

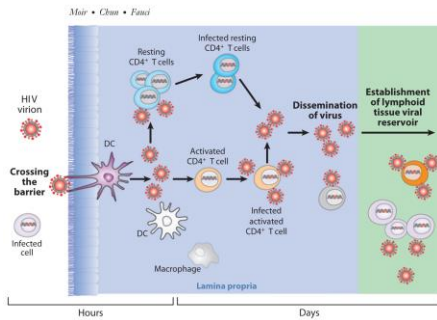
## Overview

### Genital immunology, the microbiota and HIV transmission

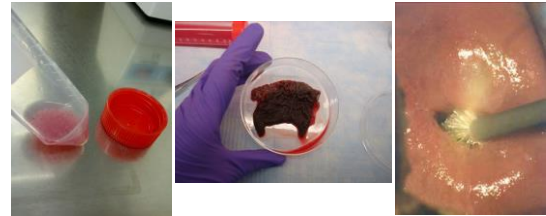
Dr. Rupert Kaul  
University of Toronto

- Genital mucosal inflammation
  - Association with HIV acquisition
- Co-infections and genital microbiome have important mucosal impacts
  - May enhance mucosal homing of susceptible T cells
  - And/or induce cytokines that alter barrier function
- Important effects on HIV shedding in an HIV+ person
  - Not covered today

### Mucosal HIV infection

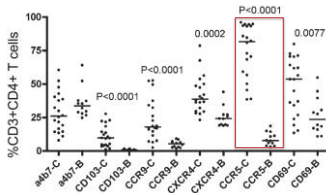


### Mucosal immune studies



- Sigmoid colon studies in Toronto
- Foreskin studies in Rakai, Uganda
- Cervical studies in Toronto, Nairobi

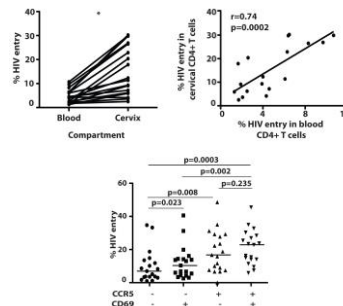
### Mucosal CD4+ cells appear more HIV susceptible



- Cervix, other mucosal sites enriched for effector memory cells
- Much higher levels of immune activation
- HIV co-receptor & integrin expression

McKinnon L. J Immunol, 2011.

### Enhanced virus entry in mucosal T cells



- Virus entry higher in cervix
- But blood, cervix correlated
- Enhanced in CD69+ and CCR5+ cells
- Also  $\alpha 4\beta 7+$ ,  $\alpha 4\beta 1+$  subsets

Joag V. Muc Immunol, 2015.

### Mucosal inflammation and HIV risk

- Cervical  $\alpha$ -defensins, cathelicidins associated with HIV acquisition in Kenyan women
  - despite *in vitro* antiviral effects
- Foreskin  $\alpha$ -defensins associated with HIV acquisition in Ugandan men
- Cervical inflammatory cytokines associated with HIV acquisition in South African women

Levinson. *AIDS*, 2009.  
 Hirbod. *PLoS Path*, 2014.  
 Passmore. *Clin ID*, 2015.

### Foreskin cytokines and HIV acquisition

	Cytokine Prevalence		Unadjusted Odds Ratio		Adjusted Odds Ratio*	
	Controls n=120	%	Seroconverters n=50	%	(95% CI)	(95% CI)
IL-8	53	52.5	44	73.3	<b>2.52 (1.28, 4.99)</b>	<b>2.58 (1.04, 6.40)</b>
MIG	23	19.7	22	36.7	<b>2.49 (1.23, 5.03)</b>	<b>3.05 (1.15, 8.06)</b>
GM-CSF	5	4.2	7	11.7	3.02 (0.92, 9.91)	
MCP-1	6	5.0	6	10.0	2.10 (0.65, 6.79)	
MIP3 $\alpha$	4	3.3	5	8.3	2.61 (0.48, 10.06)	
IL-1 $\alpha$	4	3.3	3	5.0	1.53 (0.33, 7.16)	
RANTES	3	2.5	2	3.3	1.35 (0.22, 8.30)	

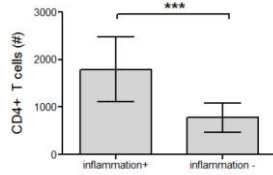
\*Conditional logistic regression (matched by visit), controlling for age, STIs (syphilis and HSV-2), and all variables associated with either seroconversion or IL-8 or MIG detectability (occupation, marital status, having multiple sexpartners, condom use, consumption of alcohol).

- Foreskin swabs collected during Rakai clinical trial of RC
  - 60 men who acquired HIV and 120 uninfected controls
- Levels of many cytokines low; more IL-8 (aOR 2.6) and MIG (aOR 3.1) among men who subsequently acquired HIV

Prodger J, *CROI* 2014.

### How is genital inflammation increasing susceptibility?

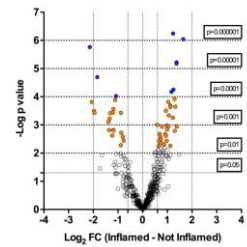
- N=96 HIV neg Kenyan women
- Inflammation if  $\geq 3/7$  pro-inflammatory cytokines in upper quartile (n=28)
- Cytobrush (cell studies) and CVL (proteomics)



Arnold K and Burgener A. *Muc Immunol*, 2015.

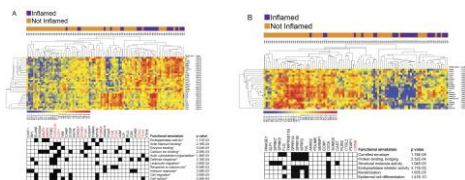
### Mucosal effects of genital inflammation: proteomic analysis

- CD4+ cell numbers doubled in the context of inflammation
- Proteome also altered: some parameters increased, others lower



Arnold K et al. *Muc Immunol*, 2015.

### Proteomic associations of FGT inflammation



- **Up-regulation** of neutrophil proteases, cell motility, actin cytoskeleton
- **Down-regulation** of antiproteases, keratinization, epithelial differentiation

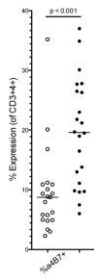
### Immune associations of clinical conditions that enhance HIV risk

- Several clinical conditions consistently associated with increased HIV acquisition risk

1. Asymptomatic HSV-2 infection (OR=2.8-3.4)
2. Bacterial vaginosis, ie: disruption in 'normal' vaginal microbiota (OR=1.6)

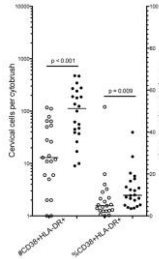
Glynn. *AIDS*, 2009.  
 Atashili. *AIDS*, 2008.

## Asymptomatic HSV2 and genital immunology



- Studies in Toronto ACB women (n=46)
  - increased  $\alpha 4\beta 7$  expression in blood
  - $\alpha 4\beta 7+$  cells are more activated
  - direct correlation with more activated cervical CD4 T cells
  - BUT no association with CV cytokines

Shannon B.  
*J Immunol*, 2014.



## Summary

- Genital mucosal inflammation
  - (i) recruits HIV susceptible target cells, and (ii) alters epithelial integrity
  - possibly mediated via different effector cytokines
- Often these things happen together, but not necessarily
  - HSV2: increased HIV target cell numbers without inflammatory cytokines
  - Dysbiosis: increased inflammatory cytokines without cell number/subset alterations
- Possible implications for populations where both are common, esp. ACB women

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