosis rate among MSM in major 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.

Diagnoses of HIV and selected STIs among MSM in the United Kingdom,1997-2006



Health Protection Agency. "Testing times, HIV and other sexually transmitted infections in the United Kingdom", 2007.

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

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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

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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."

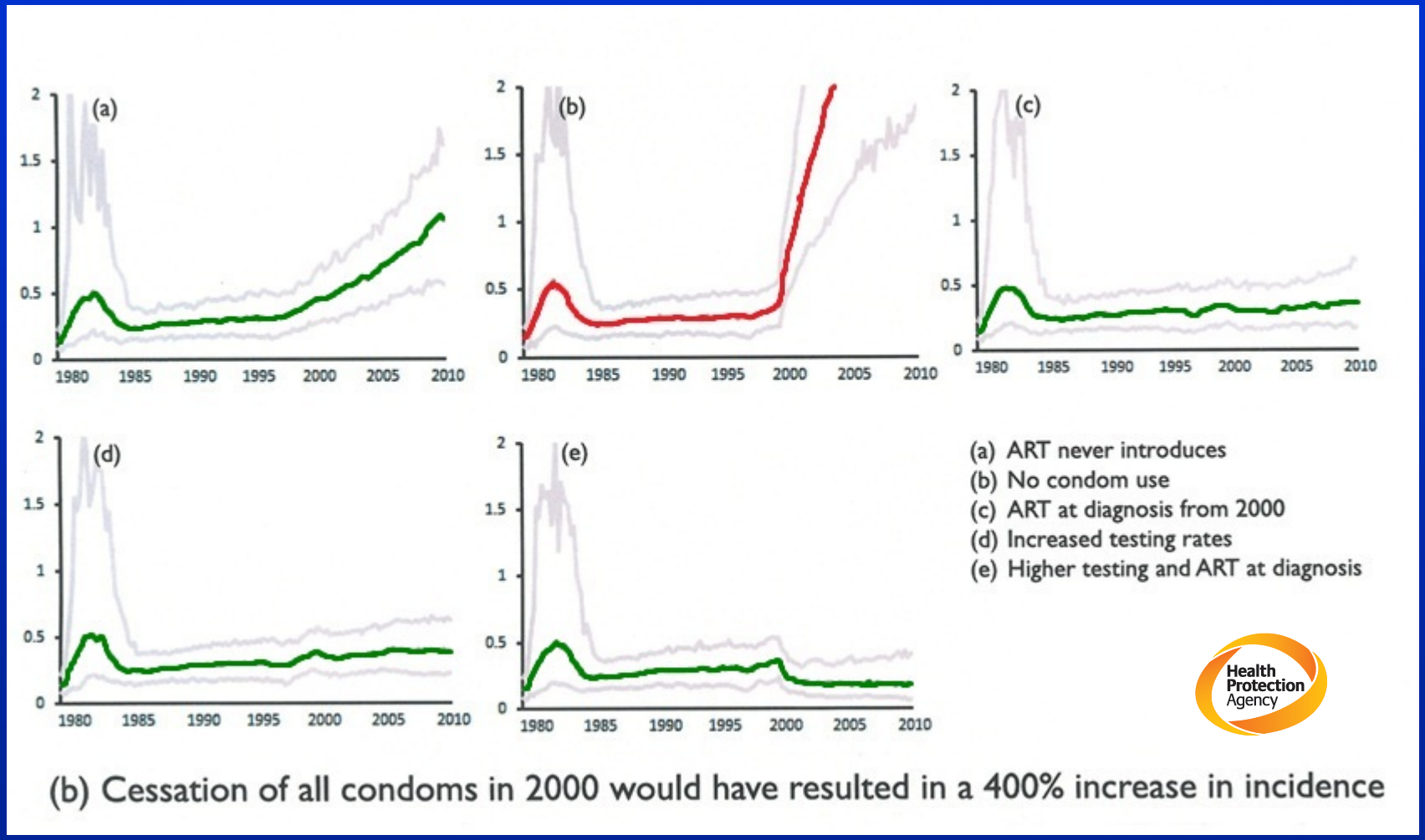
Bezemer, D. et al. *AIDS* 2008; 22: 1071-77.

Impact of ART on HIV transmission at population level

First author	Key comments and conclusions on sexual behaviour
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
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 2012	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 2012	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: Analysis of the UK epidemic, Phillips et al, 2012.



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.

Why is HIV infection difficult to manage in the MSM population?

(a) Extremely high biological risk of HIV acquisition through unprotected receptive anal sex.

(b) Effect of symptomatic and asymptomatic STI infections on HIV acquisition and transmission risk.

(c) Role of primary HIV infection (PHI) in forward transmission and the great difficulty identifying people with PHI.

(d) Complex relationship between HIV viral load levels in blood, semen and rectal tissue.

(e) Differences in HIV acquisition and transmission risk in the seminal and rectal compartments.

(f) Specific impact of high sexual role flexibility on baseline HIV transmission rates in MSM.

(g) Extent to which HIV transmission in anal intercourse occurs through direct cell-to-cell transfer rather than arising from the spread of cell free virus.

(h) Effects of large and complex sexual network structure – frequent multi-partnering, group sex, concurrency and the impact of the internet – on HIV transmission.

(i) Likelihood that there is a core group of undiagnosed MSM that will be very difficult to locate.

(j) Complex challenge provided by a minority of individuals with HIV infection who resist using condoms and are highly sexually active.

(k) Impact of unresolved alcohol, drug use and mental health issues on sexual risk behaviour.

(l) Damaging effects of social marginalisation and homophobia on MSM who are at high risk.

What are the main limitations of TasP in the MSM population?

(a) High cost of regular and widespread HIV testing and ART provision.

(b) Frequency and extent of population coverage of HIV testing initiatives.

(c) Specific problem of late HIV diagnosis in some parts of the MSM population.

(d) Consistency and durability of adherence to ART treatment schedules, especially in healthier individuals earlier in the course of HIV infection.

(e) Requirement for stability of viral load suppression on ART over many decades.

(f) Long term toxicities and side effects of various ART combinations.

(g) Emergence and spread of drug resistant HIV variants in the MSM population.

(h) Near impossibility of delivering treatment to MSM with primary HIV infection.

(i) Fact that HIV treatment does not become optimally effective in most people for several months after it has been commenced.

(j) Degree to which particular ART combinations achieve maximum viral suppression in different body compartments – blood, seminal and rectal.

(k) Increase in unprotected anal sex occurring as a direct result of ART – behavioural disinhibition and risk compensation.

(l) Difficulty of catching up with the large pool of MSM who are already infected and need priority treatment at the same time as managing newly acquired infections.

(m) Inevitability that ‘treatment for prevention’ is a complex and expensive multi-stage process, and that most of the operational demands will fall on already stretched clinical services.

Why does individual level protection not automatically result in population level protection?

Modelling sexual transmission of HIV: testing the assumptions, validating the predictions

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Current Opinion in HIV and AIDS 2010, 5:269–276

Purpose of review
To discuss the role of mathematical models of sexual transmission of HIV: the methods used and their impact.
Recent findings
We use mathematical modelling of 'universal test and treat' as a case study to illustrate wider issues relevant to all modelling of sexual HIV transmission.
Summary
Mathematical models are used extensively in HIV epidemiology to deduce the logical conclusions arising from one or more sets of assumptions. Simple models lead to broad qualitative understanding, whereas complex models can encode more realistic assumptions and, thus, be used for predictive or operational purposes. An overreliance on model analysis in which assumptions are untested and input parameters cannot be estimated should be avoided. Simple models providing bold assertions have provided compelling arguments in recent public health policy, but may not adequately reflect the uncertainty inherent in the analysis.

Keywords
male circumcision, mathematical modelling, sexual transmission, test and treat

Curr Opin HIV AIDS 5:269–276

1746-630X

Introduction

Mathematical models have played important roles facilitating understanding of HIV epidemiology and evaluating the performance of prevention initiatives [1]. From the earliest models examining the interaction between HIV and other sexually transmitted infections (STIs) [2], the effects of sexual mixing patterns between individuals by age [3] and predicting the future course of HIV epidemics [4], modelling has assisted in making projections [5], explaining past and future trends [6–8], as well as predicting the impact of existing and proposed HIV prevention initiatives [9–11]. Such analyses, in which model input parameters are believed to be estimated with sufficient accuracy, can provide quantitative predictions, often being combined with economic analyses to provide cost–effectiveness or cost–benefit projections [12**,13]. When such precision is not attainable, modelling can explore more qualitative outcomes, able to open up new directions of enquiry, such as predicting the impact of HIV prevention technologies yet to be developed (such as vaccines and microbicides).

Both qualitative models (used for broad insights) and detailed models (developed for operational purposes) may influence HIV prevention and treatment policies, yet there may also be a lack of trust due to the opaque nature of modelling methods that are used (often quite complex and technical), or conversely, overconfidence and reliance on certain methods or research groups because of lack of understanding of mathematical models in the wider stakeholder community [1]. In this review, we include a case study that has recently received a lot of attention and in which models have been used to influence the research community, policy and beyond: mathematical models of HIV testing and antiretroviral treatment as prevention ('test and treat').

From efficacy to effectiveness

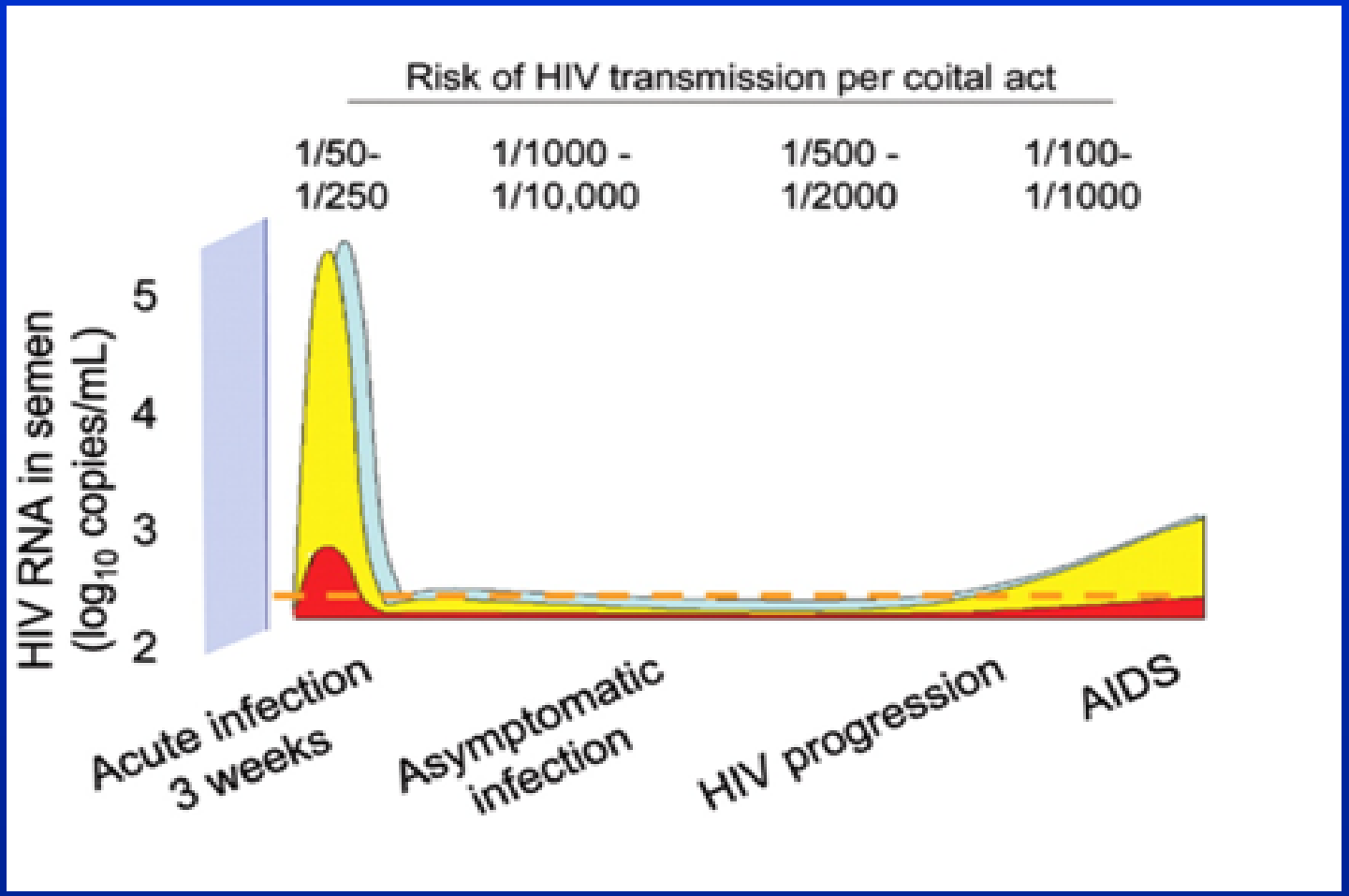
Mathematical models have proven especially useful for assessing interventions such as 'test and treat' or male circumcision, because their effect is to prevent transmission, and these interventions have individual, pairwise and population level benefits, which are very hard to estimate using empirical field studies alone. Protecting one individual from acquiring infection has an indirect protective effect on others (Fig. 1a). The efficacy of an HIV prevention intervention denotes the degree of protection against infection experienced by one individual benefiting directly from the intervention, such as the protection afforded to a man who is circumcised. Effectiveness of infectious disease interventions is more complex, as it includes the far-reaching population effects of applying the intervention to each of these individuals (as shown by the concept of herd immunity, vaccination of a

DOI:10.1097/COH.0b013e32833a51b2

- Protecting one individual from HIV infection has an indirect protective effect on others.
- The *efficacy* of a prevention intervention is the extent to which it benefits the individual directly using it.
- The *effectiveness* of a prevention intervention includes the far-reaching population effects of applying the intervention to a large number of individuals.
- "The relationship between *individual level efficacy* and *population level effectiveness* is not straightforward because of the indirect benefits of prevention, but also because people may be exposed to HIV multiple times in a lifetime."

Baggaley, R.F. Fraser, C. *Curr Opin HIV AIDS* 2010; 5: 269-76.

Efficacy: Sharply increased transmission risk in primary HIV infection



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

High rates of forward transmission events after acute/early HIV infection in Canada

MAJOR ARTICLE

High Rates of Forward Transmission Events after Acute/Early HIV-1 Infection

Bluma G. Brenner,[1] Michel Roger,[2] Jean-Pierre Routy,[3] Daniela Moisi,[1] Michel Ntemgwa,[1] Claudine Matte,[2] Jean-Guy Baril,[4] Réjean Thomas,[5] Danielle Rouleau,[2] Julie Bruneau,[6] Roger Leblanc,[7] Mario Legault,[8] Cecile Tremblay,[3] Hugues Charest,[9] Mark A. Wainberg,[1] and the Quebec Primary HIV Infection Study Group[a]

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(See the editorial commentary by Pillay and Fisher, on pages 924–6.)

Background. A population-based phylogenetic approach was used to characterize human immunodeficiency virus (HIV)–transmission dynamics in Quebec.

Methods. HIV-1 *pol* sequences included primary HIV infections (PHIs; <6 months after seroconversion) from the Quebec PHI cohort (1998–2005; $n = 215$) and the provincial genotyping program (2001–2005; $n = 481$). Phylogenetic analysis determined sequence interrelationships among unique PHIs ($n = 593$) and infections from untreated ($n = 135$) and treated ($n = 660$) chronically infected (CI) potential transmitter populations (2001–2005). Clinical features, risk factors, and drug resistance for clustered and nonclustered transmission events were ascertained.

Results. Viruses from 49.4% (293/593) of PHIs cosegregated into 75 transmission chains with 2–17 transmissions/cluster. Half of the clusters included 2.7 ± 0.8 (mean ± SD) transmissions, whereas the remainder had 8.8 ± 3.5 transmissions. Maximum periods for onward transmission in clusters were 15.2 ± 9.5 months. Coclustering of untreated and treated CIs with PHIs were infrequent (6.2% and 4.8%, respectively). The ages, viremia, and risk factors were similar for clustered and nonclustered transmission events. Low prevalence of drug resistance in PHI supported amplified transmissions at early stages.

Conclusions. Early infection accounts for approximately half of onward transmissions in this urban North American study. Therapy at early stages of disease may prevent onward HIV transmission.

An understanding of HIV-transmission dynamics is important in the design of effective prevention and treatment interventions. A number of recent studies suggest that early stages of HIV infection may disproportionately contribute to viral transmission and spread of the epidemic [1–3]. Primary HIV infection (PHI) and early stages of infection are associated with high viral burden and viral set points in blood and semen, a major determinant of HIV transmission [1, 2,4–6]. The Rakai-Uganda surveillance study showed that 43.8% (10/23) of new transmissions occurred in discordant partners at 6–15 months subsequent to seroconversions of source partners [6].

In contrast, other groups have used viral load/epidemiological/behavioral data to contend that the role of PHIs in HIV transmission may be overestimated [7–9]. Many cofactors influence transmission, including access to antiretroviral therapy and medical care, high risk behaviors, sexually transmitted diseases, and coinfections [7–9]. The findings of the North Carolina program Screening and Tracing of Active Transmission

Received 6 September 2006; accepted 3 October 2006; electronically published 16 February 2007.

Potential conflicts of interest: none reported.

Presented in part: XIV International HIV Drug Resistance Workshop, Quebec City, Canada, 7–11 June 2005 (abstract 112).

Financial support: Canadian Institutes for Health Research (grant MT-14738 for resistance genotyping in the Quebec Primary HIV Infection [PHI] cohort study and for research on PHI; Réseau SIDA of the Fonds de la Recherche en Santé du Québec (funds to recruit patients into the Quebec PHI cohort study); Quebec Ministry of Health (funds to the provincial genotypic resistance testing program).

[a] Study group members are listed after the text.

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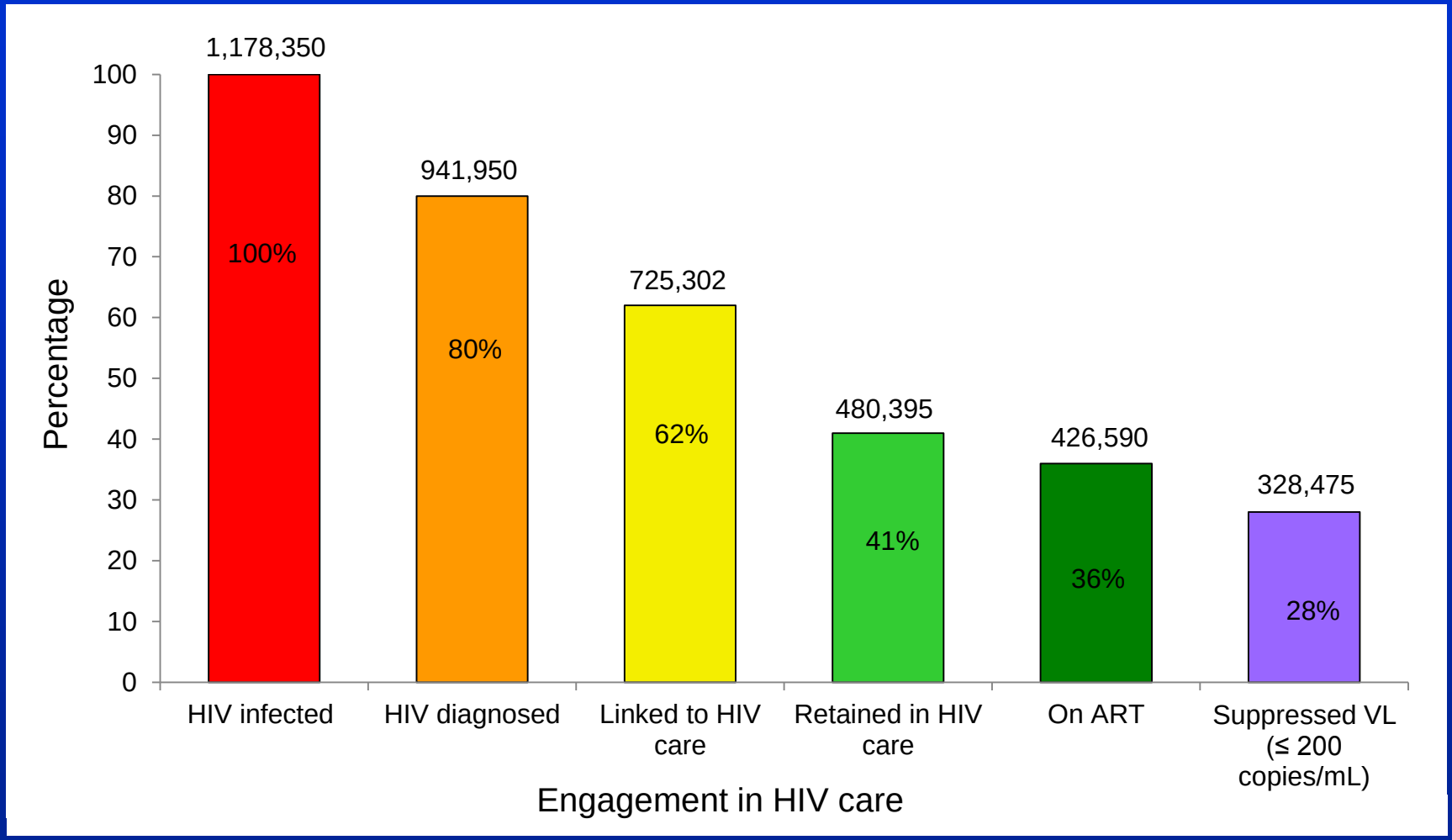
The Journal of Infectious Diseases 2007; 195:951–9

0022-1899/2007/19507-0007$15.00
DOI: 10.1086/512088

- "Acute/infection is characterized by high viremia and high viral set points in the absence of treatment. Acute/early infections are often undiagnosed…"
- "Our results show that 49% of all primary HIV infection strains in the Quebec HIV population from phylogenetic clusters, indicating that early infection may account for a major proportion of onward transmissions."
- "[P]rimary/early infection, representing <10% of the total sequenced samples in the provincial genotyping programme, disproportionately accounted for approximately half of onward transmission events."

Brenner, B.G. et al. *J Infect Dis* 2007; 195: 951-959.
Also: Brenner, B.G. et al. *J Infect Dis* 2011; 204: 1115-1119.

Effectiveness: 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; 60:1618-23

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%**)

Natural experiments highlight 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

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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

Academic Editor: John Bartlett, Duke University Medical Center, United States of America

Published July 10, 2012

Funding: No specific funding was received for writing this article.

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

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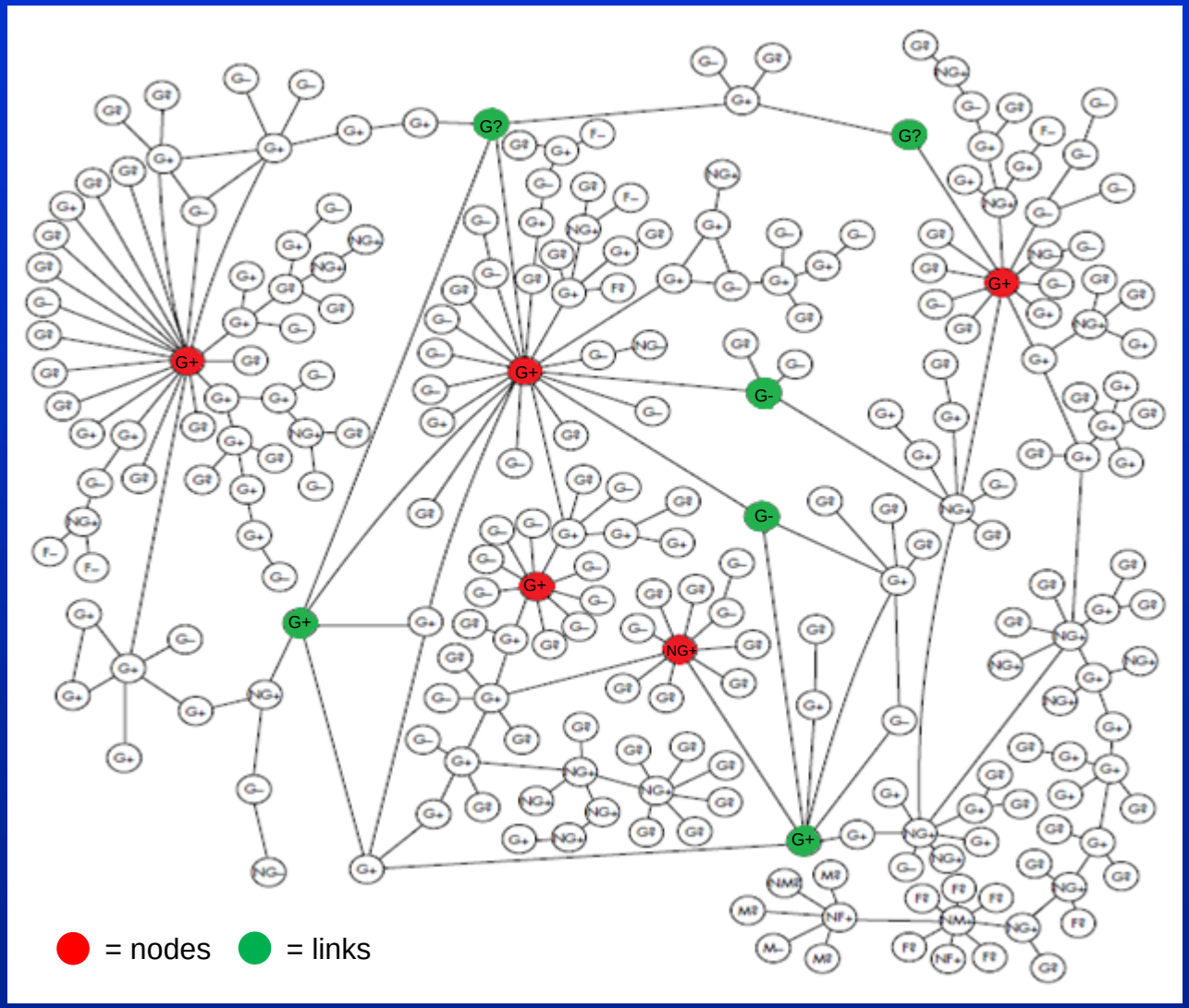
Provenance: Submitted as part of a sponsored Collection; externally reviewed.

- "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.

Sustainability: Risk network structure for HIV transmission in Colorado Springs, 1985-1999



Adapted from: Potterat, J.J. et al. *Sex Trans Infect* 2002; 78 (Suppl 1): i159-i163.

Summary: 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, concurrency and group sex.

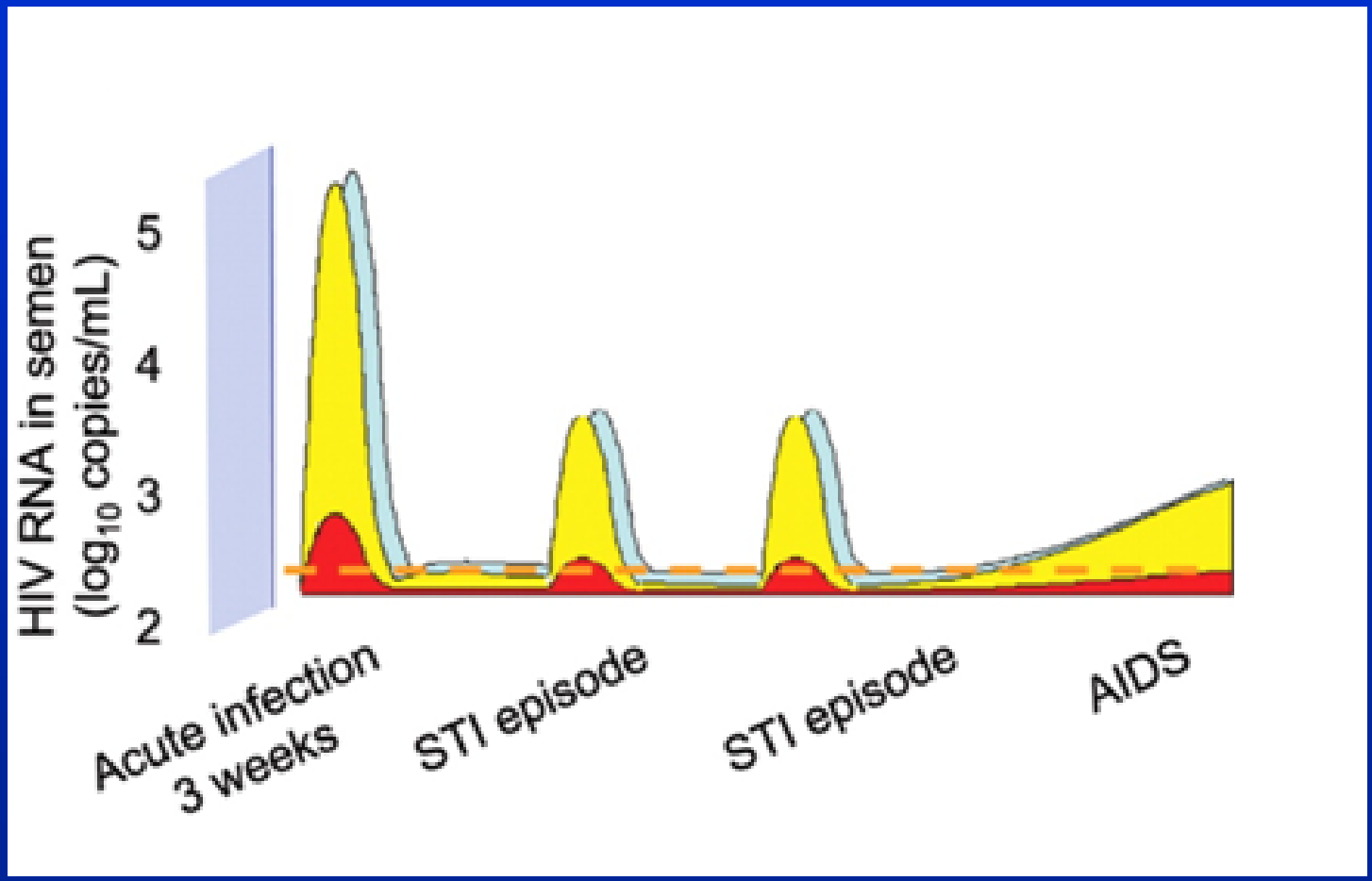
(e) Influence of the internet in sharply increasing partner availability since 2000.

(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.

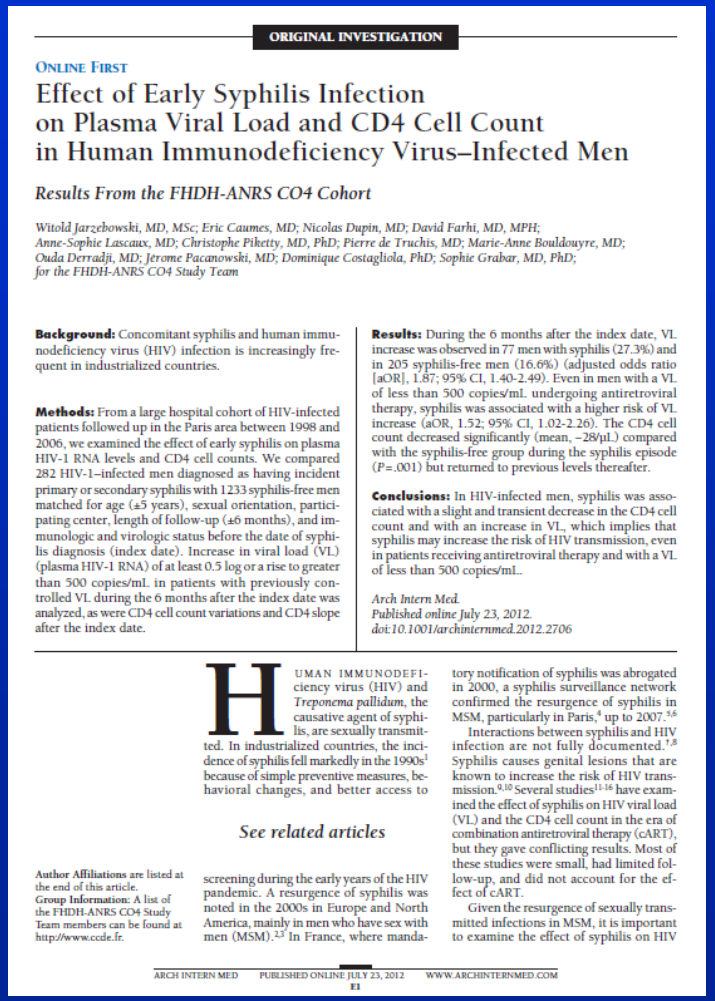
(h) Heightened risk of HIV acquisition and transmission in presence of STI co-infections.

Increased HIV transmission risk in the presence of STIs



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

Effect of early syphilis infection on plasma viral load in Human Immunodeficiency Virus-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; Jérome 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; July 23. [Epub ahead of print]

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

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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

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Received: 21 September 2011; revised: 27 February 2012; accepted: 14 March 2012.

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: 1535-43

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 site of lesions)
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

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

Conclusion

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

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

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

(d) Support vaccination for STIs in the MSM population where available.

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.

The Ministry of Health for on going funding support to the New Zealand AIDS Foundation

Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART

Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART

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Objective: The objective of this study is to estimate per-contact probability of HIV transmission in homosexual men due to unprotected anal intercourse (UAI) in the era of HAART.

Design: Data were collected from a longitudinal cohort study of community-based HIV-negative homosexual men in Sydney, Australia.

Methods: A total of 1427 participants were recruited from June 2001 to December 2004. They were followed up with 6-monthly detailed behavioral interviews and annual testing for HIV till June 2007. Data were used in a bootstrapping method, coupled with a statistical analysis that optimized a likelihood function for estimating the per-exposure risks of HIV transmission due to various forms of UAI.

Results: During the study, 53 HIV seroconversion cases were identified. The estimated per-contact probability of HIV transmission for receptive UAI was 1.43% [95% confidence interval (CI) 0.48–2.85] if ejaculation occurred inside the rectum, and it was 0.65% (95% CI 0.15–1.53) if withdrawal prior to ejaculation was involved. The estimated transmission rate for insertive UAI in participants who were circumcised was 0.11% (95% CI 0.02–0.24), and it was 0.62% (95% CI 0.07–1.68) in uncircumcised men. Thus, receptive UAI with ejaculation was found to be approximately twice as risky as receptive UAI with withdrawal or insertive UAI for uncircumcised men and over 10 times as risky as insertive UAI for circumcised men.

Conclusion: Despite the fact that a high proportion of HIV-infected men are on antiretroviral treatment and have undetectable viral load, the per-contact probability of HIV transmission due to UAI is similar to estimates reported from developed country settings in the pre-HAART era.

AIDS 2010, **24**:907–913

Keywords: Australia, cohort study, HIV, homosexuality, male, per-contact probability, transmission risk

Introduction

Most studies of per-contact probability of sexual HIV transmission have been in heterosexual people [1–4], and few estimates have been made for sex between homosexual men [5,6]. The estimation of per-contact risk in homosexual men is more complex than that of heterosexual transmission. First, sexual monogamy is more common in heterosexuals, and thus serodiscordant monogamous couples are more readily available for study

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Received: 2 November 2009; revised: 17 December 2009; accepted: 22 December 2009.

DOI:10.1097/QAD.0b013e3283372d90

- "In Australia, homosexual men have very high rates of recent HIV testing, about 70% of [diagnosed] HIV positive men are receiving HAART, and 75% of those on treatment have undetectable viral load."
- It is therefore surprising that estimates of HIV transmission risk through unprotected anal intercourse in the post-HAART era were similar to those when few HIV positive men had an undetectable viral load.
- There are several potential explanations: Primary HIV infection may have a bigger role in population spread than expected; the number of undiagnosed HIV infections may be higher that expected; HIV transmission risk by anal intercourse may not be as closely related to viral load as it is in vaginal intercourse; and STI prevalence may be higher now than in the pre-HAART era.

Jin, F. et al. *AIDS* 2010; 24: 907-13.

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." Department of Health and Human Services 2012. 1-239.

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

Increasing sexual risk behaviour amongst Dutch MSM: Mathematical models versus prospective cohort data

Research Letter

AIDS 2012, **26**:000–000

Increasing sexual risk behaviour amongst Dutch MSM: mathematical models versus prospective cohort data

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Changes in risk behaviour amongst men who have sex with men in the Netherlands were estimated by fitting a mathematical model to annual HIV and AIDS diagnoses in the period 1980–2009, and, independently, from rates of unprotected anal intercourse in a prospective cohort study in Amsterdam. The agreement between the two approaches was very good, confirming that in terms of incidence, increasing risk behaviour between MSM is offsetting benefits offered by enhanced testing and treatment.

The HIV-1 epidemic is resurgent amongst many populations of men who have sex with men (MSM) across the developed world [1]. Annual diagnoses are increasing in most age groups, and it is now clear that this is in part due to an increase in underlying incidence of infection that has occurred over the last decade [2–5].

Identifying the causes of this resurgence is key to knowing how to develop and target public health responses. Several hypotheses exist, including increased rates of unprotected sex amongst untreated or undiagnosed individuals, continuing transmission from individuals receiving treatment, increasing infectiousness due to evolutionary changes in the virus, or increased transmission due to concomitant co-infection with syphilis and gonorrhoea which are themselves increasingly epidemic [1,6]. These mechanisms of enhanced epidemic transmission are not, of course, mutually exclusive.

In earlier work, we studied the HIV-1 epidemic amongst MSM in the Netherlands using mathematical models, and longitudinal behavioural data from the Amsterdam Cohort Study (ACS) [4,5,7]. Both approaches make substantial numbers of assumptions, but aim to provide a mechanistic (as opposed to descriptive) explanation of the changing dynamics of the epidemic. These approaches were developed and published completely independently, and thus present an unusual opportunity to compare the inferences obtained from very different sets of assumptions.

The mathematical model approach is essentially integrative, starting from a number of assumptions, fitting predictions to long-term trends in annual HIV diagnoses and AIDS cases. Data on the efficacy and failure rates following antiretroviral therapy are used to constrain treatment parameters. Assumptions are then made regarding the effect of diagnosis on behaviour [8] and relative infectiousness of individuals in acute and late-stage infection [9] and during treatment. From this approach, we estimate time-changing diagnosis rates and transmission rates (denoted $\beta(t)$, where t denotes calendar year) [4,5]. The transmission function $\beta(t)$ is a compound measure of risk, including in an implicit manner the rates of new partner acquisition, of unprotected sex within partnerships, and of riskiness of each sex act, and is only estimated relative to a baseline value in the initial period of the epidemic. Changes in transmission rates related to stage of infection, diagnosis, or treatment are not included in $\beta(t)$ but are explicitly taken into account in the model.

Estimates of $\beta(t)$ depend to some extent on the underlying assumptions for other parameters. To reduce the impact of this uncertain dependency on our predictions we now extend the method to include a multivariate sensitivity analysis. Iteratively, we select input parameters randomly from a sensible range, and for each set of parameters, we refit the model to data up to 2009 following the protocol set out before [4,5].

In behavioural studies, one cannot easily measure compound risk parameters such as $\beta(t)$. It is thus necessary to choose specific questions to focus on, and then assume that the sex acts reported are good proxies for the overall drivers of the epidemic. Thus, while mathematical models are integrative, behavioural surveys are correspondingly reductive. Previously, results were presented of the Amsterdam Cohort Study amongst MSM, for whom behavioural data and HIV test results have been collected on an individual level twice a year since 1984. We chose to focus on the proportion $\varphi(t)$ of HIV-negative MSM reporting at least one unprotected anal sex act in the last six months [7]. Clearly, $\varphi(t)$ alone is not enough to fully define the risk of HIV acquisition or onwards transmission, but it is not unreasonable to assume that it is a good proxy for changes in overall risk behaviour, as it is one of the most important risk factors for HIV seroconversion [7].

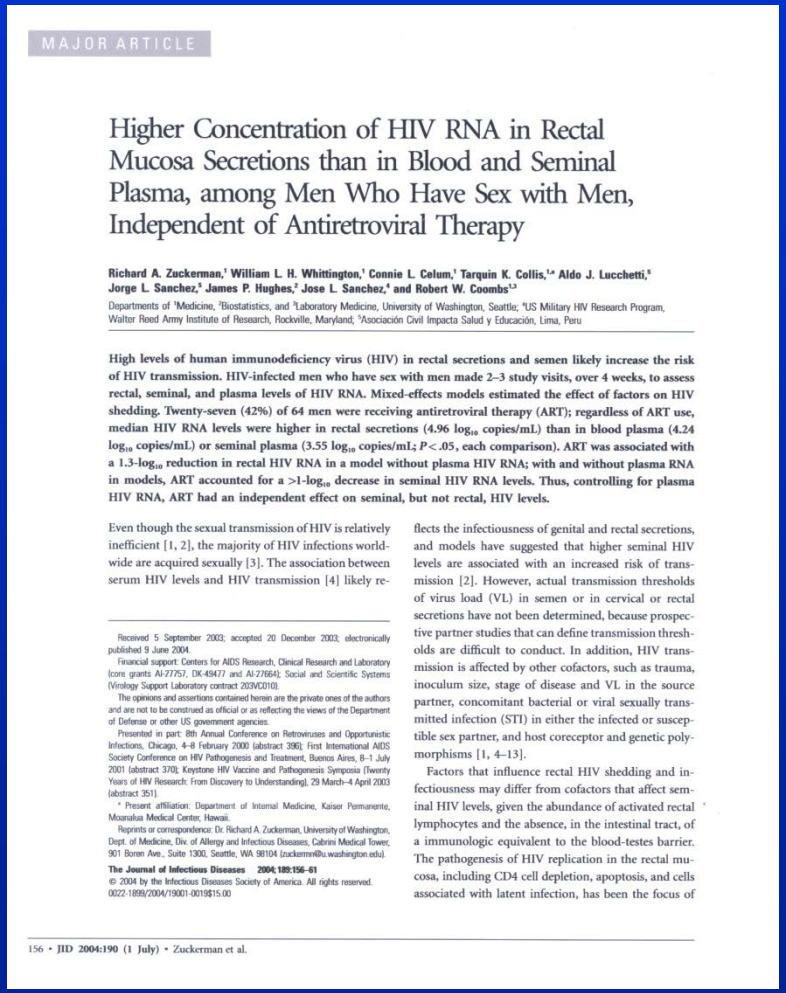
We hypothesise that the mathematical-model-estimated risk statistic $\beta(t)$ and the risk statistic $\varphi(t)$ from the ACS are both suitable summary proxies for the underlying complex patterns of risk behaviour that drive an

DOI:10.1097/QAD.0b013e3283574df9

- "The imputation from this is clear: risk behaviour reduced by approximately half from the mid-1980s through to the mid-1990s, which contributed to the self-limiting nature of the early HIV epidemic."
- "The resurgent epidemic in the Netherlands as a whole can be satisfactorily, although not exclusively, explained by increased risk behaviour, predominantly in undiagnosed individuals."
- "[I]n terms of incidence, increasing risk behaviour between MSM is offsetting benefits offered by enhanced testing and treatment."

van Sighem, A. et al. *AIDS* 2012; 26: [Epub ahead of print]

Higher concentrations of HIV RNA in rectal secretions than in blood and semen



MAJOR ARTICLE

Higher Concentration of HIV RNA in Rectal Mucosa Secretions than in Blood and Seminal Plasma, among Men Who Have Sex with Men, Independent of Antiretroviral Therapy

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High levels of human immunodeficiency virus (HIV) in rectal secretions and semen likely increase the risk of HIV transmission. HIV-infected men who have sex with men made 2–3 study visits, over 4 weeks, to assess rectal, seminal, and plasma levels of HIV RNA. Mixed-effects models estimated the effect of factors on HIV shedding. Twenty-seven (42%) of 64 men were receiving antiretroviral therapy (ART); regardless of ART use, median HIV RNA levels were higher in rectal secretions (4.96 $\log_{10}$ copies/mL) than in blood plasma (4.24 $\log_{10}$ copies/mL) or seminal plasma (3.55 $\log_{10}$ copies/mL; $P < .05$, each comparison). ART was associated with a 1.3-$\log_{10}$ reduction in rectal HIV RNA in a model without plasma HIV RNA; with and without plasma RNA in models, ART accounted for a >1-$\log_{10}$ decrease in seminal HIV RNA levels. Thus, controlling for plasma HIV RNA, ART had an independent effect on seminal, but not rectal, HIV levels.

Even though the sexual transmission of HIV is relatively inefficient [1, 2], the majority of HIV infections worldwide are acquired sexually [3]. The association between serum HIV levels and HIV transmission [4] likely reflects the infectiousness of genital and rectal secretions, and models have suggested that higher seminal HIV levels are associated with an increased risk of transmission [2]. However, actual transmission thresholds of virus load (VL) in semen or in cervical or rectal secretions have not been determined, because prospective partner studies that can define transmission thresholds are difficult to conduct. In addition, HIV transmission is affected by other cofactors, such as trauma, inoculum size, stage of disease and VL in the source partner, concomitant bacterial or viral sexually transmitted infection (STI) in either the infected or susceptible sex partner, and host coreceptor and genetic polymorphisms [1, 4–13].

Factors that influence rectal HIV shedding and infectiousness may differ from cofactors that affect seminal HIV levels, given the abundance of activated rectal lymphocytes and the absence, in the intestinal tract, of a immunologic equivalent to the blood-testes barrier. The pathogenesis of HIV replication in the rectal mucosa, including CD4 cell depletion, apoptosis, and cells associated with latent infection, has been the focus of

Received 5 September 2003; accepted 20 December 2003; electronically published 9 June 2004.

Financial support: Centers for AIDS Research, Clinical Research and Laboratory (core grants AI-27757, DK-49477 and AI-27664); Social and Scientific Systems (Virology Support Laboratory contract 203WC010).

The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of the Department of Defense or other US government agencies.

Presented in part: 8th Annual Conference on Retroviruses and Opportunistic Infections, Chicago, 4–8 February 2000 (abstract 396); First International AIDS Society Conference on HIV Pathogenesis and Treatment, Buenos Aires, 8–1 July 2001 (abstract 370); Keystone HIV Vaccine and Pathogenesis Symposia (Twenty Years of HIV Research: From Discovery to Understanding), 29 March–4 April 2003 (abstract 351).

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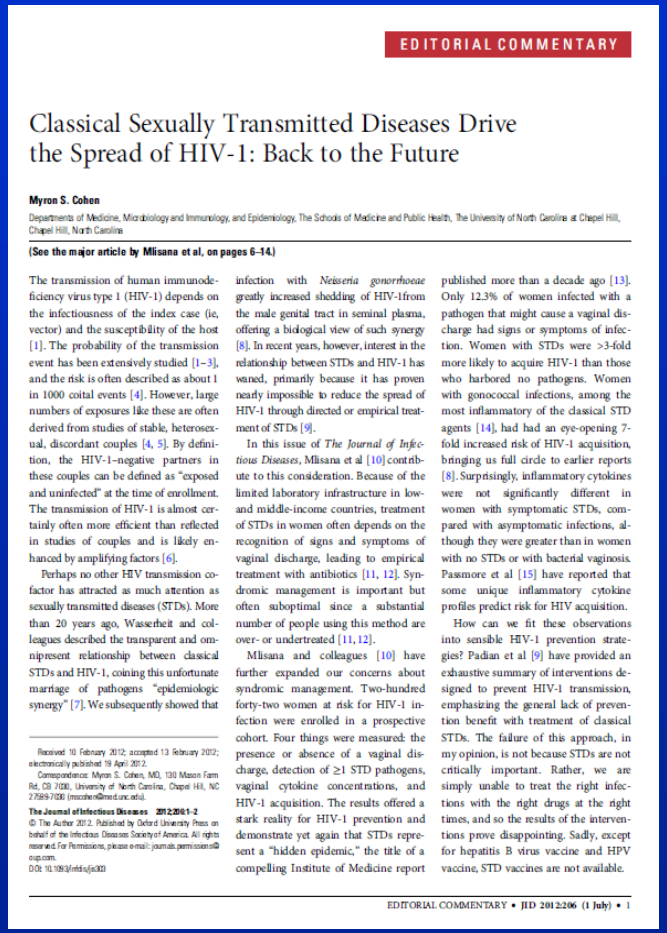
The Journal of Infectious Diseases 2004; 189:156–61

0022-1899/2004/19001-0019$15.00

- High levels of HIV in rectal secretions are likely to increase the risk of HIV transmission in unprotected anal sex
- It was found here that regardless of HAART use, median HIV RNA levels were higher in rectal secretions (4.96 $\log_{10}$ copies/mL) than in blood plasma (4.24) or seminal plasma (3.55) ($p<0.05$ each comparison)
- When controlling for plasma HIV RNA, HAART had an independent effect on seminal HIV levels, but not on those in the rectal compartment.

Zuckerman, R.A. et al. *J Infect Dis* 2004; 190: 156-161.

Classical sexually transmitted diseases drive the spread of HIV-1: Back to the future



EDITORIAL COMMENTARY

Classical Sexually Transmitted Diseases Drive the Spread of HIV-1: Back to the Future

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(See the major article by Mlisana et al, on pages 6–14.)

The transmission of human immunodeficiency virus type 1 (HIV-1) depends on the infectiousness of the index case (ie, vector) and the susceptibility of the host [1]. The probability of the transmission event has been extensively studied [1–3], and the risk is often described as about 1 in 1000 coital events [4]. However, large numbers of exposures like these are often derived from studies of stable, heterosexual, discordant couples [4, 5]. By definition, the HIV-1–negative partners in these couples can be defined as "exposed and uninfected" at the time of enrollment. The transmission of HIV-1 is almost certainly often more efficient than reflected in studies of couples and is likely enhanced by amplifying factors [6].

Perhaps no other HIV transmission cofactor has attracted as much attention as sexually transmitted diseases (STDs). More than 20 years ago, Wasserheit and colleagues described the transparent and omnipresent relationship between classical STDs and HIV-1, coining this unfortunate marriage of pathogens "epidemiologic synergy" [7]. We subsequently showed that infection with *Neisseria gonorrhoeae* greatly increased shedding of HIV-1from the male genital tract in seminal plasma, offering a biological view of such synergy [8]. In recent years, however, interest in the relationship between STDs and HIV-1 has waned, primarily because it has proven nearly impossible to reduce the spread of HIV-1 through directed or empirical treatment of STDs [9].

In this issue of *The Journal of Infectious Diseases*, Mlisana et al [10] contribute to this consideration. Because of the limited laboratory infrastructure in low- and middle-income countries, treatment of STDs in women often depends on the recognition of signs and symptoms of vaginal discharge, leading to empirical treatment with antibiotics [11, 12]. Syndromic management is important but often suboptimal since a substantial number of people using this method are over- or undertreated [11, 12].

Mlisana and colleagues [10] have further expanded our concerns about syndromic management. Two-hundred forty-two women at risk for HIV-1 infection were enrolled in a prospective cohort. Four things were measured: the presence or absence of a vaginal discharge, detection of ≥1 STD pathogens, vaginal cytokine concentrations, and HIV-1 acquisition. The results offered a stark reality for HIV-1 prevention and demonstrate yet again that STDs represent a "hidden epidemic," the title of a compelling Institute of Medicine report published more than a decade ago [13]. Only 12.3% of women infected with a pathogen that might cause a vaginal discharge had signs or symptoms of infection. Women with STDs were >3-fold more likely to acquire HIV-1 than those who harbored no pathogens. Women with gonococcal infections, among the most inflammatory of the classical STD agents [14], had had an eye-opening 7-fold increased risk of HIV-1 acquisition, bringing us full circle to earlier reports [8]. Surprisingly, inflammatory cytokines were not significantly different in women with symptomatic STDs, compared with asymptomatic infections, although they were greater than in women with no STDs or with bacterial vaginosis. Passmore et al [15] have reported that some unique inflammatory cytokine profiles predict risk for HIV acquisition.

How can we fit these observations into sensible HIV-1 prevention strategies? Padian et al [9] have provided an exhaustive summary of interventions designed to prevent HIV-1 transmission, emphasizing the general lack of prevention benefit with treatment of classical STDs. The failure of this approach, in my opinion, is not because STDs are not critically important. Rather, we are simply unable to treat the right infections with the right drugs at the right times, and so the results of the interventions prove disappointing. Sadly, except for hepatitis B virus vaccine and HPV vaccine, STD vaccines are not available.

Received 10 February 2012; accepted 13 February 2012; electronically published 19 April 2012.

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The Journal of Infectious Diseases 2012;206:1–2

DOI: 10.1093/infdis/jis303

- "Perhaps ironically, this past year was filled with great optimism in HIV-1 prevention, leading *The Economist* to focus on 'The End of AIDS' and Secretary of State Hillary Clinton to describe an 'AIDS-Free Generation'."
- "But the 'hidden epidemic' of classical STDs is squarely blocking optimal prevention of HIV-1 transmission. These STDs – symptomatic or asymptomatic – simply cannot be ignored."
- Surely this problem is no more impossible to attack or less important than any other part of the HIV-1 pandemic.

Cohen, M.S. *J Infect Dis* 2012; 206: 1-2.