# ART for Prevention of Sexual Transmission of HIV

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# Two Ideas

- HIV Transmission 2008?
- ART as Prevention?

# HIV Transmission Depends on…

***Cohen and Galvin, Nat Micro Rev 2004***
***Cohen et al JIAS online Oct 2008***

**Infectious** → **Susceptible**

Inoculum (concentration)

Phenotypic factors

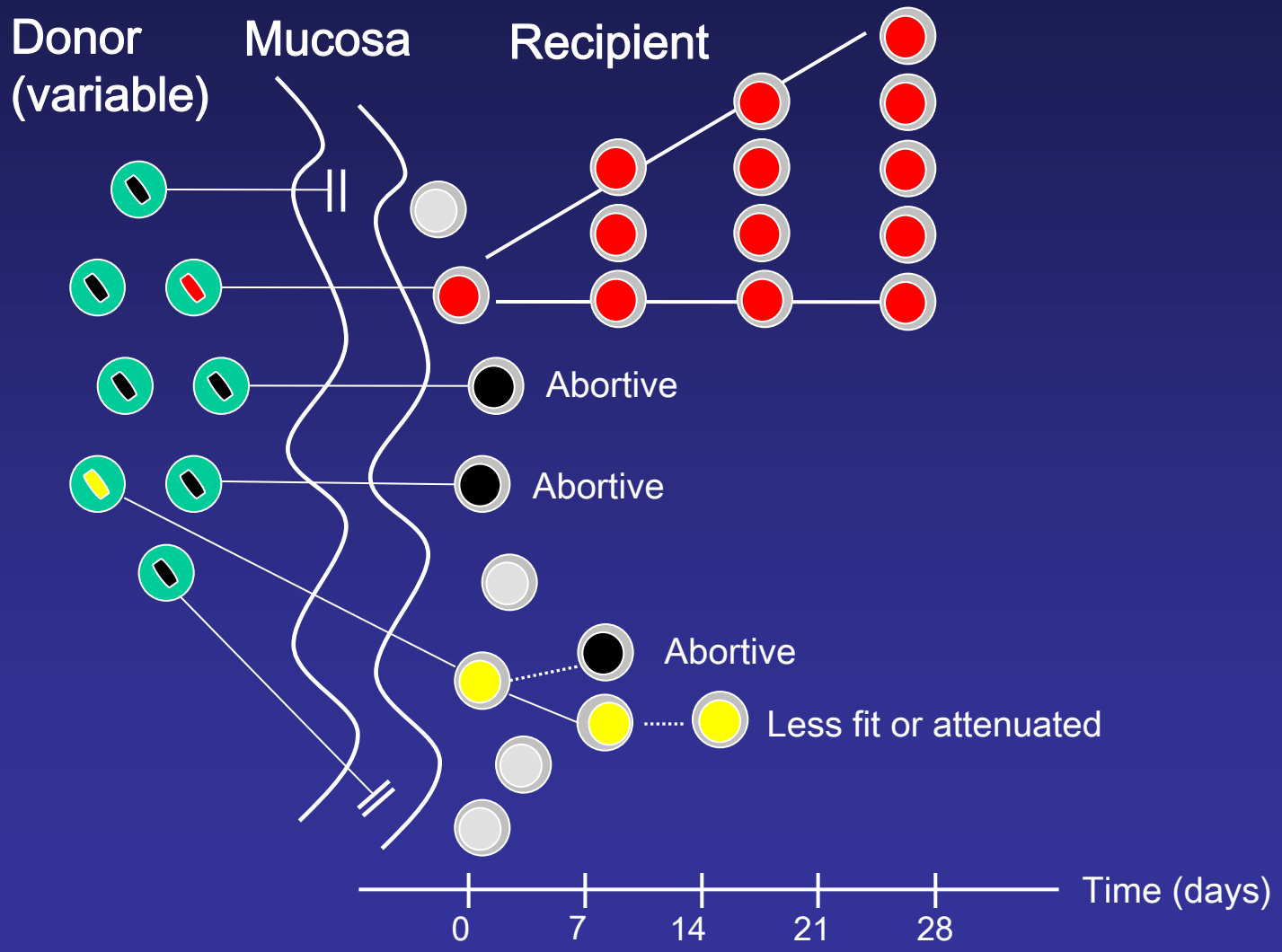
Hereditary resistance

Innate resistance

Acquired resistance

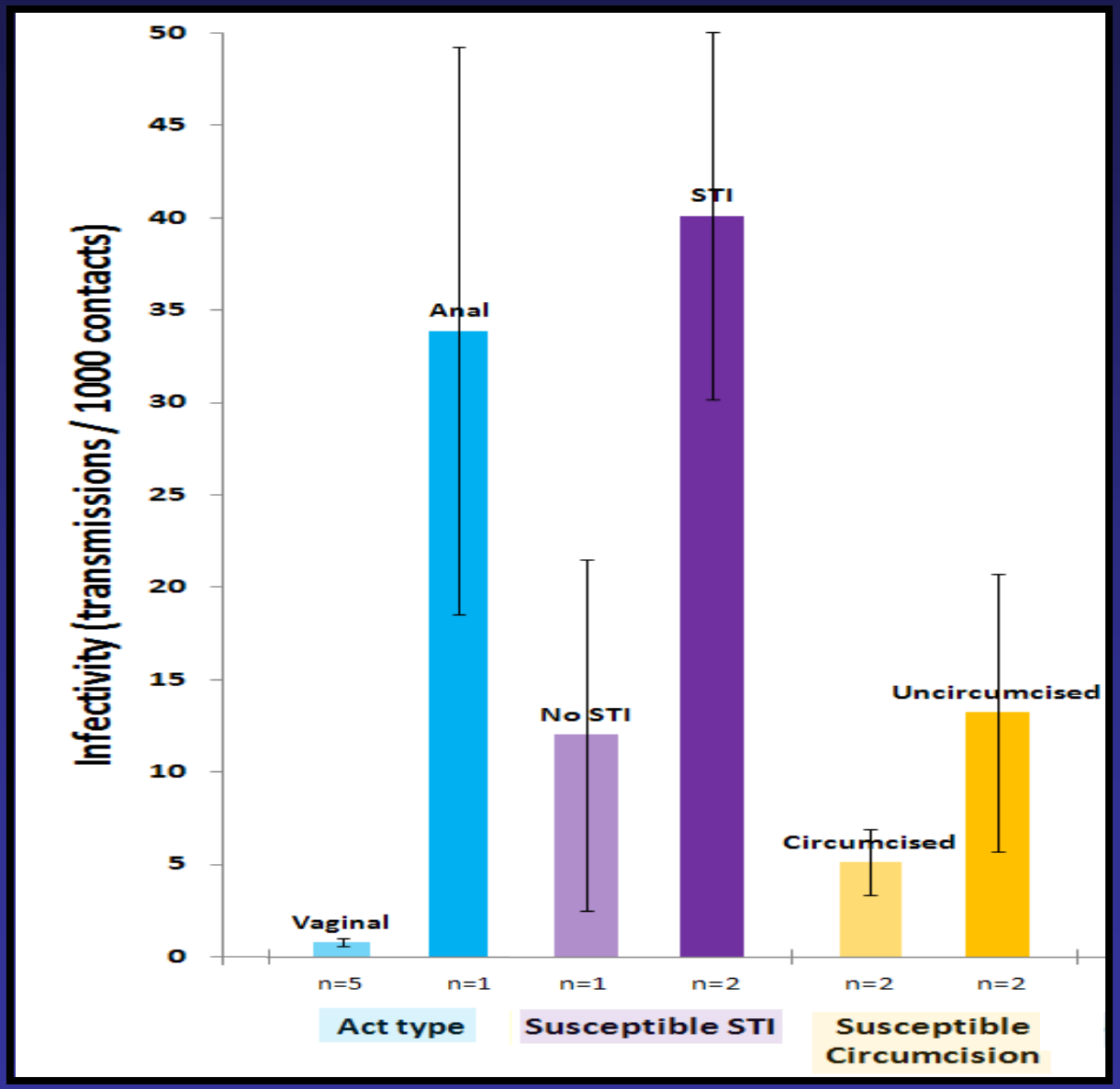
# A Single R5 Virus from “A SWARM” Infects

***Keele et al., PNAS 2008***



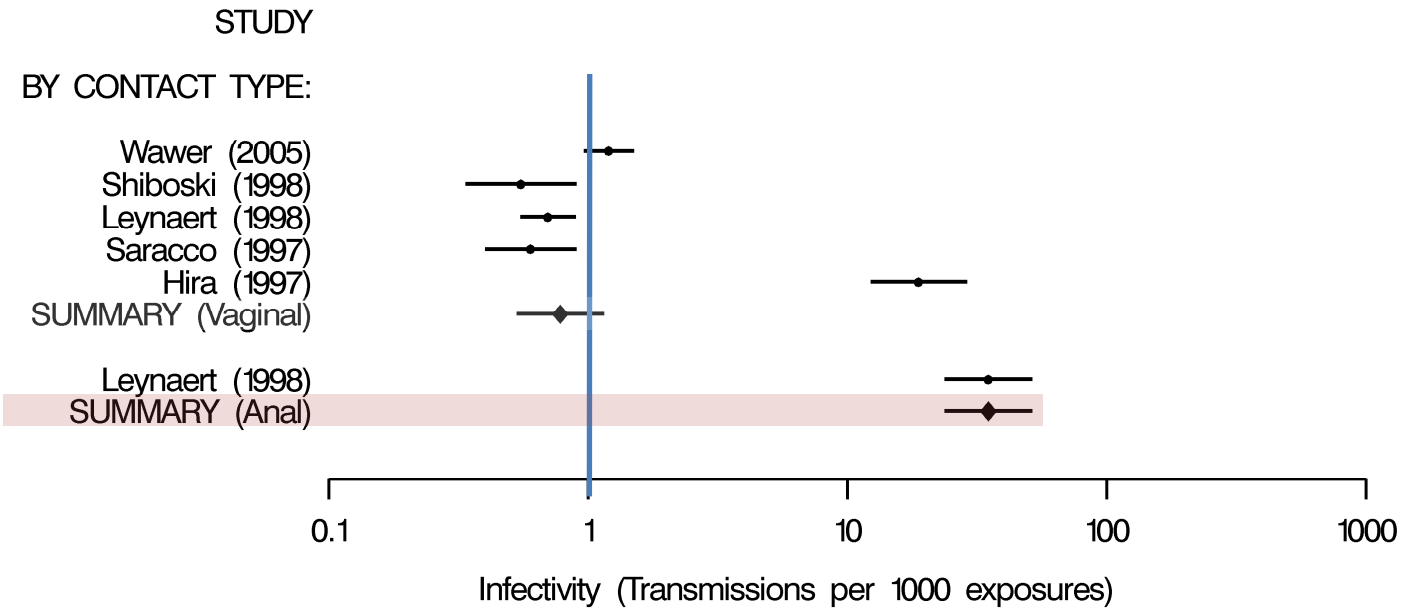
# HIV Transmission Efficiency By Cofactor

***Powers et al Lancet ID, 2008***



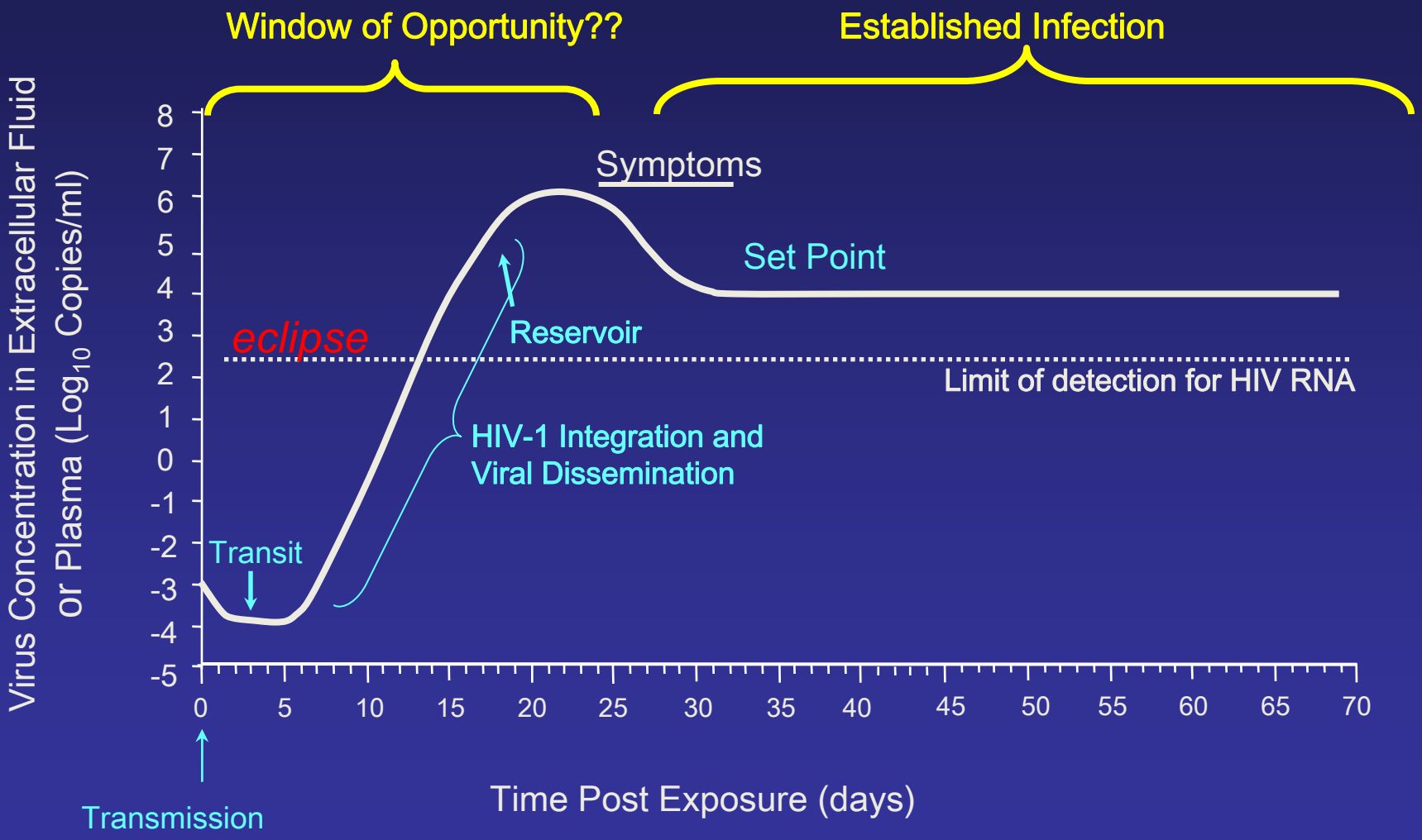
# Anal Intercourse Considered !!

## Powers et al. Lancet ID, 2008



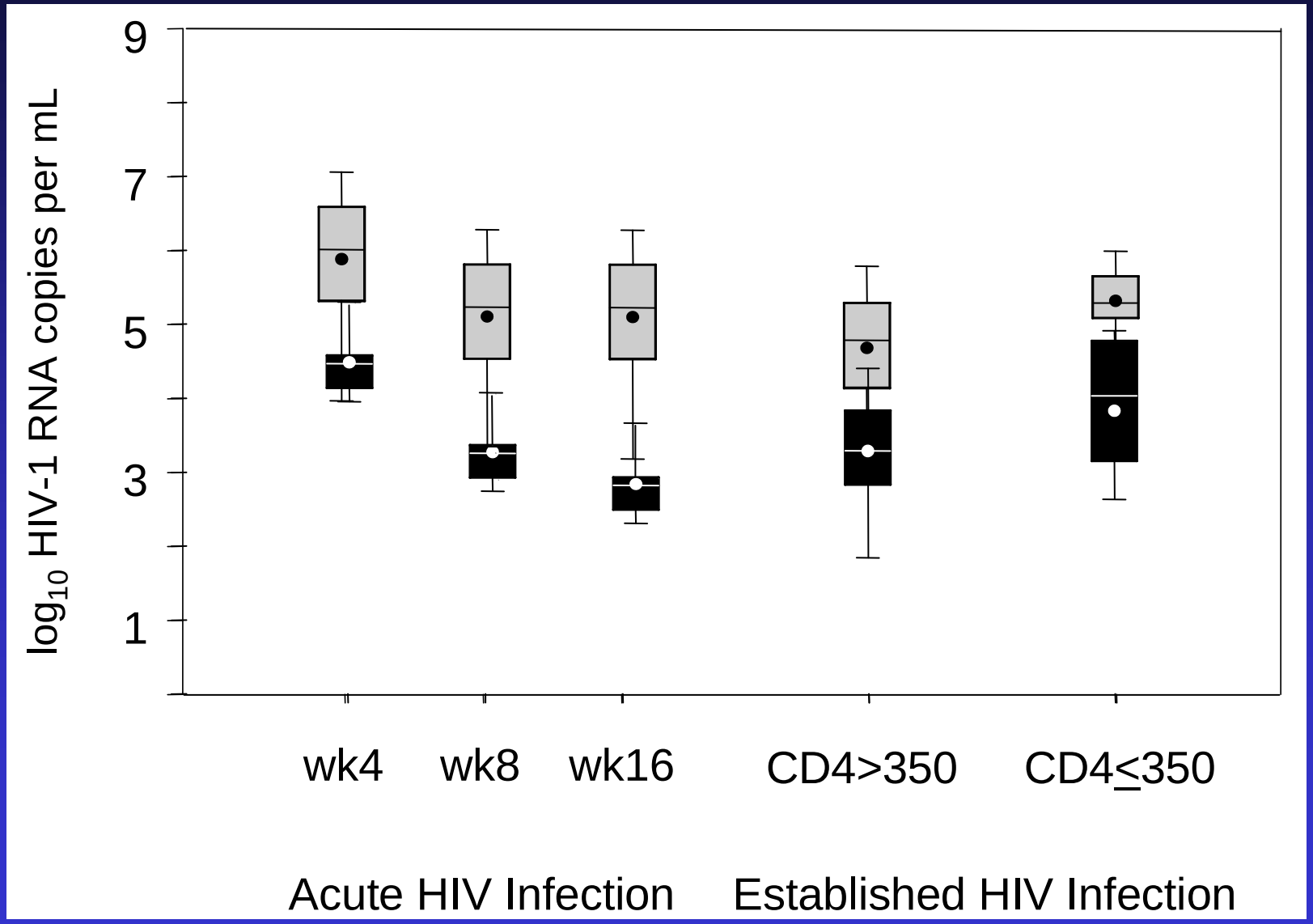
# The HIV-1 Transmission Event

***Adopted from Johnston and Fauci, NEJM,2007.***

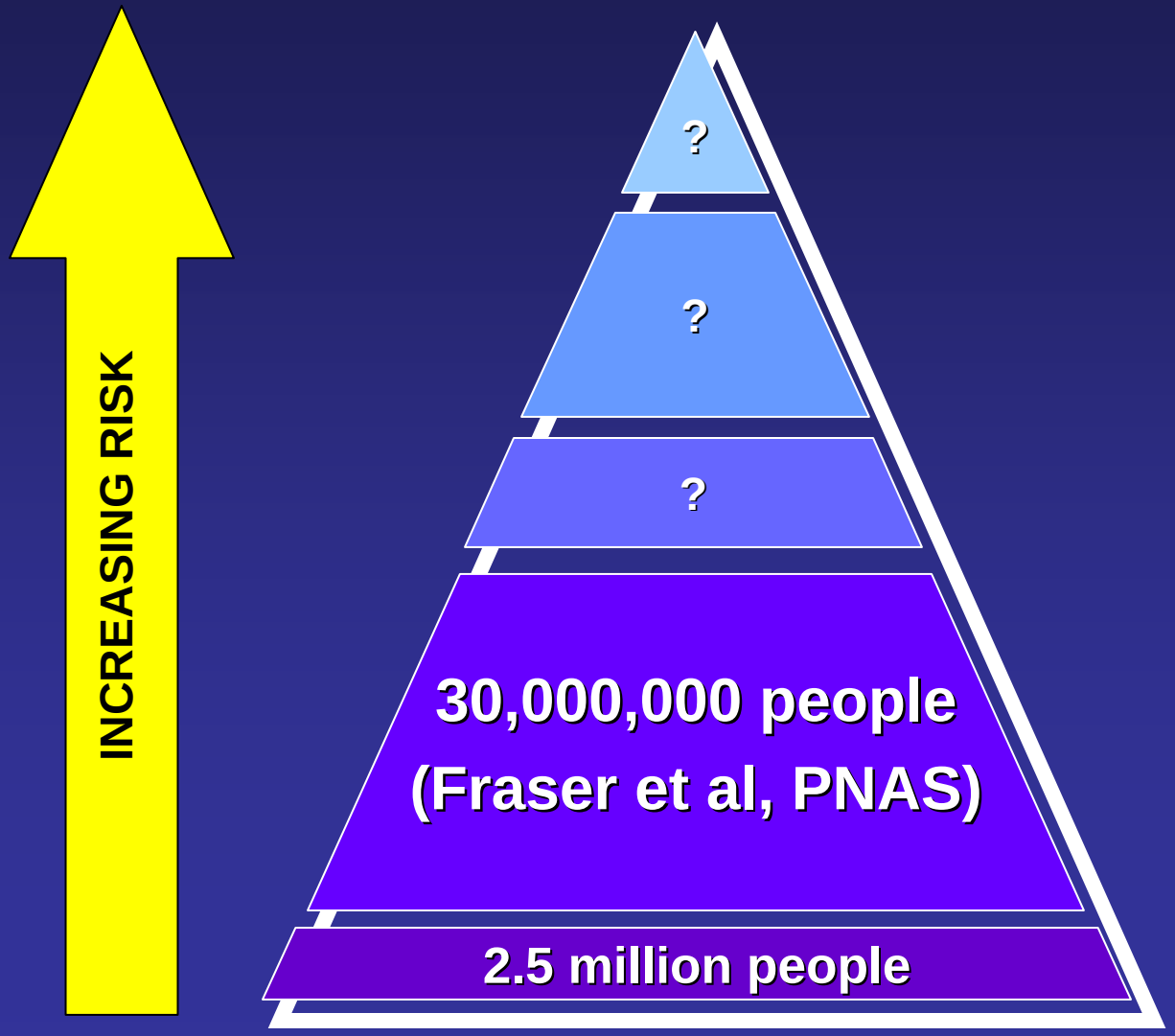


# HIV-1 Viremia and Shedding: Malawi

*Pilcher et al AIDS, June 2007*



# The Hierarchy of Transmission Risk.. From 39 Million People with HIV




Acute HIV Infection

AIDS
untreated

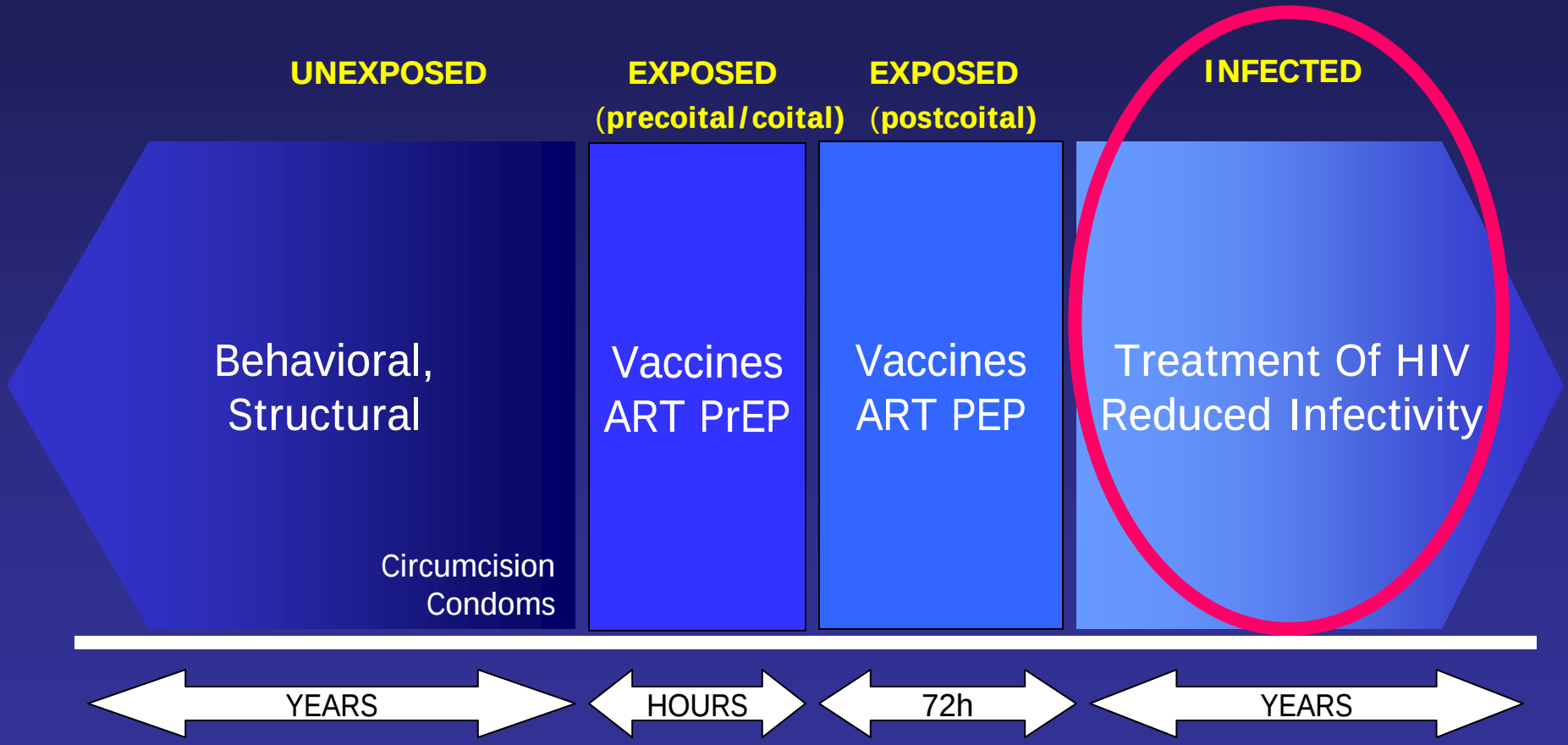
Established infection,
untreated + STD

Established infection
untreated

Established infection
on ART

# Four Prevention Opportunities

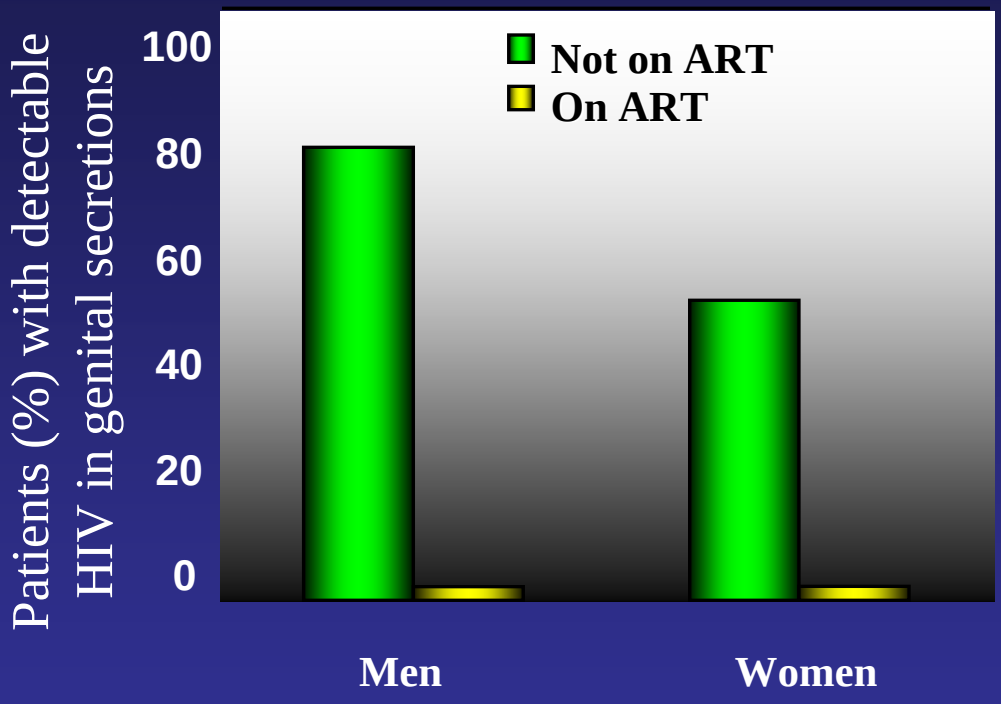
***Cohen et al, JCI, 2008***
***Cohen IAS 2008***



# ART for Secondary Prevention

***Cohen et al. Annals Int Med 2006***

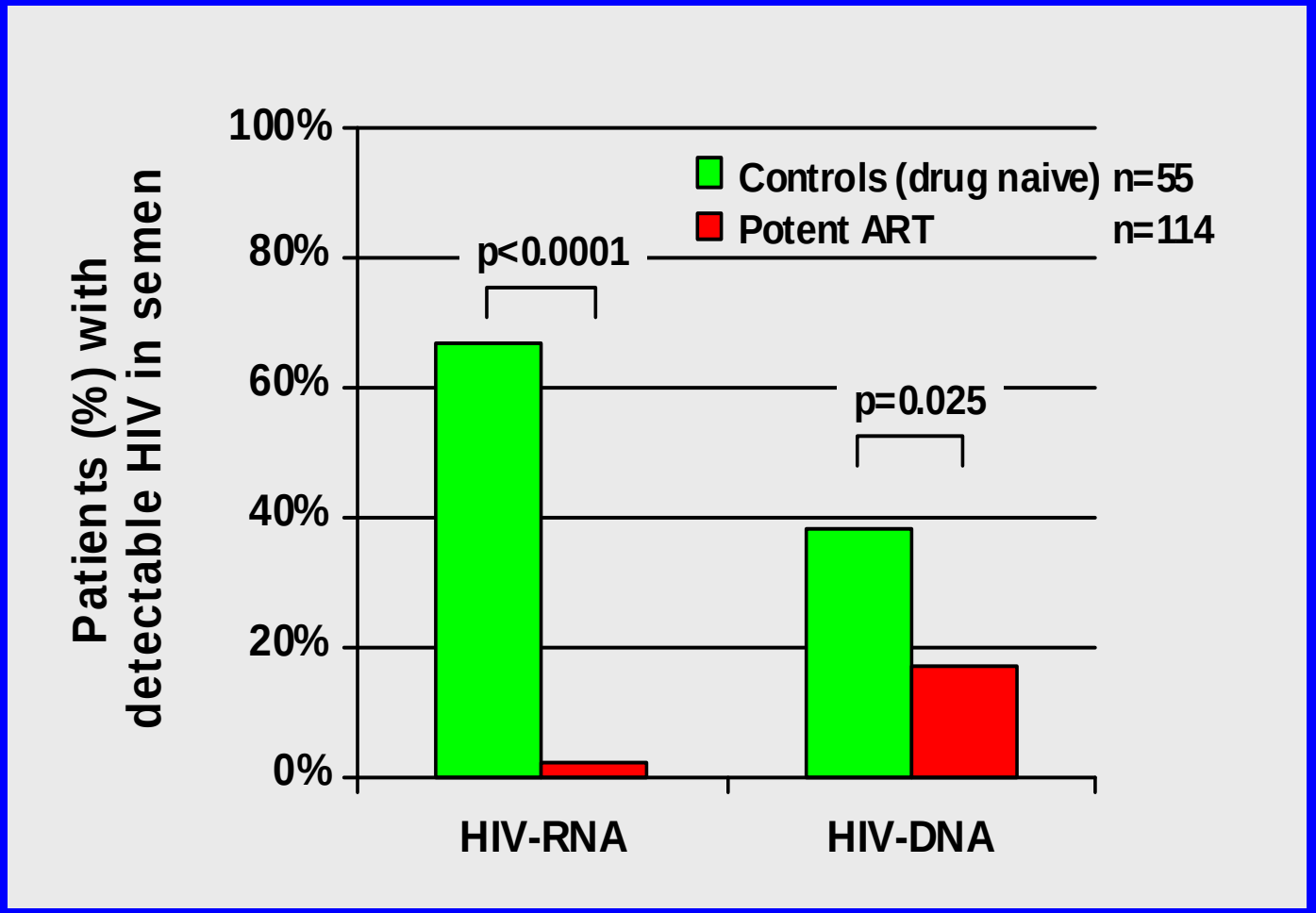
- **Strong biological plausibility for men and women**
- **Retrospective clinical studies**
- **Observation Studies of couples**
- **Ecological population studies**




***Vernazza, al., AIDS, 2000***
***Cu-Uvin et al., JAIDS, 2006***

**BUT WE DO NOT KNOW THE DEGREE OR DURABILITY OF BENEFIT FROM ART AS AN HIV-1 PREVENTION WITHIN A COUPLE** ***(Wilson et al. Lancet, 2008)***

# Semen HIV in patients with suppressed viral load



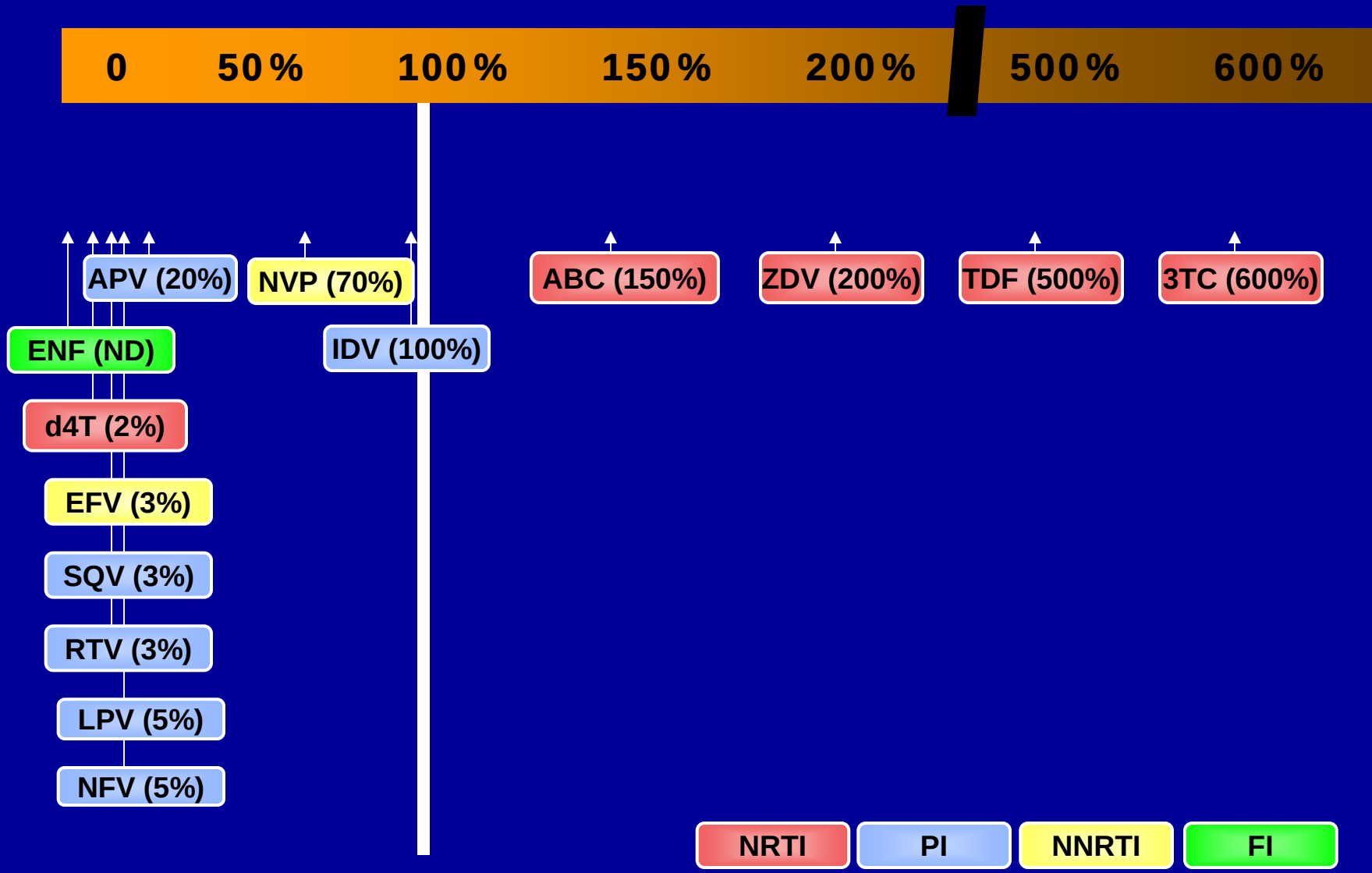

Vernazza et al., AIDS, 2000

# Male Genital Tract Exposure

*percent of blood plasma*

*Kashuba et al. and Abstract 569 (Vourvahis), 13th CROI*

*Abstracts 396 (Stekler), Abstract 618 (Katzenstein)*



# Detection of Semen HIV “Blips” Regardless of ART

+ • Zhang et al 1998—7 men on stable ART; 4 of 7 with HIV-1 proviral DNA in seminal cells; 2 of 7 with replication-competent virus in semen (no resistance mutations).

+ • Kiessling et al 1998—case report of one patient with infectious virus cultured from semen cells but not paired blood cells.

+ • Vernazza et al 2000—cohort of men on ART and all with VL<400 copies/ml, two of 111 (1.8%) patients with detectable virus in semen plasma.

+ • Nunnari et al 2002—cohort of 28 men on ART and VL<50 copies/ml; 16 of 28 had viral growth from PBMC vs. 5 of 28 from semen. Eighteen men with 2 LTR circles in PBMC suggesting recent replication; however, no semen samples had 2 LTR circles.

+ • **Sadiq et al 2002—24 men on ART x 3 months and undetectable plasma VL who develop urethritis; two of 24 patients have detectable virus in semen.**

+ • Solas et al 2003—three of 41 men on stable ART and <50 copies/ml have detectable virus in semen while undetectable in blood; all 3 patients with detectable virus in semen have multiple drug resistance mutations.

- • Lowe et al 2006—12 patients followed longitudinally x 96 weeks; all remain undetectable in blood and semen compartments.

+ • Vernazza et al 2007—PI monotherapy trial with ATV/r (ATARITMO)—excluding patients who failed, two of 15 had detectable virus in semen while blood remained <50 copies/ml.

- • Ghosn et al 2008—No shedding of HIV-1 in semen of 10 men after 48 weeks of suppression with Kaletra +/- combivir.

# Transmission During Therapy??

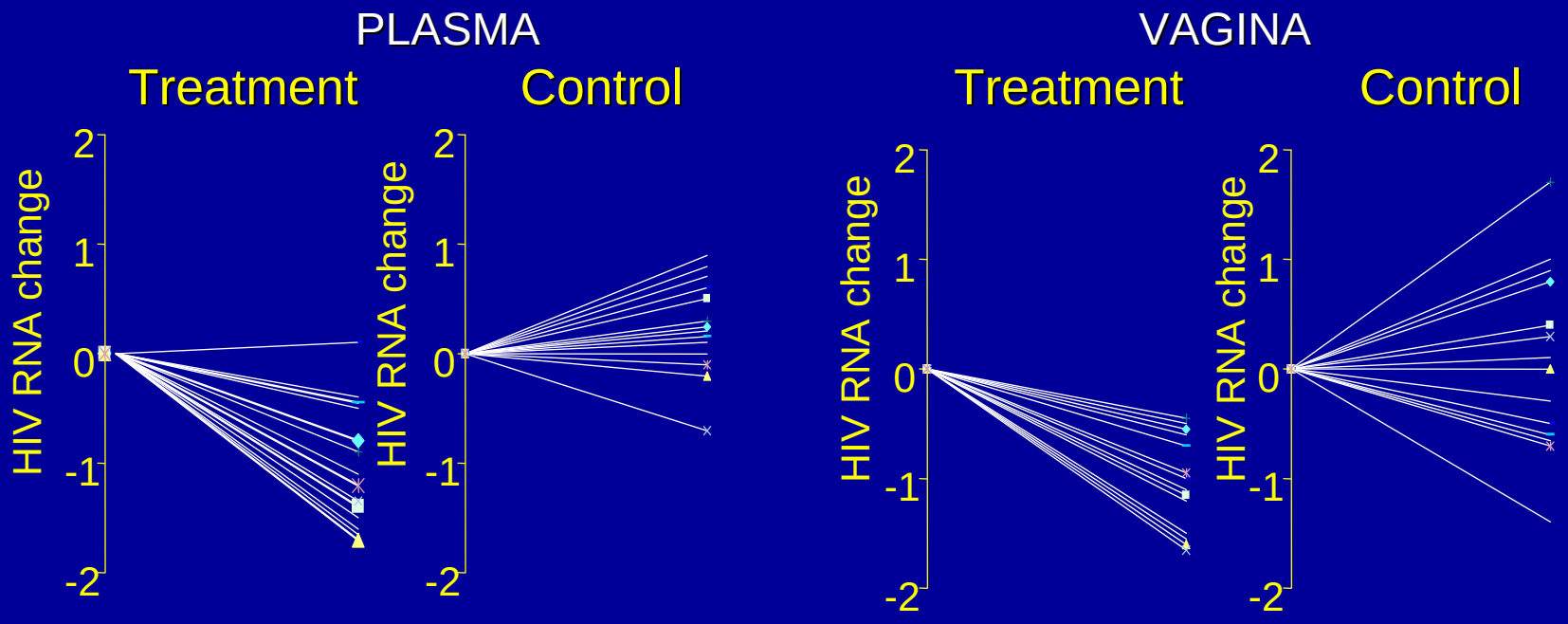
Common acquisition of resistant variants: can all patients with *de novo* resistance suffer exposure to sexual partners failing or off ART therapy?

A case report…**Sturmer art al. Antiviral Therapy 2008. 213: 641**

HIV-1 transmission in a serodiscordant couple despite successful antiretroviral therapy of the HIV-infected partner. The newly infected partner had a negative HIV-1 screening ELISA when his HIV-1-positive partner was already on antiretroviral treatment with undetectable pVL, which remained undetectable beyond the time of seroconversion in the initially negative partner. Frozen blood samples were analyzed phylogenetically from the HIV-1-positive patient and the newly infected partner before treatment and shortly after seroconversion, respectively; they showed a true relationship. The report suggested that transmission of HIV-1 can occur despite undetectable pVL.

Editorial Response, Vernazza and Hirschel…skeptical?

# Changes in HIV RNA Levels in Vaginal Lavage (Hart, Lennox et al. JID 1999.)




Controls: Women on no rx or stable for 12 wks
Cases: Unrx or stable for > 12 weeks starting at least 1 new ART
Samples obtained 2-10 weeks after change in rx

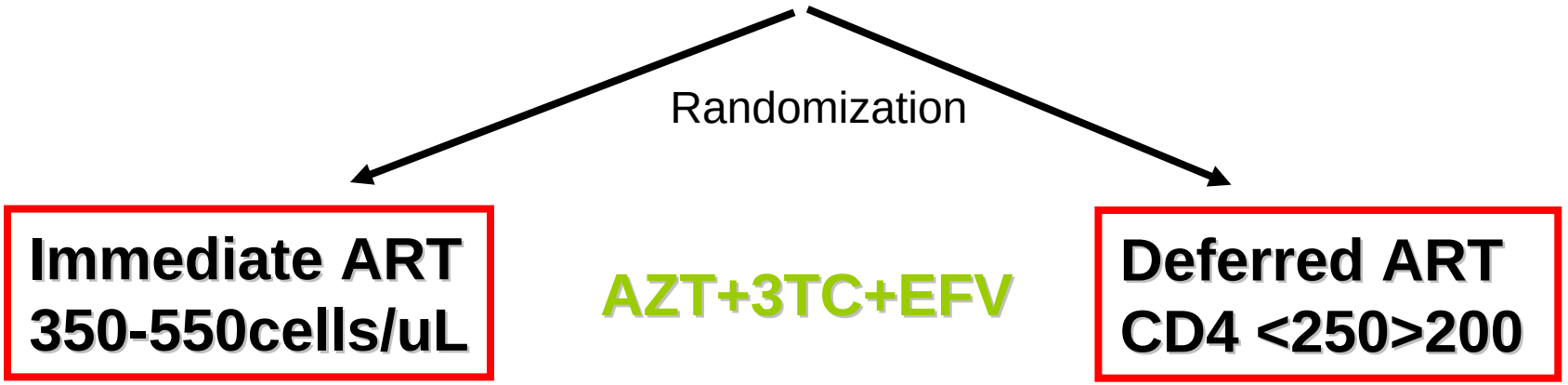
# Female Genital Tract Shedding during ART

- Cross-sectional studies estimate prevalence of women with detectable cervical or vaginal at a single point in time[1-6]:
  - HAART: 15% - 50% prevalence of shedding
  - Non-HAART: 31% - 79% prevalence of shedding
- Longitudinal studies estimate “break-through” shedding:
  - 65% of women on treatment with viremia in cervicovaginal secretions at least once over median follow-up of 21 months[7]
  - 64% of women with detectable viremia at least once during pregnancy[8]

*1 Cu-Uvin et al. (2000), 2 Fiore et al. (2003), 3 Kovacs et al. (2001), 4 Si-Mohammed et al. (2000), 5 Vettore et al. (2006), 6 Neely et al. (2007), 7 DeBiaggi et al. (2001), 8 Tuomola et al. (2002)*

# HPTN 052

**HIV-infected subjects with CD4 350 to 550cells/µL**




**Endpoints: i) Transmission Events**
**ii) OIs and Clinical Events**
**iii) ART Toxicity**

# Mathematical Modeling

- To estimate the probability of per couple or per episode transmission as a function of HIV viral load or stage of disease
- To estimate the effects of ART on per couple or per episode transmission
- To estimate the spread of HIV in a population as a function of stage of HIV disease
- To estimate the spread of HIV in a population as a function of change in sexual behavior
- To estimate the effect(s) of ART on the population level spread of HIV

…ASSUMPTIONS, ASSUMPTIONS, ASSUMPTIONS

Most confusing assumptions…behavior change

Least appreciated assumption…effect of anal intercourse

# MODELING, MODELING, MODELING

- Baggaley et al Emerg Themes Epidemiol 2005; 2:9 ( A review)
- And…more recent models (not exhaustive):
  - Abbas et al JAIDS 2006; 41:632-641
  - Wilson et al PNAS 2006; 103(38):14228-14223
  - Over et al STD 2006; 33(10):S145-S152
  - Baggaley et al PLoS Med 2006 3(4):e124
  - Bacaer et al J Math Biol 2008; 57:557-593
  - Bezemer et al AIDS 2008; 22:1071-1077
  - Lima et al JID 2008; 198:59-67
  - Salomon AIDS 2008; 22: S149-159

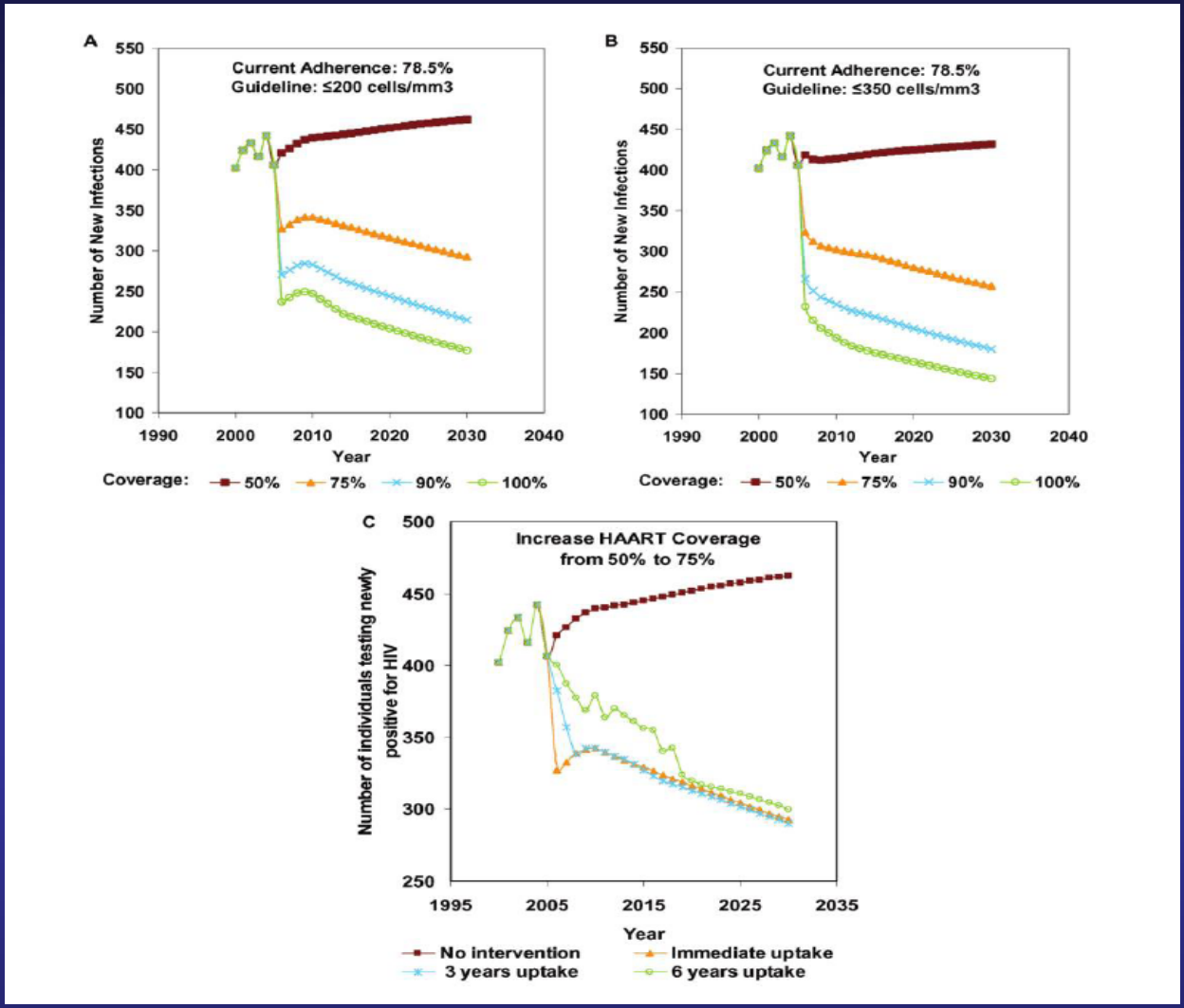



**Figure 4.** Results from the British Columbia Centre for Excellence in HIV/AIDS transmission model of the effectiveness of highly active antiretroviral therapy (HAART) uptake scenarios and coverage rates on the no. of individuals testing newly positive for HIV from 2006 through 2030. In panels A and B, we considered the effect of immediate (1-year) HAART uptake by varying coverage rates (from 50% to 75%, 90%, or 100%) and the impact of drug resistance measured indirectly through adherence (78.5% [current level]), given current guidelines (CD4 cell count ≤200 cells/mm3) (A) and new guidelines (CD4 cell count ≤350 cells/mm3) (B). In panel C, we considered the effect of HAART uptake given current guidelines (CD4 cell count ≤200 cells/mm3) and current adherence level (78.5%) and varying coverage rates from 50% to 75% and uptake scenarios (1, 3, or 6 years).

# The Big Challenge NOW

*Salomon at al. PLoS Medicine, 2005*

- Great HIV treatment success…
  - 22 antiretroviral agents available
  - More than 2 million people receiving ART
- But 2.5 million new HIV infections/yr
- HIV prevention lags far behind… and has not married treatment!!

- HIV prevention MUST marry treatment TODAY!!

# Integrating HIV Prevention and Treatment

*Salomon at al. PLoS Medicine, 2005*

## Modeling Interventions in Sub-Saharan Africa, 2004-2020

| Scenario | Millions of Total New Adult Infections | Millions of Infections Averted vs. Baseline | Millions of Total Adult Deaths | Millions of Deaths Averted vs. Baseline |
|---|---|---|---|---|
| Baseline | 52.3 | NA | 37.4 | NA |
| Treatment-centered (optimal effects) | 49.2 | 3.0 (6%) | 32.4 | 5.0 (13%) |
| Treatment-centered (mixed effects) | 57.4 | -5.1 (-10%) | 33.9 | 3.5 (9%) |
| Prevention-centered | 33.2 | 19.1 (36%) | 32.6 | 4.8 (13%) |
| Combined response (optimistic) | 23.4 | 28.8 (55%) | 27.3 | 10.1 (27%) |
| Combined response (pessimistic) | 43.6 | 8.7 (17%) | 31.6 | 5.8 (16%) |

# ART for Prevention and Equipoise?

- The idea of ART as a key part of HIV prevention has become an extremely popular idea.
- Limited observational data suggest ART will prevent HIV transmission within heterosexual couples, **but the magnitude and durability of this benefit is not known.**
- NA-Accord data suggest survival benefit in patients in the US with earlier ART (>350 CD4 cells/cubic mm).
- Many, many, many mathematical modeling exercises support or refute the prevention benefit(s) of ART…but these “exercises” are **NOT** data and they are bounded by assumptions.

# Conclusion(s)

- ART is likely to greatly reduce secondary transmission of HIV within couples, but the durability of suppression is unknown.
- The factors that increase the probability of HIV transmission in a discordant couple will not be immediately visible, and could overwhelm ART suppression.
- Under what circumstances could/should an individual couple be reassured that ART has rendered unprotected vaginal intercourse safe…or anal intercourse???
- On a population level ART is likely to be of some benefit to HIV prevention efforts, depending on magnitude of application, adherence, durability (??), and affect.