

## Progress, Challenges, Future Opportunities

**gairdner**  
LES PRIX CANADA GAIRDNER AWARDS

University of British Columbia



King K. Holmes, M.D., Ph.D.  
University of Washington  
October 31, 2013

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## VENEREAL DISEASES

AMBROSE KING  
T.D., M.B., B.S.(Lond.), F.R.C.S.(Eng.)

CLAUDE NICOL  
T.D., M.D., F.R.C.P.



Chapters featured:

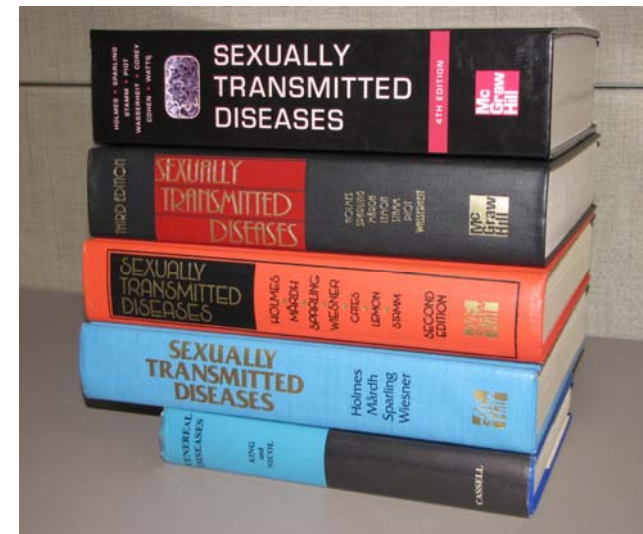
- syphilis
- gonorrhoea
- “tropical” venereal diseases
- trichomoniasis
- NGU

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- Today, there are 35 known sexually transmitted pathogens including HIV 1 and 2.
- The microbial etiology of several common STD syndromes still remains substantially undefined (e.g. NGU, MPC, PID, GUD).
- Microbiome studies will define many more.



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## 1960s: Era of contraceptives, global urbanization, the sexual revolution, the SE Asia war, and WWII baby boomers came of age

- Epidemic spread of STIs begins
- *N. gonorrhoeae*: decreased penicillin susceptibility appears in Asia
- Growing incidence of NGU and genital herpes, recognition as STDs



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## 1970s: Continued rapid spread of STI, and newly recognized STI pathogens and syndromes

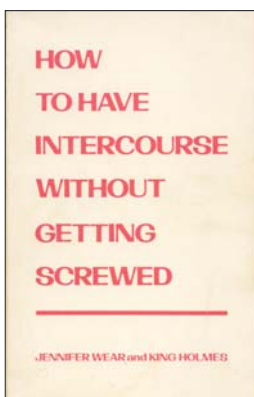
- Epidemics of syphilis, GC, and viral STI, particularly in MSM
- Penicillinase-producing *N. gonorrhoeae* appears in Philippines
- Recognition of STI impact on cancers: cervix, liver
- Recognition of STI impact on women
- “Gay Bowel Syndrome” epidemic begins in MSM

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## Despite this, aspirations for sexual freedom prevailed



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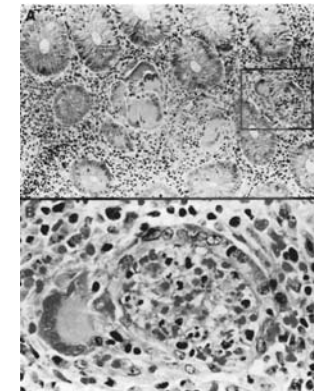
The NEW ENGLAND  
JOURNAL of MEDICINE

### *Chlamydia trachomatis* Proctitis

Thomas C. Quinn, M.D., et al.  
N Engl J Med 1981; 305:195-200. [July 23, 1981](#)  
Includes three cases of severe LGV proctitis masquerading as Crohn's disease.

### The Polymicrobial Origin of Intestinal Infections in Homosexual Men

Thomas C. Quinn, M.D., et al.  
N Engl J Med 1983; 309:576-82. [Sept. 8, 1983](#)



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## Things were getting much worse; diagnosis and treatment weren't bringing STIs under control

Journal of Homosexuality  
Volume 5, Issue 3, 1980



SYNOPSIS OF PAPERS DELIVERED AT THE CONFERENCE  
ON CURRENT ASPECTS OF SEXUALLY TRANSMITTED  
DISEASES (STDs), JUNE 1979

DOI: 10.1300/J082v05n03\_10  
David G. Ostrow & Terry Alan Sandholzer  
pages 281-285

### INTRODUCTION David G. Ostrow, MD, PhD

The final presentation on Friday was the keynote address by King Holmes, MD, PhD, Professor of Medicine at the University of Washington at Seattle, who summarized major advances as well as still unanswered questions in the specialty of STDs. Dr. Holmes's discussion suggested that behavioral and sociological factors may well be the most important areas of research and modification in the battle against the growing list of STDs.

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## HIV/AIDS era pre-HAART:1980-1996 in developed countries, 1980-2006 in LMICs

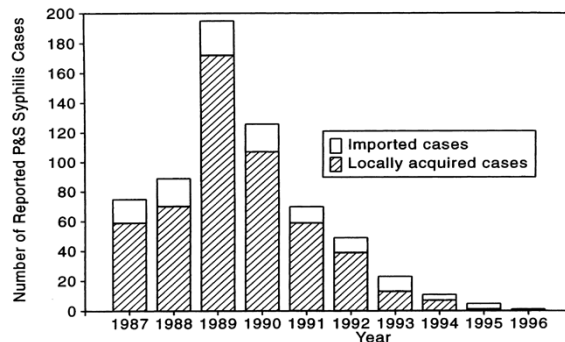
- 1980-81—PCP; KS; Gay-Related Immunodeficiency Syndrome (“GRIDS”)
- HIV incidence rises globally
- Early syphilis, other STIs begin declining in mid 80s , esp. in MSM, in developed countries
- GUD found associated with HIV in men and women
- WHO guidelines on synd. management of GUD
- Chancroid, and also syphilis and gonorrhea, began declining in LMICs, with syndromic management

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## Decline in syphilis, GC, hepatitis B, HSV-2 in No. America, West. Europe,1980s-1996



Williams LA, et al. "Elimination of primary and secondary syphilis in King County."  
Submitted to Am J Public Health, 1997.

1996

1. In Vancouver, the 11th International AIDS Conference ("One World, One Hope") highlights the effectiveness of highly active antiretroviral therapy (HAART), creating a period of optimism.

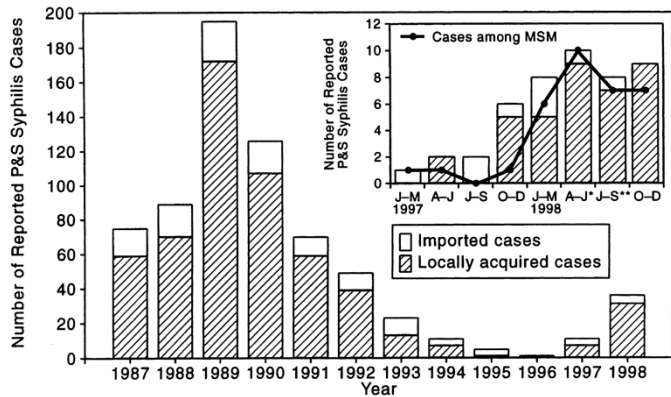


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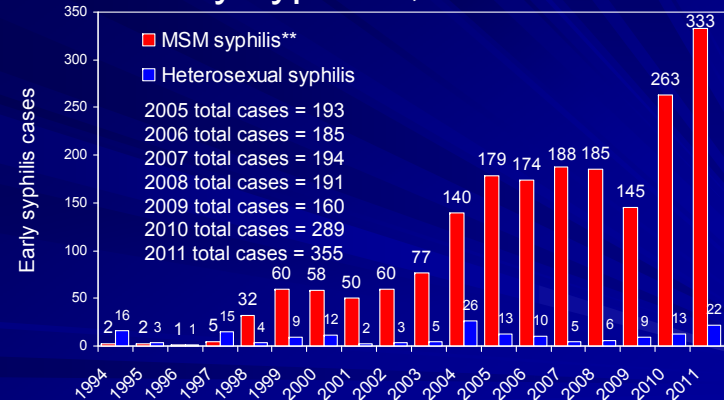
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### Oops: Elimination and reintroduction of primary and secondary (P&S) syphilis by year in King County, Washington



Williams L A, et al. "Elimination and reintroduction of primary and secondary syphilis." Am J Public Health 1999;89(7):1093-7.

### King County: Reintroduction of Early syphilis\*, 1997-2011

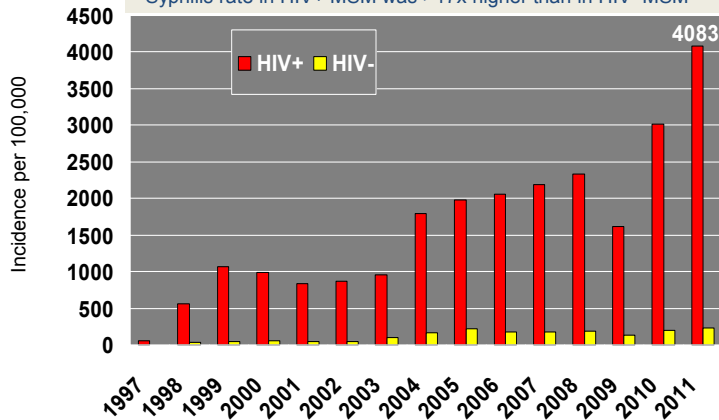


\*Reported P, S, and EL syphilis

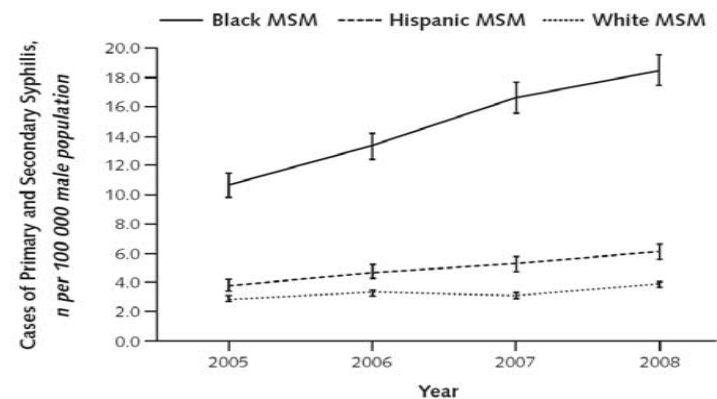
\*\*Excludes some male cases with unknown MSM status

### Early Syphilis Incidence per 100,000 Among MSM by HIV Status, King County, WA 1997-2012

- In 2011, 4.1% of all HIV+ MSM were diagnosed with early syphilis
- Syphilis rate in HIV+ MSM was >17x higher than in HIV- MSM



### Rates of primary and secondary syphilis among MSM, by race or ethnicity, in 27 US states in 2005 to 2008



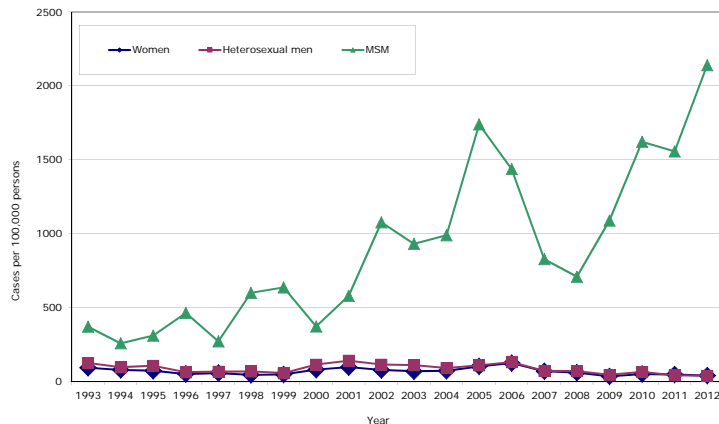
Su JR, et al. "Primary and secondary syphilis among black and Hispanic men who have sex with men: case report data from 27 states." Ann Intern Med 2011;155(3):145-151

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### Incidence of reported gonorrhea among MSM, women, and heterosexual men 15 years and older King County, WA, 1993-2012



\* In 2004, a field for gender of sex partners was added to the STD case report form. Before 2004, ascertainment of MSM status was likely less complete than in 2004 and after

### 1996-2013: Sexual behavior trends post-HAART in high income countries

- Serosorting (HIV seroconcordant sexual mixing) and seropositioning in MSM; UAI increases
- More densely connected sexual networks
- Concurrent sex partners

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### 1996-2013: Epidemiology of HIV and STI in No. America and Europe post-HAART

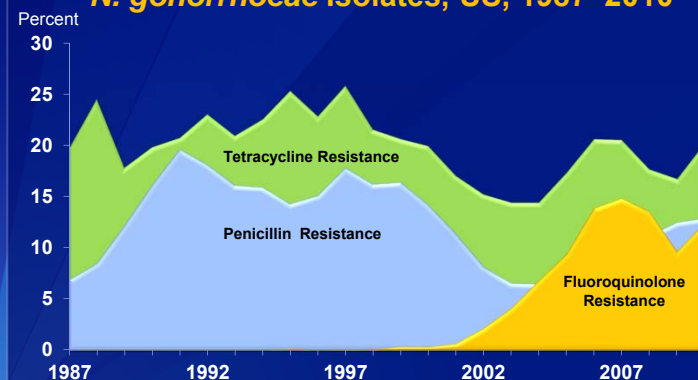
- Dramatic resurgence of some STI in MSM in US and in Western Europe, esp. in MSM
  - Syphilis, gonorrhea epidemics, LGV proctitis, hepatitis C in MSM
- GC fluoroquinolone resistance spreads from Asia to US, concentrated in MSM
- GC decreasing cephalosporin susceptibility, concentrated in MSM
- Azithromycin-resistant *T. pallidum* in US, Ireland, MSM
- US: 50,000 new cases of HIV infection annually

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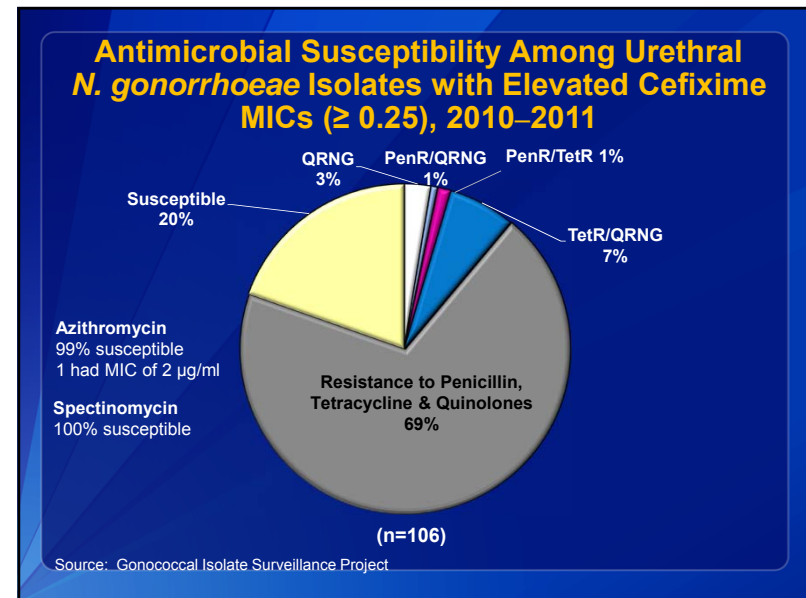
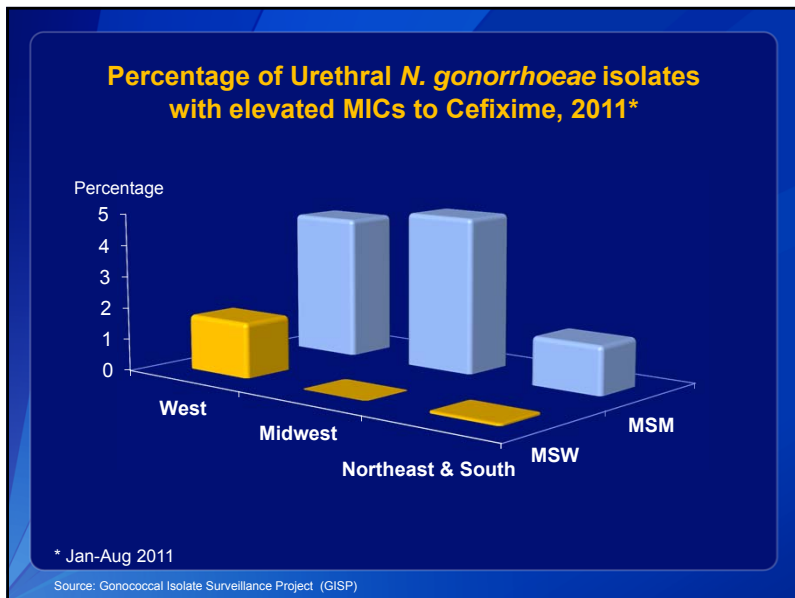
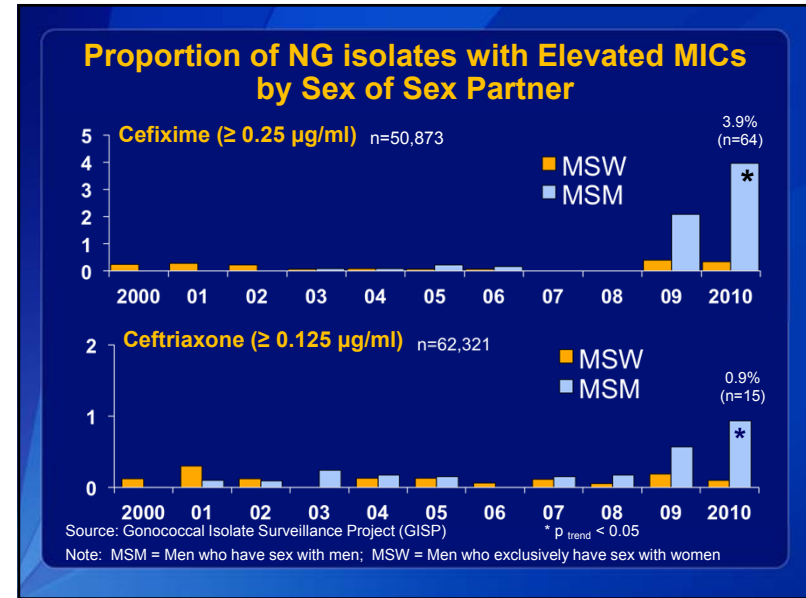
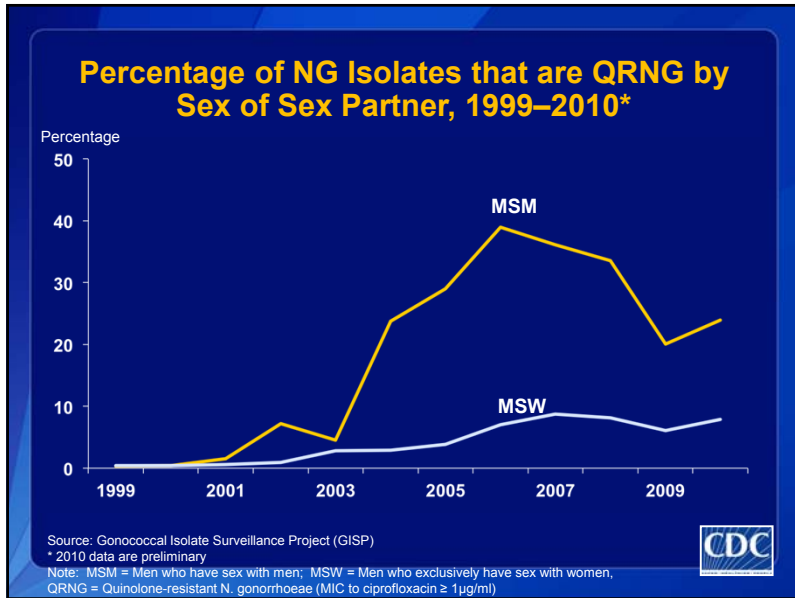
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### Prevalence of Penicillin, Tetracycline and Fluoroquinolone Resistance among Urethral *N. gonorrhoeae* Isolates, US, 1987-2010



Source: Gonococcal Isolate Surveillance Project (GISP)

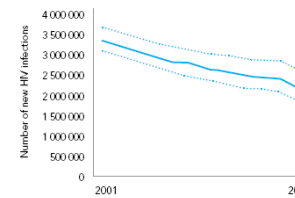


## 1996-2013: STI/HIV trends in lower income countries

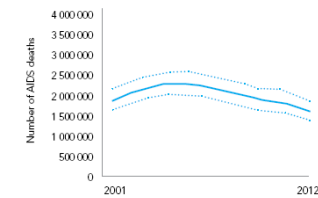
- STD syndromic management, condom promotion scaled up beginning 1990
- HAART scale up beginning mid- 1990s

## UNAIDS 2013: New HIV Infections Fall by Third

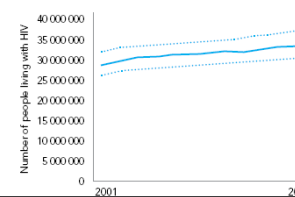
NEW HIV INFECTIONS, GLOBAL, 2001-2012



AIDS DEATHS, GLOBAL, 2001-2012

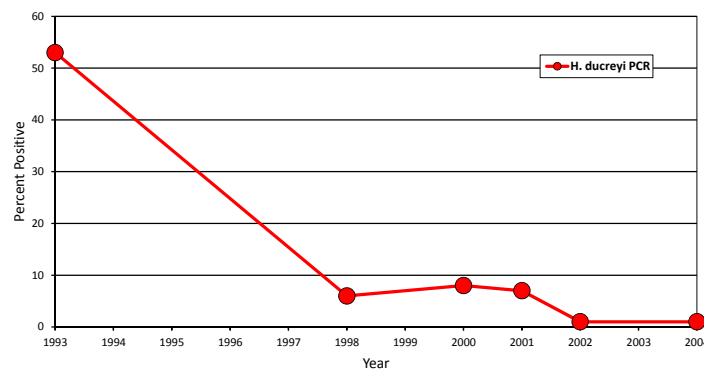


PEOPLE LIVING WITH HIV, GLOBAL, 2001-2012



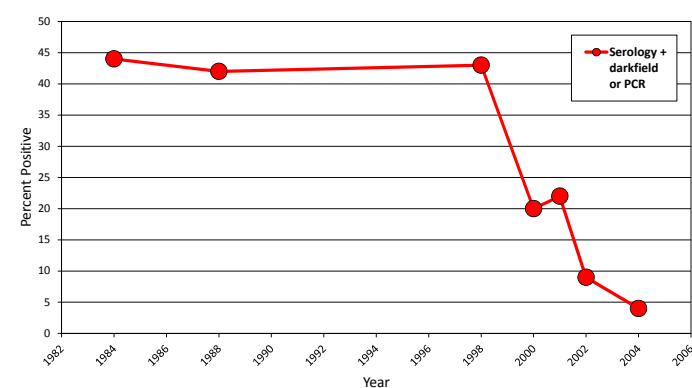
••• High estimate  
— Estimate  
••• Low estimate

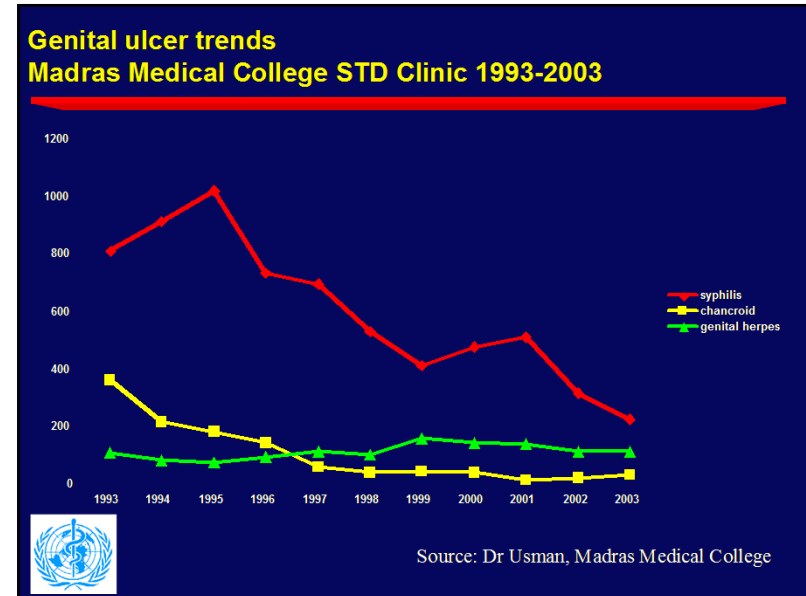
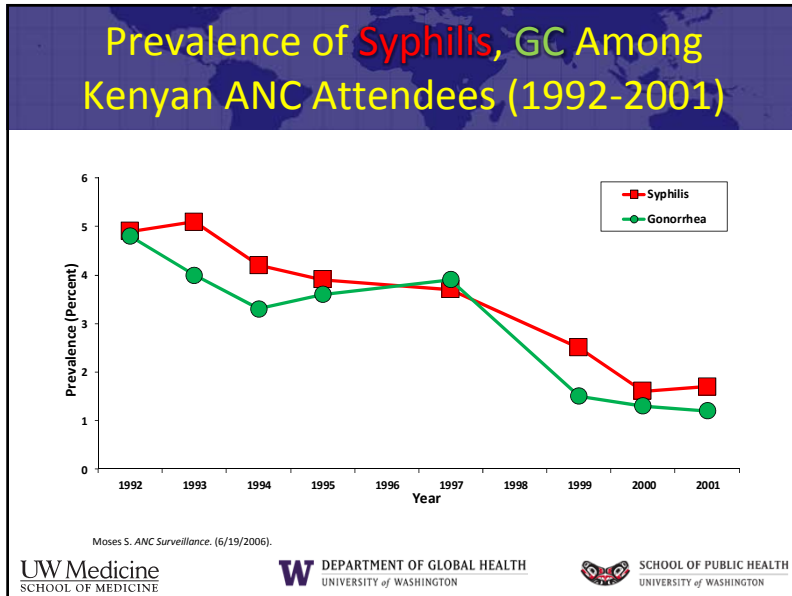
## Durban, KZN, So Africa: *Haemophilus ducreyi*



Halperin D. (March 25, 2009). "Other technologies with multi-purpose potential". Harvard University School of Public Health: Cambridge, MA. Retrieved 09/13/2011 from <http://www.cami-health.org/AP72009/PDFs/halperinrh2009.pdf>.





## Durban, KZN, So Africa: *Treponema pallidum*



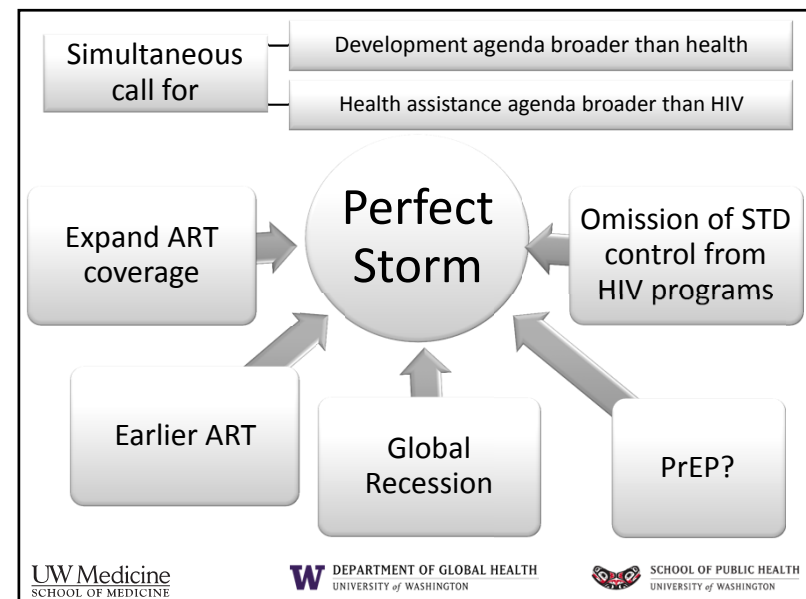


### 2010-11: New Evidence for ART and PrEP for Prevention

- CAPRISA 004: 1% tenofovir vaginal gel prophylaxis — 39% ↓ HIV acquisition
- iPrEx: daily oral Truvada for MSM — 43.8% ↓ HIV acquisition
- HPTN052: Early ART — 96% ↓ HIV transmission
- Partners PrEP: serodiscordant couples 62% (tenofovir), 72% (Truvada) ↓ HIV acquisition; even better with high adherence
- CDC PrEP TDF2: 62% ↓ HIV acquisition

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## Eight questions for the future

- 1) What will be the impact of scaled up ART on sexual behavior? (STI incidence will continue to be an indicator for unprotected sex and more connected sex networks)
- 2) Will STI epidemics accelerate even further in MSM and other populations at high risk?
- 3) Will the resurgence of STIs again increase transmission of HIV?
- 4) What will be the impact of increasing unprotected sex on emergence of new STIs (analogous to the emergence of HIV as a new STI in 1980)? On the emergence of new variants of existing STI pathogens, perhaps more virulent variants (past evidence of rapid spread enhancing virulence of other pathogens)?

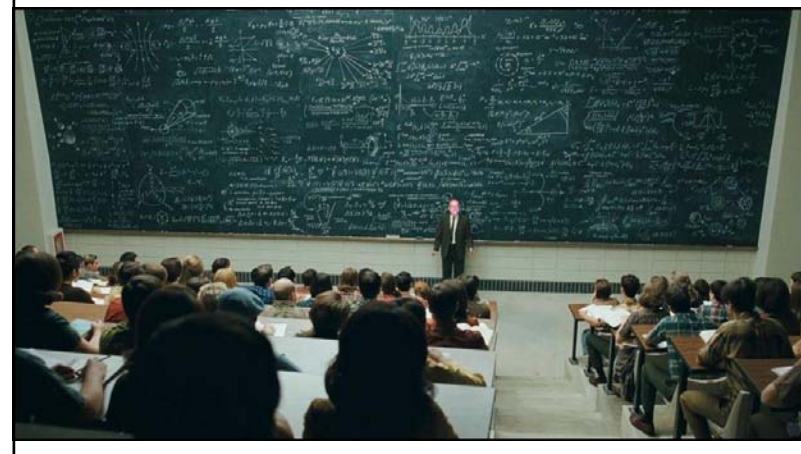
## Eight questions for the future (cont.)

- 5) What will be the impact of increasing STI incidence on antimicrobial resistance in STI pathogens (including HIV)?
- 6) Will increasing unprotected sex in the context of scaled-up ART or PrEP accelerate ARV<sup>R</sup>, similar to the emergence of azithro-resistant *T. pallidum* and multidrug-resistant GC? (How could it not?)
- 7) Will the combined negative impact of increased unprotected sexual exposure plus reemerging STI epidemics together outweigh the positive impact of increasing ART coverage on HIV transmission?
- 8) Will local, national, global resources for STI control continue to decline, despite increasingly rapid reemergence of STI, including antimicrobial-resistant STI?

## Bonus Question


- What can be done to optimize the beneficial prevention impact of scaling up ART, and reduce the risks of negative impact?

## The Science of "Complex" Interventions



**THE LANCET**

Articles



**Prevention of sexually transmitted infections in urban communities (Peru PREVEN): a multicomponent community-randomised controlled trial**

*Patricia J García, King K Holmes, César P Cárcamo, Geoff P Garnett, James P Hughes, Pablo E Campos, William L H Whittington, Peru PREVEN Study Team\**

*Lancet* 2012; 379: 1120–28

Early Online Publication, 15 February 2012  
doi:10.1016/S0140-6736(11)61846-1

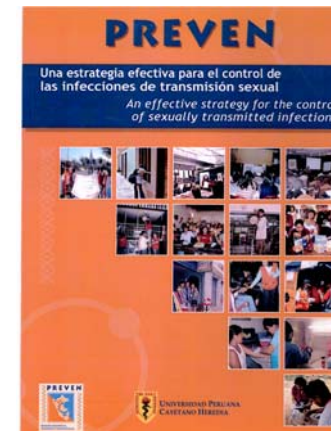
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## STI outcomes for 2006, GP (N=6556 18-29 y.o. women in 20 cities)

Intervention vs. control cities: 24% reduction in combined prevalence of any of 4 curable STIs (CT, NG, TV,  $\Sigma$ ) after 3 years ( $p=0.02$ ), comparing intervention cities vs. control cities

## STI outcomes in FSW (N=4130 in 20 cities for 2006)

Intervention vs. control cities: → 35% reduction in combined prevalence of any of 4 curable STIs (CT, NG, TV,  $\Sigma$ ) after 3 years ( $p=0.02$ ), comparing intervention cities with control cities



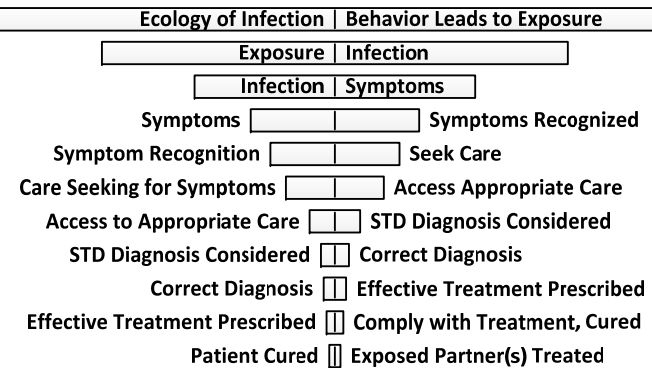
Published May 2013, with support from UNAIDS

<http://www.proyectopreven.org>

## Vancouver Collaborators!

- Bowie WR, Wang SP, Alexander ER, et al. Etiology of nongonococcal urethritis. Evidence for *Chlamydia trachomatis* and *Ureaplasma urealyticum*. J Clin Invest. 1977.
- Brunham RC, Paavonen J, Stevens CE, et al. Mucopurulent cervicitis—the ignored counterpart in women of urethritis in men. N Engl J Med. 1984.
- Money DM, Hawes SE, Eschenbach DA, et al. Antibodies to the chlamydial 60 kd heat-shock protein are associated with laparoscopically confirmed perihepatitis. Am J Obstet Gynecol. 1997.

## “STD care management”, Fig. 48-2, from Sexually Transmitted Diseases, 3rd Edition, McGraw-Hill, 1999



## The Prevention and Treatment Cascades

- Gardner EM, et al. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011 Mar 15; 52(6): 793-800.
  - Now about 1.8 million results on Google for HIV Treatment Cascade.
- Chapters 48 and 89. Sexually Transmitted Diseases, 3rd Edition. McGraw-Hill, 1999
- Prevention and Treatment Cascades now widely adapted and used:
  - GAVI, Roll Back Malaria, Stop Tuberculosis Partnership, IMCI, Reproductive Health Care, Water and Sanitation

## Conclusions

- At First, I Thought
  - Just need more and better diagnostics and treatments
- Later
  - Safer sex: change sexual behaviors
- Still Later
  - Vaccines
- Now
  - Above, plus program science for focused, efficient, cost-effective, integrated, combination interventions, with ongoing needs-assessments ; enabling policies and structural changes; and innovative integration of clinical and public health systems to expand access, coverage, and quality of interventions.

**Thank You!**