# Community Cure Meeting, EACS

# 06 November 2019

**The RIO Trial:** A randomised placebo controlled trial of ART plus dual long-acting HIV-specific broadly neutralising antibodies (bNAbs) vs ART plus placebo in treated Primary HIV Infection on viral control off ART.


Simon Collins

HIV i-Base and EATG

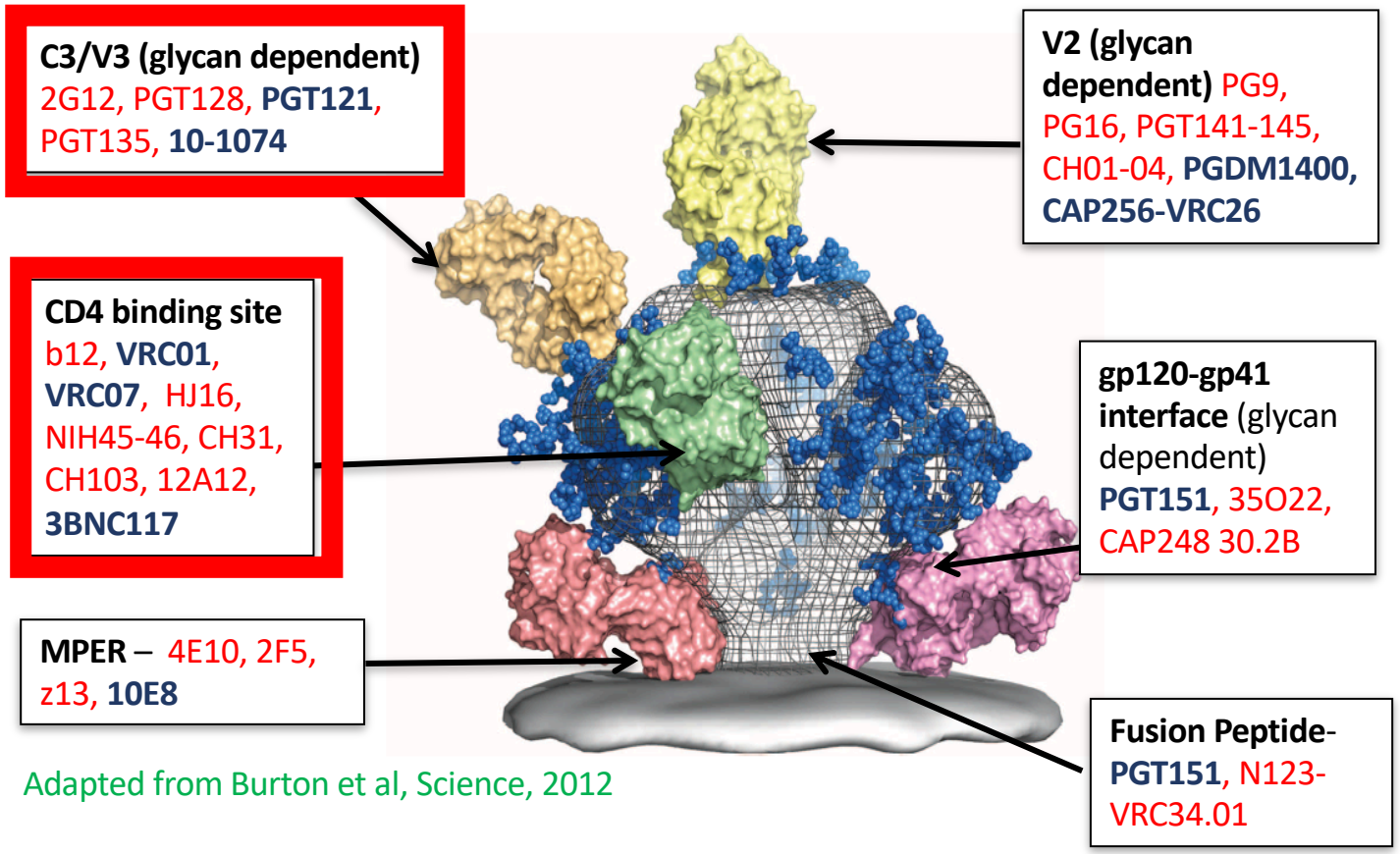
# bNAbs?

- Generated from people who develop strong antibodies to HIV.

Most people make non-neutralising antibodies – or that only affect a few strains.

- Usually after 2-3 years – ie long after infection – rare at high titres.
- Been known since early HIV research.
- Only recently able to isolate and clone for use as treatment.
- Two mechanisms – supported by in vivo studies:
  - direct antiretroviral (~1.5 log mono. 2 log dual)
  - immune modulating vaccine-type effect (after drug levels have left)
- Long acting LS formulations (M428L and N434S) extend half life x 4

# bNAb binding on HIV envelope glycoprotein:
## different target sites will reduce cross-resistance




Adapted from Burton et al, Science, 2012

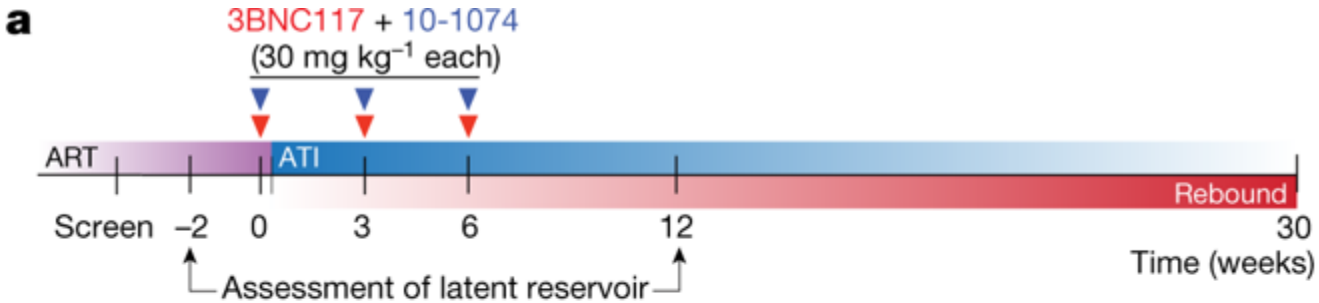
# bNAbs and HIV research

- Human studies show antiviral activity.
- Some animal studies suggest remission or cure.
- This includes ‘vaccinal effect’ after bNAbs have cleared.
  See key paper by Mendoza et al – with two people remaining off ART for >12 months, one of who is now out to >24 months
- Expanded with extended long-acting bNAbs
- Always against a background of natural (rare) ‘post treatment control’

# Mendoza et al. Nature, vol 561, p479–484 (2018)

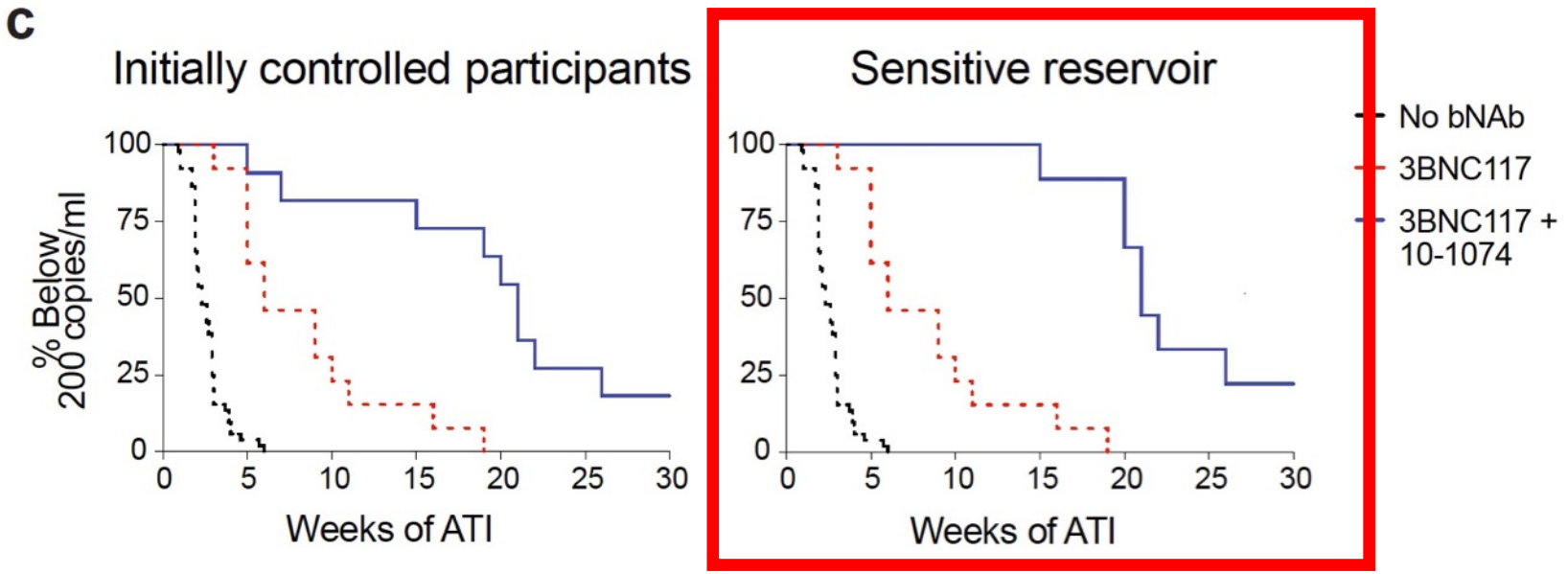
## Combination therapy with anti-HIV-1 antibodies maintains viral suppression

Pilar Mendoza[1,19], Henning Gruell[2,3,4,19], Lilian Nogueira[1], Joy A. Pai[1], Allison L. Butler[1], Katrina Millard[1], Clara Lehmann[3,4,5], Isabelle Suárez[3,4,5], Thiago Y. Oliveira[1], Julio C. C. Lorenzi[1], Yehuda Z. Cohen[1], Christoph Wyen[3,6], Tim Kümmerle[3,6], Theodora Karagounis[1], Ching-Lan Lu[1], Lisa Handl[7], Cecilia Unson-O'Brien[1], Roshni Patel[1], Carola Ruping[2], Maike Schlotz[2], Maggi Witmer-Pack[1], Irina Shimeliovich[1], Gisela Kremer[3], Eleonore Thomas[3], Kelly E. Seaton[8], Jill Horowitz[1], Anthony P. West Jr[9], Pamela J. Bjorkman[9], Georgia D. Tomaras[8,10,11,12], Roy M. Gulick[13], Nico Pfeifer[7,14,15,16], Gerd Fätkenheuer[3,4], Michael S. Seaman[17], Florian Klein[2,4,5,20]*, Marina Caskey[1,20]* & Michel C. Nussenzweig[1,18,20]*




- N=11
- Chronic HIV infection
- ART> 24 months
- bNAbs then TI

# Dual bNAbs confer control……




- Viral suppression for 5 to >30 weeks
- Median time to rebound 21 weeks vs 2.3 weeks for ART-only controls vs 6-10 weeks for single bNAb.
- Two never rebounded (now one > 24 months)
- Rebound in others due to resistance or as bNAb concentration dropped.

# Trial design

The trial is designed in two stages (n=72):

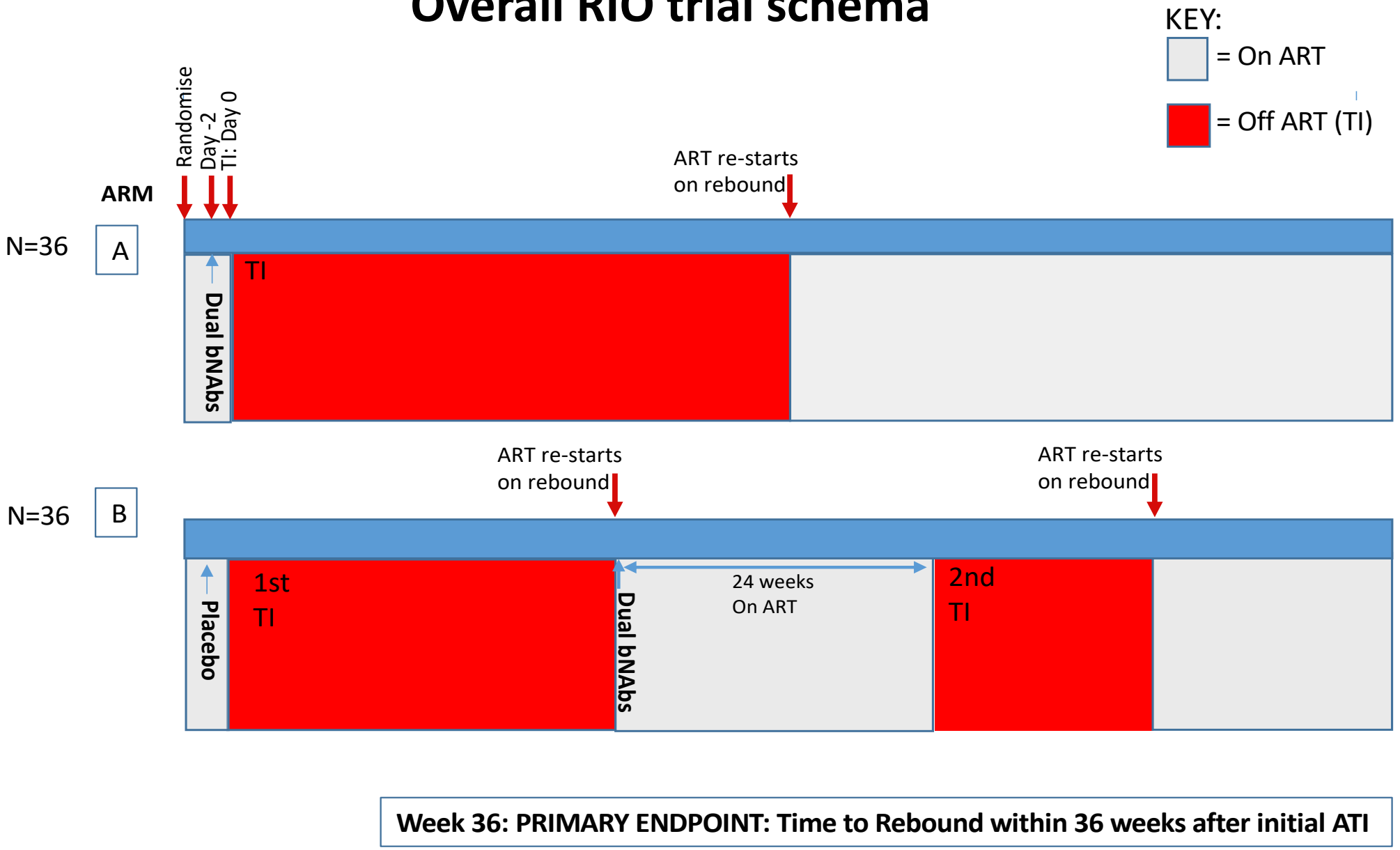
**Stage 1**

A placebo-controlled double-blinded two arm prospective phase II randomised controlled trial

**Stage 2**

For individuals randomly allocated to the placebo arm in stage 1 only, they will be offered to receive dual bNAb at ART restart once viral rebound criteria have been achieved.

# Overall RIO trial schema




**Week 36: PRIMARY ENDPOINT: Time to Rebound within 36 weeks after initial ATI**

# Trial endpoints

**PRIMARY ENDPOINT**

- Time to viral rebound* within 36 weeks after initial ATI, in the absence of ART.
- *Viral rebound is defined by HIV VL measurement from venous blood (as per local assay):
  - >1,000 copies/mL for 6 consecutive weeks
  - >100,000 copies/mL for two readings, 1 week apart
- Many secondary and tertiary endpoints.

# ART re-start criteria

- **ART will be re-started if:**
- Viral rebound confirmed by HIV VL measurement from venous blood:

  (i) sustained HIV viral load ≥ 1,000 for 6 weeks +/- 7 days

  (ii) is ≥100,000 copies for two readings, 7 days apart +/- 7 days
- CD4 count drops to < 350 cells/uL (confirmed)
- Clinical symptoms attributable to ATI
- Participant preference
- Major concerns over risk mitigation for HIV transmission.

# Cautions

- New compounds – limited safety data in humans.
- Sensitivity at baseline - ~60%+ ? (and of test).
- Risk of resistance with monotherapy (including PK tail).
- Getting true informed consent (with no belief in a cure).
- Taking a treatment interruption (STI).

    - Risks to participants (CD4, event, seroconversion etc. Also, adherence after the STI etc)

- Risks of transmission (including partner, PrEP etc)

# Thanks

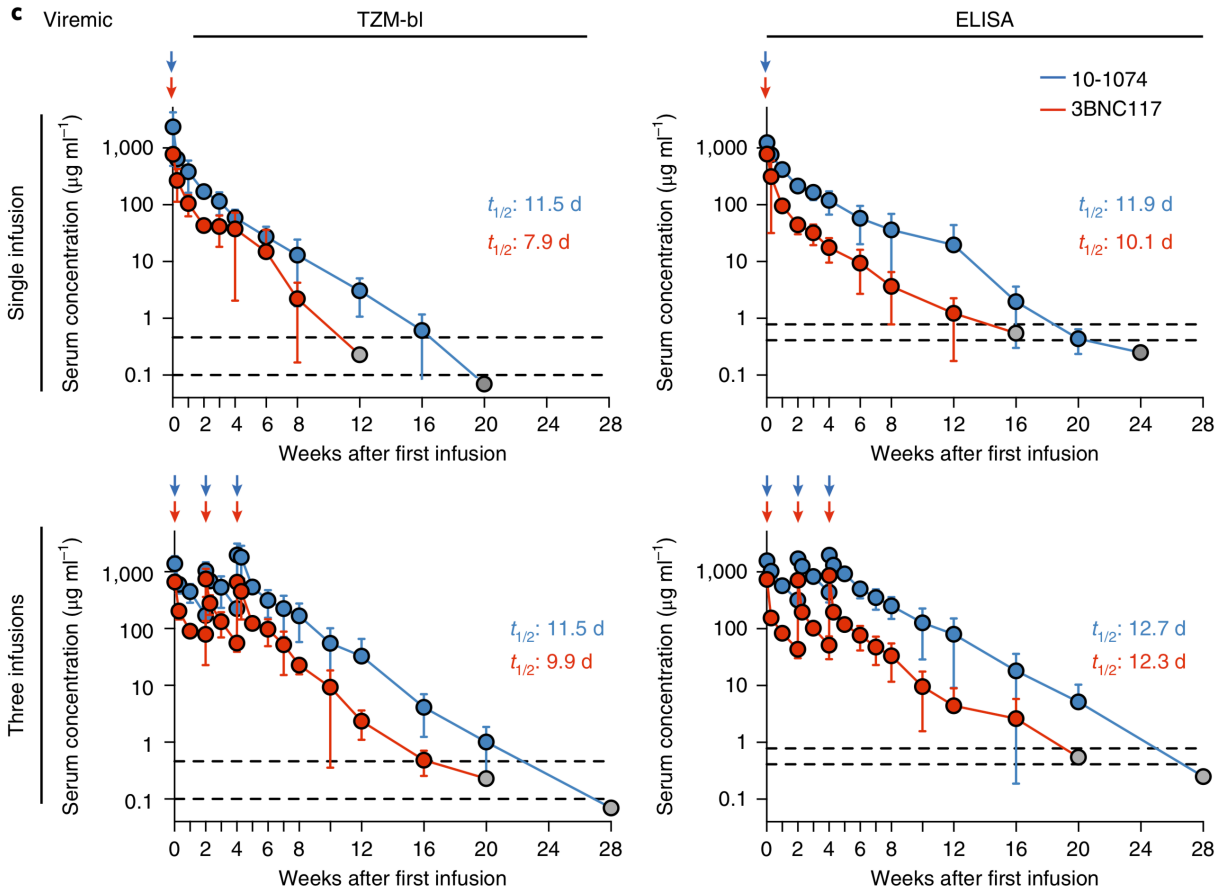
Sarah Fidler and John Frater for slides

RIO steering group.

# Back-up slides

# Why these bNAbs

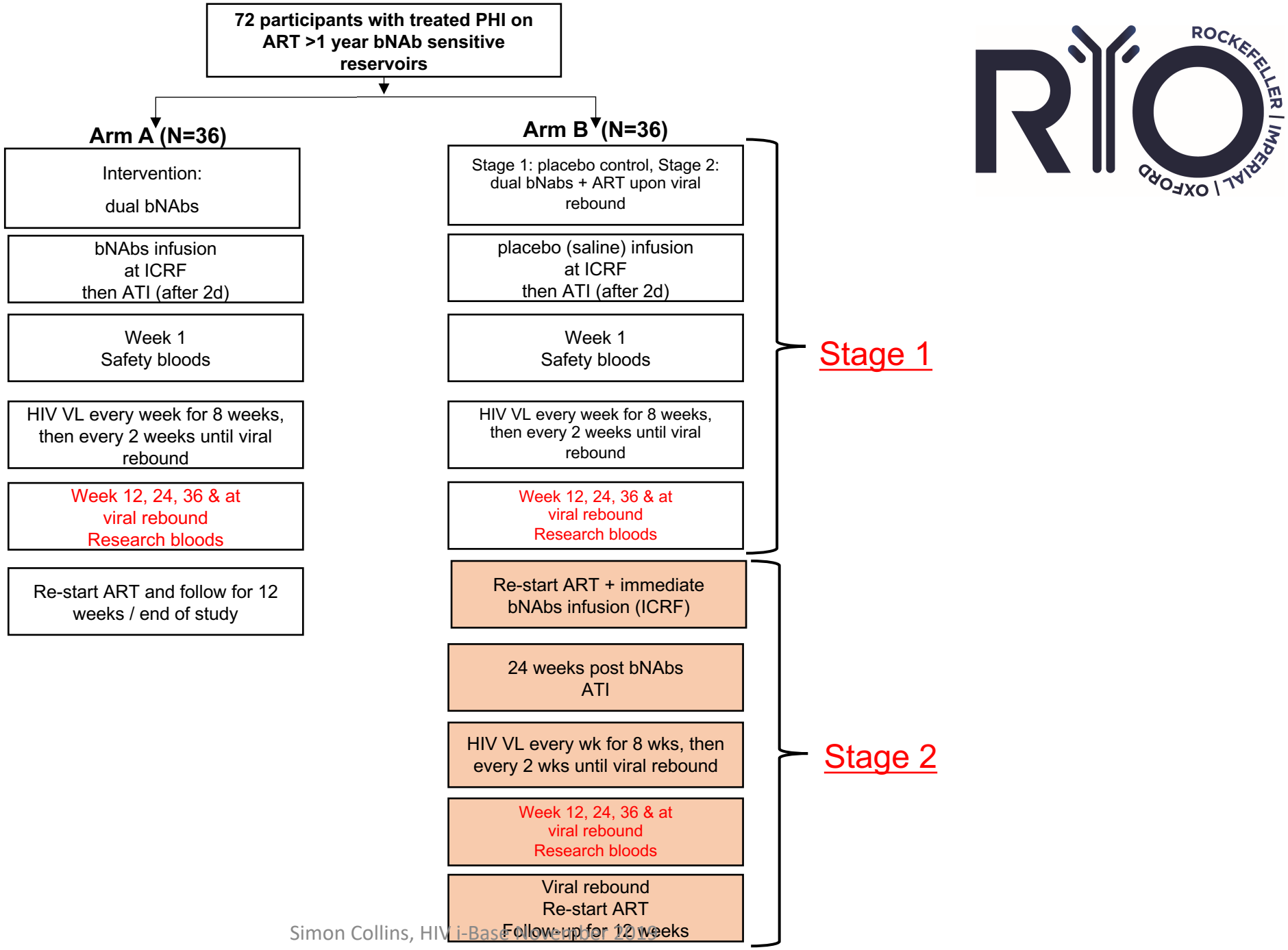
**Combined bNab 3BNC117 + 10-1074 act as antivirals in viraemic patients to reduce HIV Viral load by 2.5 log**




Bar-On et al Nature Medicine 2018 Sept. 10 1038

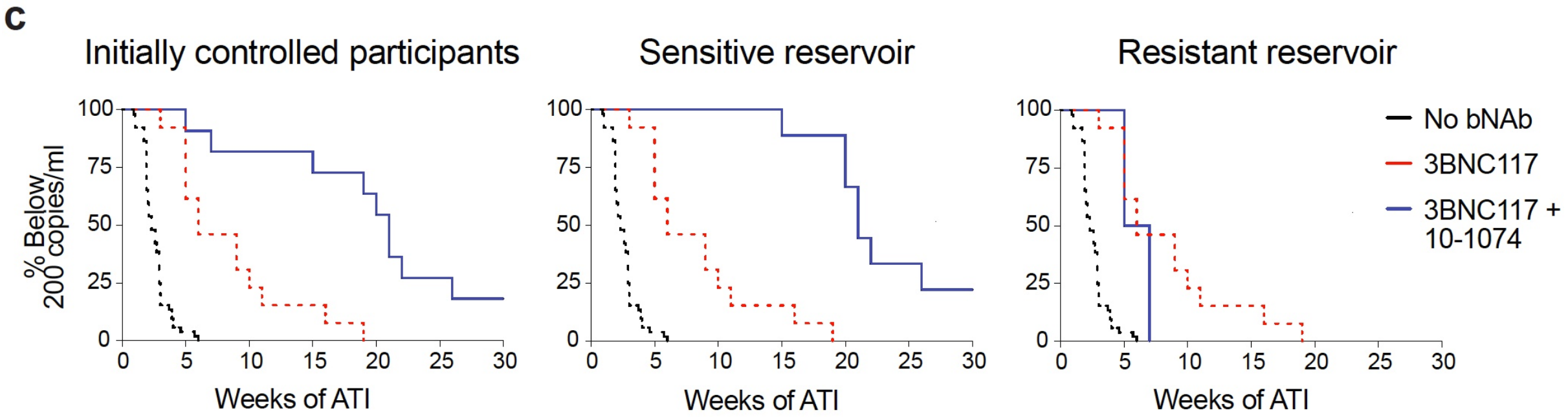
# Risks

| Risk | Risk management and mitigation |
|---|---|
| Risk of bNab administration | Anaphylaxis (none reported)<br>Mild local or systemic reactions to infusion<br>Clot formation (checked at screening) |
| Risk of ATI | Drop in CD4 count (frequent monitoring) eligibility criteria exclude low nadir or current CD4 count<br>Symptoms of viral rebound<br>Exclude any co-morbidity and co-infections, previous malignancy, OI, or CVA MI<br>ART resistance (only interrupt on bPI or INSTI avoid NNRTI |
| Risk of onward viral transmission | Access to PrEP services to any HIV-negative partners<br>Condoms<br>Pregnancy prevention for duration of study for women participants |


72 participants with treated PHI on ART >1 year bNAb sensitive reservoirs
Arm A (N=36)
Intervention:
dual bNAbs
bNAbs infusion at ICRF then ATI (after 2d)
Week 1 Safety bloods
HIV VL every week for 8 weeks, then every 2 weeks until viral rebound
Week 12, 24, 36 & at viral rebound Research bloods
Re-start ART and follow for 12 weeks / end of study
Arm B (N=36)
Stage 1: placebo control, Stage 2: dual bNabs + ART upon viral rebound
placebo (saline) infusion at ICRF then ATI (after 2d)
Week 1 Safety bloods
HIV VL every week for 8 weeks, then every 2 weeks until viral rebound
Week 12, 24, 36 & at viral rebound Research bloods
Re-start ART + immediate bNAbs infusion (ICRF)
24 weeks post bNAbs ATI
HIV VL every wk for 8 wks, then every 2 wks until viral rebound
Week 12, 24, 36 & at viral rebound Research bloods
Viral rebound Re-start ART Follow-up for 12 weeks
Stage 1
Stage 2

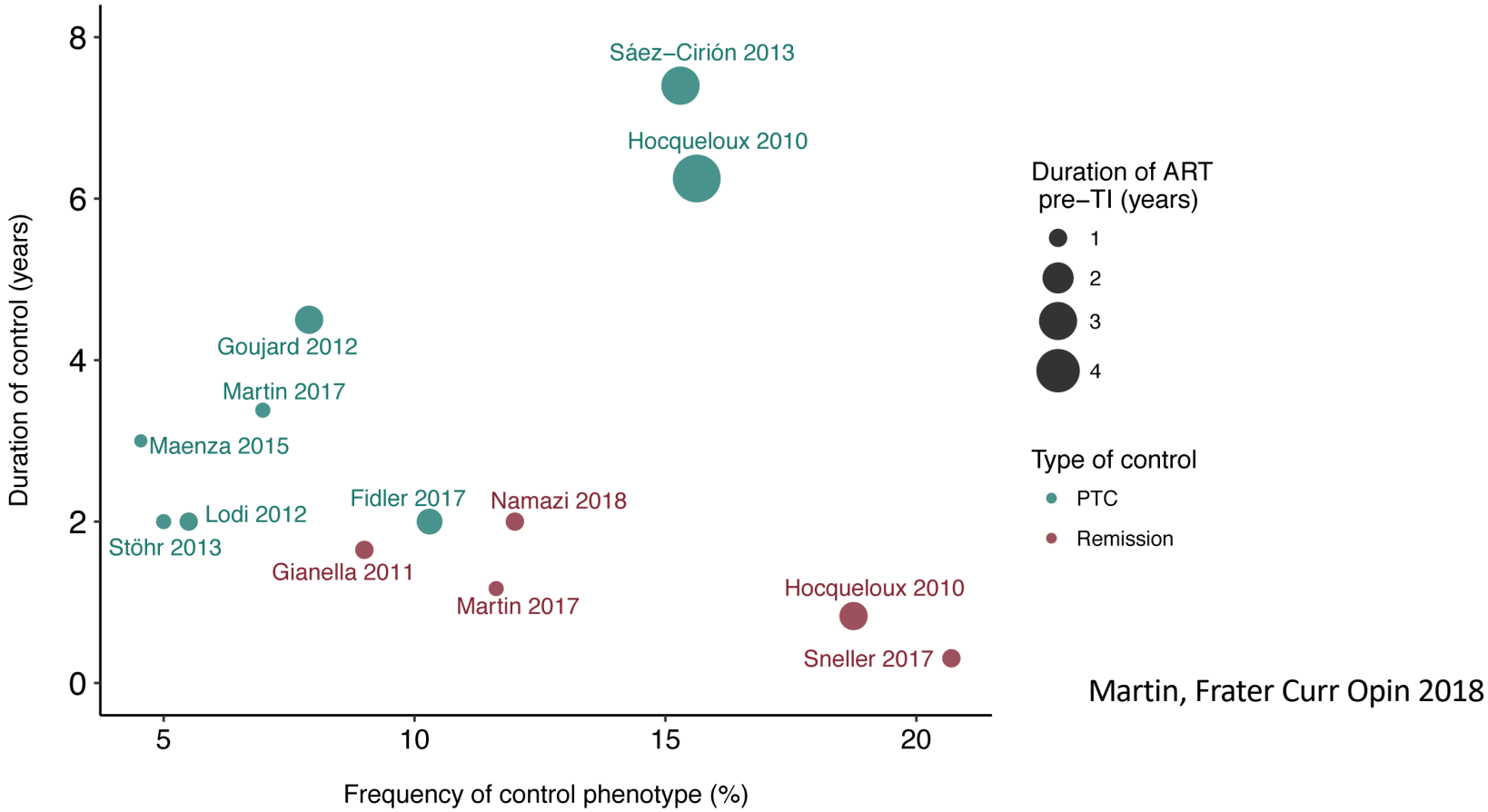
# Impact of Dual bNAb therapy given in treated HIV infection after ATI

n = 9 chronic treated HIV infection
maintained suppression out to >30 weeks




Mendoza et al Nature 2018 561 479-484

# Evidence for PTC in different studies




Martin, Frater Curr Opin 2018

In SPARTAC, 14% of those who received ART for 48 weeks were still undetectable 1 year after stopping ART

Martin 2017

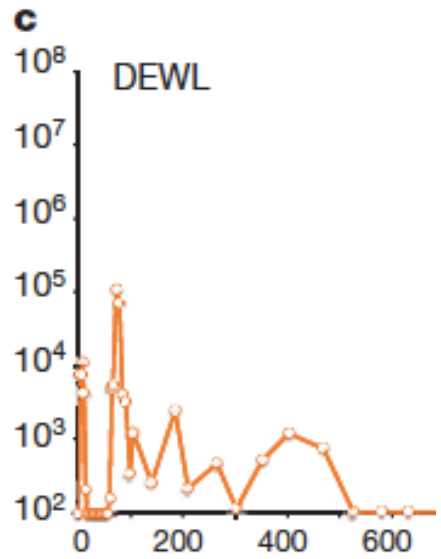
LETTER

doi:10.1038/nature21435

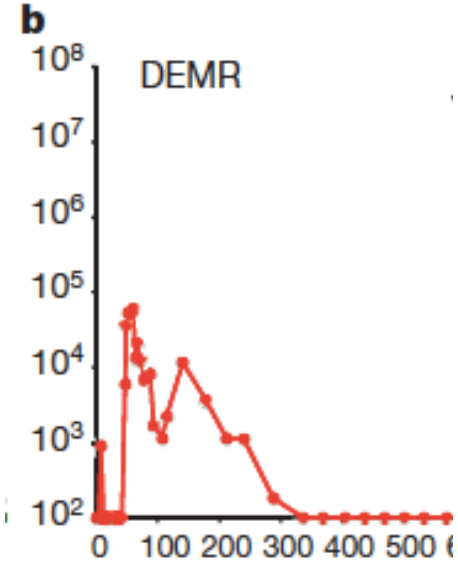
# Early antibody therapy can induce long-lasting immunity to SHIV

Yoshiaki Nishimura[1], Rajeev Gautam[1], Tae-Wook Chun[2], Reza Sadjadpour[1], Kathryn E. Foulds[3], Masashi Shingai[1], Florian Klein[4,5], Anna Gazumyan[6], Jovana Golijanin[6], Mitzi Donaldson[3], Olivia K. Donau[1], Ronald J. Plishka[1], Alicia Buckler-White[1], Michael S. Seaman[7], Jeffrey D. Lifson[8], Richard A. Koup[3], Anthony S. Fauci[2], Michel C. Nussenzweig[6,9] & Malcolm A. Martin[1]

- Rhesus macaques
- Infected with SHIV
- Given 3BNC &10-1074
- ART stopped




- Viral suppression when bNAbs present
- Evidence for post-bNAb control
- Did bNAbs induce a potent CD8 response?
  - The ‘Vaccinal Effect’



# Secondary endpoints

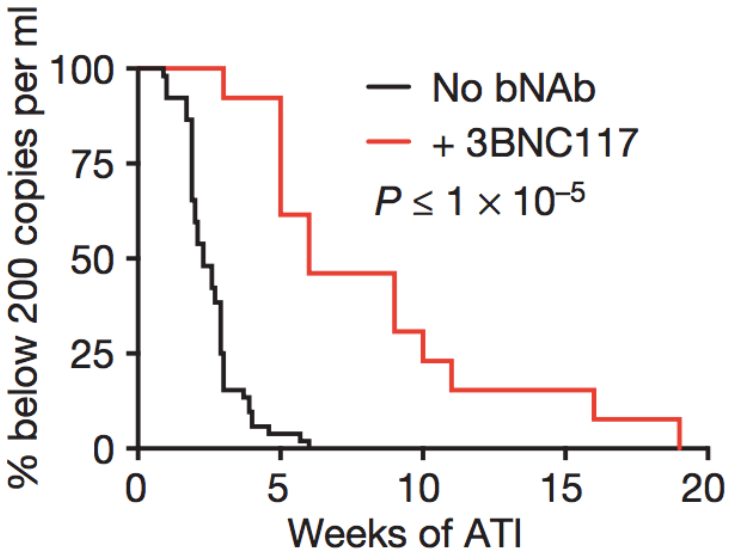
- For both Stage 1 and Stage 2, these are:
- Safety defined as Adverse Events and Serious Adverse Events by group
- Length of time undetectable in days following ATI (Arm A vs B and Arm B Stage 1 AI vs Stage 2 ATI)
- CD4 T cell counts and CD4:CD8 ratios at weeks 12, 24, 36 and 48 after randomisation, and 12 weekly until the end of study participation.
- Percentage of participants with undetectable VL at weeks 12, 24, 36 and 48 post randomisation (Stage 1; Arm A vs B) and then for Arm B participants post second ATI
- Quantitation of proviral HIV DNA and cell associated RNA
- Duration of remission by different parameters (eg VL<40, <400, <1000, +/- blips copies HIV per ml)
- Time to re-starting ART after start of ATI
- Time to undetectable HIV VL after re-starting ART
- ART presence in blood during ATI
- bNAb levels in blood
- bNAb sensitivity/resistance at viral rebound
- HIV Quality of Life measure

LETTER

doi:10.1038/nature18929

# HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

Johannes F. Scheid[1,2*], Joshua A. Horwitz[1*], Yotam Bar-On[1], Edward F. Kreider[3], Ching-Lan Lu[1], Julio C. C. Lorenzi[1], Anna Feldmann[4], Malte Braunschweig[1], Lilian Nogueira[1], Thiago Oliveira[1], Irina Shimeliovich[1], Roshni Patel[1], Leah Burke[5], Yehuda Z. Cohen[1], Sonya Hadrigan[1], Allison Settler[1], Maggi Witmer-Pack[1], Anthony P. West Jr[6], Boris Juelg[7], Tibor Keler[8], Thomas Hawthorne[8], Barry Zingman[9], Roy M. Gulick[5], Nico Pfeifer[4], Gerald H. Learn[3], Michael S. Seaman[10], Pamela J. Bjorkman[6], Florian Klein[1,11,12], Sarah J. Schlesinger[1], Bruce D. Walker[7,13], Beatrice H. Hahn[3], Michel C. Nussenzweig[1,14] & Marina Caskey[1]




July 2016

- N=13 with chronic HIV infection suppressed for >12 months
- Infusions of 3BNC117. TI 2 days later
- Up to 19 week delay in rebound vs historical controls (2.6 weeks)
- Rebound occurred with escape variants or once antibody levels had dropped

# Tertiary exploratory endpoints

- For both Stage 1 and Stage 2, these are:
- HIV-specific (humoral and cell-mediated) and innate immune responses
- Immune phenotyping and activation/exhaustion
- Host gene expression
- Viral sequence and integration site analyses
- Measures of the HIV reservoir in blood