Immune Activation and HIV Acquisition Risk

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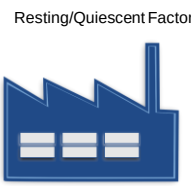
Outline

1. Immune Activation and HIV Susceptibility
2. Sex work and HIV risk
3. HESN and Immune Quiescence
4. Inducing Immune Quiescence

1) Activation = efficient production



Work force:	+	-
Supplies:	+	-
Energy Supply:	+	-
Production Protocols:	+	-
Shipping and Receiving:	+	-
Production output	+++	-

Inflammation and HIV Susceptibility

- Activated CD4+ T cell is many times more susceptible to HIV infection and produces more virus
- STIs, which cause genital inflammation, are known to be co-factors in HIV acquisition
- GML-treated monkeys reduced inflammation and lowered susceptibility to SIV infection (QS Li et al. Nature, 2009)
- STEP HIV vaccine trial – high baseline IFN-γ ELISpot correlated with HIV infection, not HIV-specific responses (Huang et al PLoS One 2014)

Caprisa 004 - Genital Inflammation and HIV Risk

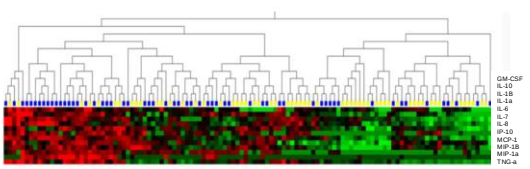
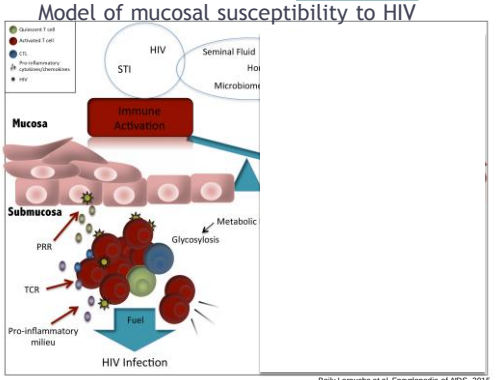


Figure 1. Unsupervised hierarchical clustering was used to visualize the variation in cytokine concentrations in individual women and to cluster women according to the similarities of their cytokine expression profiles (using Qlucore Omics Explorer). Women who later became human immunodeficiency virus

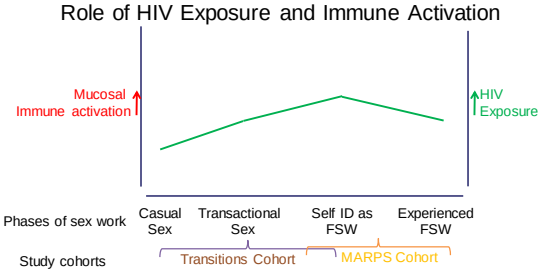
Genital Inflammation and the Risk of HIV Acquisition in Women.
Lindi Masson, Jo-Ann S. Passmore, et al Clin Infect Dis 2015

Model of mucosal susceptibility to HIV

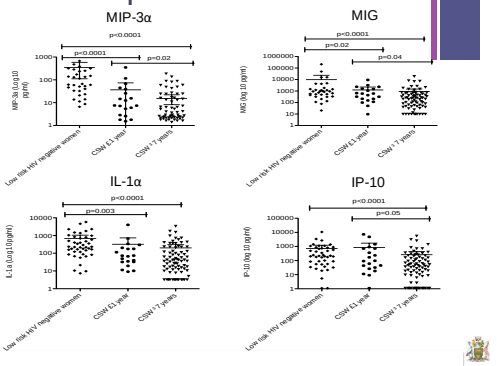


Boily-Larouche et al Encyclopedia of AIDS, 2015

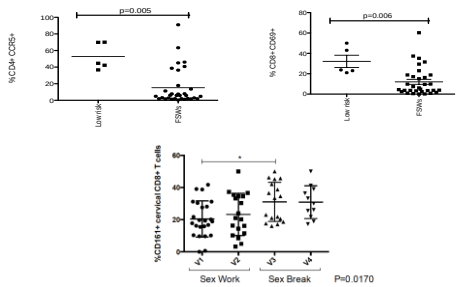
2) Conceptual Model of Sex Work and HIV Risk: Role of HIV Exposure and Immune Activation



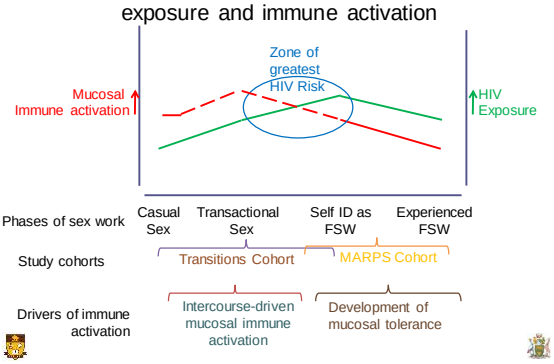
Sex work impact on inflammation



Impact of sex work on cellular activation



Conceptual model of HIV risk being driven by HIV exposure and immune activation



If ….

Immune Activation = ↑ HIV risk

….then does

Immune Quiescence = ↓ HIV risk?

3) Nairobi Sex worker cohort: T cell Immune Quiescence

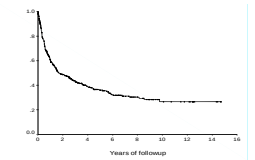
Nairobi Sex Worker Study

Pumwani cohort

- Est. in 1985, open cohort > 4000 women enrolled
- Average 4 clients/day
- most are HIV+ at entry, those not seroconvert within 2 yrs

- ~110 uninfected despite up to 500 unprotected exposures
- Exposure or co-factor determinants not different

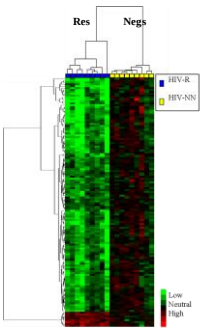
- HIV resistance defined as:
  1. No evidence of HIV infection
  2. Still active in sex work
  3. Followed in cohort for >7 years



Fowke et al Lancet 1996

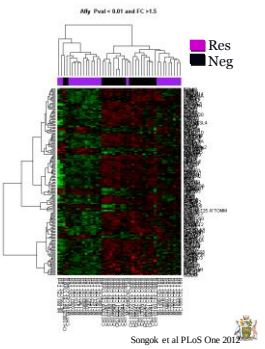
Gene expression profiling in HIV Resistants

CD4 T cells



McLaren et al JID 2010

Whole Blood



Songok et al PLoS One 2012

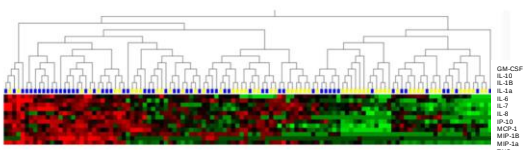
Immune Quiescence in HESN

- **Lower** overall gene expression, CD4+ T cells and whole blood
- **Lower** gene expression in HIV and T cell receptor pathways
- **Lower** resting PBMC cytokine production
- **Lower** level of cellular activation on T cell
- **Higher** T regs in the blood
- **Lower** level of FGT chemokines/cytokines
- **Lower** level of CD4+ CCR5+ T cells, lower anti-proteases at FGT
- **Normal** Antigen recall function – **not immune suppression**
- **OVERALL** Tcells seem to be resting or **quiescent**
- Termed this phenotype **T cell Immune Quiescence**

IQ in other HESN cohort

- Amsterdam MSM Cohort.
  - Lower % of activated (HLA-DR CD38, CD70) and proliferating (Ki67) CD4+ in HESN. (*Koning et al J Immunol 2005; 175; 6117-6122*)
- Discordant couples, Central African Republic
  - Lower levels of CD4 T cells activation (HLA-DR and CCR5) and reduced susceptibility to in vitro HIV-1 infection prior to PHA stimulation. (*Begaud et al Retrovirol 2006; June 22; 3:35*)
- HESN Men, Ugandan
  - Cellular immune quiescence in HESN foreskin, reduced T cell production of TNFα, IL17 (*Prodger J, et al Muc Immunol, 2014*)
- Discordant couples, Colombia
  - Hypo-neutrophil responses in HESNs *(Hernandez JC et al, PLoS One, 2015)*
- MSM, USA
  - HESN associated with low CD8+ CD38+DR+ T cell activation status (*Kuebler et al, JID, 2015*)

Caprisa 004 - Genital Inflammation and HIV Risk



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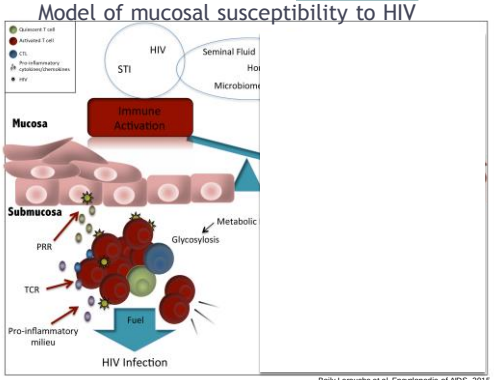


Boily-Larouche et al Encyclopedia of AIDS, 2015

4) Immune Quiescence: Can it be induced?

Hypothesis and objectives

Hypothesis:
The Immune Quiescence phenotype observed in HESN can be induced

Objectives:
- Feasibility of conducting a clinical trial phase I in low-risk women in Nairobi, Kenya (Baba Dogo and Pumwani clinics)
- Determining if drugs can induce T cell immune quiescence
- If oral administration decrease the number of HIV target cells at the female genital

Choice of Anti-inflammatory drugs

- Safe
  - FDA and Health Canada approved
  - Proven long-term track record
  - Minimal side-effects
  - Significantly speeds the development time lines
- Accessible
  - Must be accessible to areas most affected by HIV
- Affordable
  - Generic versions available
  - Low-cost

Drugs chosen

- Hydroxychloroquine - HCQ
  - nonsteroidal anti-inflammatory drug (NSAID)
  - Used to treat
    - Malaria
    - autoimmunity
  - Daily usage for prevention
    - Daily-use dose 200 mg
    - Rheumatoid arthritis – inflammatory condition
    - Lupus – autoimmune condition
  - CIHR funding - Fowke

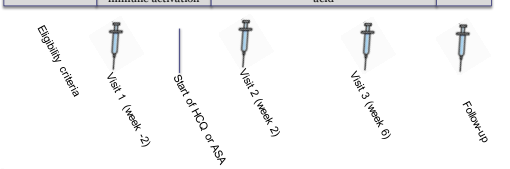
Drugs chosen

- Acetylsalicylic acid (ASA)
  - nonsteroidal anti-inflammatory drug (NSAID)
  - Used to treat
    - Headache, fever, pain
  - Daily usage for prevention
    - Daily-use dose 81 mg
    - Arthritis – inflammatory condition
    - Stroke
    - Heart disease
    - Dementia
  - Grand Challenge Canada Funding – Lajoie

Inducing Immune Quiescence -Design

Participants: 40 Low Risk – HCQ, 37 Low Risk - Aspirin

Screening visit	Month 1: Phase I: Assessment of the baseline immune activation	Month 2 and 3: Phase II: Assessment of immune activation during hydroxychlroquine or acetylsalicylic acid	Follow-up visit



Samples collected (blood, cytobrush/scraper, cervico,vaginal lavage), questionnaire
Sampling was performed 5-7 days post-menses

No drug-associated adverse events

Sample Analysis

Blood, CMC
Cytokines, Chemokines
Drug levels
Cell phenotype*

Flow Cytometry Panels

- T cell activation blood panel:
  - CD3 PeCy5
  - CD4 FITC
  - CD8v500
  - CCR5 V450
  - HLA-DR APC-h7
  - CD161 APC
  - CD95 PE
  - CD69 PeCy7
  - CCR7 PeCF594
  - CD45RA Alexa 700
- CMCs panel
  - CD3 PeCy5
  - CD4 FITC
  - CD8v500
  - CCR5 v450
  - HLA-DR APC-h7
  - CD161 APC
  - CD95 PE
  - CD69 PeCy7
  - Live/Dead ECD

Visit 1 (wk -2) vs Visit 3 (wk 6) for HCQ and ASA – No change

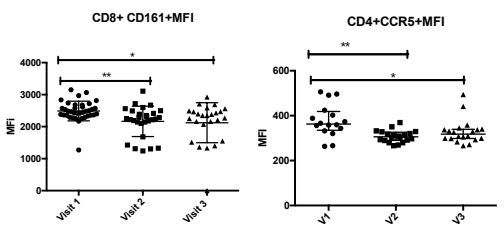
Blood

- CD4/CD8
  - CD69
  - CD95
  - HLA-DR
  - CCR7
  - CD45Ra

CMC

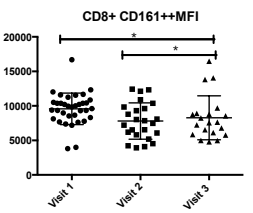
- CD4/CD8
  - CD69
  - CD95
  - HLA-DR

HCQ arm: Blood compartment

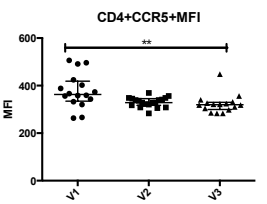


* p<0.05, ** p<0.01

ASA arm: Blood compartment



Anova p=0.008



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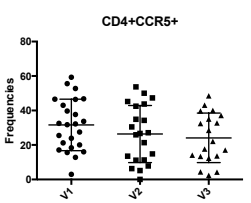
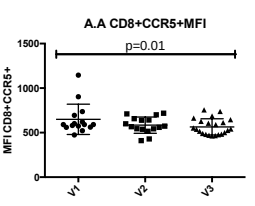
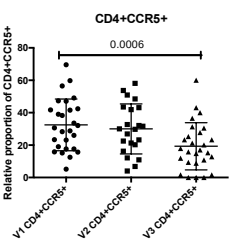
HCQ arm: FGT compartment



Reduction but did not reach significance

ASA arm: FGT compartment





Conclusion

- HCQ and ASA decrease the expression of CCR5 on CD4+ T cells at the systemic compartment
- Daily oral administration of ASA for 6 wks reduces the level HIV target cells at the female genital tract

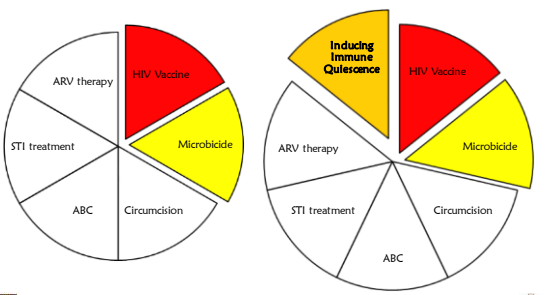
Next steps….

- Measuring Cytokines/Chemokines expression
- Measuring drug levels (blood and FGT)
- Finalizing data analysis
- Next phase of the study in high-risk population
  - Longer duration on drug regimen
  - Larger sample size
  - Mechanism of action

What does this mean?

- Reducing inflammation may help reduce HIV risk.
- Women commented the drugs were non-stigmatizing.
- Can be used with other approaches, eg microbicide or vaccine.
- As adherence is a major concern
  - would an intravaginal ring be more effective?
- Possible intervention for women transitioning to sex work????

HIV Prevention



Thanks

Collaborators	The Funders
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University of Manitoba
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Public Health Agency of Canada
Agence de santé publique du Canada

Winnipeg and Nairobi Research Teams

Laboratory of Viral Immunology

Nairobi Team:
- Lucy Mwangi
- Ken Oduor
- Domnic Ouma

Women of the Nairobi cohorts