Building Bridges Between Prevention and Treatment

Sandra Nusinoff Lehrman, M.D.

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Evolving Science Presents New Opportunities

- Acute infection
  - Role of intervention
- New drugs, novel regimens
  - Paradigm shift
- Integration of Prevention and Treatment
  - Microbicides
  - Pre-exposure Prophylaxis
  - Mother to Child Transmission

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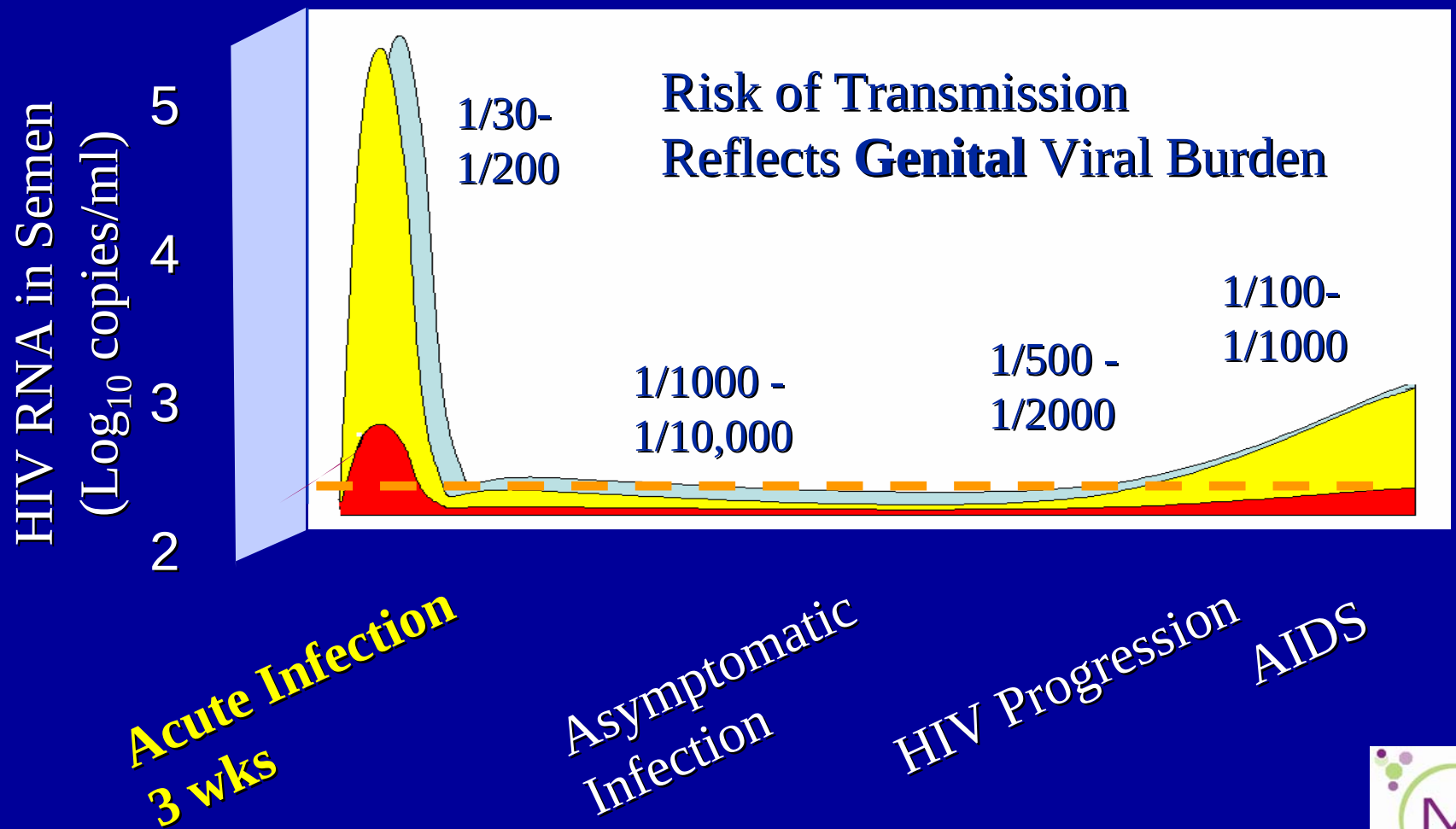
Acute Infection

Sexual Transmission of HIV
(*Cohen and Pilcher, JID May 2005*)



New Opportunities: Acute Infection

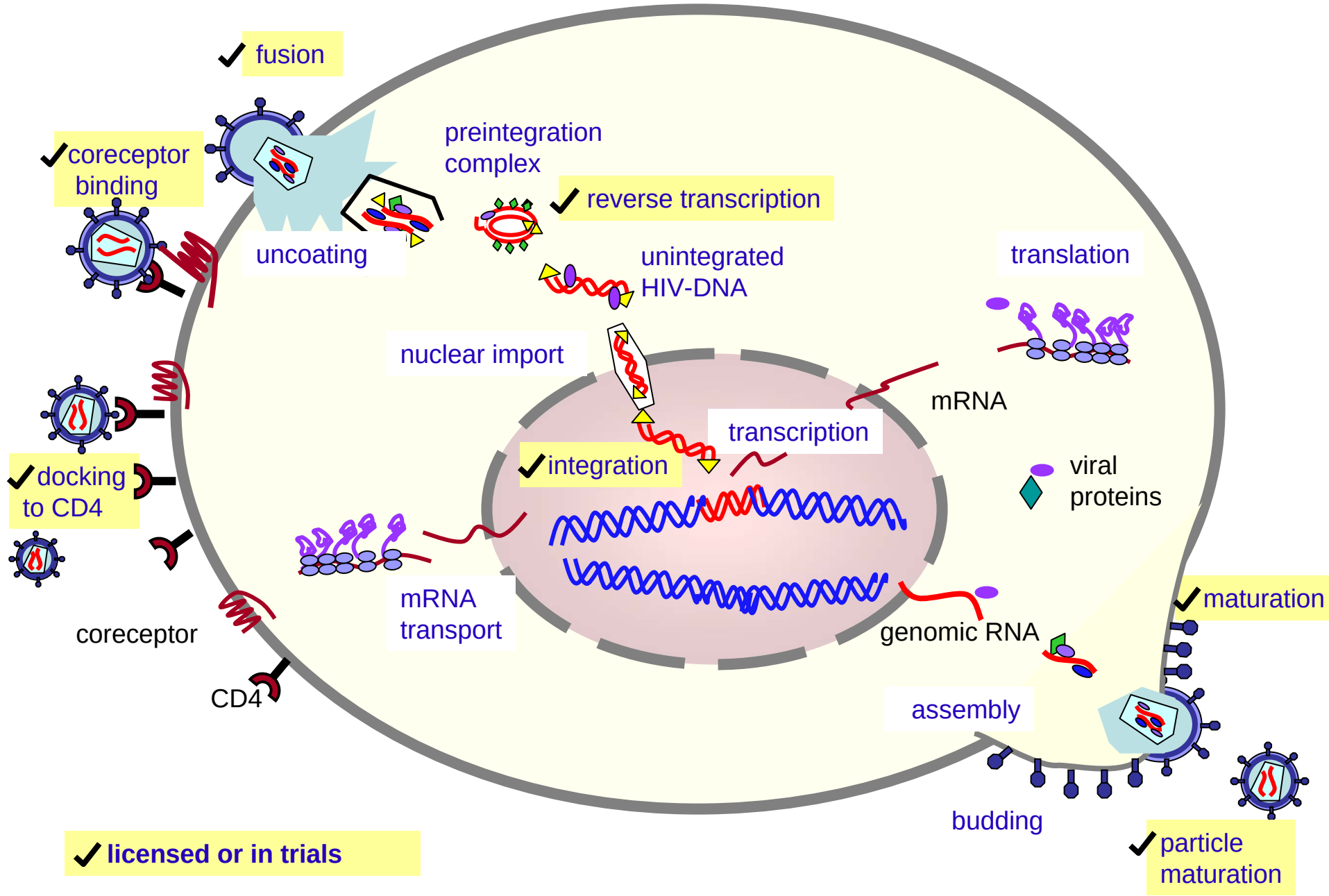
- Identify infections early via prevention trials
- Treat very early with new drug combinations which potentially might preserve T cell populations and block establishment of reservoirs
- Decrease transmissibility and modify course of disease by early attenuation of viral load

New drugs, Novel regimens

New Opportunities: Paradigm shift for treatment

- Drug regimens employing new classes
  - Integrase inhibitors – Raltegravir (MK 0518)
  - CCR5 blockers – Maraviroc

HIV Lifecycle: Targets for Intervention



Integrase Inhibitor: Week-24 Results

- Treatment-naïve patients (n=198)
  - Randomized, partially blinded 48-week study
  - Baseline
    - HIV RNA: 4.6-4.8 $\log_{10}$ copies/mL
    - CD4: approximately 300 cells/mm^3
- Regimens
  - Raltegravir: 100, 200, 400, or 600 mg bid oral administration
  - Efavirenz 600 mg qd
  - All patients lamivudine + tenofovir DF

Integrase Inhibitor: Week 24 Results

- Week 24: all groups were similar with regard to:
  - Proportion achieving HIV RNA <400 and <50 copies/mL
    - 85% to 100%
  - HIV RNA reduction by week 2
    - >2.0 $\log_{10}$ copies/mL
  - CD4 cell gain

- Most common adverse events for MK-0518:
  - Nausea, headache, dizziness, diarrhea, insomnia

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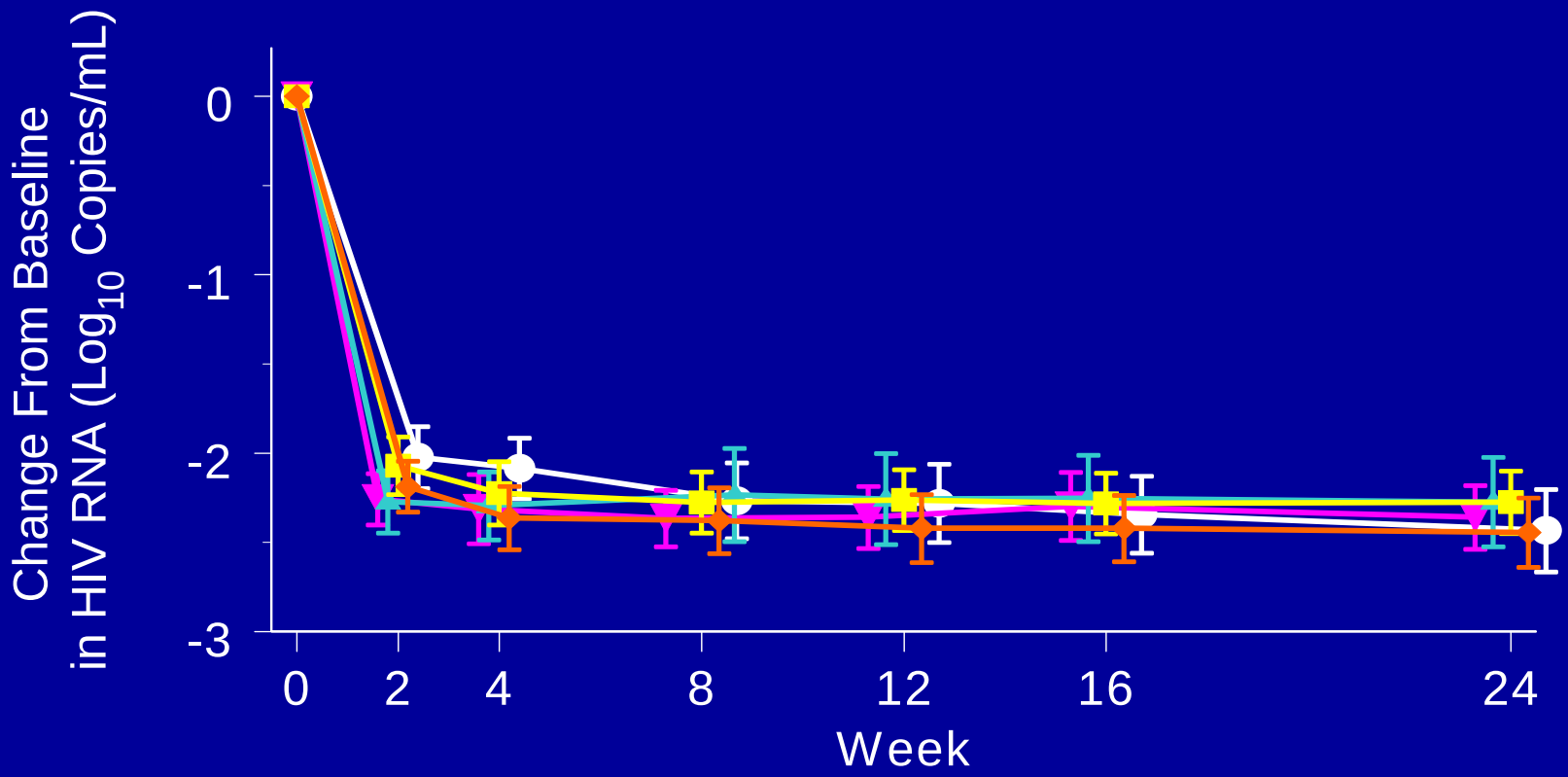
Protocol 004: HIV RNA Change from Baseline* (log_{10} copies/mL) (95% CI)

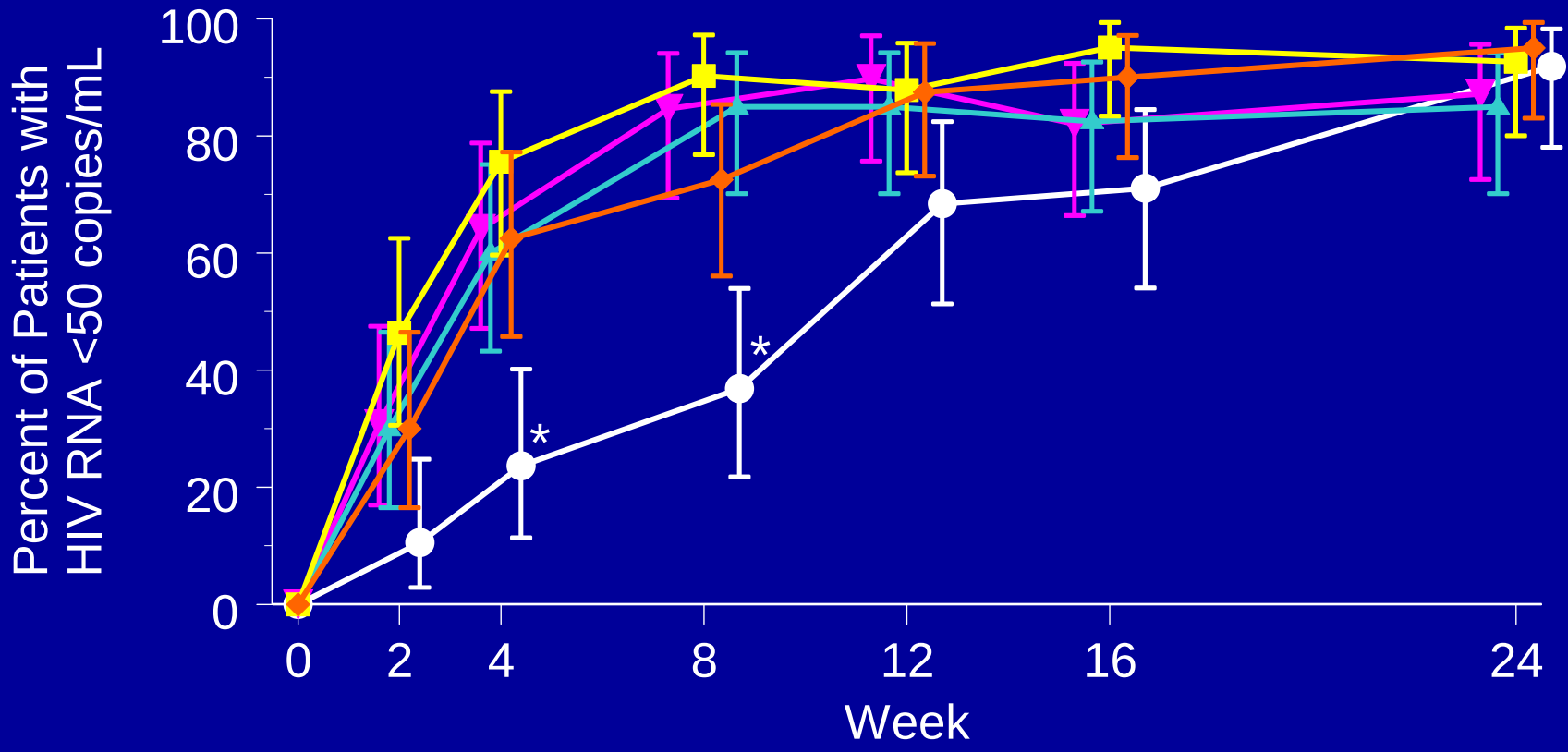


MK-0518 100mg	38	39	39	39	39	39
MK-0518 200mg	40	40	40	40	40	40
MK-0518 400mg	40	41	41	41	41	41
MK-0518 600mg	39	38	38	38	38	38
Efavirenz	37	38	38	37	38	37

*assay LoQ 400 copies/mL

IAC 2006 Abs# THLB0214

Protocol 004: Percent (95% CI) of Patients with HIV RNA < 50 copies/mL (NC=F)



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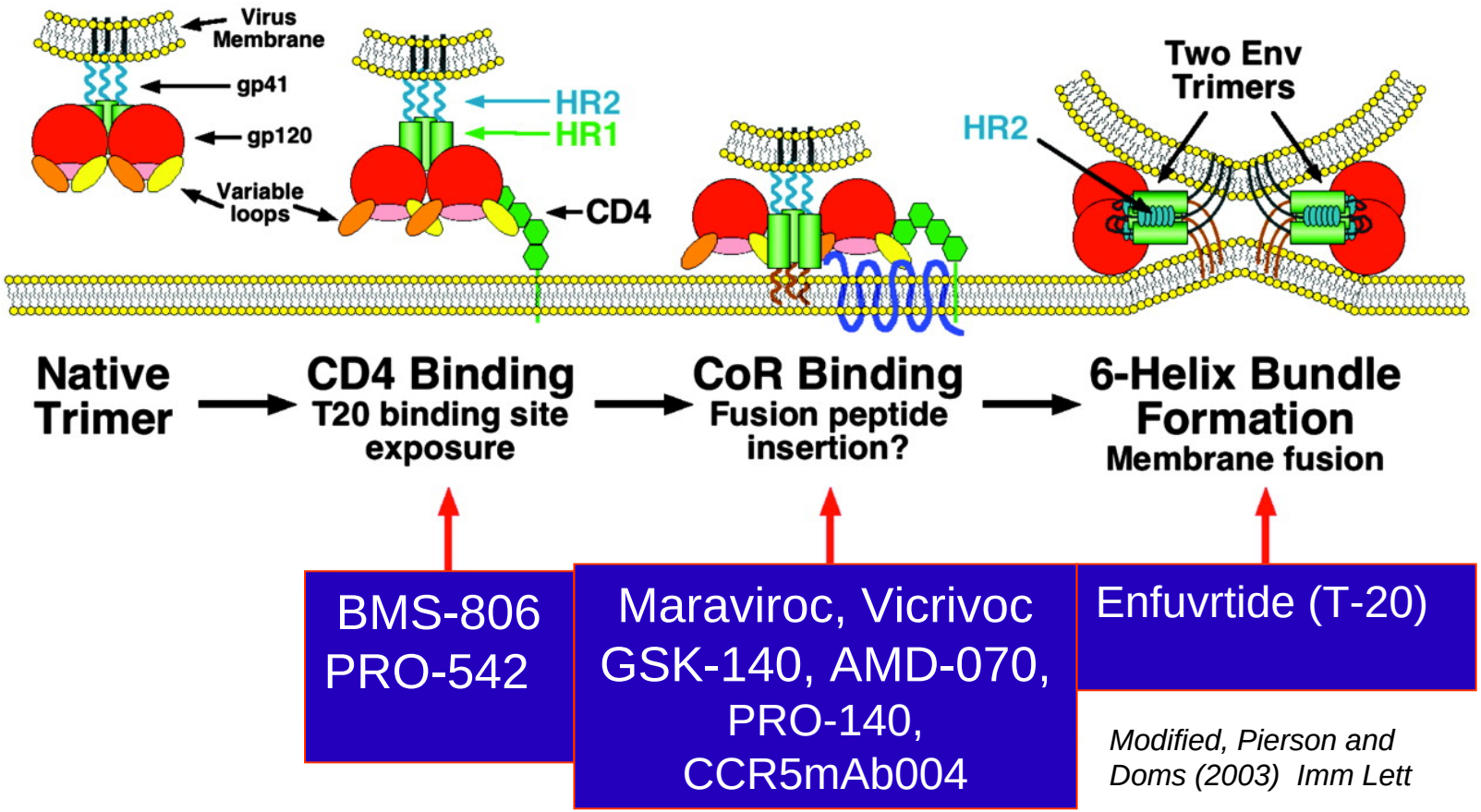
*** P < 0.001 for MK-0518 at each dose vs. EFV**

IAC 2006 Abs# THLB0214

Integrase inhibitor: Raltegravir

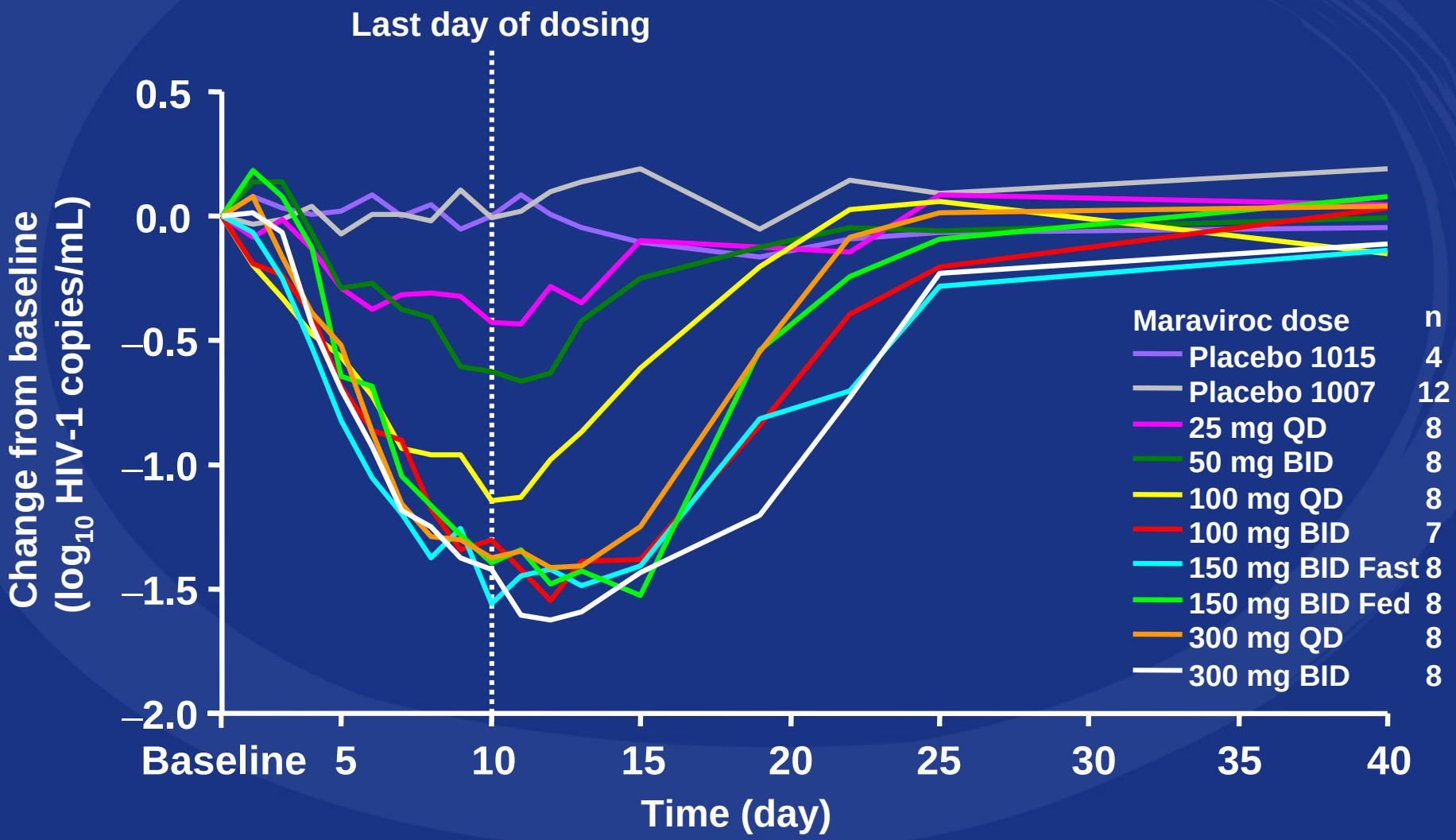
- Data reported at CROI in treatment experienced patients show 79% with less than 400 copy VL when drug added to optimized background
- CD4 responses superior to placebo added to optimized background
- Well tolerated
- Important new drug/class with potential to reduce virus in reservoirs

Targeting the entry pathway



Modified, Pierson and Doms (2003) Imm Lett

MVC Efficacy Results: Mean Reduction in Viral Load over Time



Fätkenheuer G *et al. 15th IAC* 2004; Abstract TuPeB4489

Maraviroc in Treatment Experienced Subjects: Motivate Trials

- Maraviroc (qd and bid) plus OBT demonstrated significantly increased viral suppression
- Marviroc plus OBT also resulted in significantly increased CD4 changes
- No clinically relevant differences between Maraviroc and placebo recipients with respect to adverse events

Maraviroc Motivate Studies

Patients (%) with < 50 copies

# Active Drug	PCB	QD	BID
0	3	18	29
1	9	43	43
2	19	52	53
3	55	61	58

Integration of Prevention and Treatment

Approaches to HIV Prevention

- Education and behavior modification
- Treatment/prevention of drug/alcohol abuse
- Clean syringes (i.e. “needle exchange programs)
- Condoms, other barrier methods
- Circumcision
- Interruption of transmission from mother to child
- Topical microbicides
- Prophylactic antiretroviral therapy
- Treatment of other sexually transmitted diseases
- Vaccination

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Integration of Prevention and Treatment

- Boundaries between prevention and treatment are blurring
  - Prevention mother to child transmission
  - Pre-exposure prophylaxis
  - Post-exposure prophylaxis
  - Discordant couples
  - Prevention for positives – impact of treatment on transmission

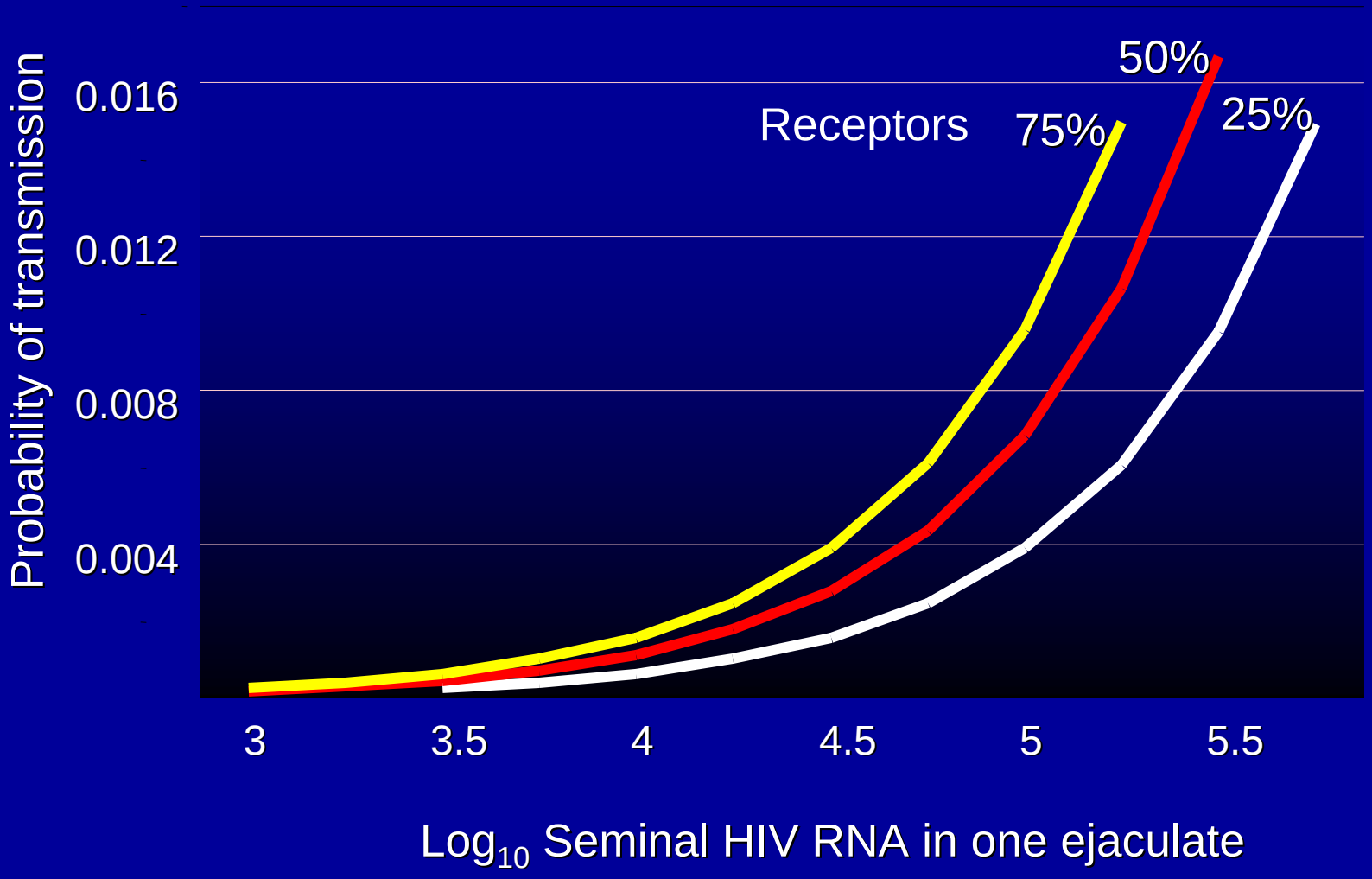
Pre Exposure Prophylaxis as a model for integration of Prevention and Treatment

High Risk Population

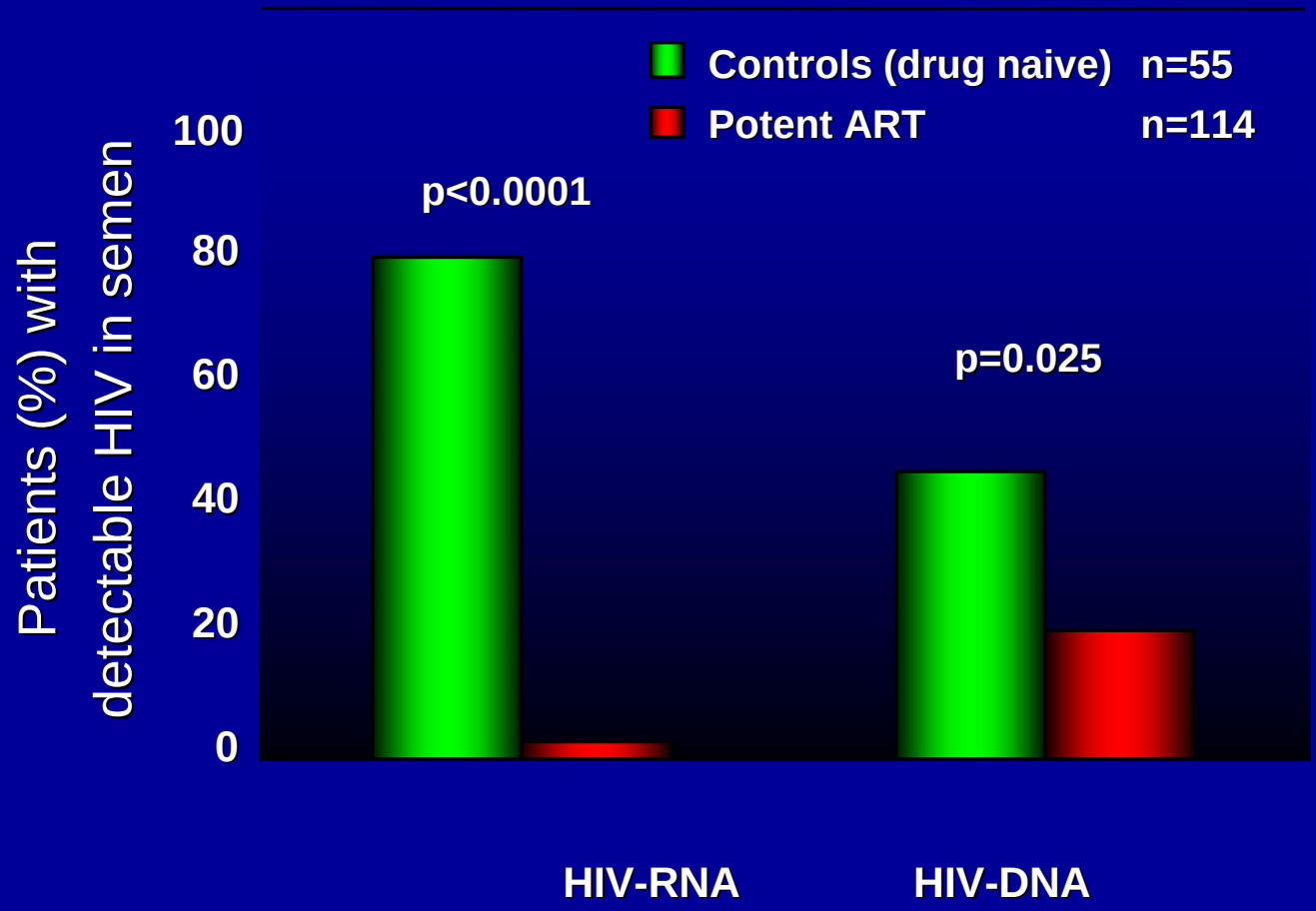
Discordant couples

Estimated HIV transmission probability

Chakraborty *et al*., AIDS 2001



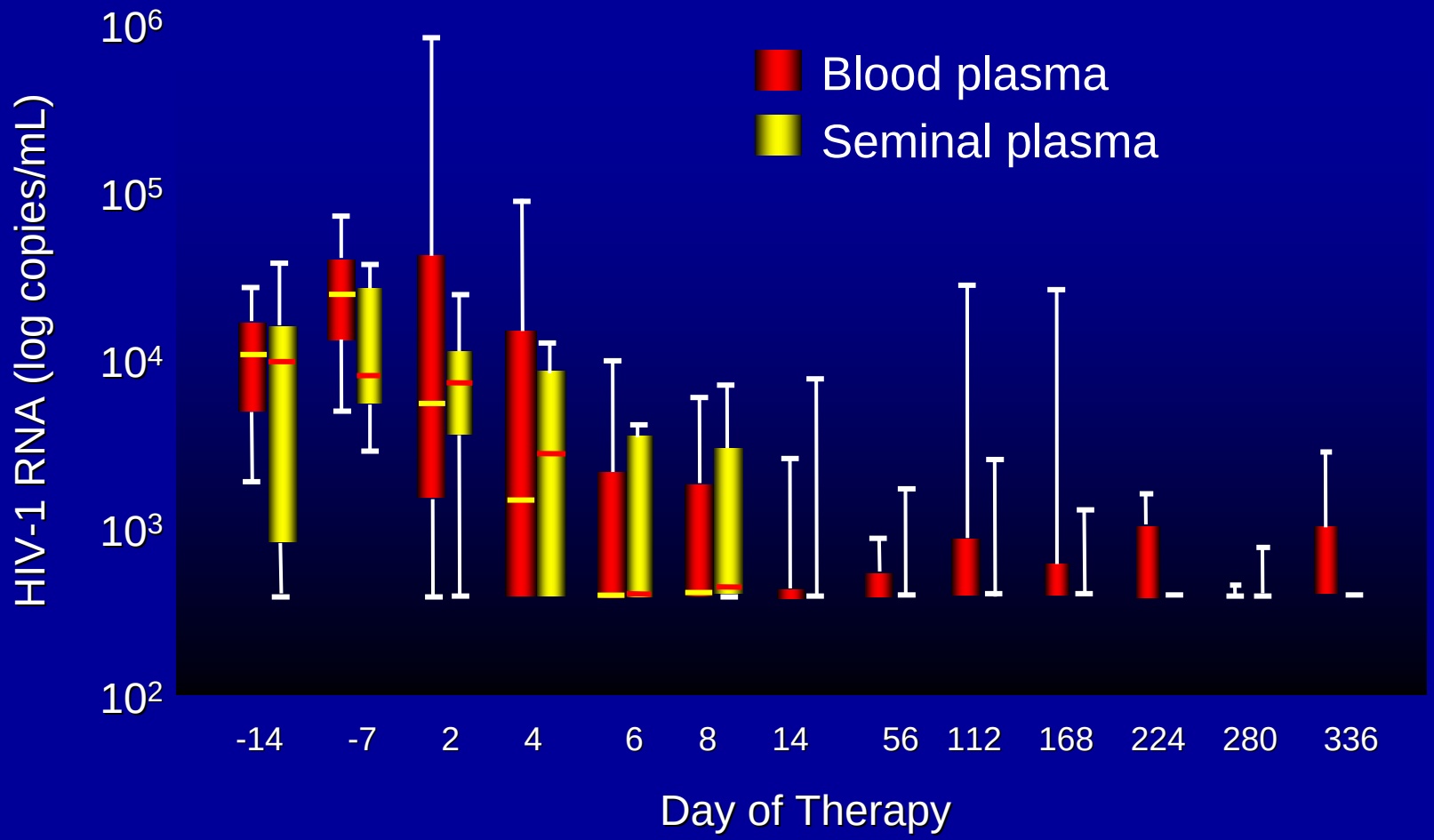
Semen HIV in patients with suppressed viral load



Vernazza, Cohen *et al.*, AIDS, 2000

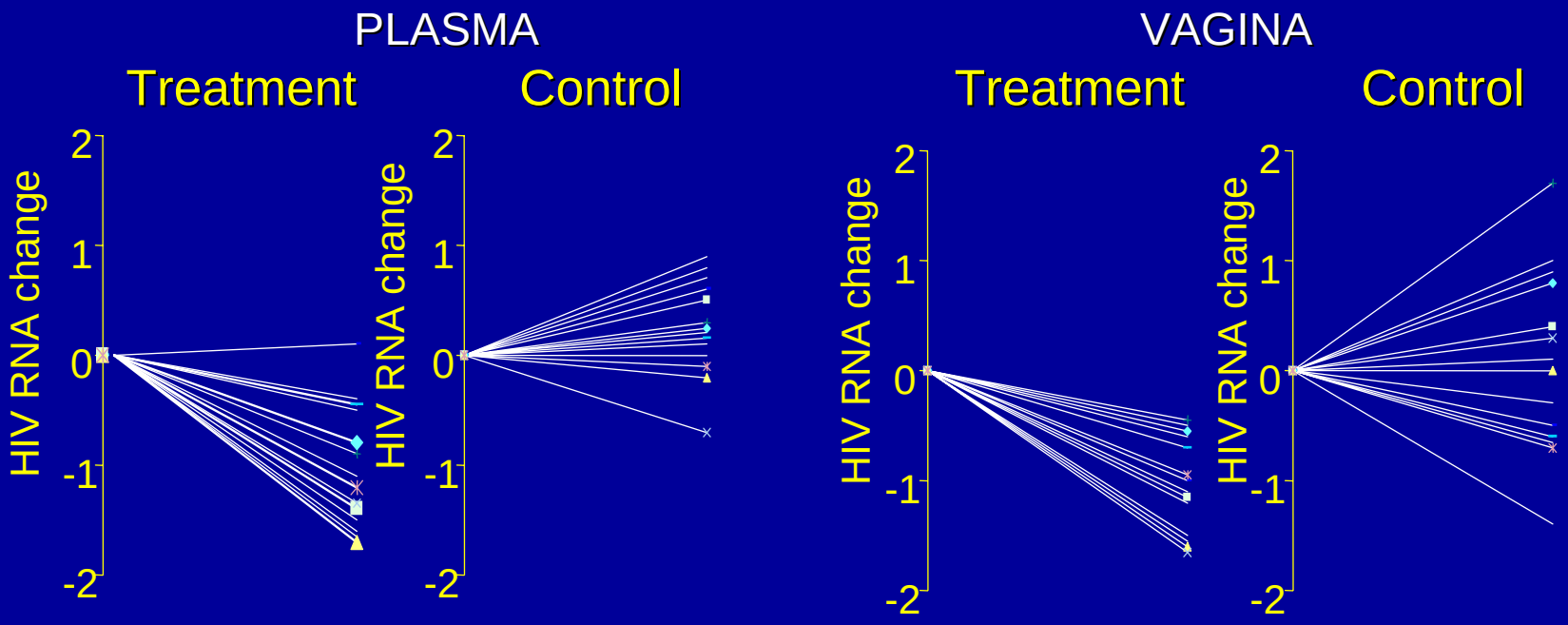
Durable HIV-RNA suppression in semen with ART

Pereira AS, Cohen *et al.* JID 180:2039; 1999



Changes in HIV RNA Levels in Vaginal Lavage

(Lennox et al.)



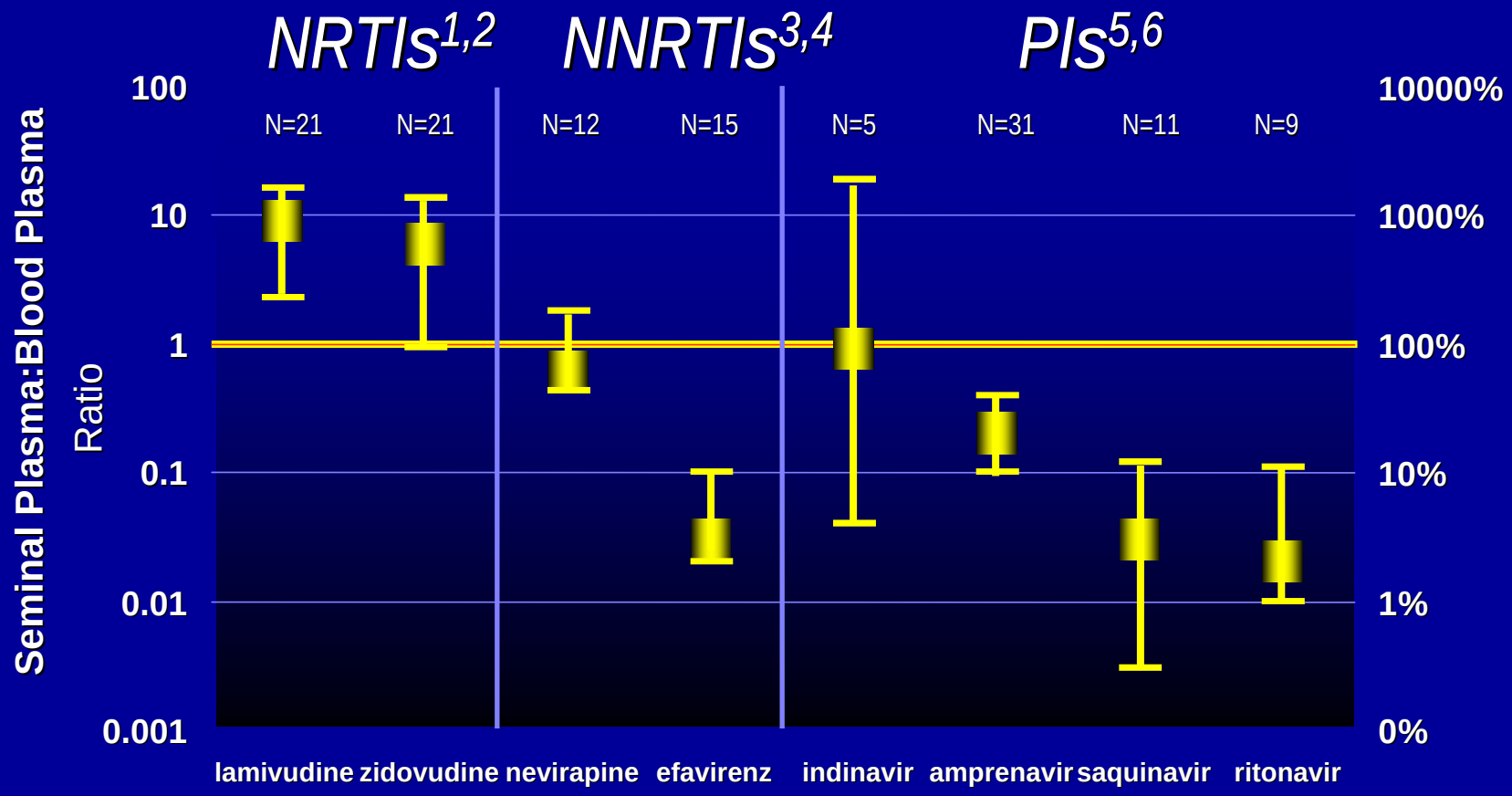
Controls: Women on no rx or stable for 12 wks

Cases: Unrx or stable for > 12 weeks starting at least 1 new ART

Samples obtained 2-10 weeks after change in rx

Antiretroviral Seminal:Blood Plasma Concentration[1,2,4-6] and AUC_{24h}[3] Ratios

(median ± minimum - maximum)



[1]Pereira et al J Infect Dis 1999, [2]Henry et al JAMA 1988, [3]Kashuba et al unpublished data, [4]Taylor et al ICAAC 1999, [5]Taylor et al 7th CROI 2000, [6]Pereira et al 7th CROI 2000

Therapeutic Reductions of HIV Viral Load to Prevent HIV Transmission: Data from HIV Discordant Couples; Rakai, Uganda

Incidence of HIV 11.8/100 patient years

VL < 3500 copies/mL	**Incidence = 2.2/100 py**
VL 3500 – 9999/mL	**12.5/100 py**
VL 25000 - 49,999/mL	**14.7/100 py**
VL >50,000/mL	**23.1/100py**

Treatment reducing VL to < 3500copies/ml would reduce HIV incidence by 81.4%.

Treatment reducing VL to < 9999 copies/ml would reduce HIV incidence by 59.9%.

Quinn *et al.* 8th International AIDS Conference, Durban, 2000 TuPEC 3391

ART for Prevention

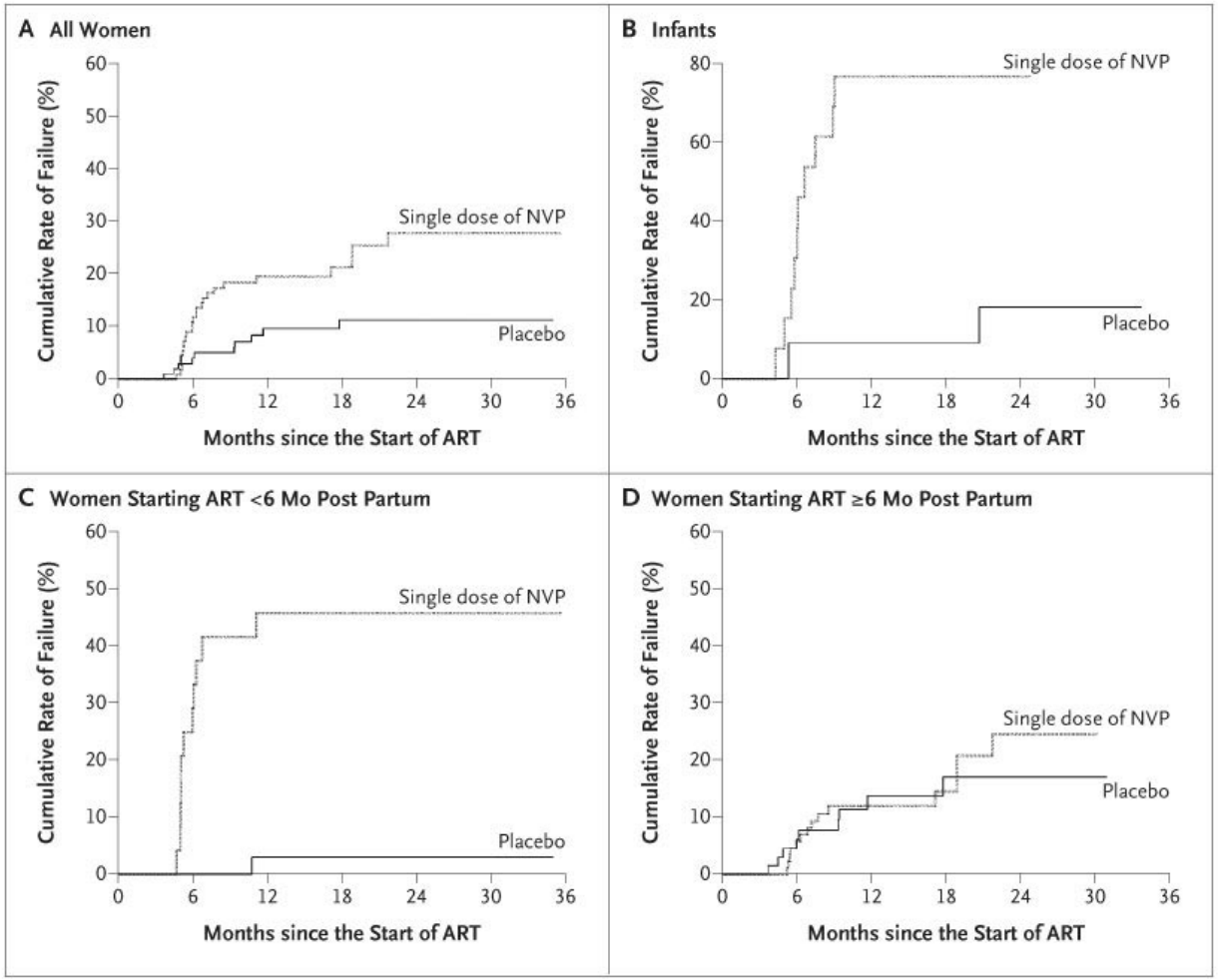
- HPTN 052 – ART for prevention of HIV transmission in serodiscordant couples
  - 87 couple pilot completed
  - Expanding to 1750 discordant pairs

ART for Prevention

- PrEP Study – Pre-exposure prophylaxis with ART for the prevention of HIV infection in MSM
- RO1 study in Peru expanding to multiple sites
  - Increased sample size to improve power
  - Greater generalizability
  - Public Health Need

Prevention of Mother to Child Transmission: Addressing Concerns for NVP Resistance

Time to Virologic Failure



Lockman S et al. N Engl J Med 2007;356:135-147

The NEW ENGLAND JOURNAL of MEDICINE

Prevention of Mother to Child Transmission: Resistance

- Evaluation of short course combination therapy post-partum to “cover the nevirapine tail”
- Two studies evaluating different drug regimens
- One, two, three and four weeks duration

Prevention of Mother to Child Transmission: Resistance

- Studies to determine outcome of subsequent therapy in women who received sdNVP and infected infants born to women receiving sdNVP
  - OCTANE - adults
  - P1060 - infants

Breast Milk as Mode of Transmission of HIV

- Remains a major challenge in prevention in developing world
- Two approaches
  - Chemoprevention - 6 week and 6 month NVP to infants
  - Immunoprophylaxis - candidate HIV vaccines to infants born to infected moms
    - Alvac safety study ongoing
    - MRK Ad 5 planned

Microbicide Research

Integrated Approaches to Prevention and Treatment

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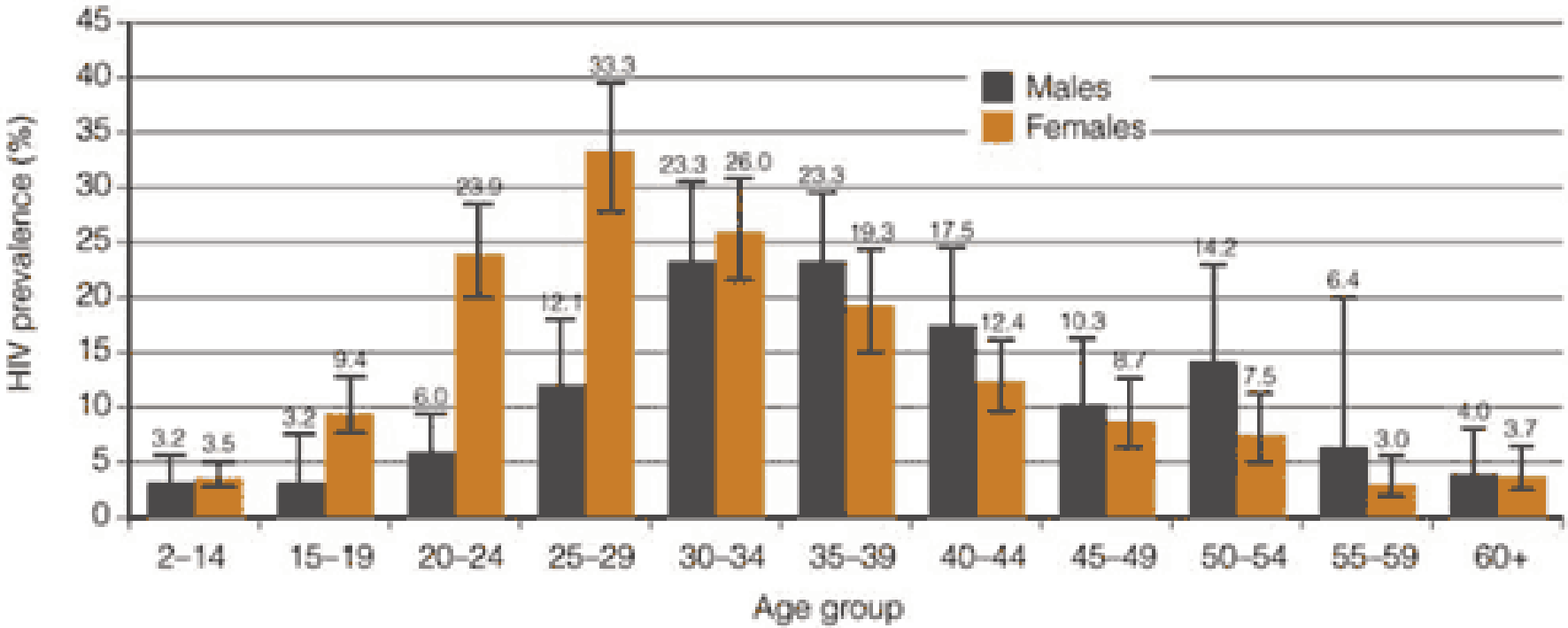
Incidence of HIV in Women in South Africa



Addressing the needs for woman controlled methods to avert HIV infection

- Vaginally applied antiviral agents
- Orally delivered drugs
- Provide a basket of options for women

HPTN 035
Phase II/IIb Safety and Effectiveness Study

- Primary Objectives
  - To evaluate safety
  - To estimate effectiveness
- Study Sites: 7 African and 1 U.S.
- Target enrollment: 3,220 women
  - 192 incident infections
- Study Arms: BufferGel; 0.5% PRO 2000/5 Gel (P); placebo gel; no treatment

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MTN 003

Effectiveness of Oral Tenofovir vs. PMPA Gel

- Rationale
  - Optimal approach to prevent sexual transmission of HIV is unknown
- Study Objectives
  - Safety
    - For both uninfected and infected women
  - Efficacy
  - Acceptability
    - Different among different populations
- Truvada arm

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History will judge us as a global community by what we will do in the next 25 years as much by what we have accomplished in the first 25 years.

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