Long-acting Antivirals – Where Are We Headed? Are We Ready?

Carl W. Dieffenbach, Ph.D.
Director
Division of AIDS, NIAID
May 3, 2018

Global HIV Statistics | 2017

People living with HIV in 2016	36.7 million [30.8 million – 42.9 million]
New HIV infections in 2016	1.8 million [1.6 million – 2.1 million]
Deaths due to AIDS-related illnesses in 2016	1 million [830,000 – 1.2 million]
Cumulative number who have contracted HIV	76.1 million
Cumulative deaths from HIV-related causes	35 million [28.9 million – 41.5 million]

UNAIDS

FDA-Approved Antiretroviral Drugs

NRTIs

- 6 multi-drug combinations
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir (TDF, TAF)
- Zidovudine

NNRTIs

- Delavirdine
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

Integrase Inhibitors

- Bictegravir
- Dolutegravir
- Elvitegravir
- Raltegravir

Post-Attachment Inhibitor

- Ibalizumab

Pharmacokinetic Enhancers

- Cobicistat
- Ritonavir

PIs

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir/ Ritonavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Entry Inhibitor

- Maraviroc

Multi-Class Combinations

- Atripla
- Biktarvy
- Complera
- Descovy
- Evotaz
- Genvoya
- Juluca
- Odefsey
- Stribild
- Triumeq

Fusion Inhibitor

- Enfuvirtide

Source: FDA, March 2018

June 19, 2010 Vol. 24, No. 10
AIDS
Official Journal of the International AIDS Society

Life Expectancy of Recently Diagnosed Asymptomatic HIV-infected Patients Approaches that of Uninfected Individuals

A. van Sighem et al. on behalf of the ATHENA National Observational Cohort Study

- **Life expectancy** for HIV-infected patients (without AIDS) aged 25 yrs at six months postinfection
  - **Men: an additional 52.7 yrs** (versus 53.1 yrs in general population)
  - **Women: an additional 57.8 yrs** (versus 58.1 yrs in general population)

What Problems are Long-acting, Sustained Release Formulations Solving?

What New Problems are They Creating?

The Bane of Therapeutics

- Adherence to drug regimens is of critical concern for chronic conditions
- Failure to adhere leads to low level viral replication and ultimately to the accumulation of HIV drug resistance (HIVDR) mutations
- Global prevalence of HIVDR is rising, mainly due to resistance to NNRTI
- Use of integrase strand transfer inhibitors (INSTIs) has been transformational
- Moving to long-acting is supposed to be the next revolution

Long-acting, Less Frequent Dosing

- **Does less frequent dosing lead to improved adherence?**
  - From the contraception literature, the answer is yes
- **What are the options for delivery?**
  - Oral dosing weekly or biweekly will soon be feasible—will this be an improvement?
- **Current injectables are bimonthly, TTP have this evolving to twice yearly**
- **For prevention, a single ARV will suffice but this may not be true for bNAbs**
- **For therapeutics, three agents with matched pharmacology, no overlapping safety concerns are required—not there yet**

Long-acting ARVs – Current Agents in Development

- Cabotegravir — INSTI (Phase 3)
- MK-8591 — NRTTI (Phase 1, 2)
- Rilpiverine — NNRTI (Phase 3)
- Albuvirtide — Fusion Inhibitor (Phase 3)
- Ibalizumab — CD4 Blocker FDA Approved (TROGARZO)
- bNAbs

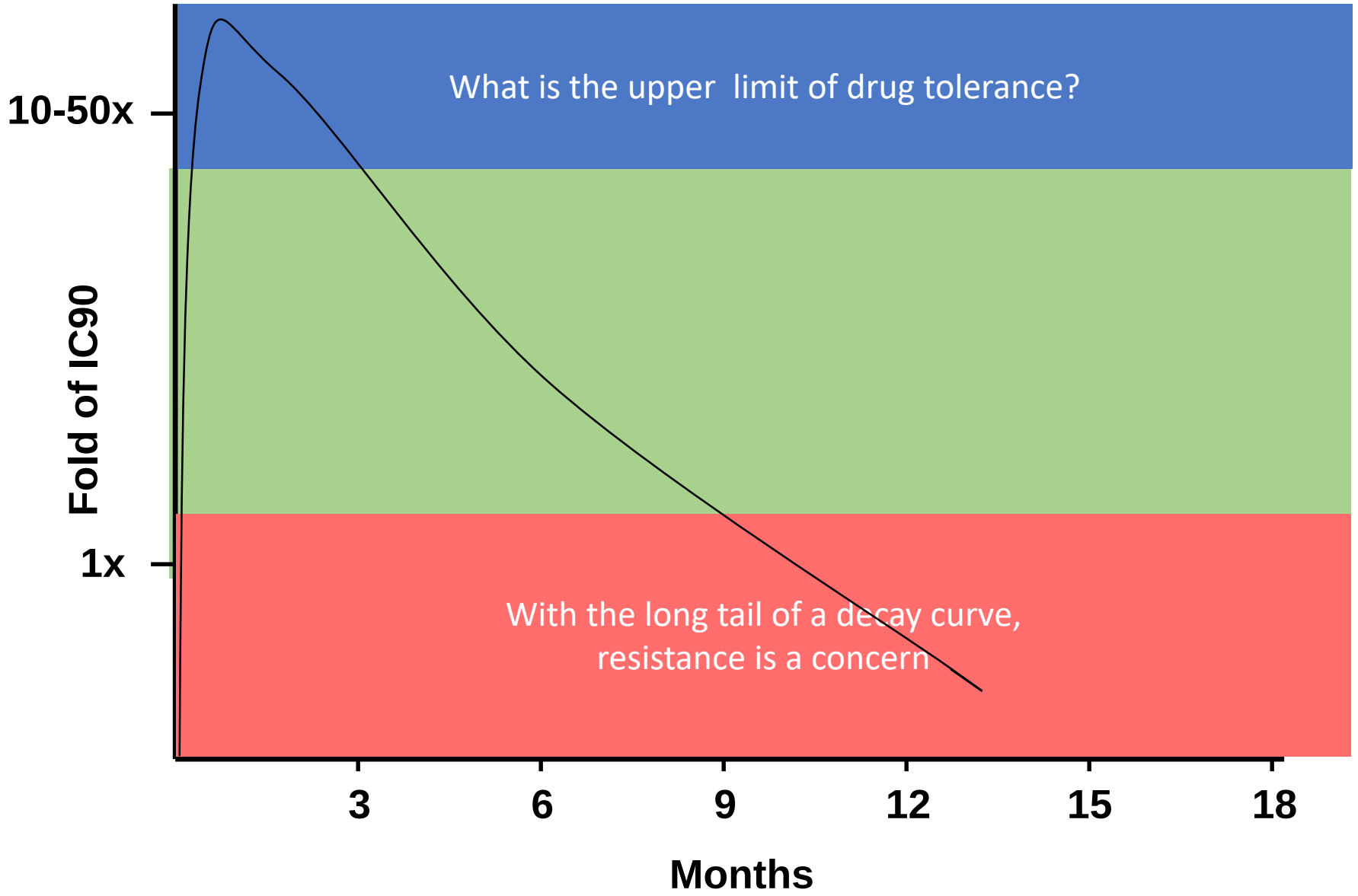
Example: Elimination of Adherence Concerns

- Single dose delivery for post-exposure prophylaxis

Adherence – My Bottom Line

- **Long-acting, sustained-release formulations do not eliminate the adherence challenges, they increase the urgency of getting patients back for redosing**
- **Need to build in a window of time where patients can be safely redosed**

Managing the Safe and Effective Zone with Long Acting Formulations



Pipeline for Prevention and Therapy

HPTN 083 Design

- **Phase 2b/3 trial CAB vs. daily oral TDF/FTC in men and transgender women who have sex with men**
  - Data on CAB activity support two-arm study design
  - Biases and challenges with daily oral tablets require double-blind double-dummy, non-inferiority design in men since a level of TDF/FTC efficacy in MSM can be estimated

- **Primary hypotheses**
  - CAB-based prevention will be non-inferior to a strategy of TDF/FTC-based prevention for HIV-uninfected MSM and TGW

HPTN 084 Design

- **Phase 2b/3 trial CAB vs. daily oral TDF/FTC in men and transgender women who have sex with men**
  - Data on CAB activity support two-arm study design
  - For women a double-blinded, double dummy superiority design has been implemented
- **Primary hypothesis**
  - CAB-based prevention will be superior to a strategy of TDF/FTC-based prevention for HIV-uninfected women

Limitations of Current Clinical Trial Designs

- The FDA is still requiring an oral lead in for all injectable and implantable formulations to evaluate the frequency of serious, early drug reactions

- Long-term transition to initiation of treatment and prevention regimens with administration of the injectable or implantable is essential

Long-Acting Injectable ARVs for Maintenance Therapy

Volume 10 • Number 4 • July 2015 www.co-hivandaids.com

Current Opinion in
HIV and AIDS

Long-Acting Antiviral Agents for HIV Treatment

DA Margolis and M Boffito

Cabotegravir+Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 32 Results

DA Margolis, W Spreen et al.

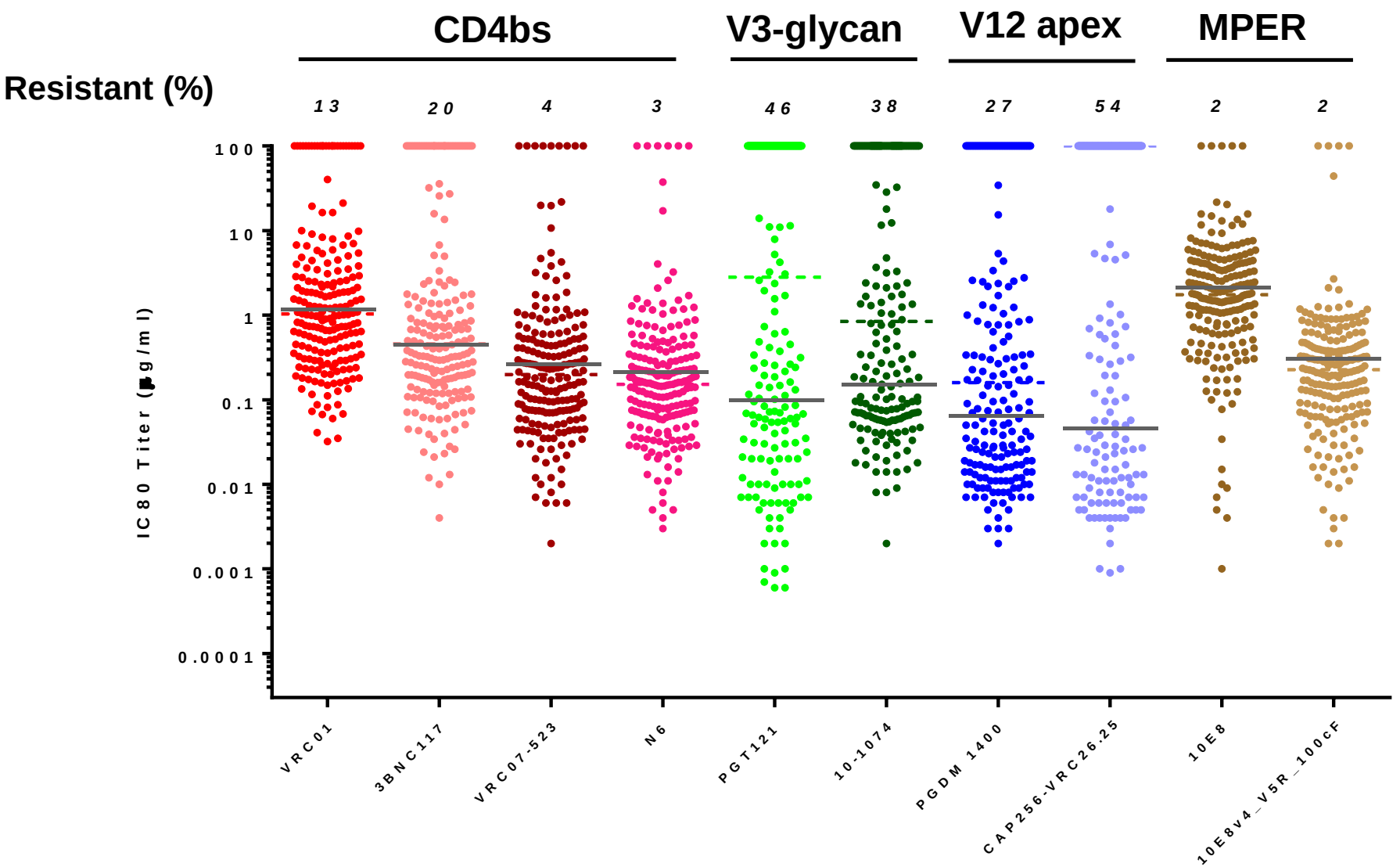
Protocol in Development: ACTG 5357

- Proof-of-concept study of long-acting cabotegravir (integrase inhibitor) + VRC01LS
- Goal: Maintain viral suppression in HIV-infected adults whose virus has been suppressed with conventional ART
- Collaborators: ViiV/GSK, NIAID VRC, DAIDS, ACTG
- Protocol chairs: Babafemi O. Taiwo, M.D., M.B.B.S. (Northwestern), Pablo Tebas, M.D. (Penn)

bNAbs

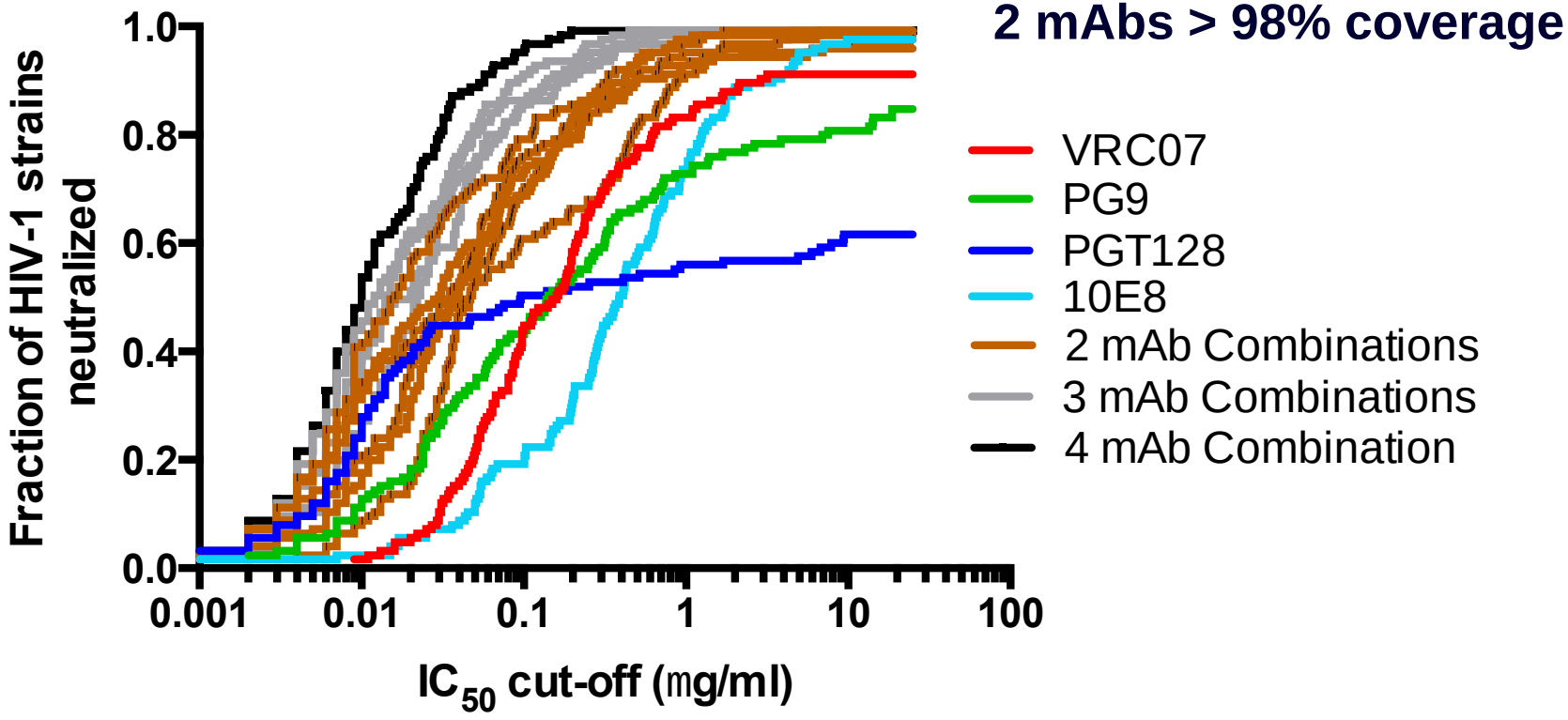
Potency and Breadth of HIV-1 Neutralizing mAbs

Multi-clade virus panel (n=208)



Multi-clade virus panel (n=208)
Bailer, Louder, McKee, Doria-Rose et al.

Broader Coverage: Two Antibodies cover > 98% of Diverse Strains Globally



Comprehensive Antibody - Vaccine Immune Monitoring Consortium

CAVIMC

Kong, Montefiori, Korber et al.
J. Virol (2015)

Passive Antibody Prevention as PrEP
HVTN703/704; HPTN 081/085

AMP = Antibody Mediated Prevention Studies
Phase 2b Efficacy (proof-of-concept)

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults

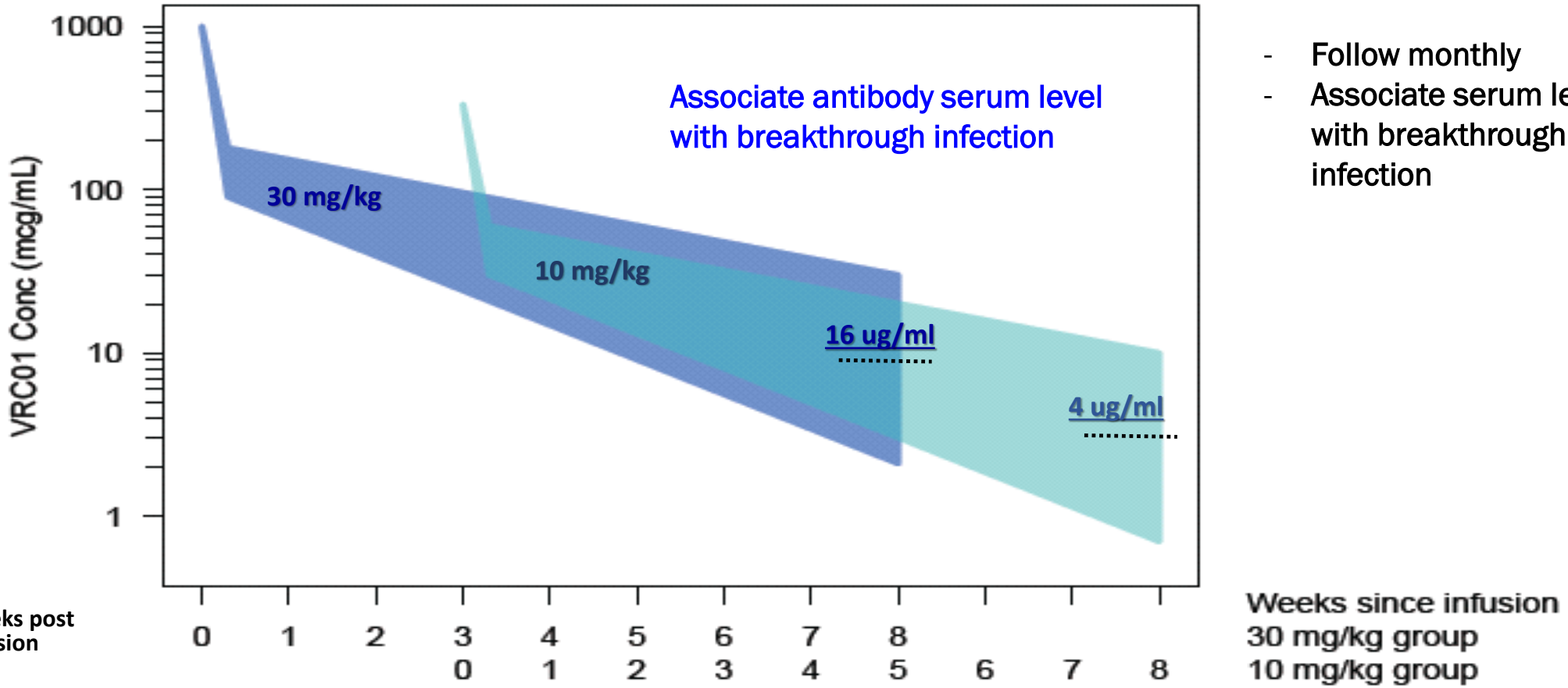
Chairs: Lawrence Corey, HVTN
Myron S. Cohen, HPTN

Co-chairs: Srilatha Edupuganti
Nyaradzo Mgodi

Mike Cohen (HPTN) ← **DAIDS NIAID** → Larry Corey (HVTN)

VRC01 Concentrations Over Time

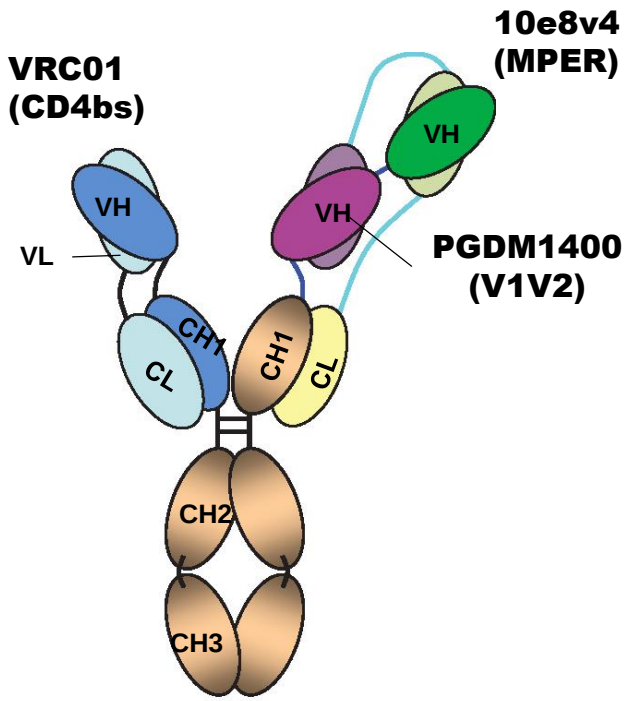
HVTN104: Mayer et al. PLoS Med (2017)



- Follow monthly
- Associate serum level with breakthrough infection

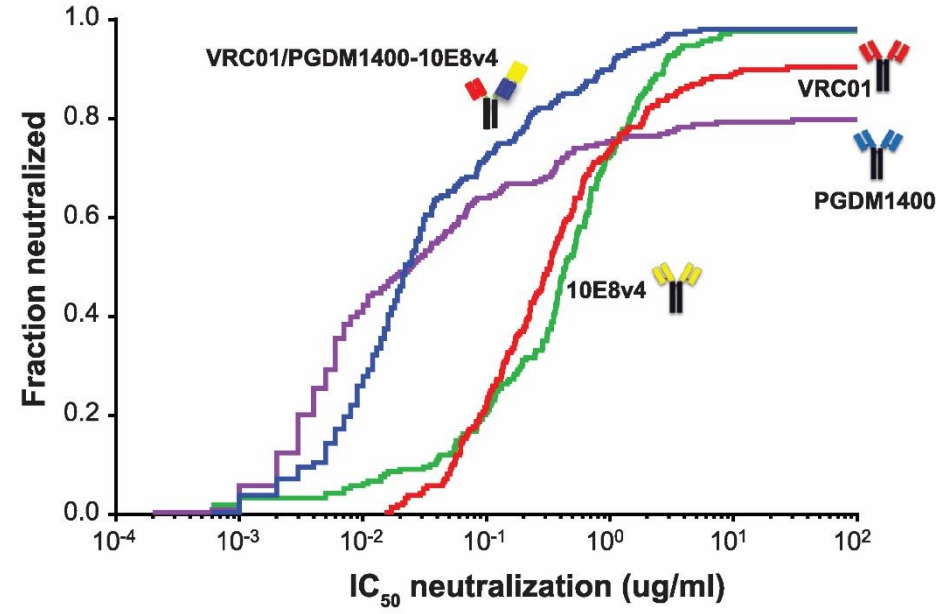
Sanofi/VRC Tri-specific Antibody

CODV-Fab (Sanofi)



- All 3 Fabs active
- Normal IgG PK in macaques
- GMP manufacturing in progress

Potent against 98% of viral strains



- **GMP manufacture: Sanofi**
- **Two Phase ones mid 2018 (VRC/NIAID)**

Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques
Ling Xu1, Amarendra Pegu, Z-Y Yang et al (Science 2017),

Conclusions/Questions

- For long-acting prevention, maintaining and enhancing adherence is essential
- To help address adherence challenges, a range of methods of delivery and duration of coverage will be important
- For prevention, we will see a steady improvement and refinement in products
- For therapy, additional agents need to advance so that LA three drug combinations can be evaluated