



## Age, sexual experience and mucosal inflammation: What do we know?

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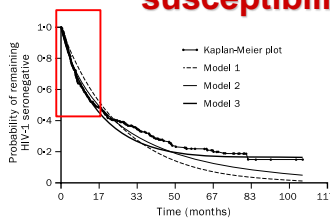
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## Overview

- Recent data on host predictors of HIV acquisition
  - Mucosal cytokines & chemokines
  - Mucosal proteomics
  - Systemic CD4+ T cell correlates
- Potential impact of age & sex work
  - Particularly at the start of sex work



## A spectrum of HIV susceptibility



**KwaZulu Natal, SA:**  
Peak incidence in women aged 20-24 years

**CAPRISA 004:** 2/3 of infections in first 2/5 of follow up

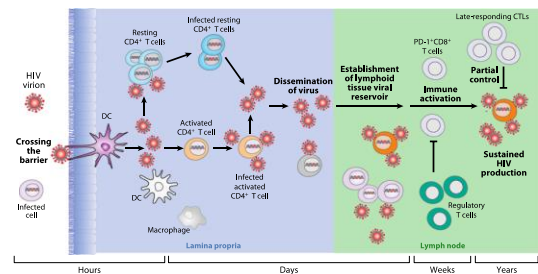
**VOICE:** incidence of >7% in the first year compared to 5% overall

	Majengo (80-90s) <sup>1</sup>	SWOP City, Majengo (2008-11) <sup>2</sup>
HIV incidence	42/100 PY	2/100 PY
Declining annual risk per year in sex work	17%	23%

<sup>1</sup> Fowke et al *Lancet* 1996; <sup>2</sup> McKinnon et al, *AIDS and Behav* 2015



## Mucosal immunology of HIV transmission



Moir et al *Annu Rev Pathol Mech Dis* 2011



## Mucosal Inflammation is a strong predictor of HIV risk

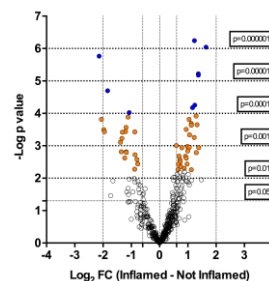
	Acquired HIV	Remained uninfected
Inflammation + *	19	6
Inflammation -	39	52
Total	58	58
Pair-matched OR (95% CI)	3.2 (1.3, 7.9)	
P value	0.014	

\* Upper quartile for 5 of 9 inflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-8, IP-10, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ )

Masson, Passmore et al *Clin Infect Dis* 2015



## Proteins associated with elevated mucosal cytokines



Kenyan cohort (all HIV-)

Inflammation+ (n = 28)  
Inflammation- (n = 68)

3 / 7 cytokines in the upper quartile (MIP-3 $\alpha$ , RANTES, IL-8, MIP-1 $\beta$ , IL-1 $\beta$ , IL-1 $\alpha$ , and GM-CSF)

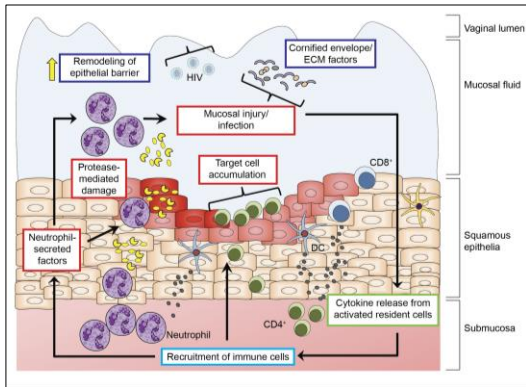
455 CVL proteins detected by LC-MS/MS

Blue - Sidak-Bonferroni alpha of 5% (p < 0.000005)

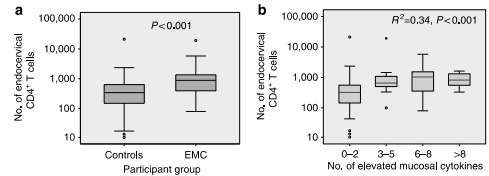
Orange - false discovery rate q value of 5% (p < 0.0032)

Arnold, Burgener et al, *Mucosal Immunology* 2015



Arnold, Burgener et al *Mucosal Immunology* 2015

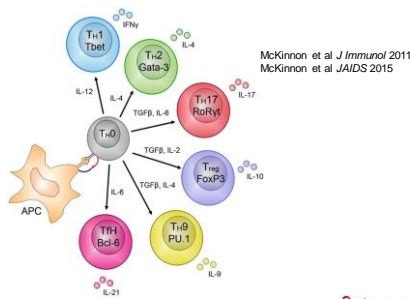
## Elevated mucosal cytokines associated with a >2-fold increase in endocervical CD4+ T cells



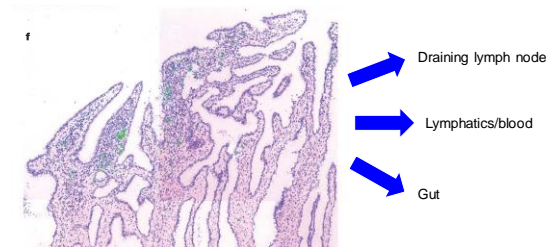
11/14 cytokines correlated positively with the # of mucosal T cells



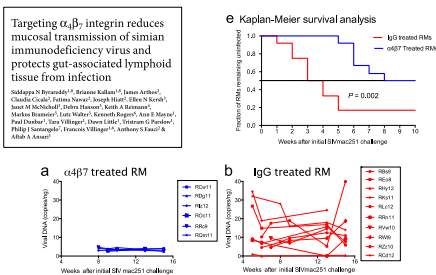
## CD4+ T cells are immunologically heterogeneous

Russ et al. *Frontiers in Genetics* 2013

## HIV target cells & viral dissemination

Li et al. *Nature* 2009

## Blockade of α4β7 protected non-human primates from low dose repeat vaginal SIVmac251 challenge

Byrareddy et al, *Nature Medicine* 2014

## Summary of Part 1

- Several host immune factors, measured pre-infection, are associated with higher rates of HIV acquisition during prospective follow-up
- Is inflammation a surrogate for some other biological process? What is the mechanism by which inflammation increases HIV transmission? Are there any 'host targets'?
- Can these markers be validated in different cohorts? Younger populations? Sex workers? Can these be used for risk stratification?



## Per-coital rates of HIV acquisition: Age as a co-factor

- Powers et al. Meta-analysis (2008)
  - Those under 30 years of age were 15x more likely to acquire HIV per contact
- Gray et al. (2001) Prospective cohort of HIV serodiscordant couples.
  - Highest per-coital rates were in women 15-24 years of age
- Hughes et al. (2012) Prospective trial of HIV serodiscordant couples.
  - 18% decrease in risk (95% CI 6-29) for uninfected partner by 5 years of age



## Co-factors, age, and mucosal immunology

- Adolescent mucosal immune system still developing
  - Ectopy increased in younger women
- Younger women have higher levels of mucosal cytokines (Masson et al *CID* 2015, Yi et al *Am J Reprod Immunol* 2012)
- Young NHP more easily infected by SIV
- First contact with co-factors of transmission occurs shortly after sexual debut
  - Exaggerated mucosal impact?



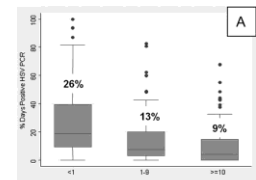
## Age effects for transmission co-factors?

- **DMPA:** Highest HIV risk in 18-20 year old women (HR 9.3, 2.7-31.7) compared to the 21-24 year old group (HR 2.0, 1.1-3.6)
- **HPV:** Peak prevalence in CAPRISA004 was in the 18-19 years group (81%), 2.8x increased risk of HIV acquisition, greater risk with HPV clearance. Mucosal impact poorly defined.
- **HSV2:** (next slide)
- **Bacterial STIs:** (slide after that)



## Rapid acquisition of HSV2 and increased rates of HSV2 shedding in the first year post-infection

Age group	HSV2 % prevalence (n/N)
≤15	4.1 (24/590)
16-17	8.6 (46/537)
18-19	22.6 (48/212)
20-22	36.1 (30/83)



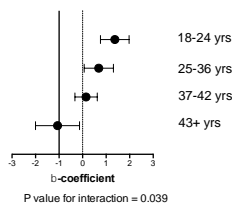
\* Based on data from 14 schools, grades 9-10

Q Abdoal Karim et al *Sex Trans Infect* 2014; Phipps et al *J Infect Dis* 2011



## Are STIs more inflammatory in younger populations?

Effect estimate for NG and IL6 by age



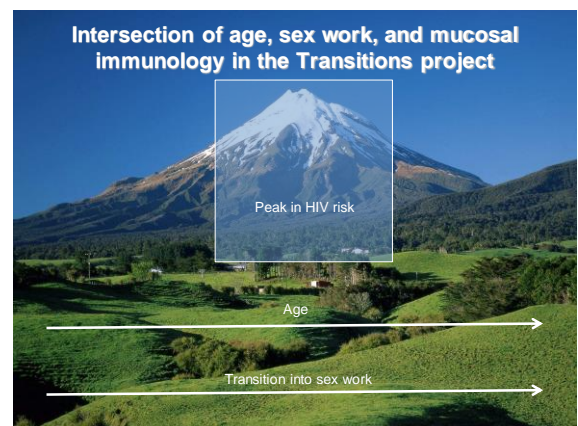
P value for interaction = 0.039

Similar results for Age-NG interactions seen for MCP1, IL8, GRO, IL10, IL1B, etc., and also for other STIs

Need to show in additional and younger populations

Effect due to differences in immunity? Tolerance?

Further analysis of Masson et al., *Sex Trans Infect* 2014



## Intersection of age, sex work, and mucosal immunology in the Transitions project

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- Does the age at the time of sex work transition matter? Or the duration/nature of the transition? How heterogeneous are these variables?
- What is the impact of frequency of sex & whether it is with one or more partners?
- What is the impact of condom exposure in a transactional setting vs. low condom use observed with regular partners and boyfriends?
- How do HIV risk proteins/cells change over time/SW transition?
- What are the interactions between overlapping co-factors?
- How do mucosal host interactions with STIs / the microbiome change over time?
- What is the impact of vaginal practices (common in FSW, but in the general population)?



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