PxWire A Quarterly Update on HIV Prevention Research | Vol. 8 No. 2 | April–June 2015 | AVAC Global Advocacy for HIV Prevention

Antibodies

What is it?

- Passive immunization is the transfer of pre-made antibodies to a person. Passive immunization using today's pre-made antibodies can involve infusion delivered in a clinic setting over a period of 30 minutes or more.
- An alternative approach using vectors and genes that can be turned into 'antibody factories' within the body is also under investigation.
- Both infusion and gene therapy approaches differ from immunization with vaccines that teach the body how to make its own defenses.

What could it do?

- Laboratory-made broadly neutralizing antibodies (bNAbs) against HIV could provide protection against infection in HIV-negative people.
- It might be possible to formulate these bNAbs so that a single dose could provide protection for months at a time.
- Testing bNAbs for HIV prevention can also provide proof-of-concept for developing HIV vaccine candidates.
- This strategy is being considered used for prevention of HIV acquisition in adults and/or breastfeeding infants.
- It is also being explored as a treatment modality and perhaps as part of a cure strategy to eliminate viral reservoirs.

Key Facts

- bNAbs are isolated from the blood of people living with HIV. A handful of individuals make these potent immune responses.
- The most potent bNAbs come from months of co-evolution with virus during chronic infection. They have unique characteristics.
- Some have atypically long regions in the CDR43 loop—a portion of the "arms" of the Y-shaped antibody protein. Others undergo a lengthy process of maturation to become potent against HIV. It will take a long time to create vaccines that elicit such responses.

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Product Name(s)	Phase of Research	Research Description	HIV Status of Population	Class of Drug	Location
Antibodies*					
3BNC117	Phase I	• Phase I trial in HIV-negative people and people living with HIV looking at safety, tolerability and virologic impact associated with different doses found safety in all groups and sustained viral load reductions at the highest dose. Further treatment and prevention studies are planned.	− +	Broadly neutralizing antibody	Germany, US
AAV vector encoding PG9 antibody	Phase I	• Ongoing Phase I trial is establishing safety and optimal doses of a gene-therapy approach to passive immunization.	−	Broadly neutralizing antibody	UK
CAP256-VRC26	Pre-clinical	• Targeting the V1V2 binding site in development for treatment and prevention, currently in preclinical phase.	N/A	Broadly neutralizing antibody	South Africa
Ibalizumab (TMB-355)	Phase I, II	• Ibalizumab has completed Phase I and II trials in HIV-negative individuals and people living with HIV. It is currently available for treatment (as part of combination therapy) via compassionate access programs.	− +	Monoclonal antibody targeting the CD4 binding site	US
PGT121	Pre-clinical	• Targets the V3 region of gp120 and has shown potency in reducing viral load in SIV-infected non-human primates. It is being developed as a possible treatment and/or a component of a cure strategy for people living with HIV.	N/A	Broadly neutralizing antibody	US
VRC01	Phase I	• Targets the gp120 binding site recently being evaluated in a dose escalation study looking at safety, acceptability, PK and PD in people living with HIV. Preliminary results have been reported showing an impact on viral load. • HVTN 104 is phase 1 trial evaluating safety and drug levels of this antibody in HIV-negative adults. Concept note for follow-on efficacy trial has been developed. • Phase I saftey trial in infants is also being explored. Planned treatment trials will look at VRC01 + ART in acute infection. Additional trials in HIV-positive and -negative individuals are planned.	− +	Broadly neutralizing antibody	US

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Long-Acting Injectable (LAI) Antiretrovirals (ARVs)

What is it?

- Antiretroviral drugs given via injection that persist in the blood for long periods of time.
- LAI ARVs need to be dosed every few months. Single-drug LAI PrEP regimens being evaluated utilize injections (one in each buttock) every eight to 12 weeks.
- Two-drug LAI treatment regimens being evaluated utilize injections every four or eight weeks.

What could it do?

- In HIV-positive people, LAI ARVs could simplify treatment and change the way ARVs are delivered.
- In HIV-negative people, the same ARVs could be long-acting PrEP. This could reduce the burden of adherence and make it easier for some people to take, although issues of regular testing to monitor for HIV infection need to be addressed, as they do for all PrEP strategies (right now PrEP is a daily oral strategy).

Key Facts

- Trials of LAI ARVs start with a lead-in phase where people take oral formulations of the same drugs to establish safety and tolerability in a formulation that can be discontinued. (Injectable ARVs cannot be removed from the body.)
- The drugs used as injectables have unique properties that allow them to be formulated into doses suitable for injection. Many other common ARVs can't be used in this way.
- The current suite of trials will provide information that could launch expanded trials in 2016/7 designed to test for efficacy and possible licensure for both treatment and prevention purposes.

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Product Name(s)	Phase of Research	Research Description	HIV Status of Population	Class of Drug	Location
Long Acting Injectable ARVs					
GSK744 (cabotegravir, GSK1265744)	Phase II	• Ongoing ECLAIR trial evaluating safety and tolerability of injections every 12 weeks in HIV-uninfected men in the US. • HPTN 077 evaluating the safety, tolerability and pharmacokinetics in HIV-uninfected men and women.	−	Integrase strand transfer inhibitor	Brazil, Malawi, South Africa (HPTN 077), US (HPTN 077 and ECLAIR)
TMC278 (rilpivirine, Edurant)	Phase II	• Phase I trial evaluating the safety, acceptability, pharmacokinetics and pharmacodynamics of different dosing regimens underway in men and women in the US. • Phase II placebo-controlled HPTN 076 trial is evaluating safety, acceptability, drug presence in the genital tract of injections at eight week intervals among women in sub-Saharan Africa and the US and also gather information on HIV acquisition.	−	Nonnucleoside reverse transcriptase inhibitor	South Africa, US, Zimbabwe
TMC278/GSK744	Phase IIb	• A two-drug combination being tested as a "maintenance" regimen in people living with HIV who have achieved virologic suppression on triple-combination oral ARVs.	+	Nonnucleoside reverse transcriptase inhibitor plus integrase strand transfer inhibitor	Canada, France, Germany, Spain, US

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	What is it?	What could it do?	Key Facts
 **Preventive Vaccines**	• Seeks to teach to the immune system how to protect itself against infection by a pathogen.	• AIDS vaccines have been a key part of the prevention research agenda for nearly three decades. • Existing preventive vaccines for other diseases involve one or a series of immunizations, and can provide long-term or even lifelong protection. • Protection isn't always complete and may wane over time. • The one AIDS vaccine strategy to show efficacy to date (in RV144) involved six immunizations and protection waned after one year. • Current research is focused on improving on these results as well as exploring other vaccine candidates entirely.	• There is a robust pipeline of AIDS vaccine work, some of which overlaps with the investigations of passive immunization. • In Southern Africa, work continues on a suite of trials designed to build on the evidence from the RV144 trial. • A range of early-phase trials of other novel candidates to establish the safety and immunogenicity of other novel candidates are getting underway in 2015.

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Product Name(s)	Phase of Research	Research Description	HIV Status of Population	Class of Drug	Location
Preventive Vaccines*					
Ad26/MVA/gp140	Phase I/II	• Trial testing safety and immunogenicity of various regimens containing Ad26 vector (a cold-causing virus, altered to not cause illness) and a "mosaic" immunogen, designed to induce immunity against a range of HIV subtypes.	–	Adenovirus 26/ Modified Vaccinia Ankara Mosaic/ glycoprotein 140	South Africa, Thailand, US
ALVAC/AIDSVAX	Phase III follow-up and Phase I	• RV305 is taking place among participants from original RV144 trial to assess impact of additional boosts. • RV306 is testing the boosted regimen among new participants.	–	Pox-protein	Thailand
ALVAC/gp120/ MF59 adjuvant Clade C	Phase I/II	• HVTN 100 is testing an RV144-like regimen that has been altered with goal of optimizing for southern Africa. • First trial in the "development track" of post-RV144 trials sponsored by the Pox-Protein Public-Private Partnership (P5).	–	Pox-protein	South Africa
ALVAC, DNA, Protein, MF59, AS01B adjuvant (various combinations)	Phase I/II	• Suite of trials in the P5 "research track" will evaluate various vaccine combinations to identify correlates of immunity that could improve future regimens.	–	Pox-protein	Malawi, Mozambique, South Africa, Switzerland, Tanzania, US, Zambia, Zimbabwe

New Frontiers in HIV Prevention, Treatment and Cure

Development of 3BNC117 Monoclonal antibody

Sarah J. Schlesinger

April 21, 2015

HIV-1 Treatment and Prevention - Challenges

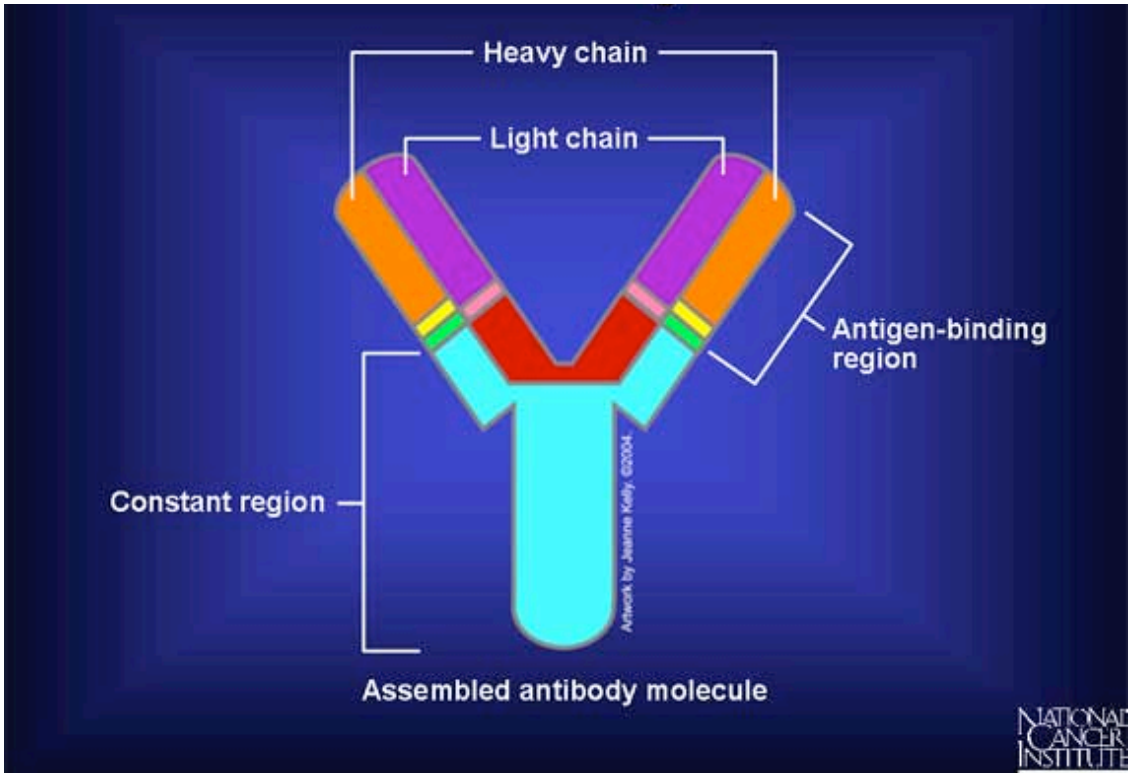
- ART is highly effective, however **cannot eradicate** HIV-1 infection
- Despite substantial increase in coverage**, only 38% of adults and 24% children** in need are currently receiving ART (UNAIDS Report 2015)
- New infection rates remain high **(2.1 million in 2013)**
- Engagement in HIV-care remains a challenge (**< 25% HIV+ with VL < 20 in the US**)
- An effective vaccine is not available – results from large efficacy phase 3 trials won't be available until 2020
- A major challenge to an effective vaccine is the rapid establishment of a viral reservoir
  - Vaccines that block infection (sterilizing immunity)

B-Cell Lymphocytes

Antibody-producing cells of “bursal” origin. Produce immunoglobulin in response to antigen.

Antibody

Immunoglobulin produced by B-cells;
may be neutralizing or non-neutralizing.



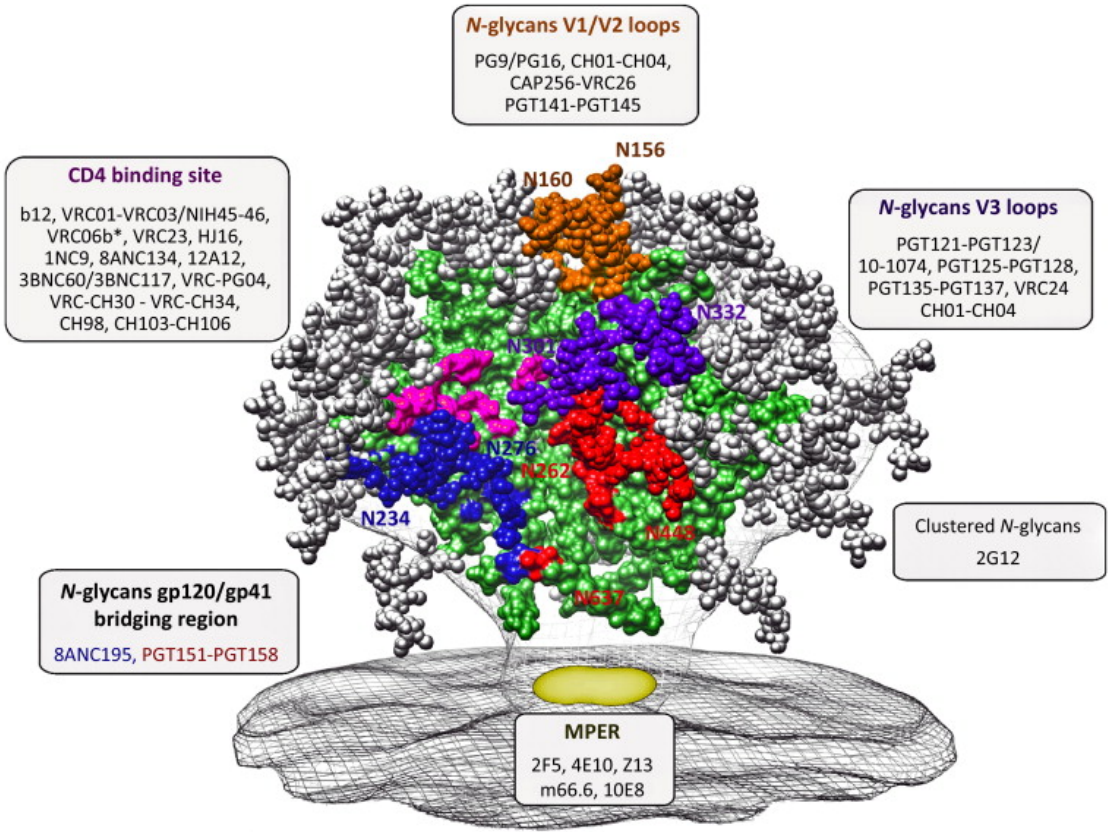
Passive Immunization is Effective against many Infectious Diseases

Virus Pathogen	Passive Immunization leads to Protection	Vaccine Licensure
Measles	Concentrated Human gamma globulin (Janeway, CA **1945**)	1957
Polio	Red Cross gamma globulin (Hammon WM, **1953**)	1954
Varicella	VZV-gamma globulin (Zaia JA, **1983**)	1995
Hepatitis B	Hep B immune globulin (Beasley RP, **1983**)	1984
Hepatitis A	Immune serum gamma globulin (Conrad ME, **1987**)	1995
CMV	Polyclonal Ig for prophylaxis of transplant-associated infection (**1990**)	-
RSV	mAb (palivizumab) for prophylaxis of high risk infants (**1998**)	-

Adapted from Barney Graham

A fraction of HIV-1 infected individuals generate neutralizing antibody responses in 2-3 years post infection

- Single cell cloning methods allowed the isolation of new highly potent bNAbs

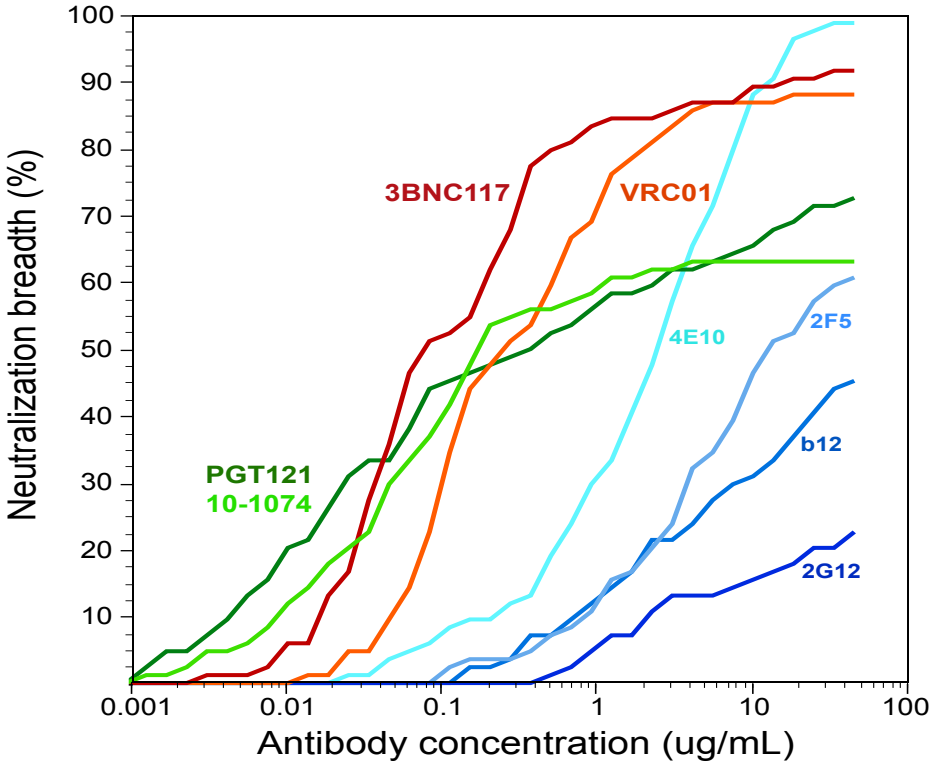


Adapted from Mouquet *et al.*, Trends Immunol 2014

Anti-HIV Antibodies Tested in Humans

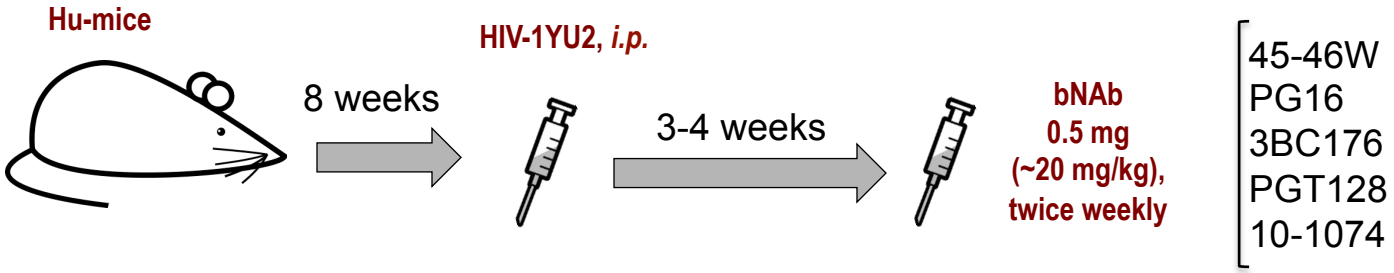
Antibody	Target	Clinical Setting	Safety	Antiretroviral effects
HIVIGLOB	Polyclonal	Pregnant women and infants	Safe	p24 Ag cleared, no change in VL
F105 (Posner, 1998)	CD4 binding site	Viremic, on ART Single infusion	Safe	No effect by viral culture
2G12, 2F5 (Armbruster, 2002)	Carb epitope gp120 MPER gp41	Viremic (10K), ART naive	Safe	Transient reduction in VL (0.6 log)
4E10 and 4E10,2F5,2G12 (Armbruster, 2004)	Glycan gp120 MPER gp41	Viremic (100K), ART naive	Safe	No significant change in VL
2G12, 2F5, 4E10 (Trkola, 2005)	Glycan gp120 MPER gp41	ART interruption	Safe	Delay to viral rebound in few; 2G12 resistance
2G12, 2F5, 4E10 (Mehandru, 2007)	Glycan gp120 MPER gp41	ART interruption	Safe	Viral rebound in most; 2G12 resistance
KD-247 (Matsushita, 2015)	V3 loop	Viremic, ART naive	Safe	Transient VL reduction (0.6 log); V3 loop mutations
VRC01	CD4 binding site	HIV-infected, on/off ART Two doses, 1-40 mg/kg	Safe	Ongoing

Can new generation antibodies effectively control HIV-1 Infection?

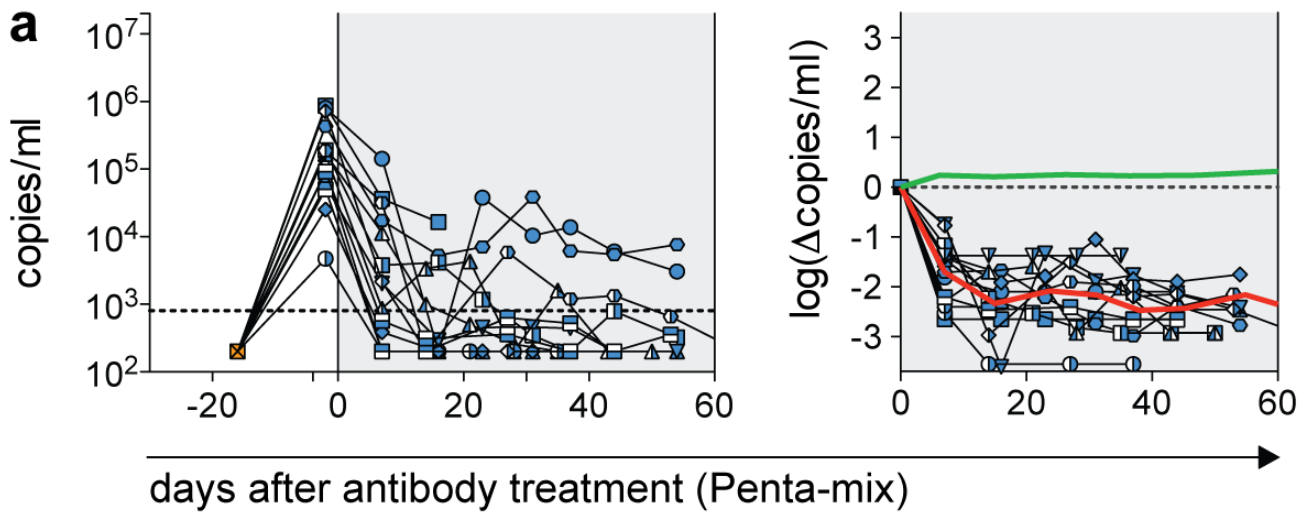


VRC01, Wu *et al.*, Science 2010; 3BNC117, Scheid *et al.*, Science 2011; PGT121, Walker *et al.*, Nature 2011; 10-1074 Mouquet *et al.*, PNAS 2012

A Combination of Five bNAbs Suppresses Viremia in hu-Mice

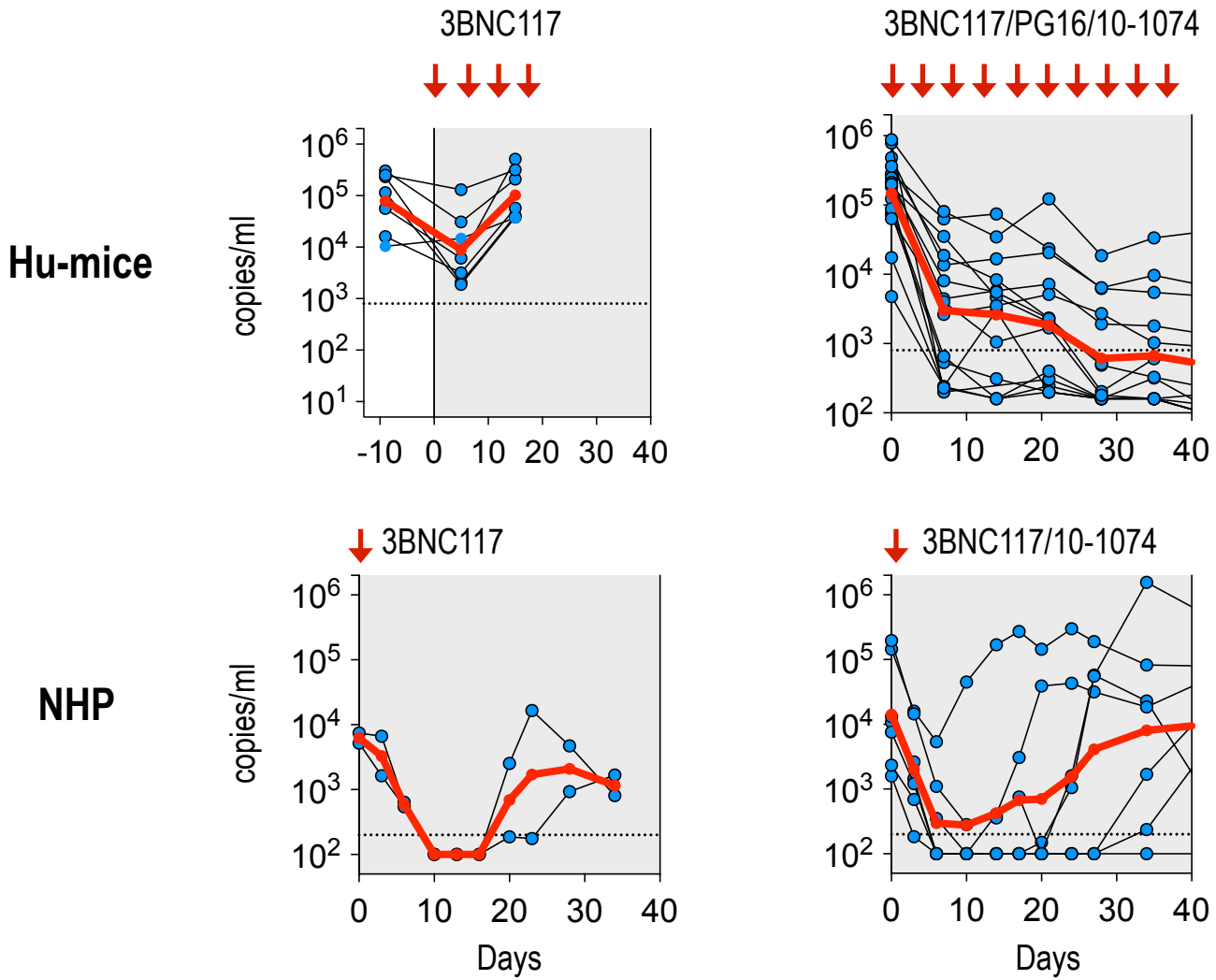


bNAb monotherapy led to transient decline in viremia followed by viral rebound
Rebounding viruses harbored escape mutations



Klein F et al., Nature 2012

bNAbs in HIV-1infected Hu-Mice and SHIV-infected NHP

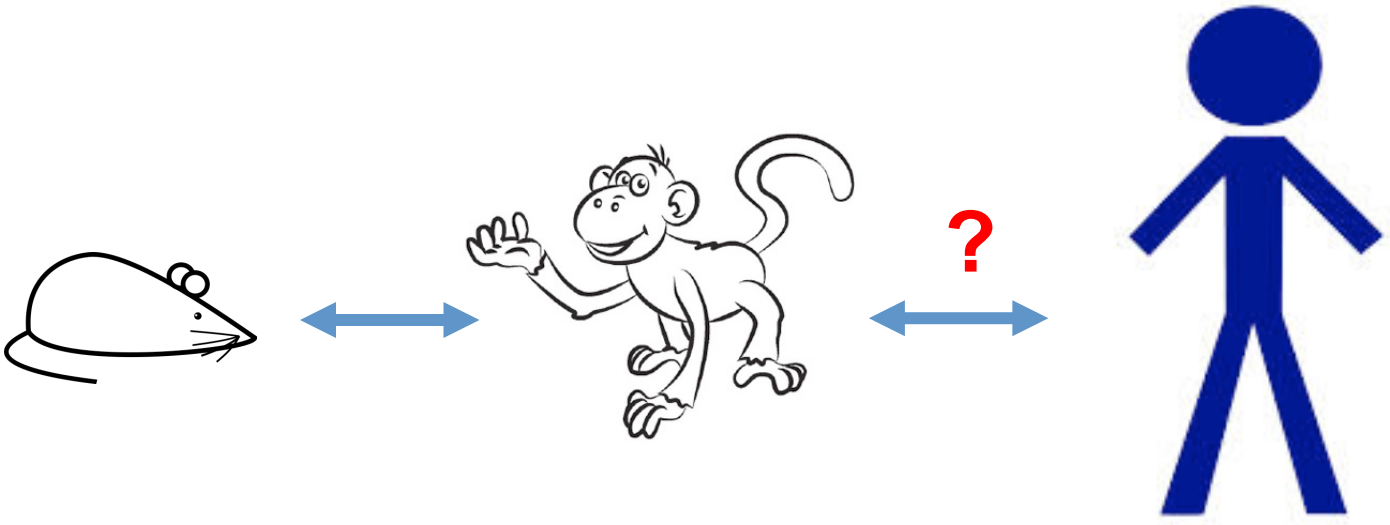


Klein *et al.*, Nature 2012; Horwitz *et al.*, PNAS 2013; Shingai *et al.*, 2013

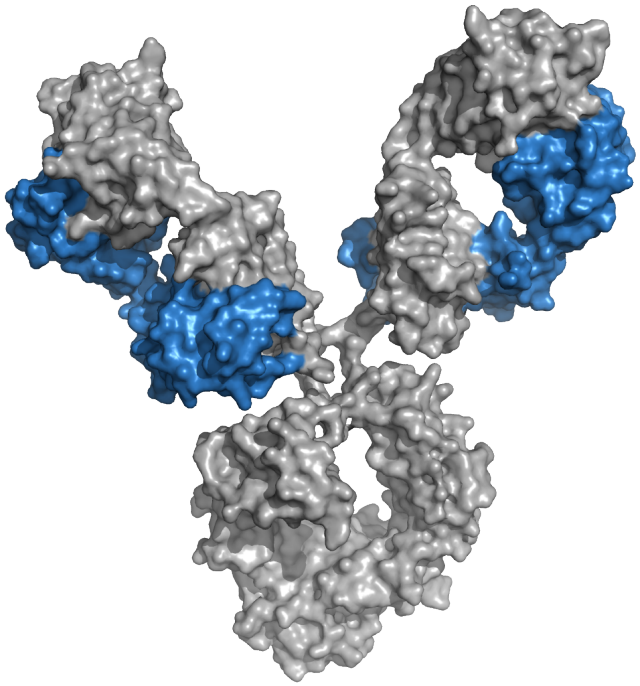
Preclinical Evaluation of bNAB-mediated Therapy

- 3BNC117 can effectively suppress HIV-1 viremia in humanized mice, but there is rapid escape (Klein *et al.*, Nature 2012; Horwitz *et al.*, PNAS 2013)

- 3BNC117 can rapidly decrease viremia in NHPs and in most cases maintain suppression until mAb decays (Shingai *et al.*, Nature 2013). Similar results were obtained with PGT121 and 10-1074 (Barouch D. *et al.*, Shingai *et al.*, Nature 2013)



Clinical Investigation of bNAb 3BNC117 (MCA-0835)



3BNC117

- Human monoclonal IgG1 k antibody
- Targets CD4bs on HIV-1 Env
- IC_{80} on a combined group of 95 tier 2 viruses of 1.4 µg/ml
- 5 mg/kg was effective in protecting animals against intrarectal challenge in NHP
- 10 mg/kg induced rapid decline in plasma viremia (hu-mice, NHPs)

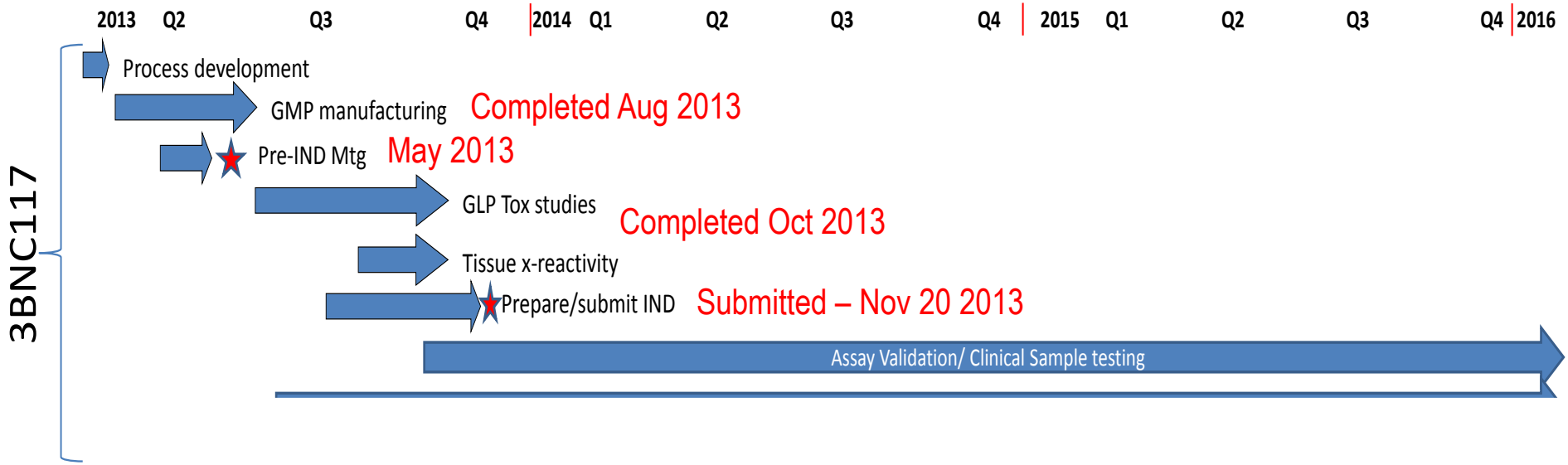
Scheid *et al.*, Science 2011

Potential Clinical Applications of 3BNC117 and other HIV-1 NAbs

- Prevention in high risk individuals
  - If favorable PK profile and potency in humans
  - If antibodies can be formulated for subcutaneous administration

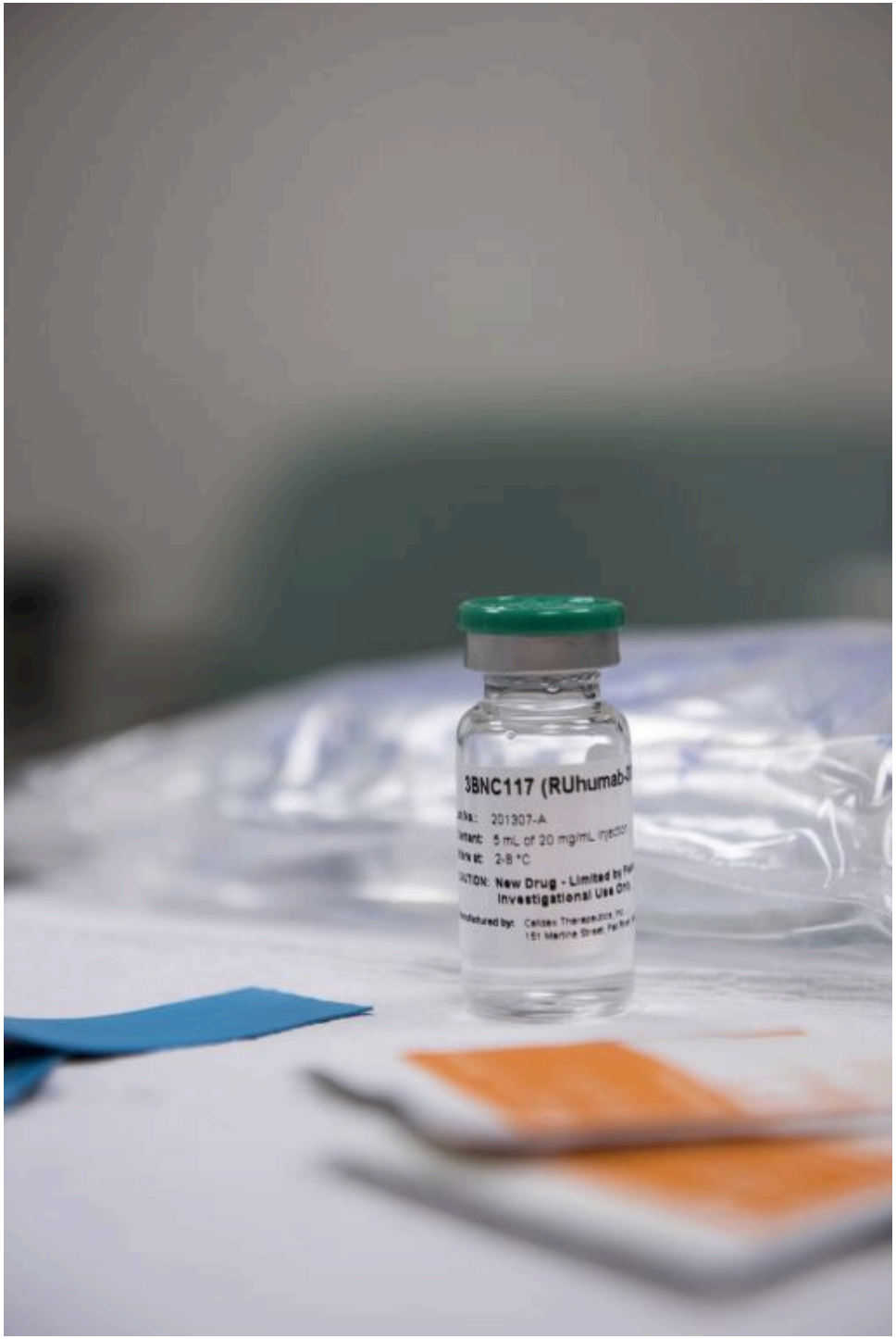
- Adjuncts to conventional ART
  - In intensification regimens
  - During ART-interruption
  - Eradication strategies

3BNC117 – From the Lab to the Clinic
First-in-Man Study



- FDA "Ok to proceed Letter" – Dec 19 2013
- Rockefeller IRB approval – Jan 14 2014
- First 3BNC117 infusion – Feb 12 2014

3BNC117 for Clinical Use



Protocol MCA-0835 - Study Objectives:

Primary:

Safety, tolerability and pharmacokinetics profile of a single intravenous infusion of 3BNC117 in HIV-infected and uninfected individuals

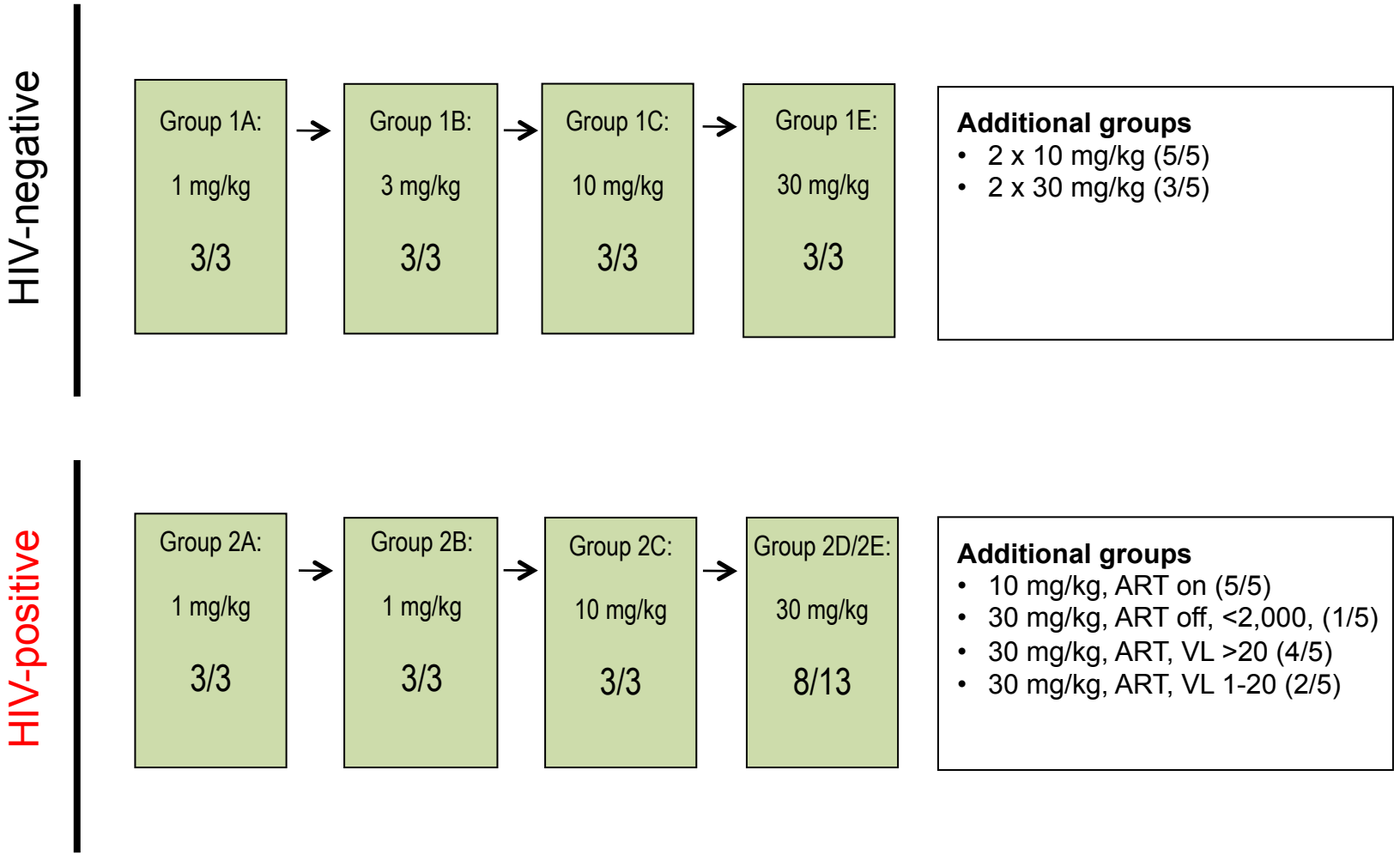
Secondary:

Effect of 3BNC117 on plasma HIV-1 RNA levels and the frequency and magnitude of induced anti-3BNC117 antibodies.

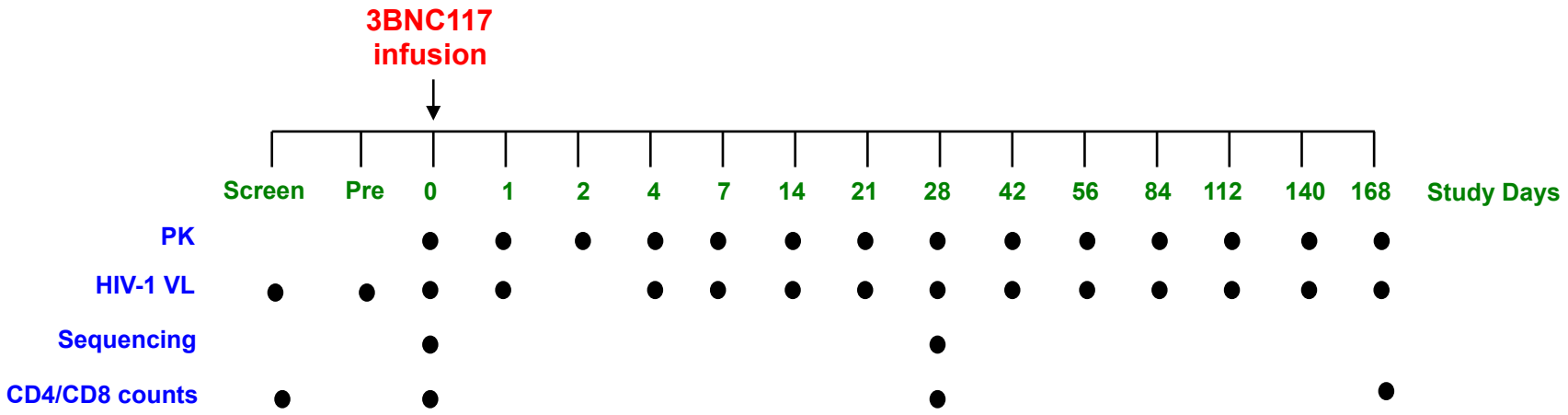
Exploratory:

Genotyping of escape variants that might arise, cell-associated HIV-1 RNA and DNA levels, 3BNC117 levels in cervicovaginal and rectal secretions, and HIV-1 specific T and B cell immune responses following administration of 3BNC117.

First-in-man Study of bNAb 3BNC117
Study Groups



Study Design



3BNC117 study – Enrollment and Safety

Enrollment

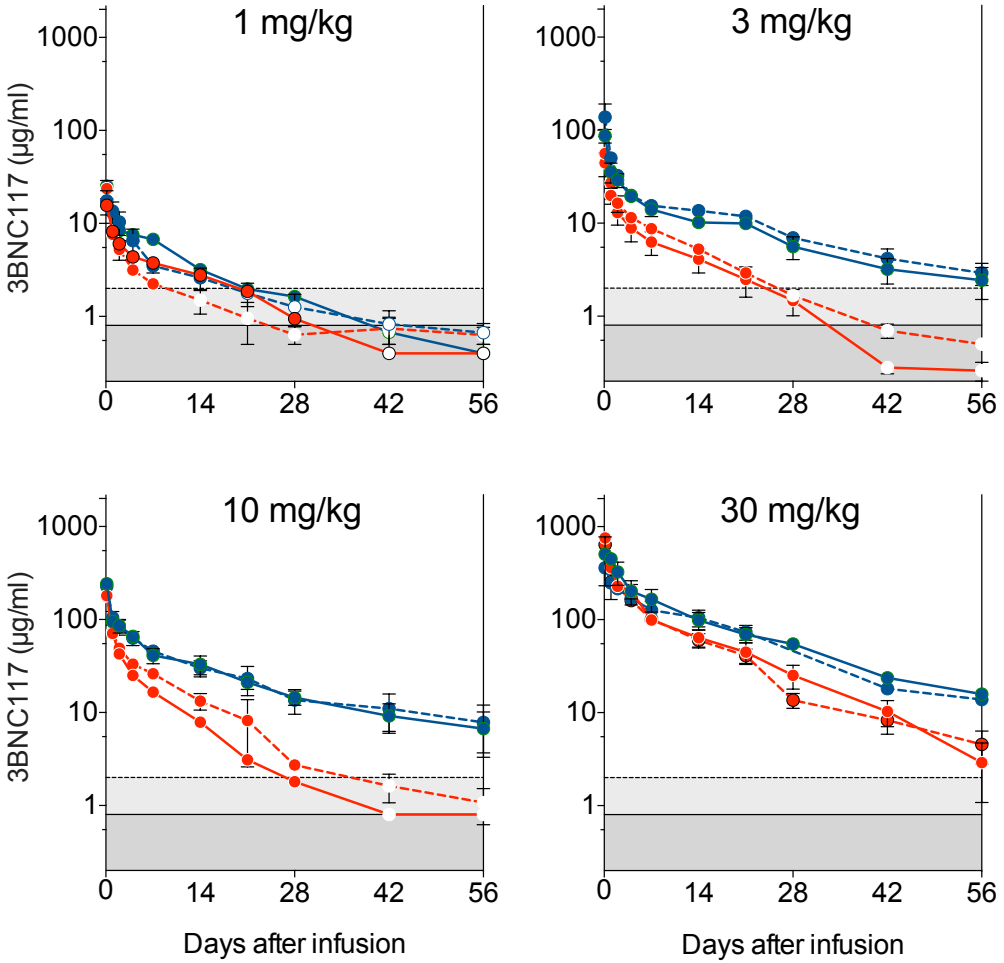
- 49 subjects enrolled
- 15 completed follow up

- 29 HIV-1-infected (16 off ART and 13 on ART)
- Baseline HIV-1 VL in subjects off ART: 640 – 53,470 cp/ml

Safety for subjects receiving 1, 3, 10, and 30 mg/kg

- No SAEs
- Well-tolerated; most reported AEs graded as mild (transient fatigue and headache)

3BNC117 Pharmacokinetics



	HIV-infected	HIV-uninfected
Average Half-life	9.6 days	17.6 days
Cmax (30 mg/kg)	669.8 (410.2 - 976.4)	495.9 (360.8 - 765.0)

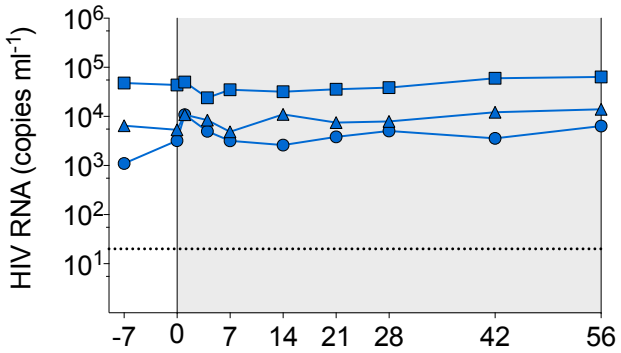
Summary – Safety and PK

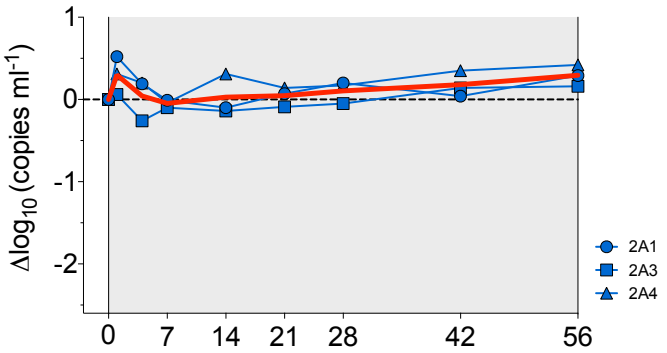
- 3BNC117 has been generally safe and well tolerated at doses up to 30 mg/kg in HIV-uninfected and HIV-infected individuals, on and off ART.

- 3BNC117's half-life is approximately 2.5 weeks in HIV-uninfected individuals. In viremic HIV-infected individuals, it is slightly shorter.

Single 3BNC117 infusion – Antiviral activity

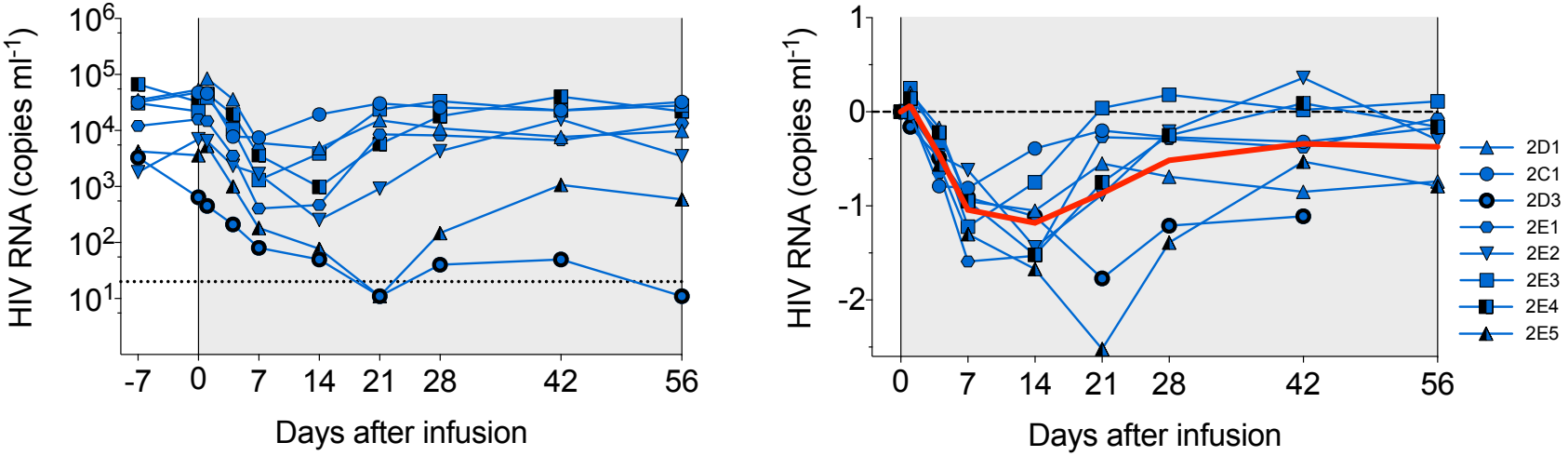
1 mg/kg





Single 3BNC117 infusion – Antiviral activity

30 mg/kg



Summary – Virologic Effects

- A single administration of 1 or 3 mg/kg led to small effects on plasma viremia but altered 3BNC117-sensitivity.
- A single administration of 30 mg/kg led to decline in plasma viremia in all individuals treated of up 2.5 logs (average 1.48 log). Plasma viremia remained significantly reduced for 28 days.
- Decline in viremia correlated with baseline sensitivity to 3BNC117 and to starting viral load.
- 3BNC117 selected resistant viral strains in some but not all viremic individuals treated.
- The long term effects on viremia and on host immune responses remain to be determined.

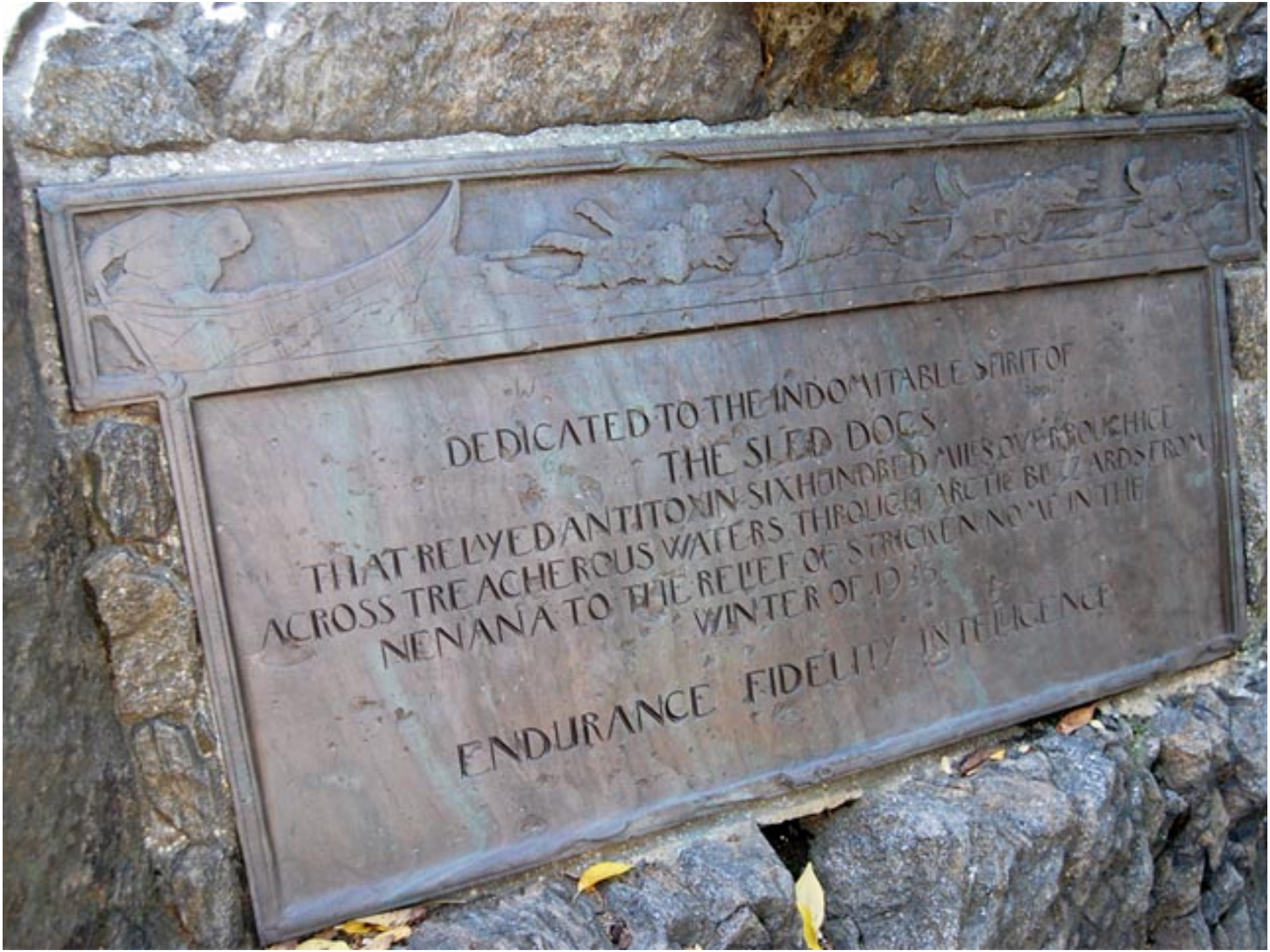
Future 3BNC117 studies

- Evaluate the effects of 3BNC117 on host immune responses (Florian Klein, Till Schoofs)
- Evaluate if 3BNC117 alters levels of CA-HIV-1 RNA and DNA (Josh Horwitz, Julio Lorenzi)

- Future Clinical Studies:
  - Can 3BNC117 **prevent virologic rebound** when ART is discontinued? (Johannes Scheid)
  - Can 3BNC117 **affect the size of the reservoir**, alone or in combination with a latency reversing agent?
  - Will **3BNC117 in combination 10-1074** lead to more significant effects on viremia (longer lasting)?

Balto

Central Park,
near East 67th Street


DEDICATED TO THE INDOMITABLE SPIRIT OF
THE SLED DOGS
ENDURANCE FIDELITY INTELLIGENCE

Acknowledgements

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