

14TH ANNUAL CONFERENCE
OF THE BRITISH HIV ASSOCIATION (BHIVA)



Dr Anna Maria Geretti

Royal Free Hospital and
RF & UC Medical School, London

23-25 April 2008, Belfast Waterfront Hall, Northern Ireland, UK

Top Ten Papers 2007-2008

Anna Maria Geretti



Strategy

- Peer-reviewed articles from the last 12 months
- Intentionally excluded HAART trials

Topics:

- *HIV transmission*
- *Treatment outcomes*
- *Complications of disease or treatment*
- *HCV co-infection*

Herpes Simplex Virus (HSV) Suppression with Valacyclovir Reduces Rectal and Blood Plasma HIV-1 Levels in HIV-1/HSV-2–Seropositive Men: A Randomized, Double-Blind, Placebo-Controlled Crossover Trial

Richard A. Zuckerman,¹ Aldo Lucchetti,⁶ William L. H. Whittington,² Jorge Sánchez,⁶ Robert W. Coombs,^{2,3} Rosario Zuñiga,⁶ Amalia S. Magaret,³ Anna Wald,^{2,3,4,5} Lawrence Corey,^{2,3,5} and Connie Celum^{2,4}

¹Section of Infectious Disease and International Health, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Departments of ²Medicine, ³Laboratory Medicine, and ⁴Epidemiology, University of Washington, and ⁵Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle; ⁶Asociación Civil Impacta Salud y Educación, Lima, Peru

The Journal of Infectious Diseases 2007; 196:1500–8

Background:

- HSV-2 infection ↑ the risk of HIV transmission and acquisition
- HSV-2 suppression ↓ HIV load in plasma and female genital tract

Study design

- HIV-1/HSV-2 seropositive ARV-naïve MSM, CD4 >200 (n=20)
- Valacyclovir 500mg bd or placebo for 8 wks →
- Washout for 2 wks →
- Cross-over for 8 wks
- Median 46 (31-48) clinic visits
- Blood, rectal secretion, genital and perianal skin swabs
- Pill count: median 96.2% (65.8-100%) adherence

Main outcomes

Table 2. Rates of herpes simplex virus (HSV) and HIV-1 detection and mean log₁₀ HIV-1 levels for 20 HIV-1/HSV-2-coinfected men who have sex with men.

Category	Both arms	Arm	
		Placebo	Valacyclovir
HSV detection rate, external anogenital or rectal mucosal sample	356/2155 (17)	309/1071 (29)	47/1084 (4) ^a
HSV detection rate, rectal mucosal sample only	124/904 (14)	112/446 (25)	12/458 (3)
Rectal mucosal HIV-1 detection rate	620/844 (73)	333/427 (78)	287/417 (69) ^b
Rectal mucosal HIV-1 level, mean ± SD, log ₁₀ copies/mL	4.90 ± 1.04	5.00 ± 1.04	4.80 ± 1.04 ^a
Plasma HIV-1 detection rate	284/288 (99)	143/145 (99)	141/143 (99)
Plasma HIV-1 level, mean ± SD, log ₁₀ copies/mL	4.32 ± 0.72	4.50 ± 0.71	4.14 ± 0.69 ^a

NOTE. Data are no. with detectable HIV-1 RNA or HSV DNA by polymerase chain reaction/no. of samples obtained, unless otherwise indicated. Observations begin on the second day for each study arm. Undetectable HIV-1 levels have been imputed to the midpoint between zero and the lower limit of detection.

^a *P* < .001, compared with placebo.

^b *P* = .02, compared with placebo.

▪ Valacyclovir vs placebo

Log₁₀ rectal HIV-1 level -0.16 (p=0.0008) 31% reduction

Log₁₀ plasma HIV-1 level -0.33 (p<0.0001) 53% reduction

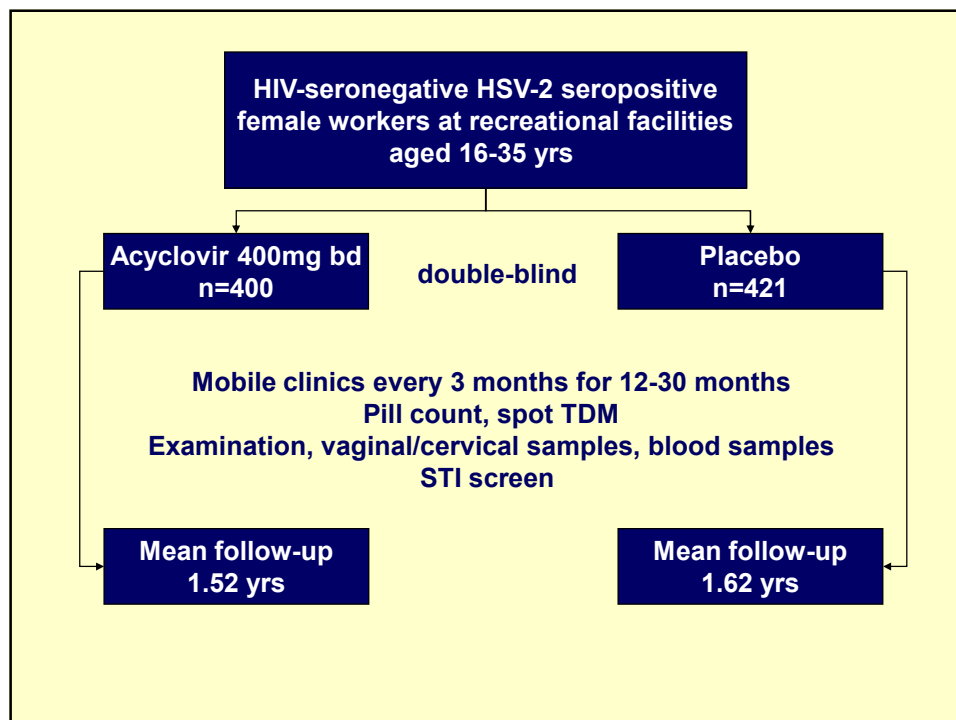
▪ HIV reduction coincided with HSV reduction

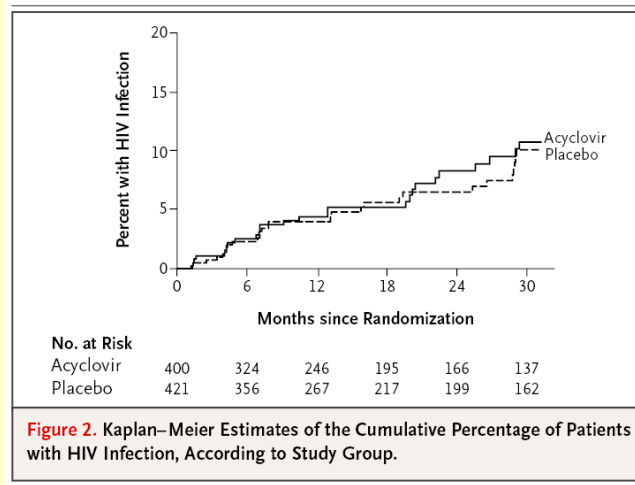
Effect of Herpes Simplex Suppression on Incidence of HIV among Women in Tanzania

Deborah Watson-Jones, M.D., Ph.D., Helen A. Weiss, Ph.D.,
Mary Rusizoka, Dip.Med., John Changalucha, M.Sc., Kathy Baisley, M.Sc.,
Kokugonza Mugeye, Dip.Med., Clare Tanton, M.Sc., David Ross, M.D., Ph.D.,
Dean Everett, Ph.D., Tim Clayton, M.Sc., Rebecca Balira, M.Sc.,
Louise Knight, M.Sc., Ian Hambleton, Ph.D., Jerome Le Goff, M.Sc., Ph.D.,
Laurent Belec, M.Sc., Ph.D., and Richard Hayes, D.Sc.*

N Engl J Med 2008;358:1560-71

From the London School of Hygiene and Tropical Medicine, London (D.W.-J., H.A.W., K.B., C.T., D.R., D.E., T.C., L.K., I.H., R.H.); the African Medical and Research Foundation (D.W.-J., M.R., K.M.) and the National Institute for Medical Research (J.C., K.B., C.T., D.E., R.B., L.K., I.H.) — both in Mwanza, Tanzania; and the Laboratoire de Microbiologie, Hôpital Saint Louis (J.L.G.), and INSERM Unité 743 and Université Paris V (L.B.) — both in Paris.





- **Spot urinary TDM: acyclovir in 33-67% of samples in acyclovir group and 5-10% of samples in placebo group**
- **HSV-2 DNA: in 3.8% of vaginal/cervical samples in acyclovir group vs 4.7% of samples in placebo group**
 - **1.7% vs 5.0% if $\geq 90\%$ adherence**

Conclusions

- **No evidence that acyclovir (400mg bd) decreases the incidence of infection with HIV**
- **Possible explanations:**
 - *chance, bias due to loss of follow-up*
 - *low HSV-2 replication*
 - *limited power to detect moderate effects, outweighing effects of other risk factors*
 - *suboptimal adherence, insufficient antiviral potency*
- **Potential benefit not excluded**
- **Not a viable public health intervention**

Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREAThE network

Bujan L, Hollander L, Coudert M, Gilling-Smith C, Vucetich A, Guibert J, Vernazza P, Ohl J, Weigel M, Englert Y, Semprini AE. *AIDS* 2007;21:1909-14

- Retrospective multicentre study
- 1036 HIV-serodiscordant couples
- 580 pregnancies obtained from 3315 reproduction cycles
 - IUI: pregnancy per cycle 15.1%, pregnancy per couple 42.7%
- 463 live births from 533 pregnancies with known outcome
- All 967 women tested ≥ 6 months after treatment were HIV-
- Probability of contamination = zero [95% CI 0-0.09]

Mortality in HIV-infected Ugandan adults receiving antiretroviral treatment and survival of their HIV-uninfected children: a prospective cohort study

Jonathan Mermin, Willy Were, John Paul Ekwaru, David Moore, Robert Downing, Prosper Behumbiize, John R Lule, Alex Coutinho, Jordan Tappero, Rebecca Bunnell

Lancet 2008; 371: 752-59

Centers for Disease Control and Prevention-Uganda, Global AIDS Program, National Center for HIV, Viral Hepatitis, Sexually Transmitted Disease, and Tuberculosis Prevention, Centers for Disease Control and Prevention, Entebbe, Uganda (J Mermin MD, W Were MB, J P Ekwaru MSc, D Moore MD, R Downing PhD, P Behumbiize, J R Lule MB, J Tappero MD, R Bunnell ScD); Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada (D Moore); The AIDS Support Organisation, Kampala, Uganda (A Coutinho MB); and Centers for Disease Control and Prevention-Kenya, Coordinating Office for Global Health, Centers for Disease Control and Prevention (J Mermin), Nairobi, Kenya

Background

- Access to ART in Africa limited by high ARV cost, lack of trained health-care providers, poorly equipped clinics, distance to health centres, transport costs
- A home-based ART programme may overcome some of the barriers

Study population

- Observational cohorts
- 1373 HIV+ persons
- 4601 HIV- household members
- Households visited every week by trained lay providers
- No clinic visits scheduled

- Adherence >95% for 87-97% of quarterly assessments
- VL <400
 - 91% at 3 months
 - 96% at 6 and 24 months

2001:
No intervention cohort
n=466
Median follow-up 154 days

2001-2003
CTX* cohort
N=399
Median follow-up 532 days

2003-2005
CTX* + ART**
N=1045
Median follow-up 749 days

*Co-trimoxazole
** d4T/3TC/NVP or EFV

Findings-1

Deaths	HIV-infected	Household
Total	233 (17%)	40 (1%)

- Males at greatest risk of mortality
adj HR 1.4 [95% CI 1.07-1.90; *p*=0.017]
- 99% of deaths medically-related

	adjHR	95% CI	<i>P</i>
▪ CTX vs no intervention			
47% ↓ mortality	0.53	0.34-0.82	0.0046
36% ↓ hospitalisation	0.64	0.45-0.90	0.0114
<i>Greatest benefit on mortality at CD4 ≤50</i>			
▪ ART+CTX vs CTX alone			
55% ↓ mortality ≤16 wks	0.45	0.27-0.74	0.0018
92% ↓ mortality >16 wks	0.08	0.06-0.13	<0.0001
43% ↓ hospitalisation	0.57	0.42-0.76	0.0001
<i>Benefit on mortality across all CD4 strata after wk 16</i>			

Findings-2

ART+CTX vs no intervention	adjHR	95% CI	P
95% ↓ mortality	0.05	0.03–0.08	<0.0001
93% ↓ orphanhood	0.07	0.04–0.13	<0.0001
81% ↓ mortality in uninfected children <10 yrs	0.19	0.06–0.59	0.004

Conclusions

- High rate of success of ART programme
- Significantly reduced mortality
- Reduction in orphanhood
- Reduction in mortality of HIV- children
- Greatest benefit seen >16 wks of ART

Risk of extensive virological failure to the three original antiretroviral drug classes over long-term follow-up from the start of therapy in patients with HIV infection: an observational cohort study

Andrew N Phillips, Clifford Leen, Alan Wilson, Jane Anderson, David Dunn, Achim Schwenk, Chloe Orkin, Teresa Hill, Martin Fisher, John Walsh, Deenan Pillay, Loveleen Bansal, Brian Gazzard, Philippa Easterbrook, Richard Gilson, Margaret Johnson, Caroline A Sabin, for the UK Collaborative HIV Cohort (CHIC) Study*

Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London, UK (Prof A N Phillips PhD, T Hill PhD, L Bansal MSc, Prof C A Sabin PhD); University of Edinburgh, Western General Hospital, Edinburgh, UK (C Leen MD); ^aWilson's Hospital, London, UK (J Anderson FRCP); Medical Research Council Clinical Trials Unit, London, UK (D Dunn PhD); North Middlesex University Hospital, London, UK (A Schwenk FRCP); Barts and The London NHS Trust, London, UK (C Orkin MRCP); Brighton and Sussex University Hospital NHS Trust, Sussex, UK (M Fisher FRCP); St Mary's Hospital, London, UK (J Walsh MBBS); Department of Infection, BfU/CMS, Centre for Infection, Health Protection Agency, London, UK (Prof D Pillay FRCP); Chelsea and Westminster NHS Trust, London, UK (B Gazzard FRCP); King's College Hospital, London, UK (P Easterbrook FRCP); Mortimer Market Centre, Royal Free and University College Medical School (BfU/CMS), London, UK (R Gilson MD); and Royal Free NHS Trust and BfU/CMS, London, UK (Prof M Johnson FRCP)

Lancet 2007; 370: 1923-28

- 7916 patients who started HAART with ≥3 drugs
- Virological failure: VL >400 despite >4 months of continuous drug use
- Extensive triple class failure: 3 subclasses of NRTIs +1 NNRTI + ≥1 PI/r
- 167 patients during 27441 py of follow-up

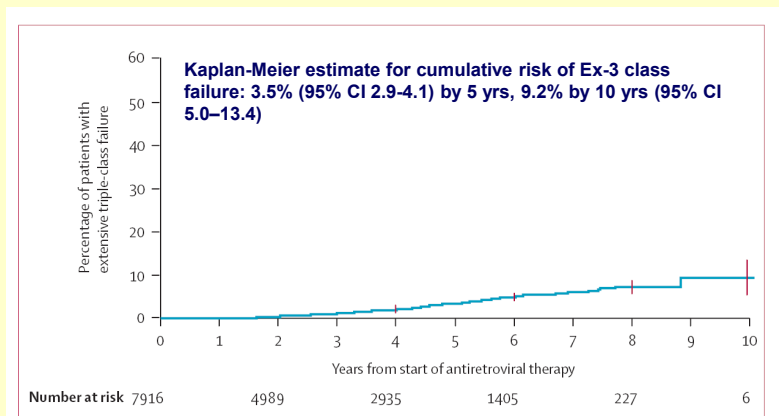


Figure: Cumulative risk of extensive triple-class virological failure
95% CIs are shown at 2 year intervals.

	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Sex (women vs men)	1.39 (0.98-1.96)	0.06
HIV-exposure group				
Homosexual men	1.00	..	1.00	..
Heterosexual	2.11 (1.53-2.90)	<0.0001	2.26 (1.50-3.40)	<0.0001
Other	1.56 (0.87-2.80)	0.14	1.66 (0.91-3.03)	0.10
Age (per 10 years older)	0.77 (0.63-0.94)	0.01	0.70 (0.57-0.87)	0.001
Calendar year of ART (per year more recent)	0.95 (0.85-1.05)	0.31	0.86 (0.77-0.96)	0.006
CD4-cell count (per 100 per μ L higher)	0.67 (0.59-0.76)	<0.0001	0.68 (0.60-0.77)	<0.0001
Viral load (per log higher)	1.17 (0.97-1.42)	0.10
Initial regimen				
Two NRTI+NNRTI	1.00
Two NRTI+PI	0.93 (0.65-1.33)	0.68
Two NRTI+PI/r	0.84 (0.41-1.74)	0.64
Three NRTI	1.48 (0.77-2.86)	0.24
Other	0.71 (0.39-1.27)	0.25
AIDS before ART	1.61 (1.16-2.24)	0.005

ART=antiretroviral therapy. PI/r=ritonavir-boosted protease inhibitor.

Table 3: Hazard ratio for development of extensive triple-class failure according to baseline factors

By 10 yrs the risk of Ex-3 class failure 5.5% [95% CI 3.5-7.5] vs 12.1% [5.1-19.1] for pre-treatment CD4 counts >200 or <200

Conclusions

- **Low risk of extensive triple class failure over time in patients starting HAART, especially in those who started therapy in recent years with CD4 >200**
- **Higher risk in younger patients and heterosexuals**

The prevalence and incidence of neurocognitive impairment in the HAART era

Robertson KR, Smurzynski M, Parsons TD, Wu K, Bosch RJ, Wu J, McArthur JC, Collier AC, Evans SR, Ellis RJ. *AIDS* 2007;21:1915-21

- 1160 Caucasian and Afro-American
- ACTG cohort, 50% ARV-naïve
- Prevalent mild-moderate neurocognitive impairment: 26%
 - Associated with low nadir CD4 count
 - Associated with low current CD4 count
- Incident neurocognitive impairment: 21%
 - No significant virological and immunological predictors

Metabolic effects of growth hormone-releasing factor in patients with HIV

Falutz J, Allas S, Blot K, Potvin D, Kotler D, Somero M, Berger D, Brown S, Richmond G, Fessel J, Turner R, Grinspoon S. *N Engl J Med.* 2007;357:2359-70

- Multicenter, randomised, placebo-controlled study
- Tesamorelin by daily sc injections for 26 wks in patient on HAART with excessive abdominal fat defined by waist circumference and waist to hip ratio (n=412)

	Tesamorelin	Placebo	P
Visceral fat (by CT)	- 15.2%	+ 5%	<0.001
Subcutaneous fat (by DEXA)	+ 0.4%	+ 1.7%	0.05
Limb fat (by DEXA)	+ 0.6%	+ 3.8%	0.006
Triglycerides (mg/dl)	- 50	+ 9	<0.001
TC/HDL-C	- 0.31	+ 0.21	<0.001
ILGF-I	+ 81%	- 5%	<0.001
Discontinuations	22.7%	16.1%	0.12

Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis

Andrew E Grulich, Marina T van Leeuwen, Michael O Falster, Claire M Vajdic

Lancet 2007; 370: 59-67

National Centre in HIV
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Research, University of New
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(Prof A E Grulich PhD,
M T van Leeuwen MPH,
M O Falster BPsych[Hons],
C M Vajdic PhD)

Background

- Only a few types of cancer recognised as directly related to immune deficiency in people with HIV
- Studies in transplant recipients suggest a wider range of cancers that could be associated with immune deficiency

- 7 studies of people with HIV (n = 444172) and 5 of solid organ transplant recipients (n = 31977)

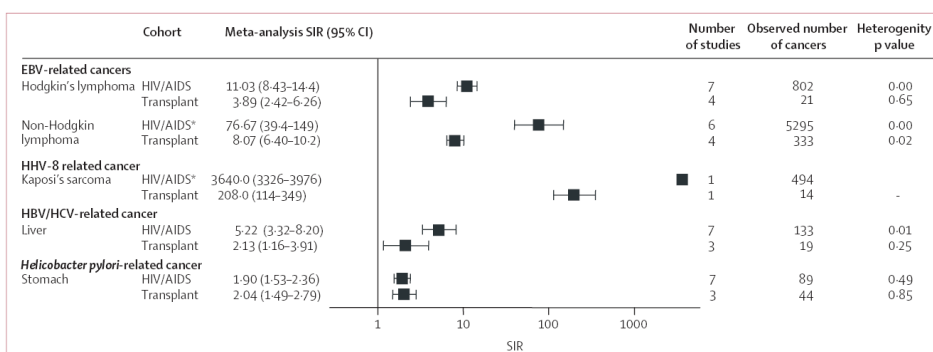
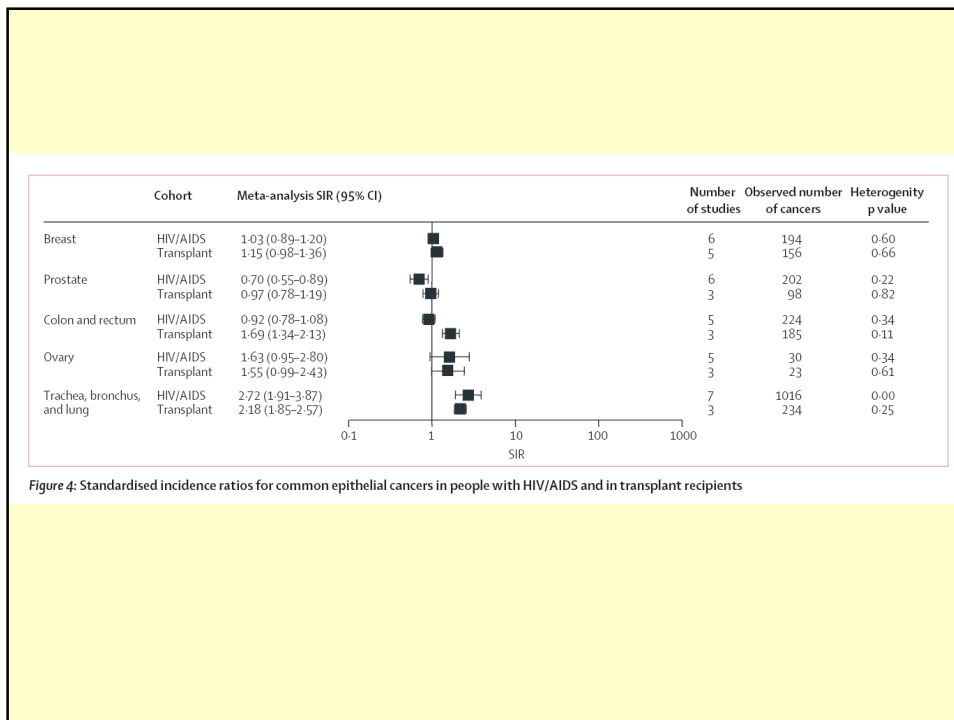
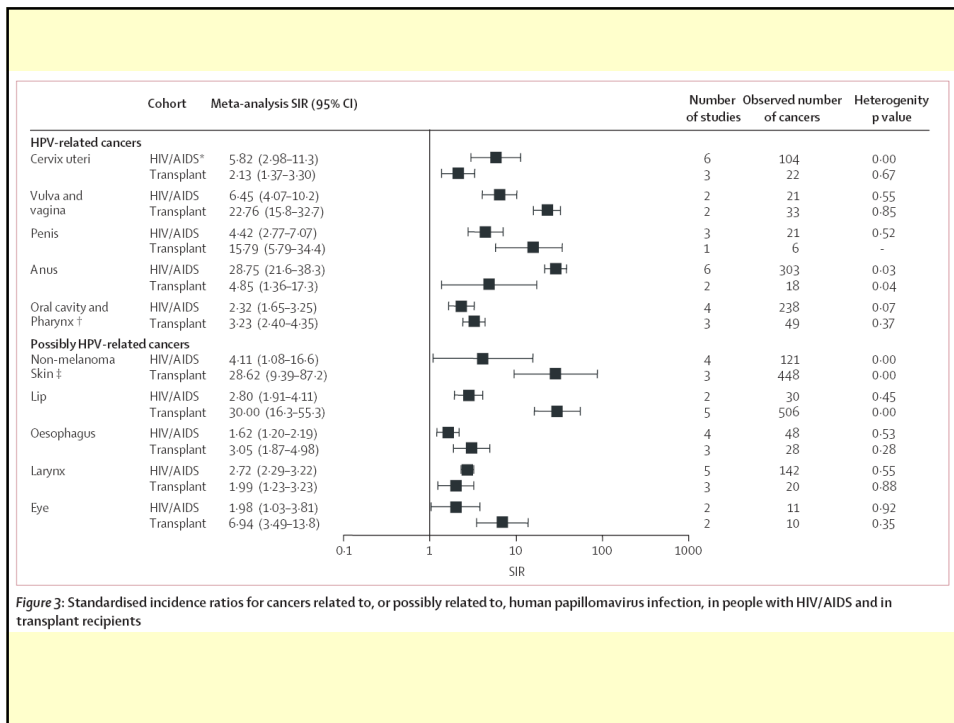


Figure 2: Standardised incidence ratios for cancers related to infection with Epstein-Barr virus, human herpesvirus 8, hepatitis B and C virus, and *Helicobacter pylori* in people with HIV/AIDS and in transplant recipients



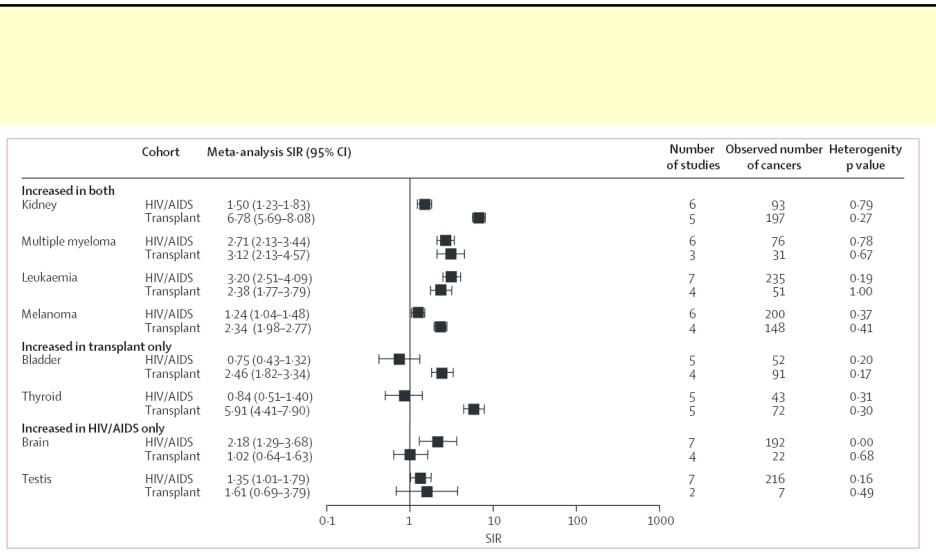


Figure 5: Standardised incidence ratios for other cancers occurring at increased rates in one or both populations

Conclusions

- 20/28 types of cancer examined showed increased incidence in both groups
- Most common epithelial cancers did not occur at increased rates
- The pattern of increased risk similar in both groups
- Many - but not all - cancers that occurred at increased rates were those with a known or suspected infectious cause

<p>Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. <i>Danta et al. AIDS 2007;21:983-91</i></p>	
<ul style="list-style-type: none"> ● MSM with acute HCV [1999-2005] ● 7 monophyletic clusters from 111 cases, largest with 43 sequences ● 60 cases matched to 130 HCV- controls, self-administered questionnaire <p>Cases:</p> <ul style="list-style-type: none"> ● 82.8% did not report IDU ● More piercing, more sexual partners, higher levels of high-risk sexual behaviour and rough sexual practices, more history of STIs, more likely to have shared drugs via a nasal or anal route 	

<p>Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. <i>Danta et al. AIDS 2007;21:983-91</i></p>	<p>Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. <i>Van de Laar et al. J Infect Dis 2007;196:230-8</i></p>
<ul style="list-style-type: none"> ● MSM with acute HCV [1999-2005] ● 7 monophyletic clusters from 111 cases, largest with 43 sequences ● 60 cases matched to 130 HCV- controls, self-administered questionnaire <p>Cases:</p> <ul style="list-style-type: none"> ● 82.8% did not report IDU ● More piercing, more sexual partners, higher levels of high-risk sexual behaviour and rough sexual practices, more history of STIs, more likely to have shared drugs via a nasal or anal route 	<ul style="list-style-type: none"> ● Retrospective HCV Ab tests on 1836 MSM [1984-2003] <p><i>HCV incidence per 100 py:</i></p> <ul style="list-style-type: none"> ● 0 in HIV- MSM ● 0.18 in HIV+ MSM ● 0.87 after yr 2000 <p>● 3 monophyletic clusters</p> <p><i>MSM who acquired HCV:</i></p> <ul style="list-style-type: none"> ● High rates of ulcerative STIs (59%) and rough sexual techniques (56%), denied IDU

SNAHC pilot Surveillance of Newly Acquired Hepatitis C in MSM



Objectives

- To inform decision process for national roll out
- Assess the burden of disease and monitor trends
- Investigate risk factors
- Develop information systems for public health actions

SNAHC - Surveillance of Newly Acquired Hepatitis C in men who have sex with men

Reported by: Name, Position

1. Date of FIRST hepatitis C (HCV) diagnosis
 Pos (First positive test date) Neg (Last negative test date)
 Documented? Y N

2. HCV markers at diagnosis
 HCV-RNA Pos Neg NK
 HCV-AB Pos Neg Equivocal NK

3. Genotype (if available)

4. a Confirmed case (anti-HCV sero-conversion)
 Date of LAST negative HCV-AB test
 Documented? Yes No
 Sample obtained through routine screening
 Sample tested retrospectively using stored serum

4. b Establishable case (HCV-RNA pos and HCV-AB neg)
 Date of LAST negative HCV-RNA test
 Documented? Yes No

5. Evidence of acute hepatitis at diagnosis
 ALT rise > 2.5 upper normal limit Yes No NK
 Evidence of acute HAV infection? Yes No NK
 Evidence of acute HIV infection? Yes No NK

6. Reason for HCV test - tick as appropriate
 Routine HCV screen
 Clinical symptoms suggestive of acute hepatitis
 Raised ALTs at routine LFT screen
 Known contact of HCV+
 History of injection drug use
 STI diagnosis
 Other (please specify)

7. a HIV status
 Pos (First positive test date) Neg (Last negative test date)
 Documented? Y N

7. b If Yes, on ARV at HCV diagnosis? Yes No NK

7. c Last CD4 count before HCV diagnosis: _____ Cells/mm³

8. Ethnicity (Please tick)
 White
 Mixed
 Asian or Asian British
 Black or Black British
 Other

9. Country of birth

10. Injection drug use: Ever injected drugs? Yes No NK

10. a If YES, which type?
 Opiates/stimulants
 Steroids/other performance enhancing drugs

10. b If YES, date last used? _____

10. c Ever used needles or syringes received from someone else? Yes No NK

10. d If YES, date last used? _____

SNAHC - Surveillance of Newly Acquired Hepatitis C in men who have sex with men

Section C

11. Did the patient have a sexual health screen in the last 12 months? Yes No NK

11. a If YES, any STIs diagnosed in the last 12 months?
 GC (please circle: pharyngeal/ urethral/ rectal) CT (pharyngeal/ urethral/ rectal)
 LGV (pharyngeal/ urethral/ rectal) Early Syphilis HIV Other

12. Approximate number of sexual partners in previous 2 months
 None 1 2 to 4 5 to 10 11 to 19 20 or more NK

13. Sexual Practices - Has the patient engaged in or experienced any of the following within the last 2 months - please tick as appropriate

	No	Yes Protected	Yes Unprotected	Yes unknown	NK
Insertive anal intercourse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Receptive anal intercourse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Insertive fisting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Receptive fisting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14. Recreational drug use - Did the patient use any of the following substances in the last 12 months?
 Yes No NK

14. a If YES, please indicate
 Ecstasy Cocaine Ketamine GHB Methamphetamine Speed
 Viagra/other PDE5 inhibitors Heroin LSD Crack other _____

14. b Did the patient have sex under the influence of these drugs? Yes No NK

14. c If YES, please indicate the frequency
 Seldom Occasionally Often

15. Any other comments:

Please return to: Dr Sam Lattimore, HIV/STI Department, Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, or Fax: 0208 200 7868
 For queries contact Dr Sandra Collier, T: 0207 793 2612, Dr Sam Lattimore T: 0208 327 7426, or Murad Ruf T: 0208 327 7345, OR email: scollier@hpa.gov.uk with 'SNAHC' in the subject field

SNAHC pilot
Surveillance of Newly Acquired
Hepatitis C in MSM



Newly acquired hepatitis C in MSM will be defined as:

Definite Case: Documented anti-HCV seroconversion

HCV antibody positive with documented negative HCV antibody within the previous 36 months

Probable Case

HCV RNA positive AND HCV antibody negative or equivocal

London, Brighton, Eastbourne, Hastings, Oxford, Southampton

Murad Ruf [Murad.Ruf@hpa.org.uk]



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23-25 April 2008, Belfast Waterfront Hall, Northern Ireland, UK