Broadly Neutralizing Antibodies Against HIV

Qing Ma

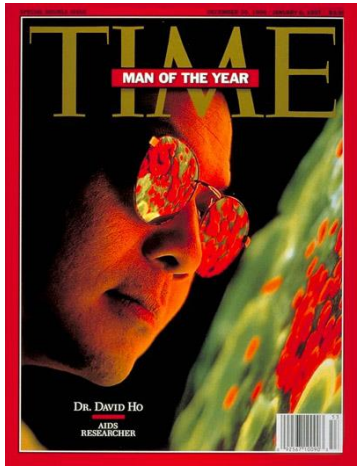
University at Buffalo
School of Pharmacy and Pharmaceutical Sciences

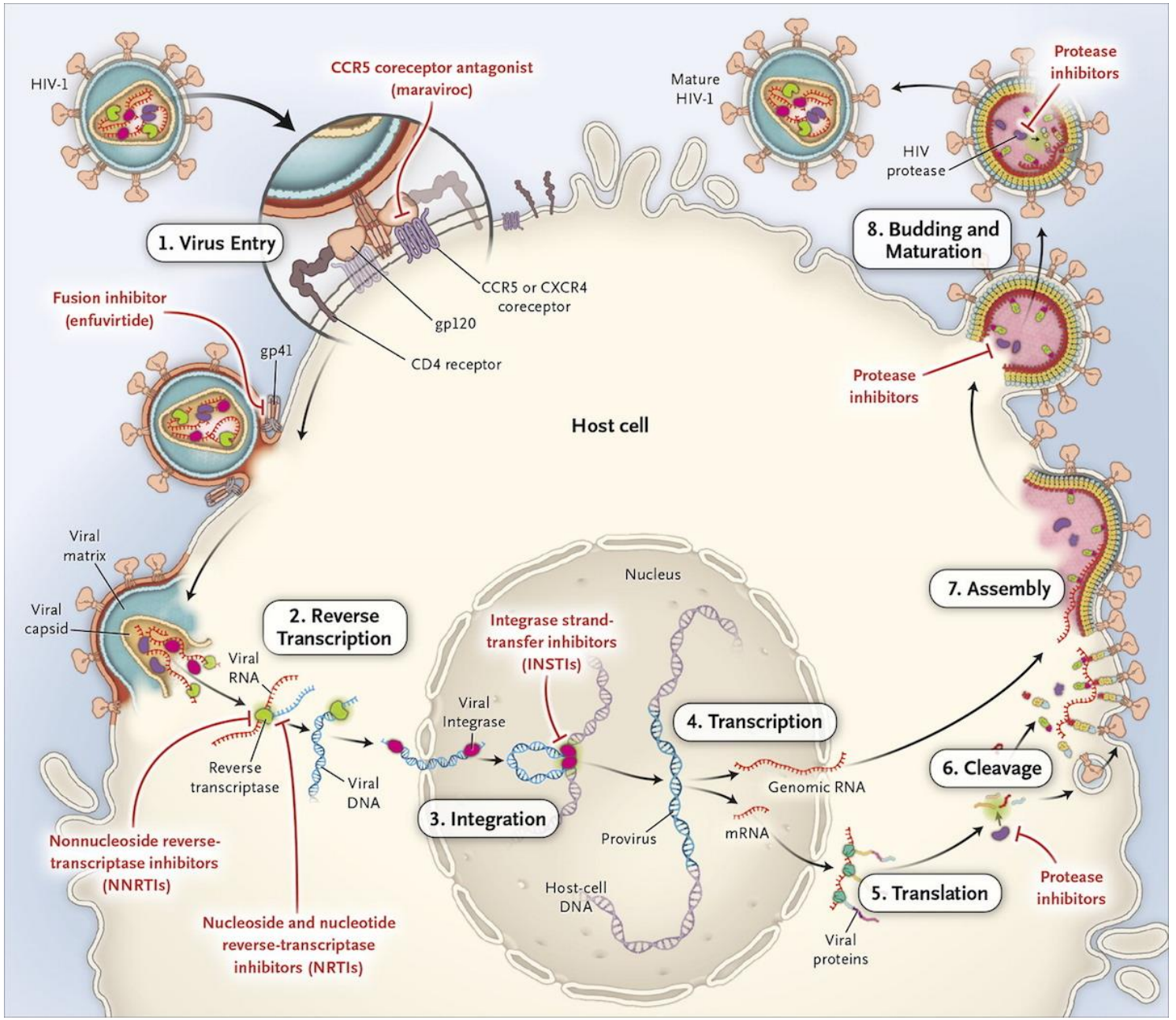
University at Buffalo

Quiz!

- Question 1: Do we have an approved monoclonal antibody against HIV?
- **Answer 1: Yes. Ibalizumab (Trogarzo®, FDA 2018, EMA 2019)**
- Question 2: Is it commonly used?
- **Answer 2: Maybe not. It was approved as an orphan drug.**
- Question 3: is it a broadly neutralizing antibody (bNAb)?
- **Answer 3: No.**
- Question 4: so what are broadly neutralizing antibodies?
- **Answer 4: …**

HIV Life Cycle





https://www.hiv.uw.edu/go/antiretroviral-therapy/general-information/core-concept/all#antiretroviral-regimens-initial-therapy

FDA Approval of HIV Medicines

1981: First AIDS cases are reported in the United States.

'85-'89

1987
Zidovudine (NRTI)

'90-'94

1991
Didanosine (NRTI)

1992
Zalcitabine (NRTI)

1994
Stavudine (NRTI)

'95-'99

1995
Lamivudine (NRTI)
Saquinavir (PI)

1996
Indinavir (PI)
Nevirapine (NNRTI)
Ritonavir (PI)

1997
Combivir (FDC)
Delavirdine (NNRTI)
Nelfinavir (PI)

1998
Abacavir (NRTI)
Efavirenz (NNRTI)

1999
Amprenavir (PI)

'00-'04

2000
Didanosine EC (NRTI)
Kaletra (FDC)
Trizivir (FDC)

2001
Tenofovir DF (NRTI)

2003
Atazanavir (PI)
Emtricitabine (NRTI)
Enfuvirtide (FI)
Fosamprenavir (PI)

2004
Epzicom (FDC)
Truvada (FDC)

'05-'09

2005
Tipranavir (PI)

2006
Atripla (FDC)
Darunavir (PI)

2007
Maraviroc (CA)
Raltegravir (INSTI)

2008
Etravirine (NNRTI)

'10-'14

2011
Complera (FDC)
Nevirapine XR (NNRTI)
Rilpivirine (NNRTI)

2012
Stribild (FDC)

2013
Dolutegravir (INSTI)

2014
Cobicistat (PE)
Elvitegravir (INSTI)
Triumeq (FDC)

'15-'19

2015
Evotaz (FDC)
Genvoya (FDC)
Prezcobix (FDC)

2016
Descovy (FDC)
Odefsey (FDC)

2017
Juluca (FDC)

2018
Biktarvy (FDC)
Cimduo (FDC)
Delstrigo (FDC)
Doravirine (NNRTI)
Ibalizumab-uiyk (PAI)
Symfi (FDC)
Symfi Lo (FDC)
Symtuza (FDC)
Temixys (FDC)

2019
Dovato (FDC)

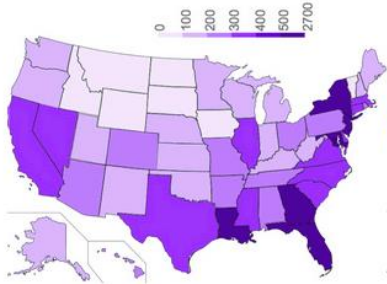
Drug Class Abbreviations:
CA: CCR5 Antagonist; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor; **PAI:** Post-Attachment Inhibitor

AIDSinfo

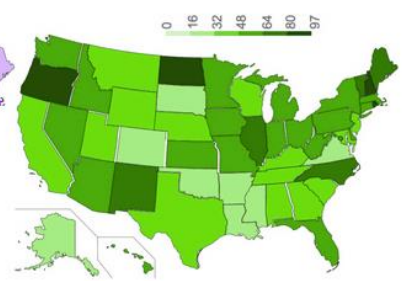
Note: Drugs in gray are no longer available and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.

The aging HIV population: new challenges and market opportunities

HIV DIAGNOSED PER 100K POPULATION



HIV DRUG TREATED PERCENTAGE



944,000
HIV Diagnosed

49%
HIV Patients over 50 yrs old

57%
Drug treated

HIV: from a devastating epidemic to a manageable chronic disease (WHO 2017)

MedicineToday 2014; 15(2): 16-26
PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

HIV infection as a chronic disease

Optimising outcomes

DAVID BAKER MB ChB, DCH, Dip Med (Sexual Health); **CATHY PELL** MB BS(Hons), MM(Sexual Health), FAChSHM; **BASIL DONOVAN** MD, FAChSHM, FAFPHM, FRCPI

Key points

- The rate of new HIV infections is increasing so all practitioners need to consider 'could this be HIV?'
- Life expectancy for people living with HIV infection can approach that of the general population.
- Current management focuses on treating HIV as a chronic disease.
- Most patients need lifelong treatment with antiretroviral therapy (ART).
- Improvements in ART mean that patients can expect a simple regimen with few or no side effects.
- Guidelines for preventive care of other health problems are similar to those for the general population.

Provided they receive regular care, the life expectancy of patients newly diagnosed with HIV infection in the developed world can approach that of the general population. For most people this will mean lifelong daily medication with a combination of antiretroviral drugs.

The success of antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection into a manageable chronic disease. The life expectancy for a patient newly diagnosed with HIV infection in the developed world can approach that of the general population provided they receive regular care. For most people this will mean lifelong daily medication with a combination of antiretroviral drugs. This article reviews the long-term monitoring and management of people with HIV infection and discusses the role of the GP in this care.

WHO HAS HIV IN AUSTRALIA?

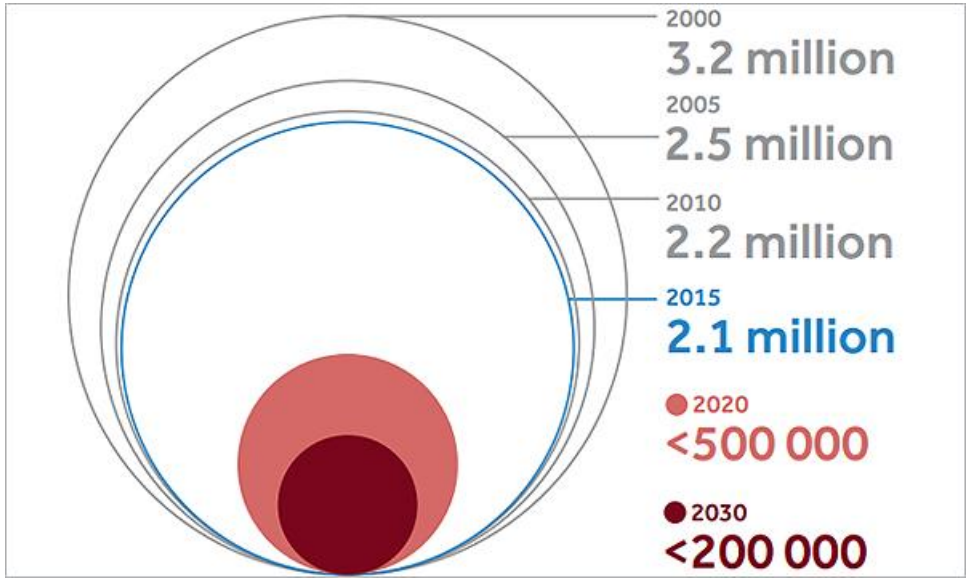
More than 25,000 people are living with HIV in Australia, with approximately 1250 new infections per year.[1] In 2012, the average age of people newly diagnosed with HIV infection was 37 years, and about 86% were male; most infections are in men who have sex with men (MSM).[2] The number of new infections has been steadily increasing since 1999, and the rate of HIV diagnosis in 2012 was 5.4 per 100,000 population (Figure 1).[1] The cumulative total of cases of HIV infection reported in Australia to the end of September 2012 is 32,578, and 10,859 of these progressed to acquired immunodeficiency syndrome (AIDS), with 6852 deaths.[2]

Many patients who became infected with HIV in the 1980s have survived and are now ageing and presenting with increasing comorbidities that require comprehensive care from a range of practitioners.

WHAT ARE THE MAJOR CAUSES OF MORTALITY?

With improved treatment (antiretroviral therapy [ART]), fewer patients living with HIV are experiencing AIDS and related mortality. For more

Dr Baker is a GP in Sydney, NSW, and medical advisor to the Australasian Society for HIV Medicine. Dr Pell is Director at Taylor Square Private Clinic, Sydney, NSW. Professor Donovan is Senior Specialist at Sydney Sexual Health Centre, Sydney Hospital, and Professor and Head of the Sexual Health Program at The Kirby Institute, University of New South Wales, Sydney, NSW.

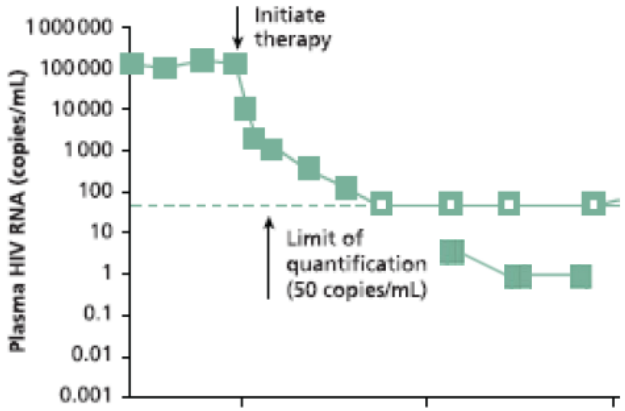


World Health Organization

Initiation of ART is associated with . . .

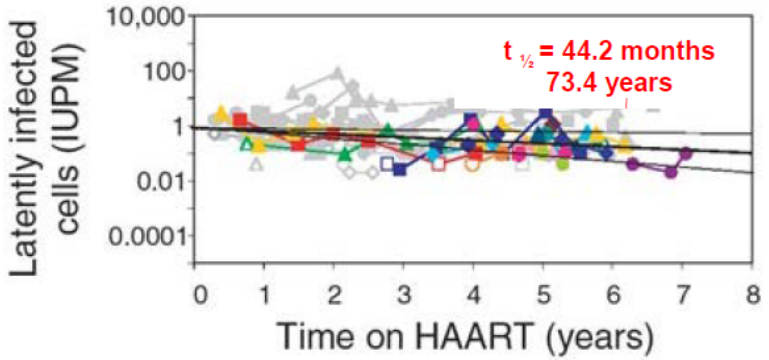
1. Dramatic drop in plasma RNA[1]

- 10,000-50,000-fold decrease in first months
- Below limits of detection of commercial assays

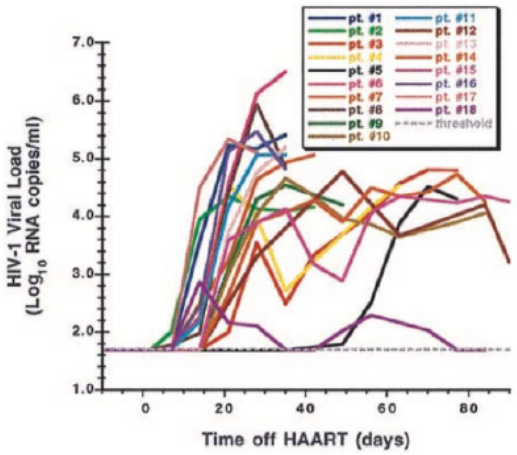


HIV RNA by single copy assay (SCA)

2. Persistence of HIV in memory CD4 cells[2] (latent reservoir)



3. Long-lived HIV latent reservoir leads to HIV rebound when ART is stopped



[1]Siliciano R, Top HIV Med, 2010;
[2]Siliciano J et al, Nature Med, 2003;
[3]Davey RT et al, PNAS, 1999

From: R. Gandhi ACTG Cure

CURE Transformation Science Group (TSG)

- One of the major TSG in AIDS Clinical Trial Group (ACTG https://actgnetwork.org/)
- Mission: **CURE** through "sterilizing cure" or "functional cure"

Fully characterize the HIV reservoirs in blood and tissues

Understand by what means people have been cured

Identify the most promising new therapies: broadly neutralizing antibodies

Current CURE TSG Organizational Structure

Pablo Tebas
Chair

Marina Caskey
Vice Chair

28 Investigators + Other Representatives

- Virologists
- Clinicians
- Immunologists
- DAIDS, DMC, SDAC
- Pharmacologists
- Community

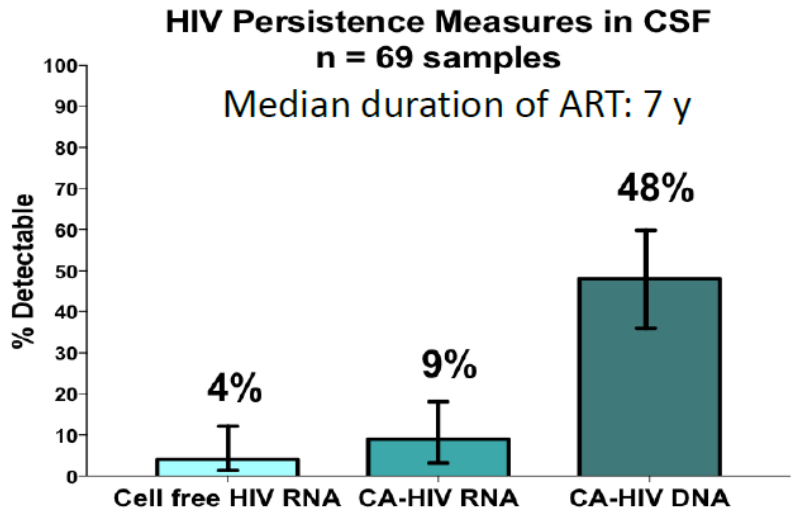
Cure Research Goal #1: Define and Measure the HIV Reservoir

HIV reservoir: population of cells that harbor HIV and the lead to viral rebound when ART is stopped

From: R. Gandhi ACTG Cure

Other Challenges in Measuring HIV Persistence: HIV in Cerebrospinal Fluid

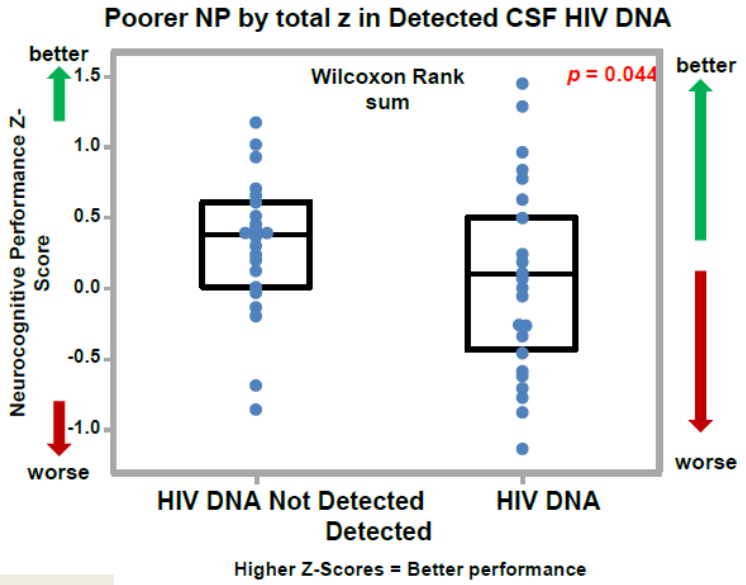
HIV DNA Persists in CSF in Half of Those on Long-term ART



Boxes indicate % positive; bars represent 95% confidence intervals

CA: cell-associated

Participants with CSF HIV DNA have worse neurocognitive performance



NP: neurocognitive performance

Is HIV in CSF replication competent? Legacy effect?

Spudich S, Robertson K et al, JCI, 2019

From: R. Gandhi ACTG Cure

Quiz 2

Timeline

1995:

Brown was diagnosed with HIV in 1995 while studying in Berlin, Germany.

2007:

In 2007 he underwent a procedure known as hematopoietic stem cell transplantation to treat leukemia (performed by a team of doctors in Berlin, Germany, including Gero Hütter).

2010:

He chose to come forward in late-2010.

2012:

In July 2012, Brown announced the formation of the Timothy Ray Brown Foundation in Washington, DC, a foundation dedicated to fighting HIV/AIDS.

Cure Research Goal #2: Evaluate interventions to reduce/control HIV

Early ART

Inducing HIV expression (latency reversal)

Enhancing immunity (anti-PD-1, bNAbs*)

* bNAbs: Broadly neutralizing antibodies

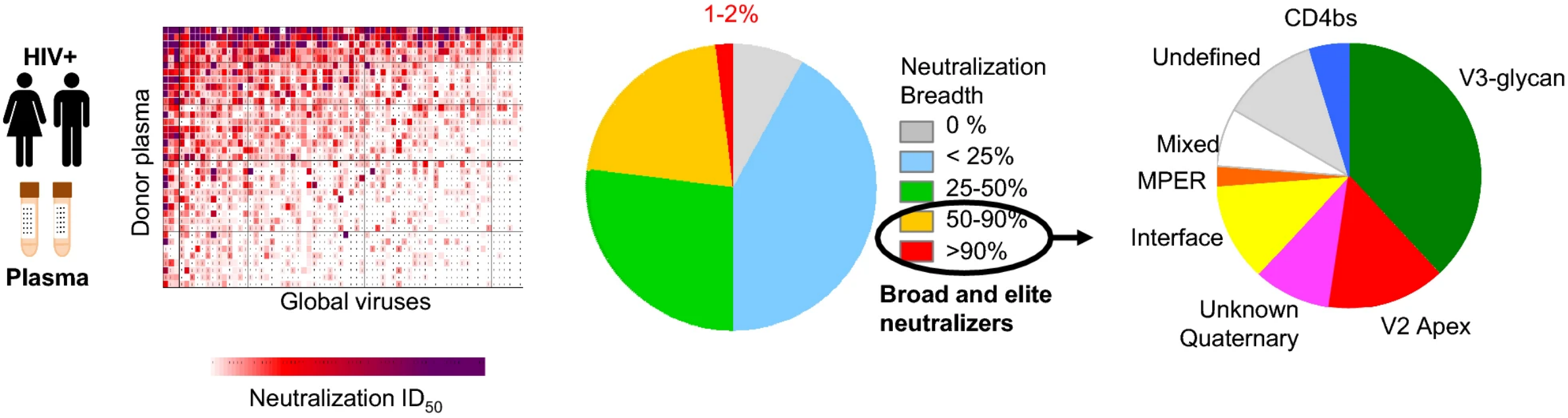
From: R. Gandhi ACTG Cure

bNAb Pharmacology: Three Concepts

- Breadth
- Potency
- Fc receptor modification

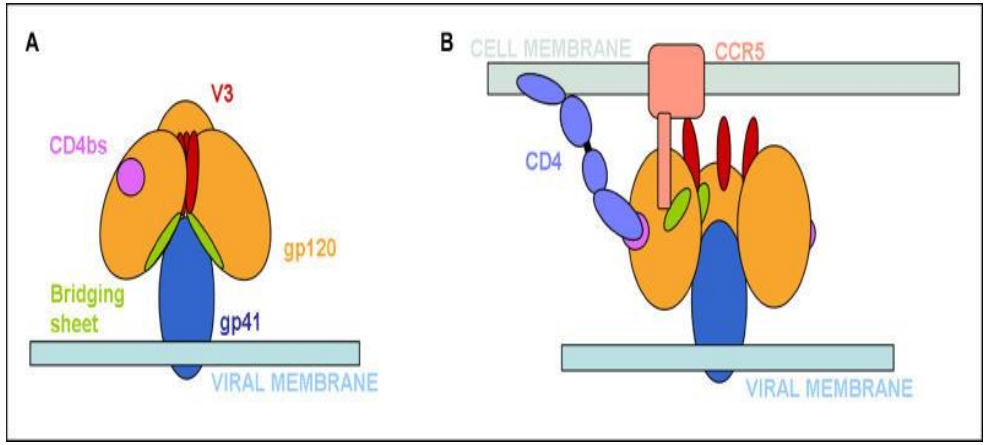
Identifying bNAbs from Elite Neutralizers

Screening of plasma for breadth → Classification of broad neutralizers → Mapping the targets of bNAbs

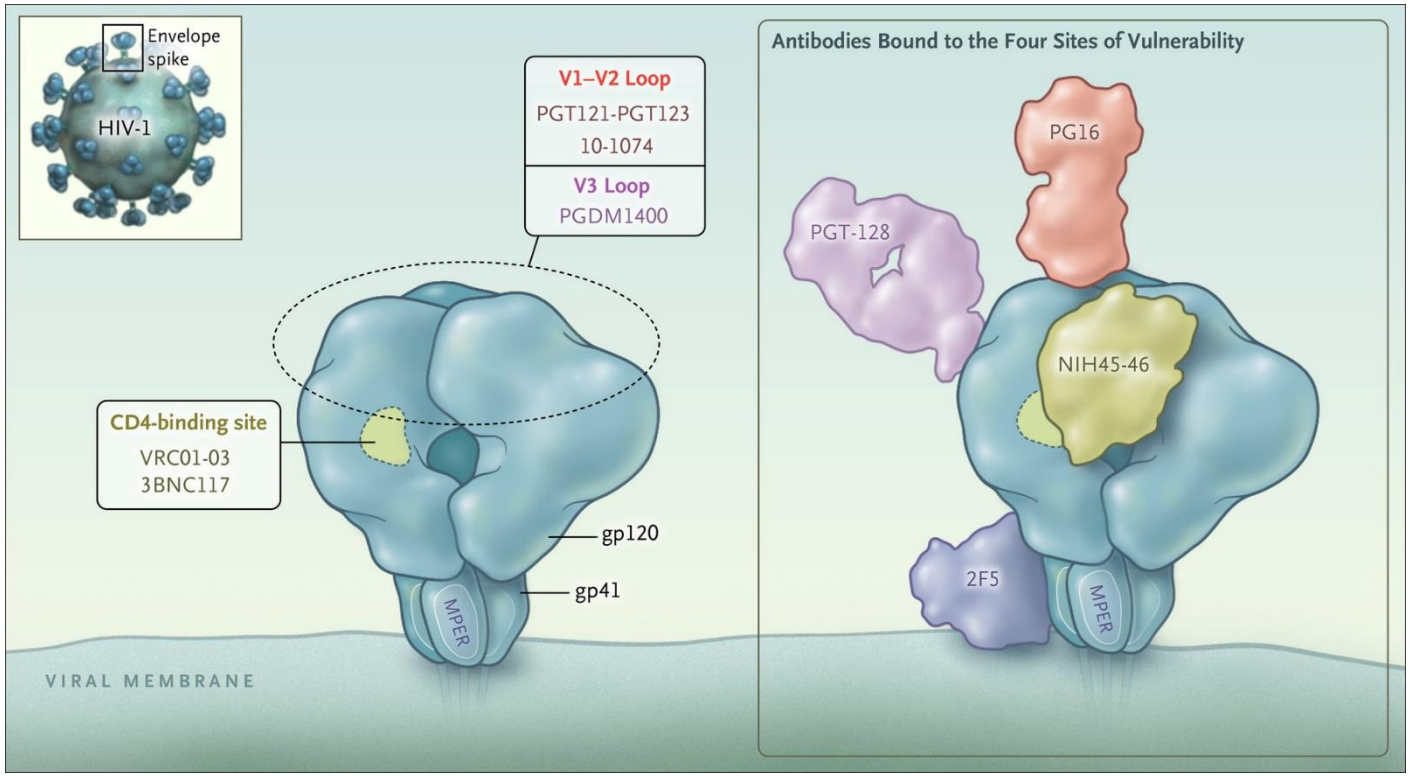


Landais E, Moore PL. Retrovirology. 2018; 15: 61.

Sites Identified as Targets for bNAbs

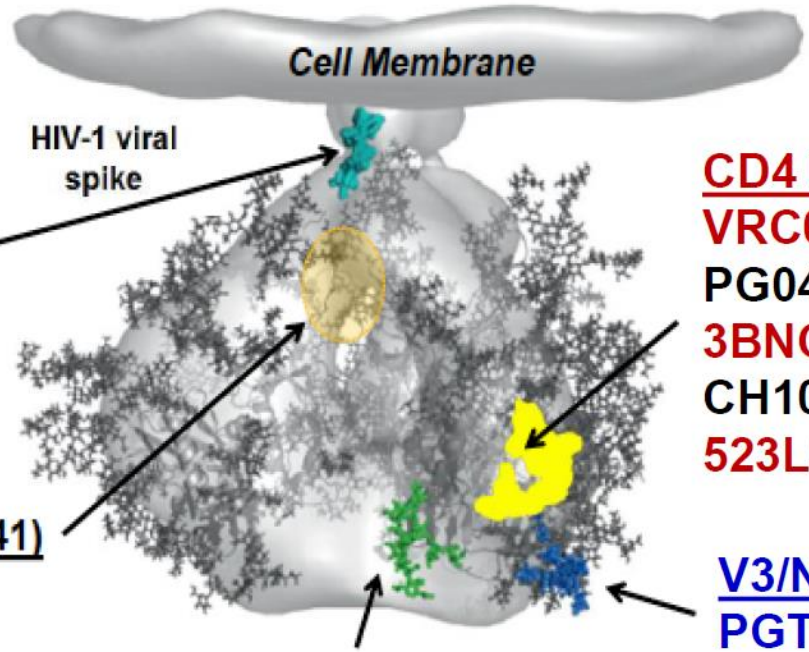


Zanetti G. Cryo-Electron Tomographic Structure of an Immunodeficiency Virus Envelope Complex *In Situ*. PLoS Pathog. 2006 Aug; 2(8): e83.



Caskey M, Klein F, Nussenzweig MC. N Engl J Med 2016; 375:2019-2021

Broadly Neutralizing Antibodies



Gp41 MPER:
2F5, 4E10, 10E8, 10E8v4 V2

CD4 Binding Site:
VRC01, VRC01 LS, PG04, CH31, 3BNC117, 12A12, CH103, VRC07-523LS, N6

Trimer (gp120/41)
8ANC195
PGT151
35022

V3/N332 Glycan Supersite
PGT121, PG128
10-1074

V1V2 Glycan:
PG6, PG9 (GS-9277), GSPG16, CH01-04, PGT 141-145, PGMD1400, CAP259-VRC26.25

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups

Adapted from Mascola, CROI 2017

2019 bNAb Update

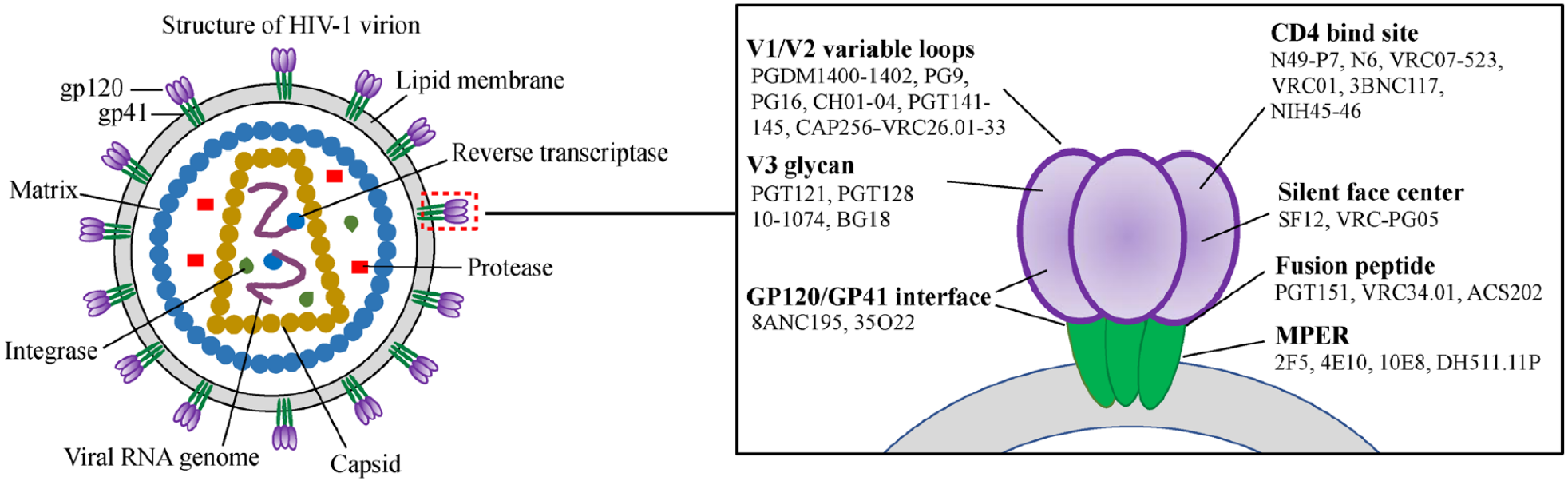
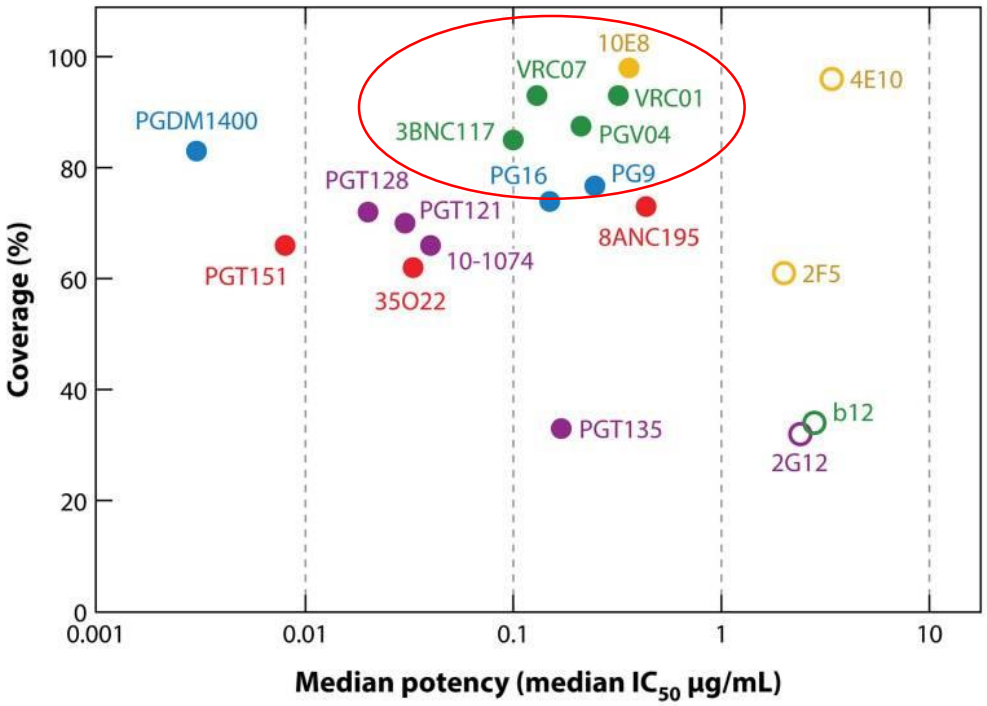


Fig. 1 Schematic diagram of HIV-1 and epitopes for bNAbs on trimeric HIV envelope spike glycoproteins.

Wang Q, Zhang L. Broadly neutralizing antibodies and vaccine design against HIV-1 infection. *Front Med* 2019.

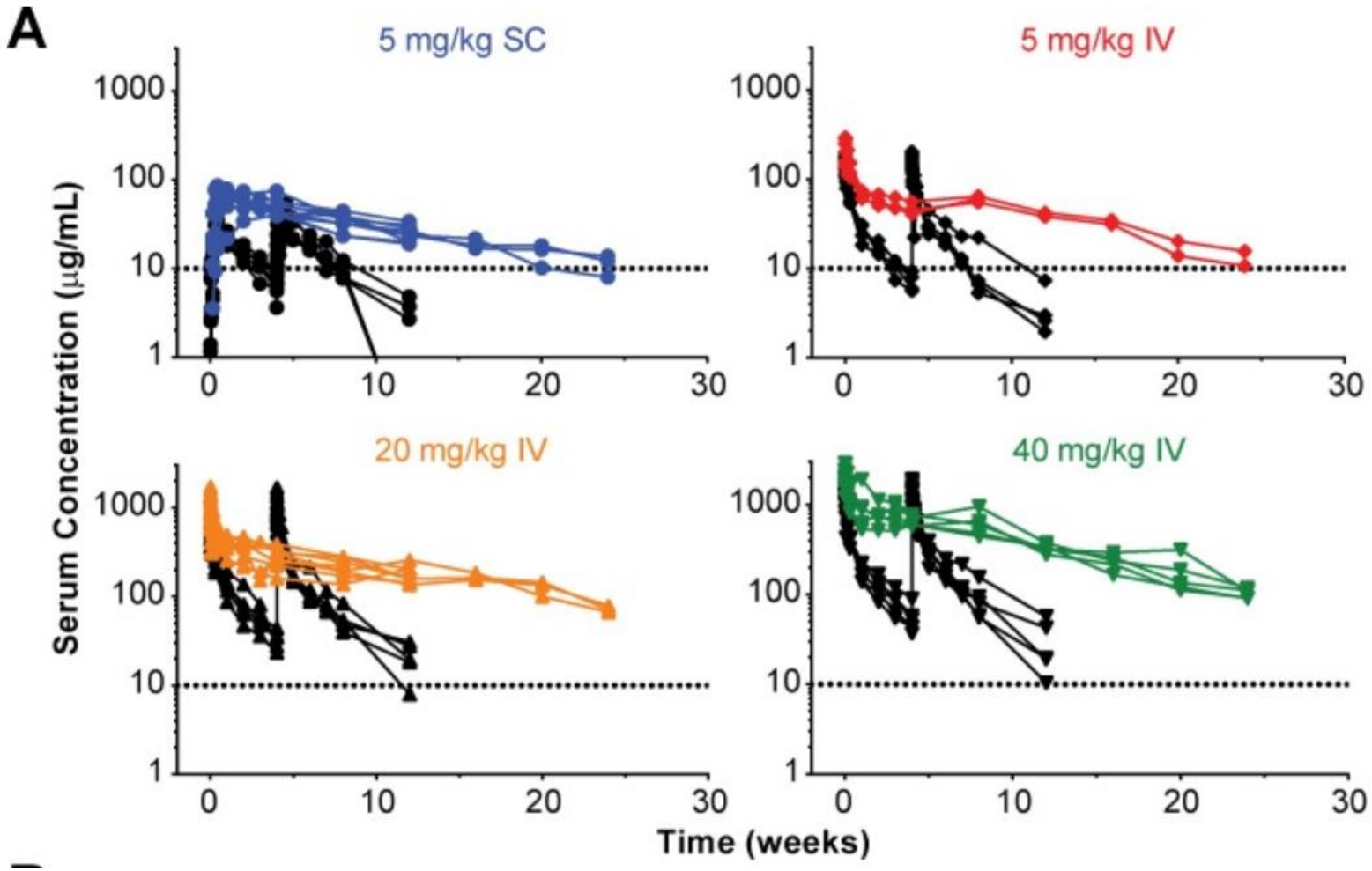
Broadly Neutralizing Assay: A Translational Target For Dose Finding to Balance Potency and Coverage

- *In vitro* assay reflecting cell free virus neutralization
- bNAb dose escalation studies in animals utilize serum concentration decay profiles to identify a "target" concentration for clinical studies
- Does this "target" concentration vary?
  - Preventing HIV infection
  - Treatment to lower HIV viral load
  - Sustaining viral suppression following ART interruption, *i.e.*, analytic treatment interruption (ATI)
  - Reducing latent viral reservoir following latency reactivation



Burton DR, Hangartner L. Broadly Neutralizing Antibodies to HIV and Their Role in Vaccine Design. Ann Rev Immunol. 2016; 34: 635–659.

Fc Modification – VRC01 to VRC01LS



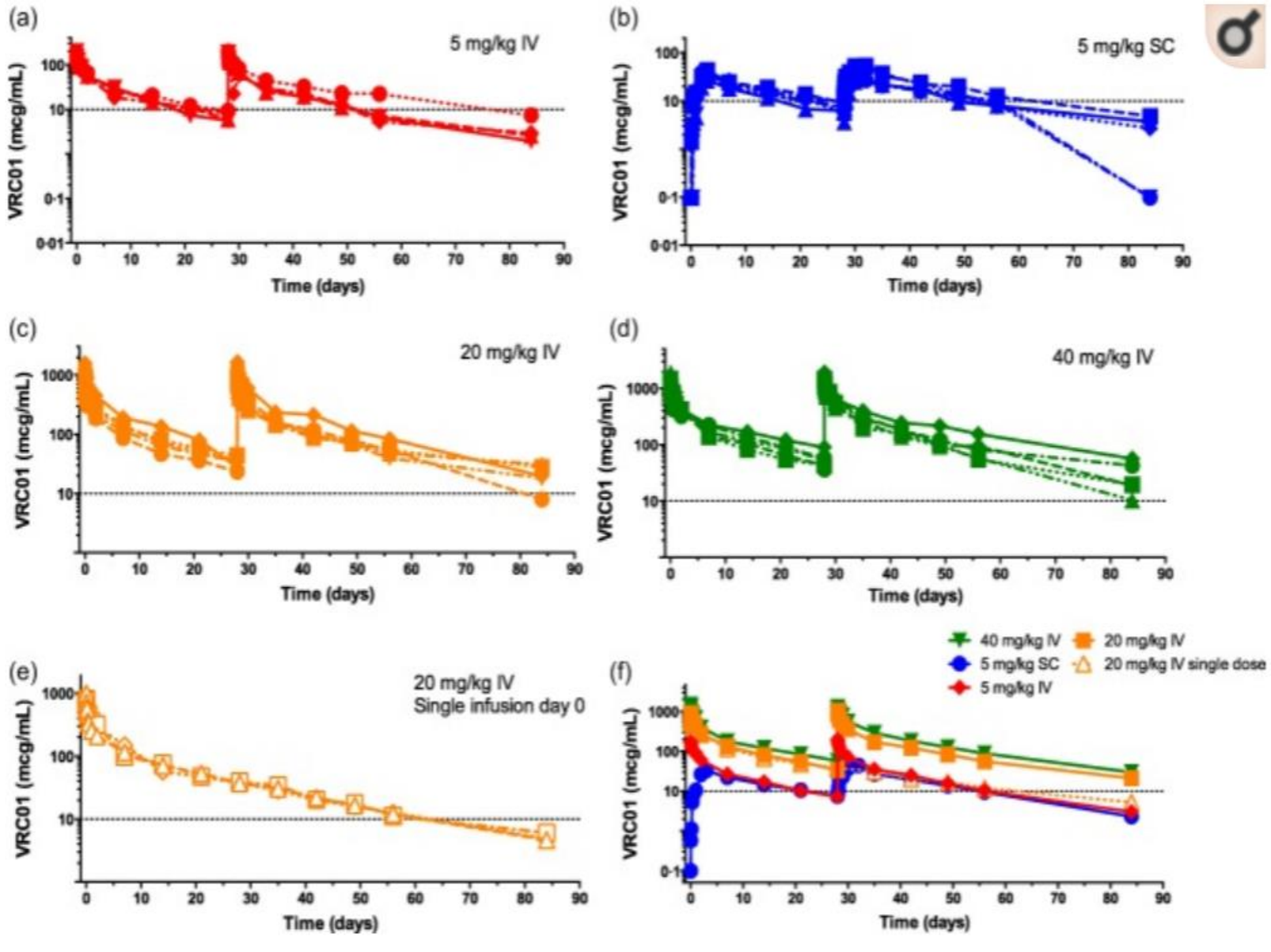
- Fc modification M428L/N434S yields VRC01LS
- Reduced cellular degradation results in prolonged serum half-life
- Altered clinical pharmacology leads to longer period of viral suppression post-ATI.

Gaudinski MR, et al. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults. PLoS Med. 2018 Jan 24;15(1):e1002493.

Lessons Learned from bNAb Trials

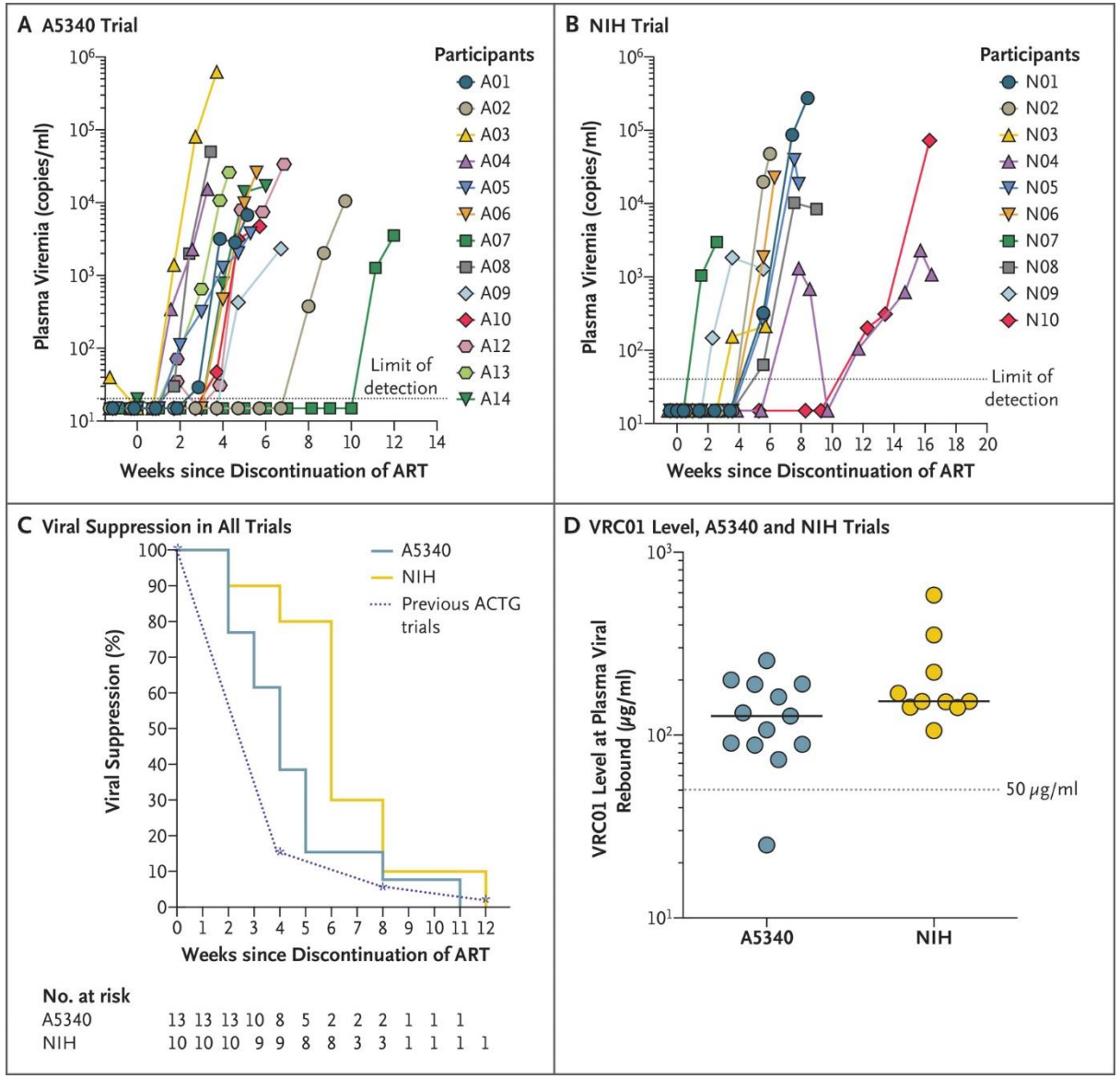
- Viral rebound following first generation bNAbs
- Viral rebound following a single bNAb
- Viral rebound following dual bNAbs

First Generation bNAb: VRC01 in Healthy Adults



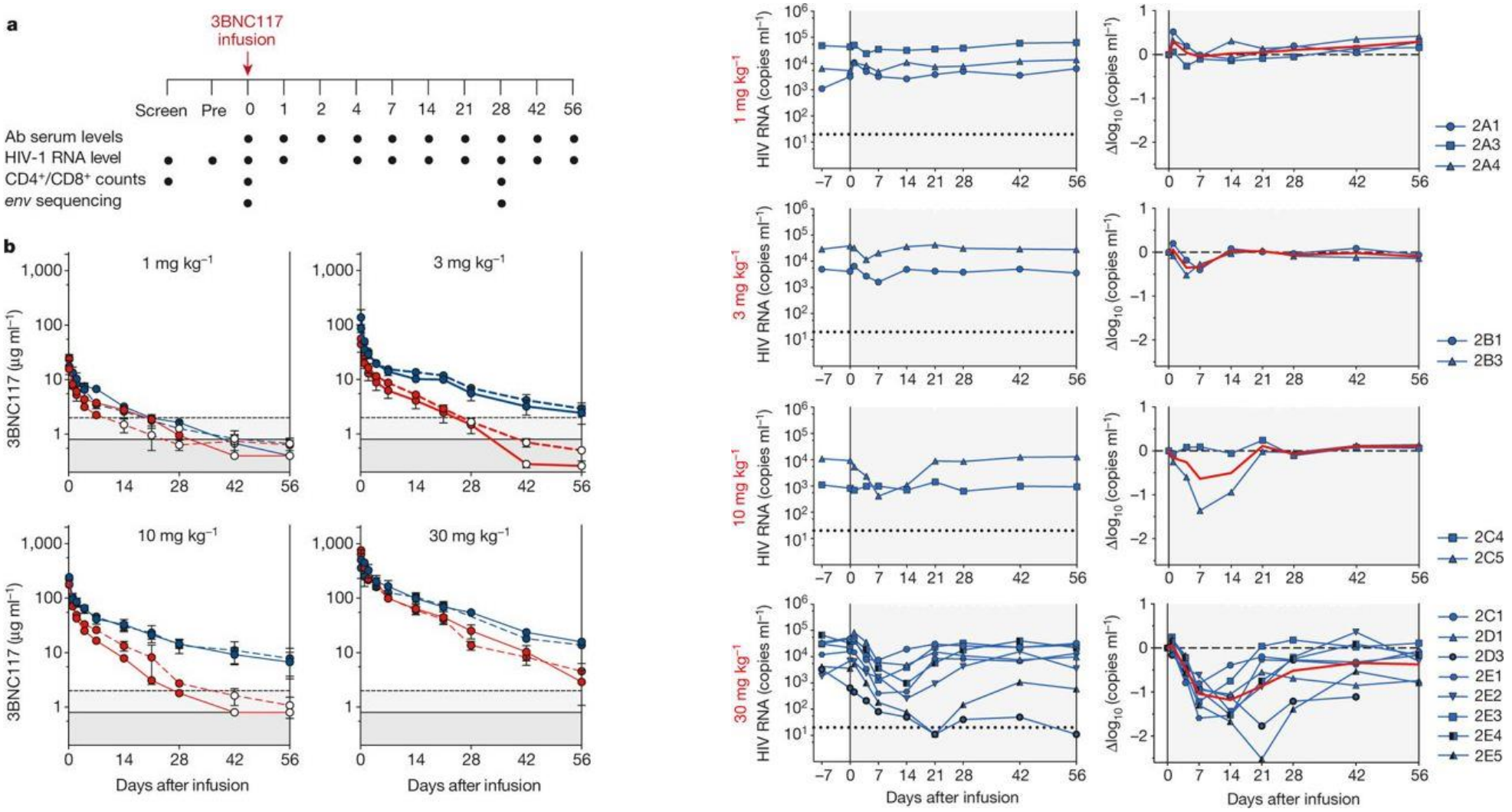
Ledgerwood JE, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. Clin Exp Immunol. 2015 Dec;182(3):289-301

Viremia and VRC01 Concentrations after ART Discontinuation



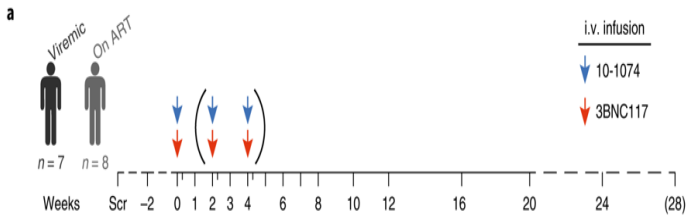
Bar KJ et al. Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption. N Engl J Med 2016; 375:2037-2050

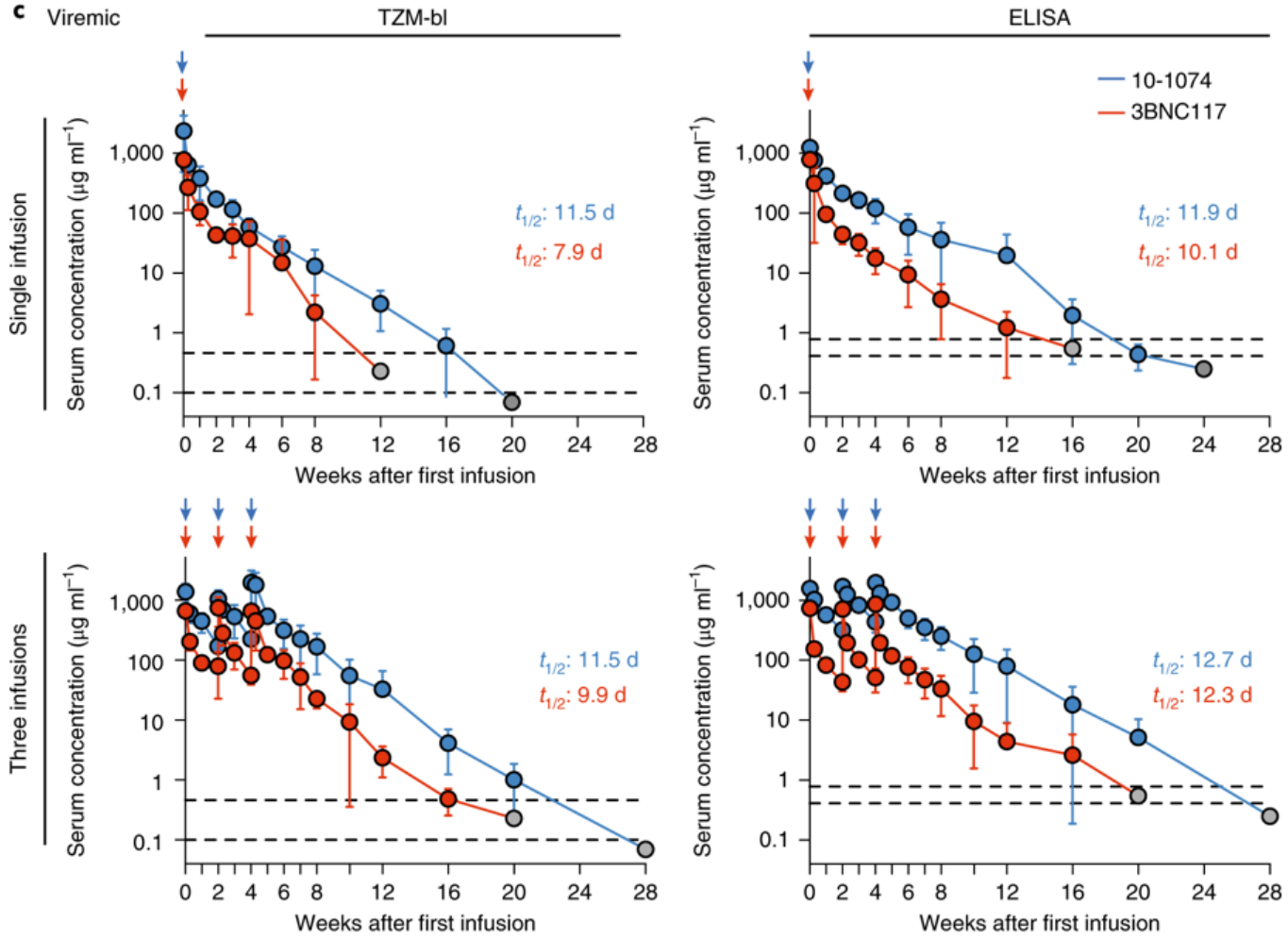
Single bNAb: 3BNC117 PK/PD



Caskey M, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature 2015, 522, 487–91.

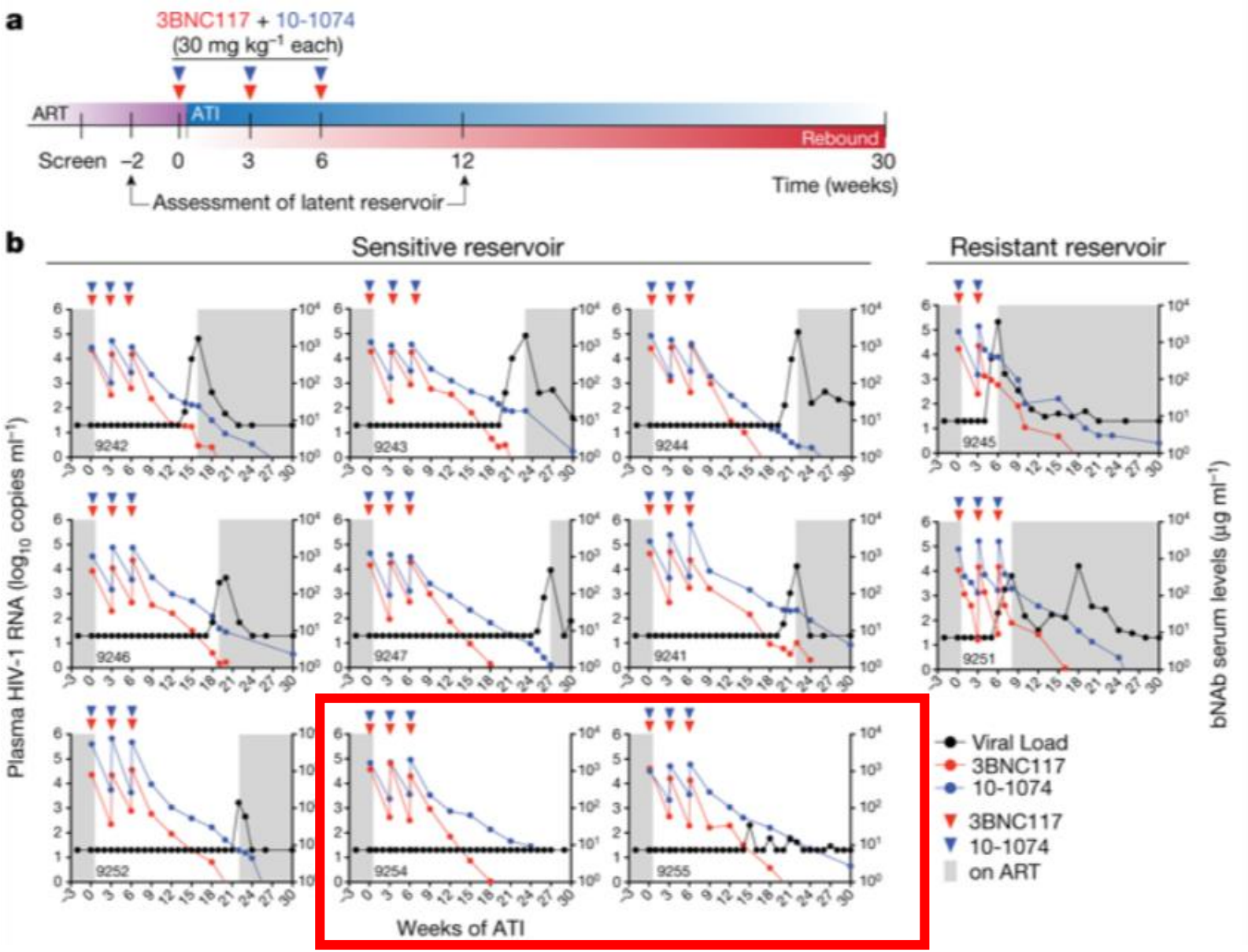
Dual bNAb Pharmacokinetics: 3BNC117 and 10-1074





Bar-On Y et al. Safety and antiviral activity of combination HIV-1 broadly neutralizing antibodies in viremic individuals. Nature Med 2018, 24, 1701–7

Dual bNAb: 3BNC117 + 10-1074 PK/PD



Mendoza P, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature 561, 479–484 (2018)

ACTG bNAb Trials: Coming Soon

- A5364: Phase I Study of Safety and Ability of 3BNC117-LS and 10-1074-LS in Combination to Durably Prevent Viral Relapse During a Monitored Analytical Treatment Interruption
- A5386: IL-15 Superagonist (N-803) with and without Combination Broadly Neutralizing Antibodies (VRC07-523LS and 10-1074)
- A5387: Phase I Study to Evaluate the Effect of PGT121.BIJ414.LS and VRC07-523LS in Combination with TLR9 agonist Lefitolimod on the HIV Reservoir and on Viral Rebound after ATI in Participants with HIV
- A5388: A Randomized Clinical Trial of Combination HIV-Specific Broadly-Neutralizing Monoclonal Antibodies (PGT121.BIJ414.LS and VRC07-523LS) Combined with ART Initiation during Acute HIV Infection to Induce HIV Remission
- A5389: Study to Evaluate Effect of Two bNAbs on HIV rebound PGT121.BIJ414.LS and VRC07-523LS)
- A5390: ATI in Participants Who Received VRC01 or Placebo and Became HIV-Infected During the AMP Studies (non-interventional)

bNAbs: Challenges and Opportunities

- Challenges
  - Need more research in understand optimal combinations as ART development
  - bNAbs might not be accessible to sanctuary sites, such as brain
- Opportunities
  - Strategies for immune enhancement, *e.g.*, bNAbs, expanded
  - New approaches including combinations are moving into clinical trials

Acknowledgements

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There is no buffalo in Buffalo…