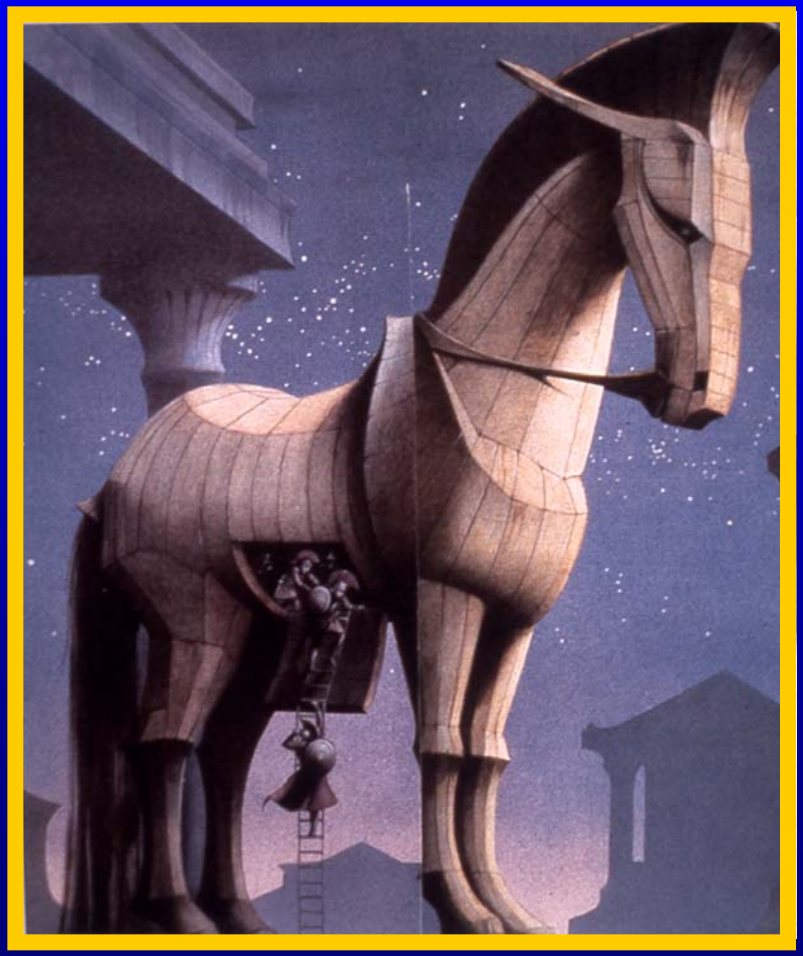
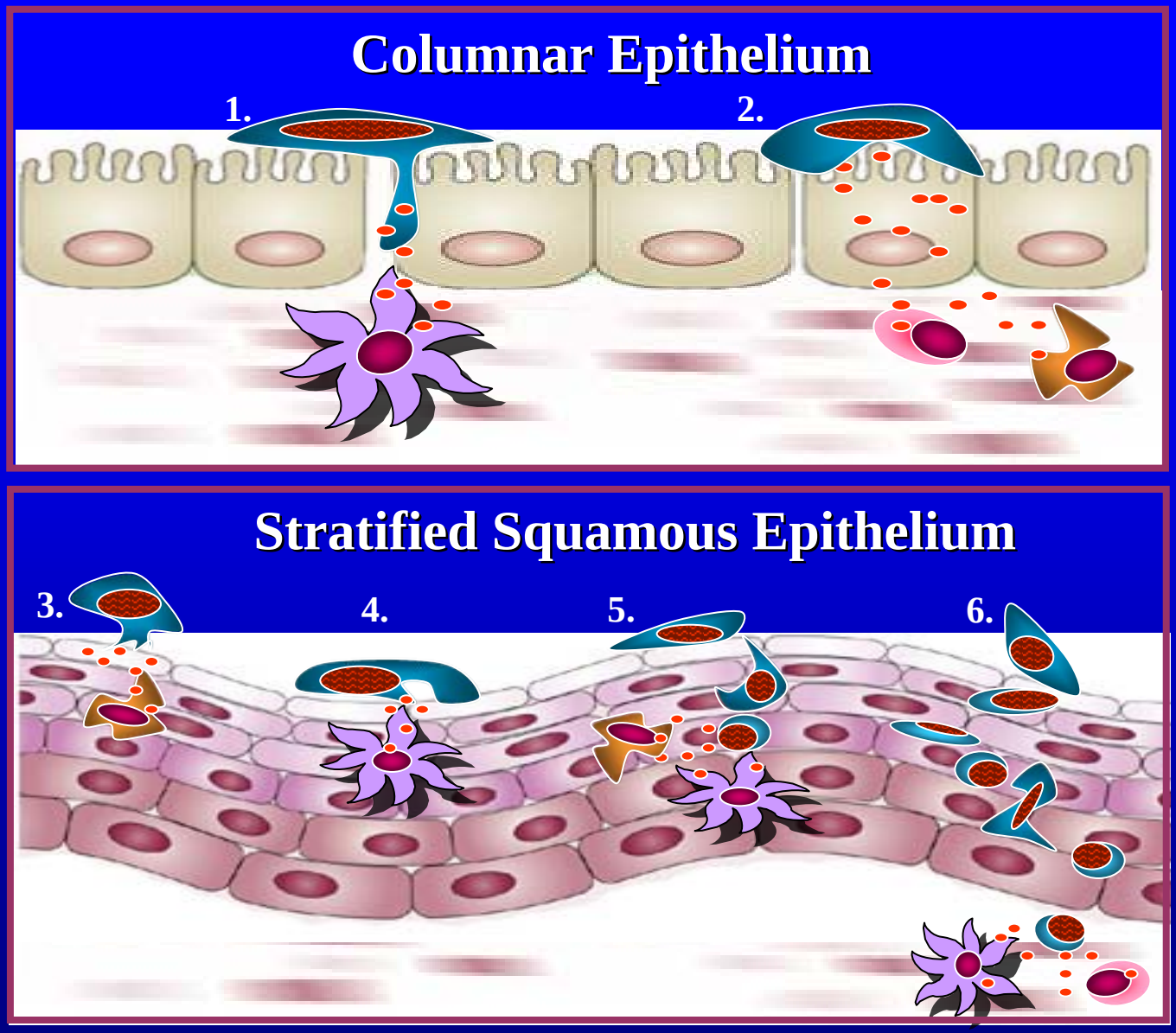
Cell-associated HIV transmission: the neglected pathway

Trojan Horse Leukocytes in AIDS Transmission

Anderson DJ, Yunis EJ. NEJM 1983



- T cells and macrophages in semen could transmit HIV
- Intracellular virus is protected from antibodies and antimicrobial proteins
- Cell-to-cell HIV transfer is highly efficient


Columnar Epithelium
1.
2.
Stratified Squamous Epithelium
3.
4.
5.
6.
Dendritic cell/ Langerhans cell
HIV virions
Infected leukocyte/ macrophage
Resident leukocyte
Resident macrophage

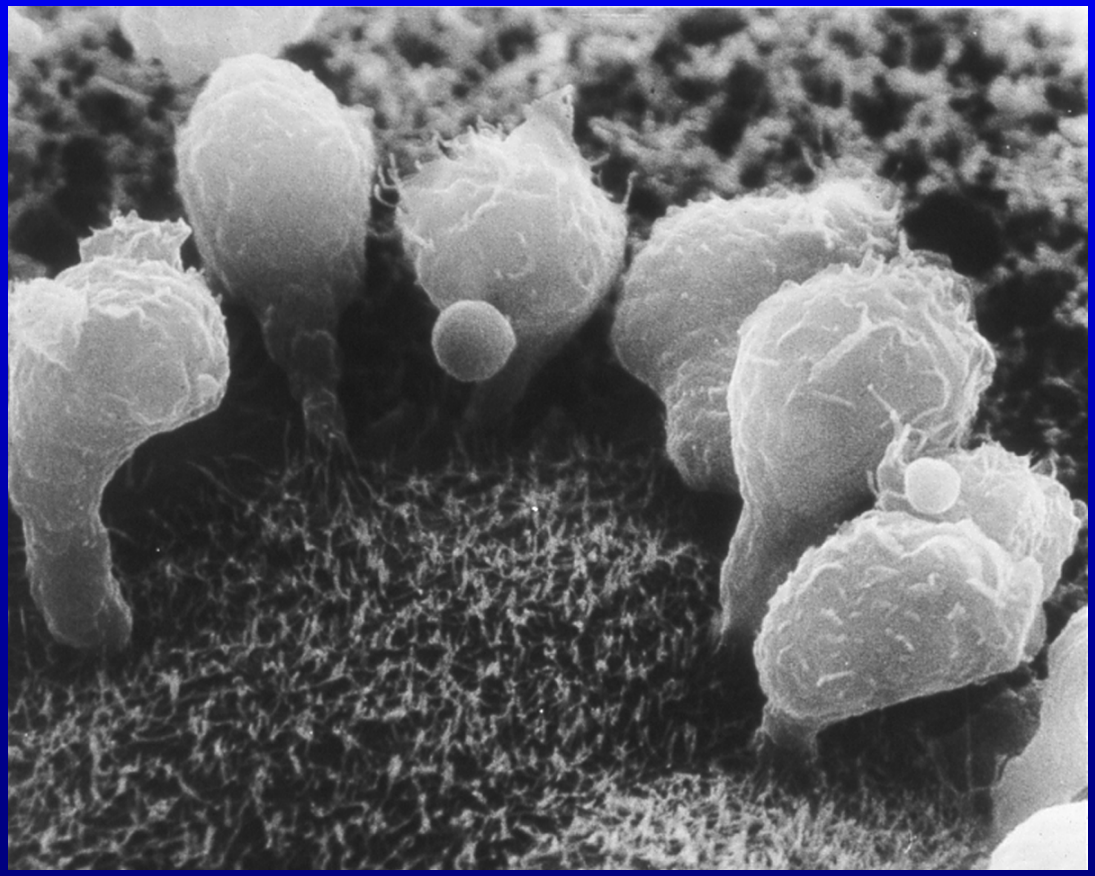
Questions:

- What are the infectious cells in semen?
- How long do they survive?
- Does CA-HIV have a distinctive genotype?
- What are the molecular events that can be targeted by HIV prevention strategies?
- What are the best in vitro and animal models to study CA-HIV transmission?
- Can CA-HIV transmission be blocked with antibodies, microbicides, ARVs?

In Vitro Tissue Models of Cell-Associated HIV Transmission

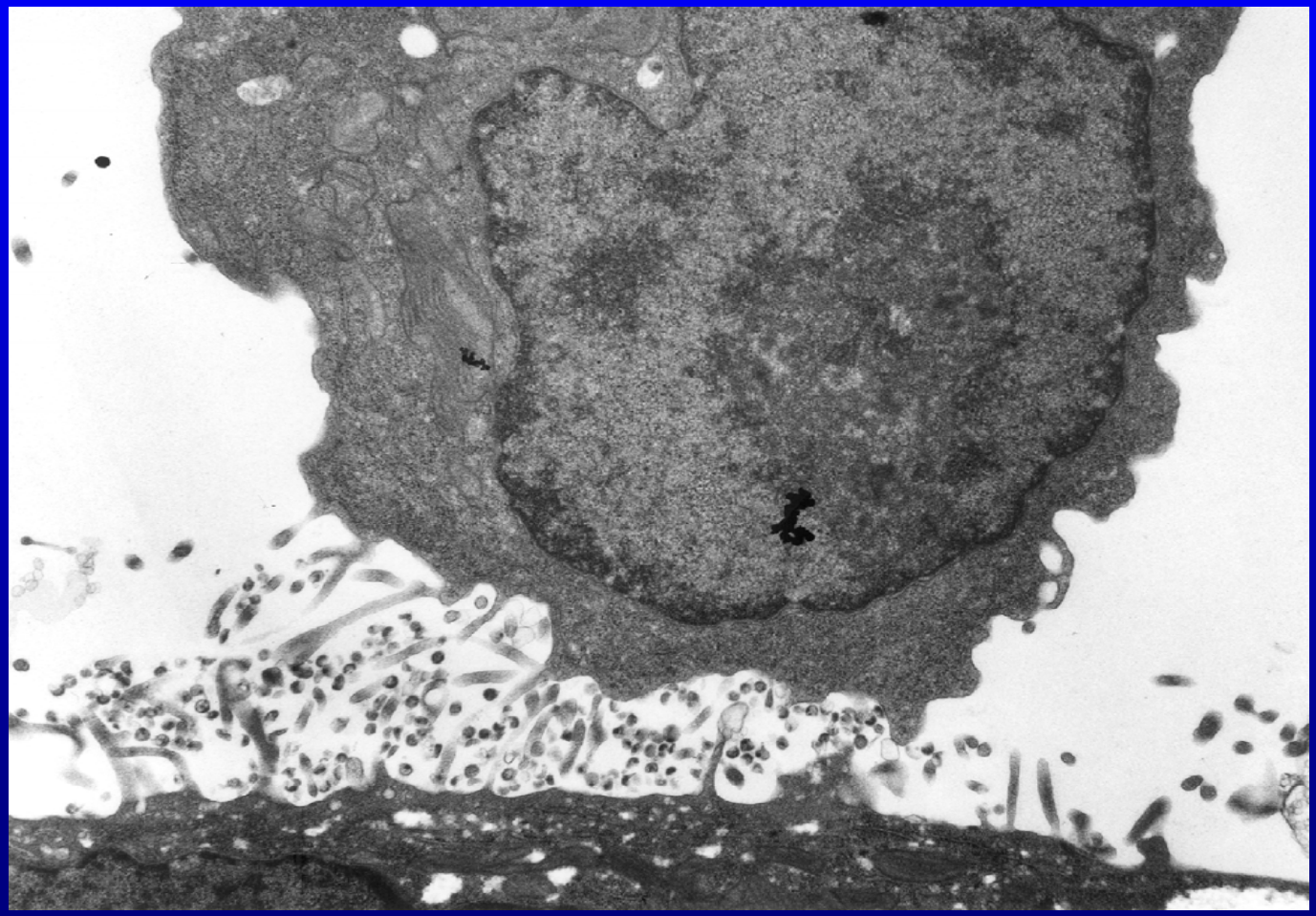
- Microscopic studies
- Transcytosis assays
- Explant assays

Adhesion of leukocytes to epithelial cells



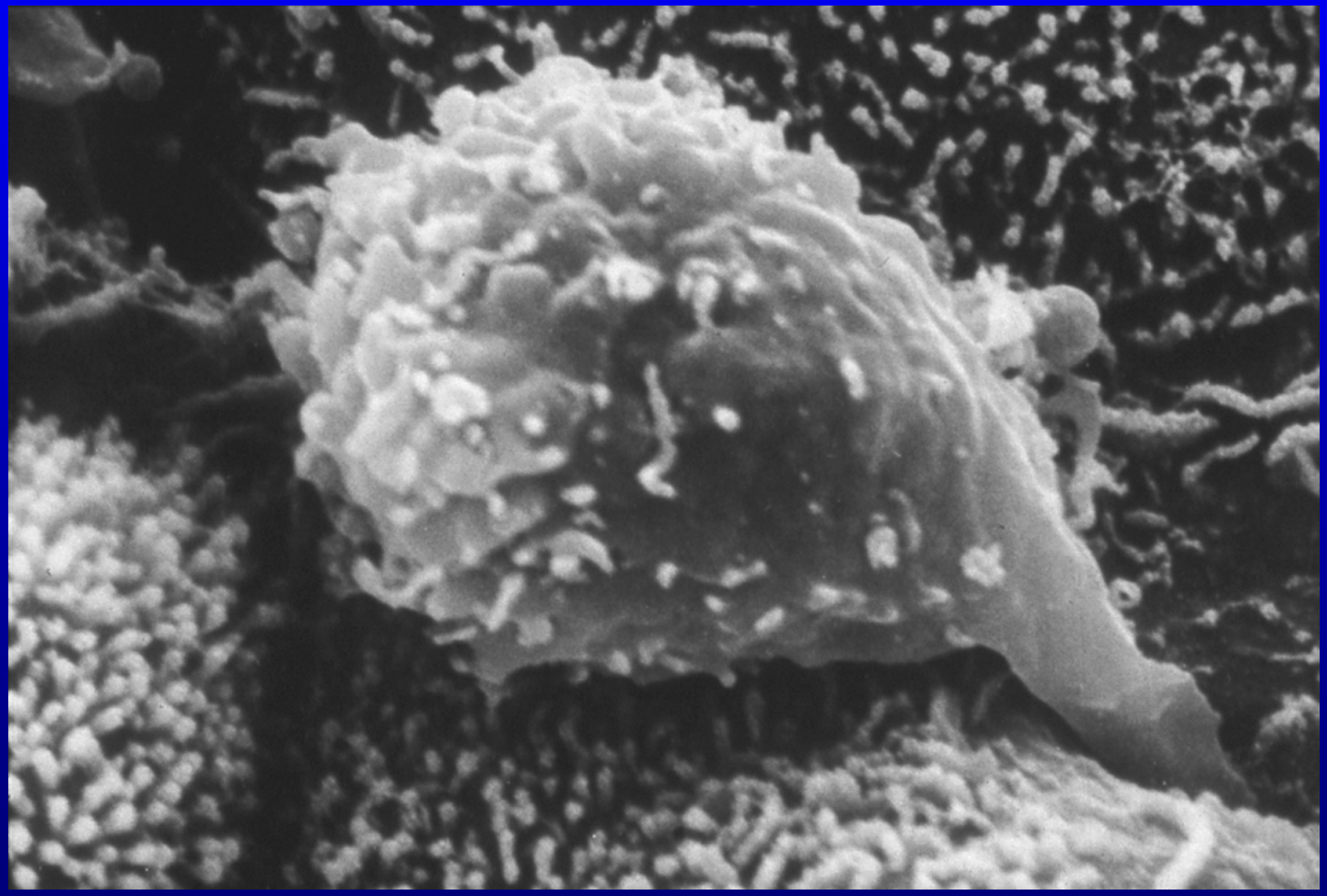
D Phillips 1997

Directional HIV shedding towards epithelial surface

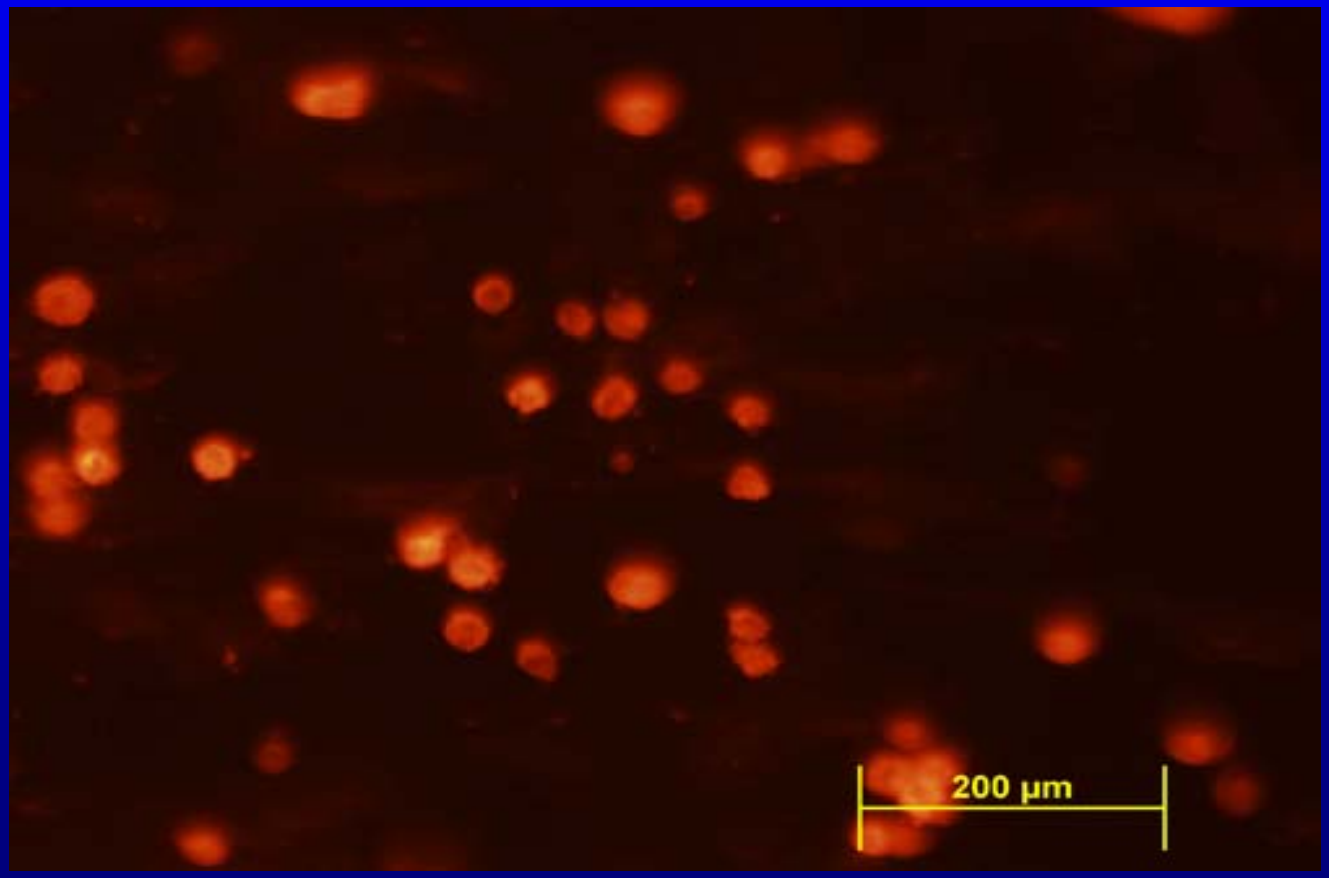


Phillips 1997

Macrophage beginning to infiltrate endocervical explant

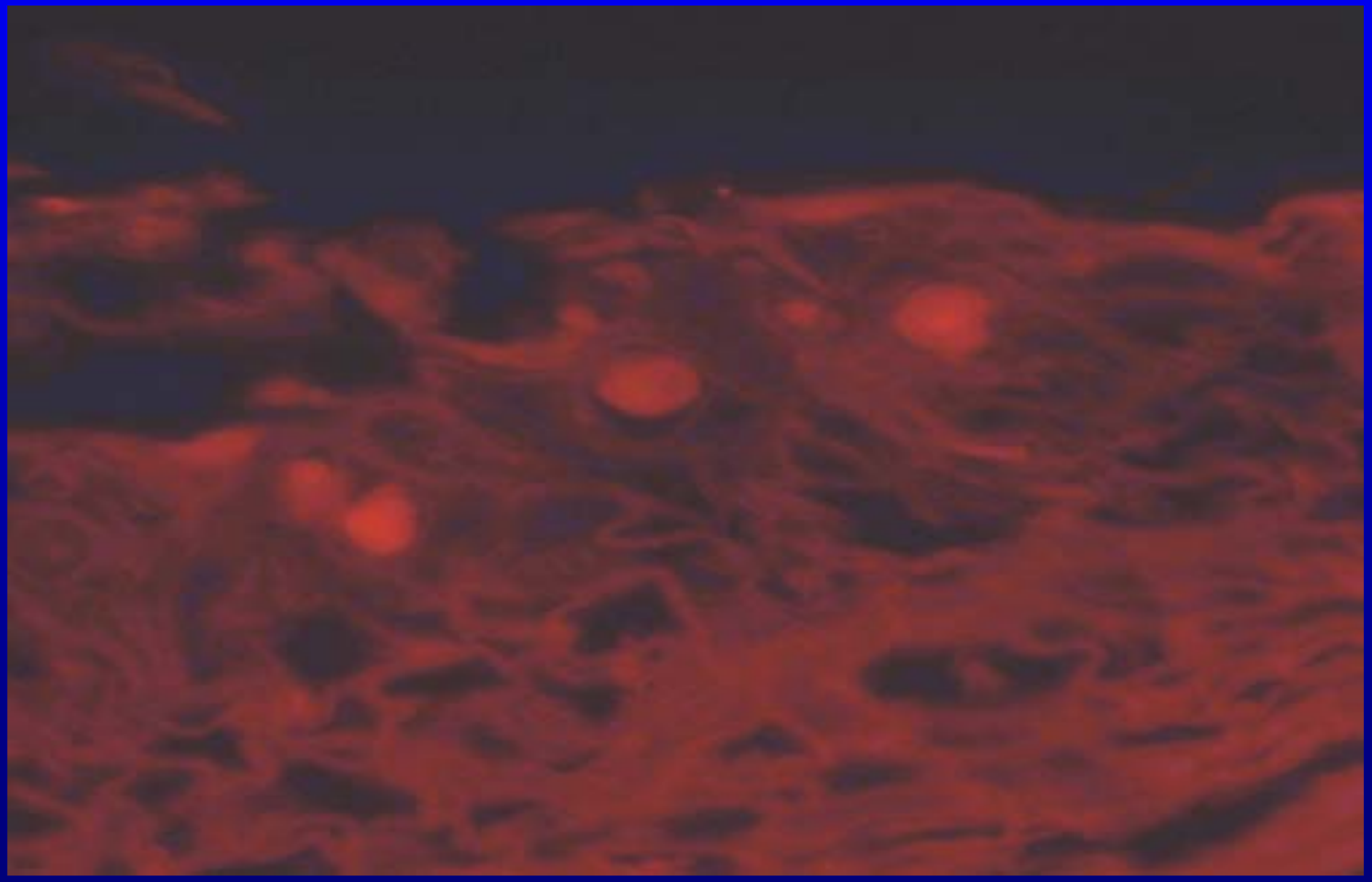


Macrophages attached to surface of VEC tissue



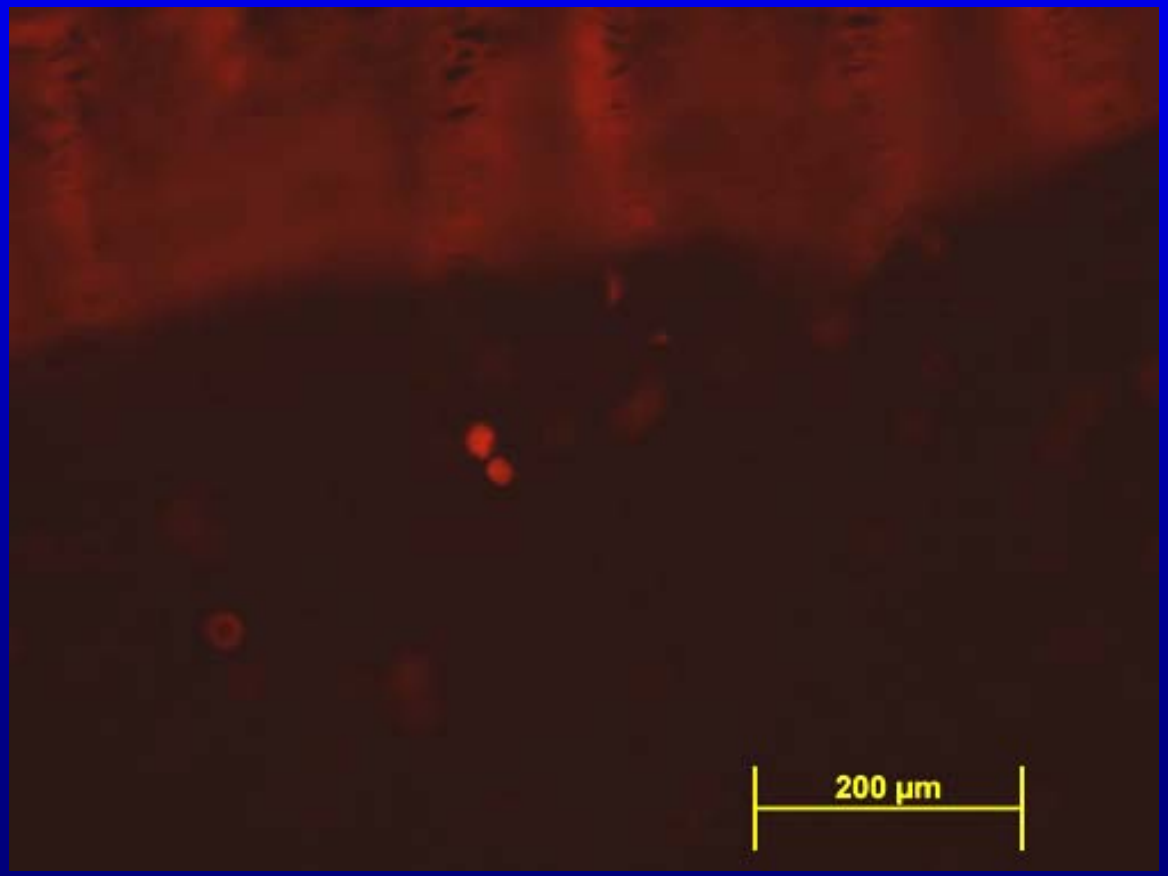
30 min

Macrophages infiltrating VEC stratified squamous epithelium



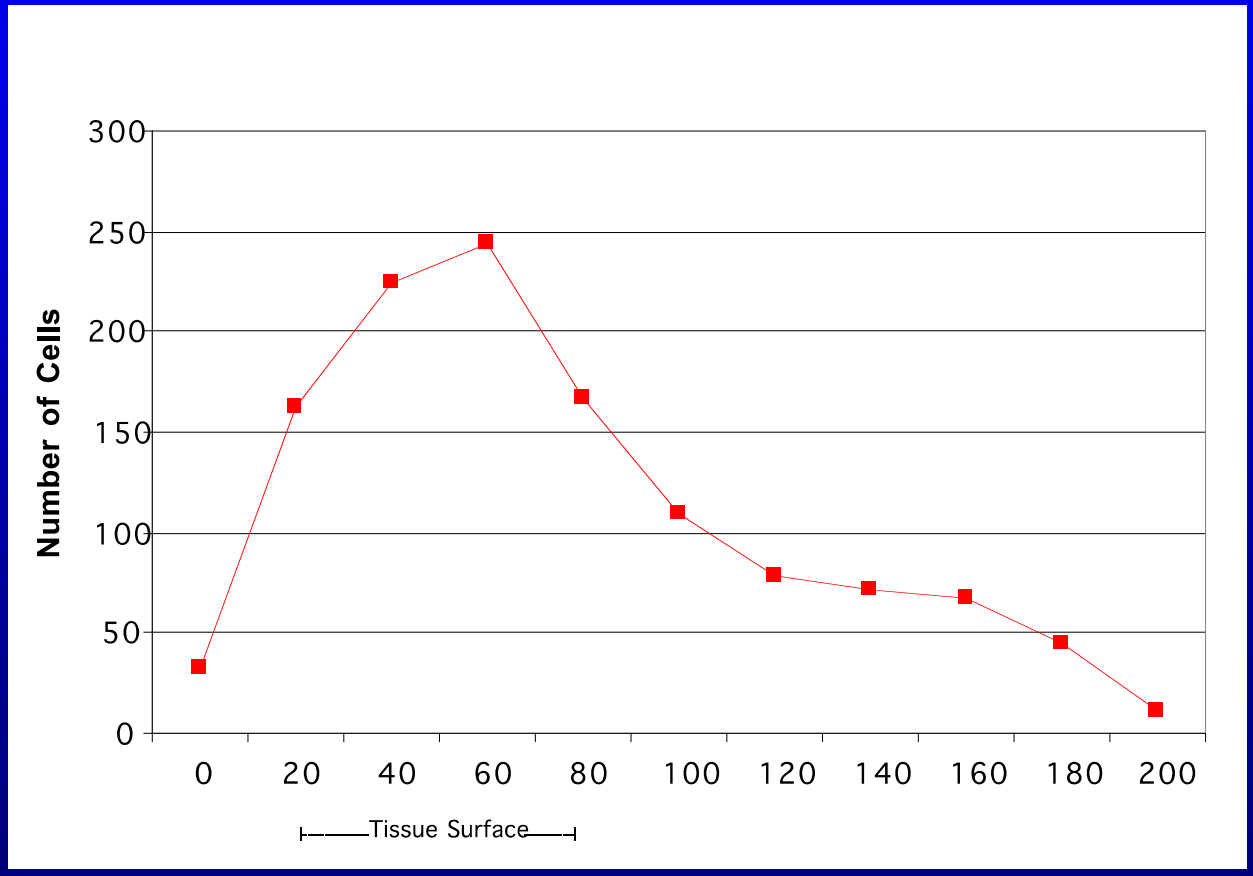
1 hr

Macrophages have crossed the epithelium and are located in the lamina propria

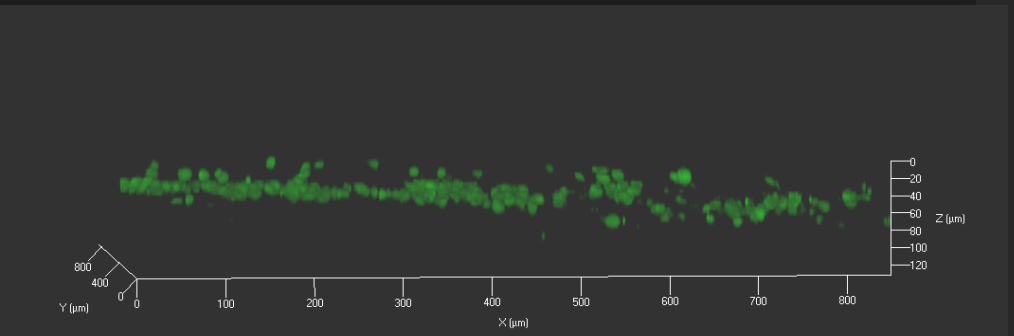


4 hrs

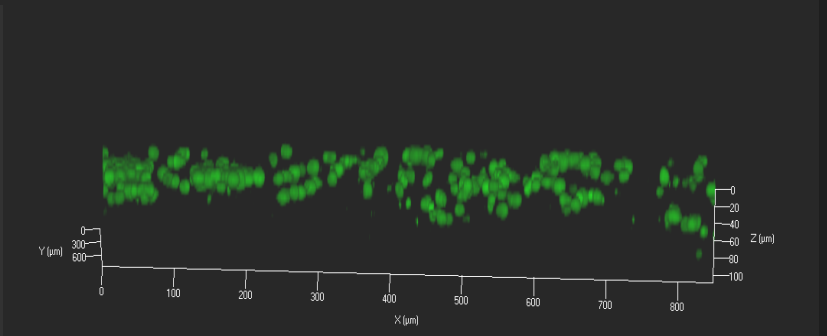
JPEG graph of infiltrating cells



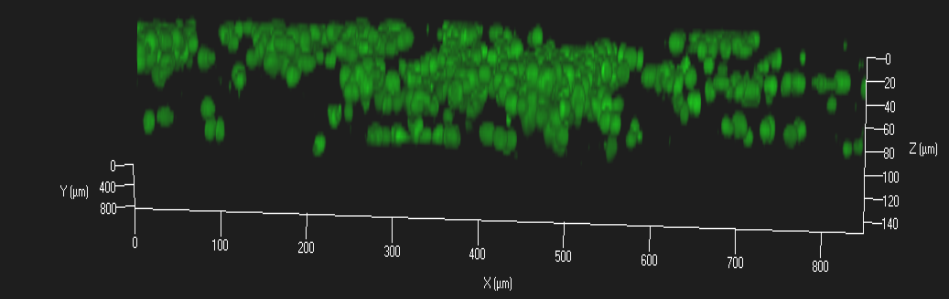
TNF-a treated VEC tissue is more permeable to macrophage infiltration



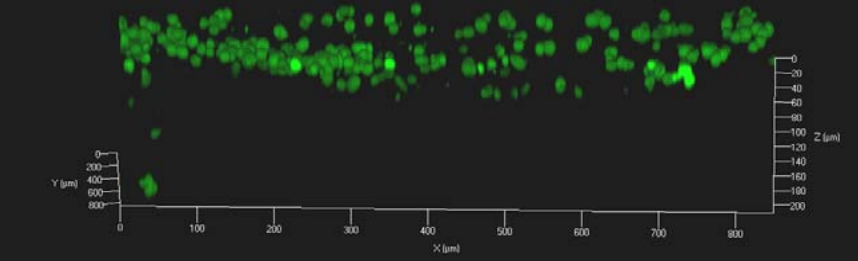
PBS treated control



0.1ug/mL TNF

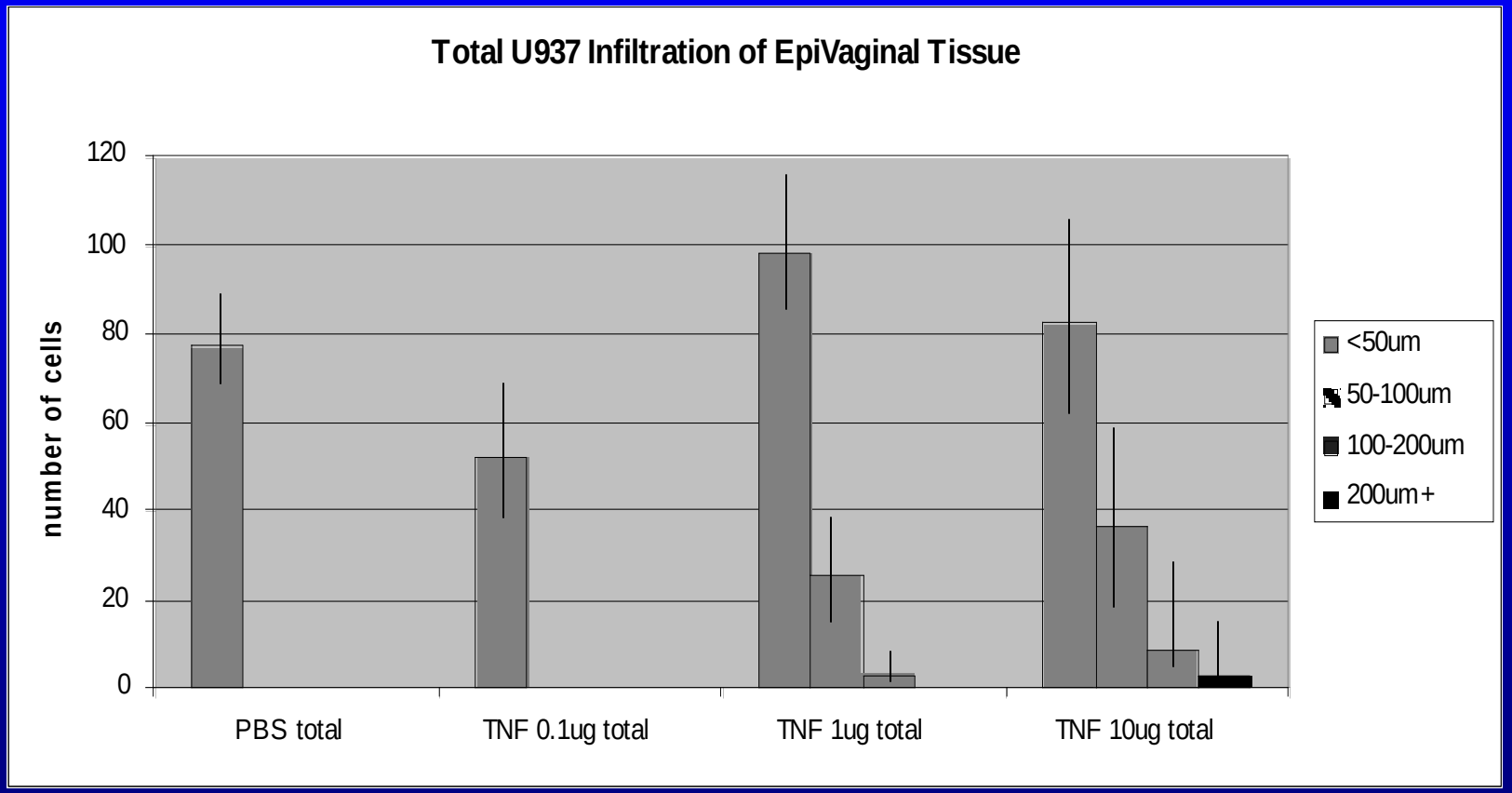


1ug/mL TNF



10ug/mL TNF

Quantitation of infiltrating cells in TNF-a treated VEC tissue



Evidence for cell-associated HIV transmission: in vitro models

- HIV-infected leukocytes are more efficient than free virus at transmitting HIV across polarized epithelial monolayers via transcytosis

  (Tan et al 1993; Chancey et al 2006; Bomsel 1997;VanHerrewege 2007)

- Both infected cells and free virus infect subepithelial cells in the cervical explant model

  (Collins et al 2000)

Recent In Vitro Studies

- SIV-infected PBMCs crossed the mucosal epithelium of rectal explant tissues and infected target cells.

  Kolodkin-Gal D. et al. J Virol 2013

- HIV-infected PBMCs crossed themucosal epithelium of human urethral explant tissues and infected subepithelial macrophages
- *Ganor Y et al Mucosal Immunology 2013*

Summary of Cell-Associated HIV Transmission Models

	Cervicovaginal	Rectal	Urethral
Polarized Epithelial Monolayers	+	+	
Tissue Explants	+	+	+
Organotypic Cultures	+		