



HIV and Syphilis: A syndemic with no end in sight?

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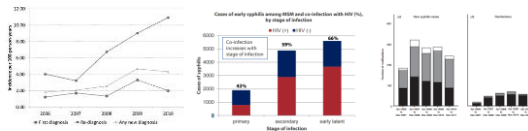
Outline

- Brief epidemiology
- Interventions
- Chemoprophylaxis/PrEP
- Treatment
- Subtyping
- Neurosyphilis
- Cytokines and markers of disease status



Epidemiology of HIV and syphilis

Syphilis notifications in HIV positive gay and bisexual men continue to increase



Canada
300x rate in general pop
Burchell et al
BMC Infectious Diseases 2015

USA
50% cases in HIV pos
Su et al
STD prevention 2014

NSW, Australia
49% in HIV pos
87% of reinfections
Botham et al
Sex health 2013



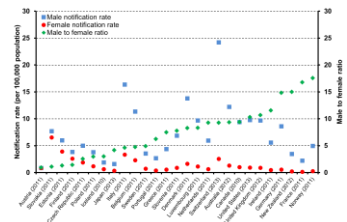
Syphilis notifications in high income countries

Male to female ratio increasing in 17/28 OECD countries

Proportion of cases in MSM >50%

No country succeeded in significantly reducing trend between 2000-2013

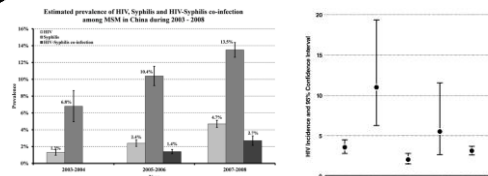
None report HIV status systematically



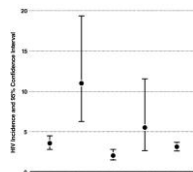
Read et al, Sex Health 2015



Not just high income countries....



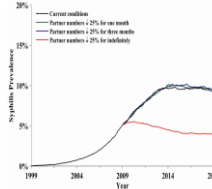
Chow et al PLoS one 2011



Rates of syphilis >10%/yr in Brazil, 7% in South Africa, 6% Thailand
Solomon et al CID 2014



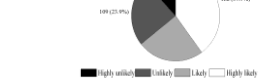
Syphilis control: sexual behaviour



Gray RT et al. Sex Transm Dis 2011
McCann PD et al. Sex Transm Dis 2011

Would MSM do it for 3m?

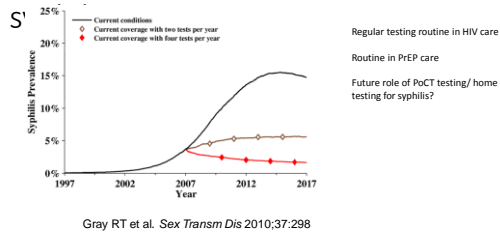
Personal benefit



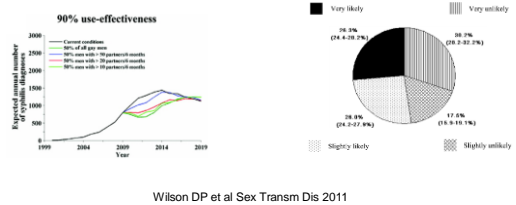
Community benefit



Syphilis control: increase MSM



Syphilis control: Chemoprophylaxis



Doxycycline prophylaxis pilot: Bolan et al STD 2015

30 HIV positive GBM randomised

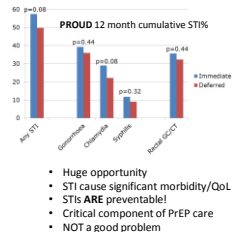
- 15 received 100mg od doxycycline

- Followed for 48 weeks
- 77% retention rate; drug levels reasonable
- 1 gastro reflux

Outcome	Number of Visits with Outcome		p-value	OR (95% CI)
STI Co-infection	Doxycycline Arm	CM Arm		
Gonorrhoea or Chlamydia Only	4	8	0.18	0.34 (0.08-1.56)
Syphilis Only	2	7	0.10	0.24 (0.04-1.33)
Any STD (Gonorrhoea, Chlamydia, Syphilis or any combination thereof)	6	15	0.02	0.27 (0.09-0.83)

STIs and HIV PrEP- "a good problem to have?"

- PROUD: high baseline prevalence (>50% incidence any STI- 10% syphilis)
- IPERGAY: 10% syphilis incidence
- Kaiser Cohort- San Francisco = 50% STI at 12 months
 - 5.5% syphilis (CI95: 3.3-9.1%)
- Behaviour/condom change-
 - No change in partners
 - less condom use



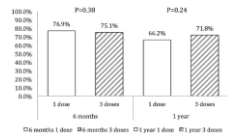
How much benzathine is enough?

478 patients – US Military HIV cohort
All had syphilis of <1yr duration
Stratified by treatment

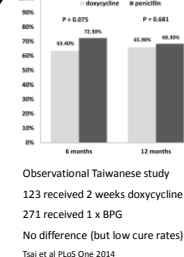
Serologic Response	Total (N = 478)	1 Dose of BPG* (n = 141)	≥2 Doses of BPG* (n = 252)	Other** (n = 85)
3 mo	31%	33%	29%	33%
6 mo	66%	69%	66%	60%
9 mo	84%	86%	85%	80%
12 mo	91%	92%	92%	86%

Ganesen et al *CID* 2015

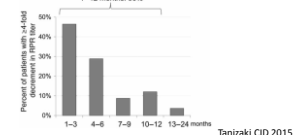
578 HIV patients across Taiwan
Compared RPR at 6, 12 months
N= 295 1x BPG vs n= 273 3xBPG



Can we use other treatment for syphilis in HIV+ve?



Japan: 3g Amoxicillin + probenecid
286 HIV pos men: Observational
1/3 late/unknown duration with RPR ≥1:8
Excluded neurosyphilis
150 on cART, median CD4 390
Overall 95% cure rate at 24 months



Treatment guidelines for early syphilis and HIV

US CDC 2015:

1 x 2.4 MU BPG for early syphilis

If no treatment response, give 3 x BPG unless CSF shows neurosyphilis

No need for enhanced regimens

No need for LP unless neuro signs

BASHH & European & Australian

1 x 2.4 MU BPG for early syphilis

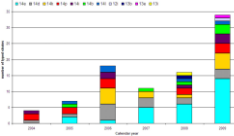
No need for LP unless signs (BASHH more permissive)

Despite this: Australian data shows 40% of HIV pos are treated with enhanced regimens- no difference in cure

Read et al Sex Health 2015

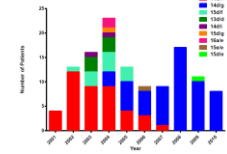
What can syphilis subtyping tell us about syphilis and HIV?

1998 CDC classification- ARP/TPR



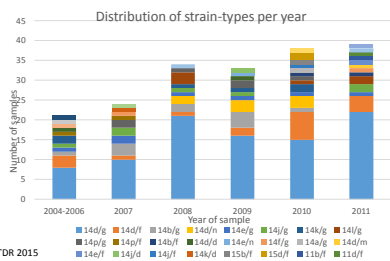
11 strains in Melbourne
No conspicuous relation to HIV status
Azzato et al J Clin Micro 2012

Enhanced in 2010- CDC + TRAP 20



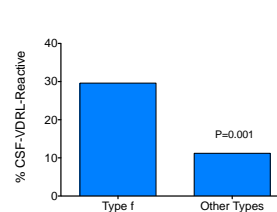
Multiple strains in Seattle, 14d/f replaced with 14d/g over time
Grimes et al STD 2012

Distribution of strain types over time in Sydney- no relation to HIV status



Read et al ISSTD 2015

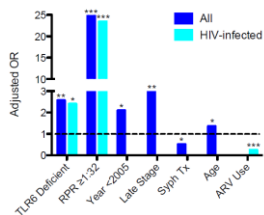
Strain Type and Neurosyphilis



	Adj OR	P-value
RPR	1.8	<0.001
Type f	3.5	0.02
> 2005	0.7	0.4

Slide courtesy Christina Marra

Neurosyphilis and host immunity



Graph courtesy Christina Marra

Impairment of innate immunity

Natural polymorphisms of TLR

Reduced opsonisation?

Higher levels of serum TNF in HIV pos who developed NS vs those who didn't- more immune activation/dysregulation

May explain OR for NS with cART of 0.2

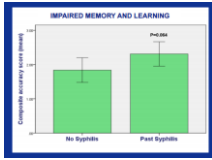
What's new in neurosyphilis and HIV?

Tuddenham- STD 2015

Confirmed finding that negative serum RPR predicts absence of NS

Patient and laboratory characteristics	Data by NS status		P	Crude OR (95% CI)*
	With NS (n = 30)	Without NS (n = 92)		
RPR titer [†]	256 (13-1,152)	128 (4-1,152)	0.639	
Median (range)	88 (100)	88 (94)	0.364	41.86 (0.34-1,000)
≥1:16 (n [%])	30 (100)	82 (89)	0.119	73.17 (0.68-1,000)
≥1:32 (n [%])	28 (93)	75 (82)	0.154	3.17 (0.69-14.63)
≥1:256 (n [%])	22 (73)	55 (60)	0.200	1.85 (0.75-4.60)
≥1:2048 (n [%])	14 (45)	45 (49)	0.834	1.19 (0.52-2.75)

Relation between Neurosyphilis and HIV neurocognitive impairment?



CHARTER study:
Case control study
Prior syphilis OR of 2.6 for learning impairment (controlled for methamphetamine use), and greater number of domains with reduced function

No relation to current CSF findings

Marra et al 2013 Int J STD AIDS

Significant for reinfection
Vera et al HIV Med 2012

Need for better markers of disease activity

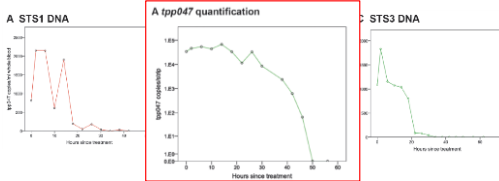
TP-PCR in blood- pooled sensitivity meta-analysis- Gayet-Ageron STI 2012

Specimen, n (%) per stage	Primary	Secondary	Early	Latent	Neurosyphilis	Congenital	All stages
Blood	10 (33.3%)	13 (52.0%)	7 (9.1%)	10 (83.3%)	1 (11.1%)	6 (85.7%)	42
Urothelium	27 (90.0%)	18 (72.0%)	20 (90.9%)	9 (10.0%)	0 (0.0%)	0 (0.0%)	65

	Odds ratio	95% CI	p-value
Age	0.983	0.939-1.029	0.457
Baseline RPR, per 1-log ₁₀ increase	1.184	0.967-1.437	0.087
Secondary vs. primary syphilis	4.967	2.016-12.238	<0.001
Early latent vs. primary syphilis	0.762	0.273-2.176	0.603
CD4 count (10-cells/mm ³ decrease)	1.030	1.006-1.036	0.006
Plasma HIV RNA load, log ₁₀	0.824	0.594-1.142	0.245
CART	1.005	0.362-2.787	0.992

No association with HIV and spirochaetemia
Wu et al Clinical Microbiology and Infection 2013

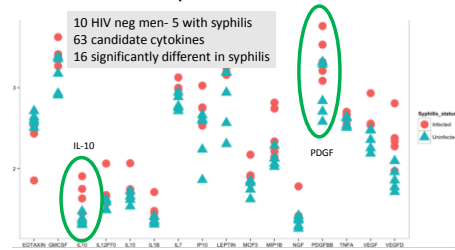
Quantitative TP-PCR changes post treatment



Half life 5.7 hours, clearance 56 hours

Tipple et al PLoS Neglected Trop Dis 2015

Inflammatory markers and infection



Bristow et al ISSTD 2015

HIV-positive patient on ART (CD4+=380, VL=15,000) with recent syphilis infection, PET Scan

First visit (RPR = 1:64) pre-treatment with probable syphilitic aortitis



PICASSO Study
NIH/NIAD R01 AI099727

Follow up visit (RPR 1:16) post-treatment without aortitis



Slide courtesy Jeff Klausner

Summary- Maybe there is light at the end of the tunnel?

- Overlapping epidemiology of HIV and syphilis continues
- Greater understanding of range of prevention options
- Evidence that current treatments do work in HIV
- Role of prophylaxis and molecular epidemiology
- Evolving data on biological basis for possible risk of neurosyphilis
- Development of better tools to establish disease activity
- Significant social and structural challenges- but never give up.



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