Art of ART 2019
HIV cure 101. Progress and challenges

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Overview

- Barriers to HIV Cure
- Framework for HIV Cure strategies
- Cases of HIV remission off ART
- Broadly Neutralising antibodies
- Combination interventions
- Post Treatment Control

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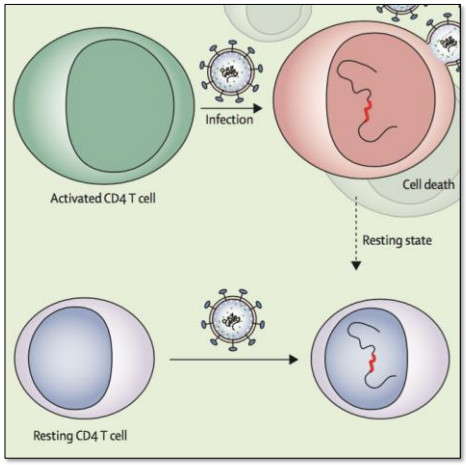
HIV latency

Latent infection = integration of HIV DNA into host genome with virus production

Established by:
- Survival of an activated infected T cell, which reverts to a memory state, or,
- After direct infection of a resting CD4 T cell

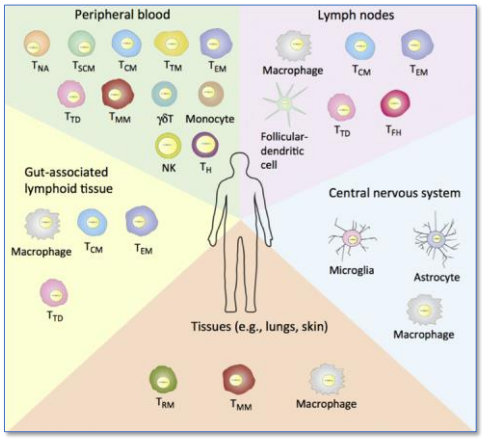


Maartens, Lancet, 2014

Tissue reservoirs

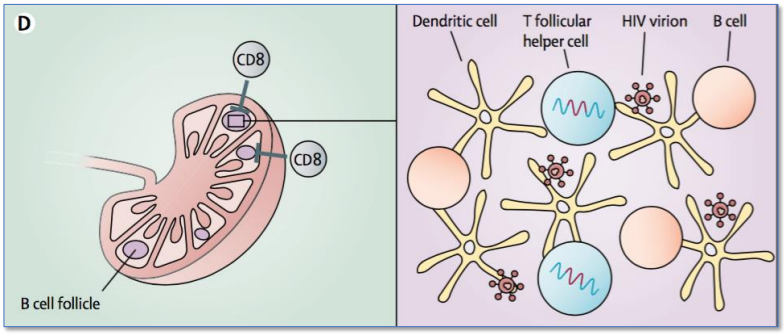
Main sites of latent HIV infection:

- CD4+ memory T cell subsets in peripheral blood
- Lymphoid tissue
- Gut-associated lymphoid tissue
- Central nervous system



Barton, Trends in Microbiology, 2016

Lymph Node B cell follicles



Pitman, Lancet HIV, 2018

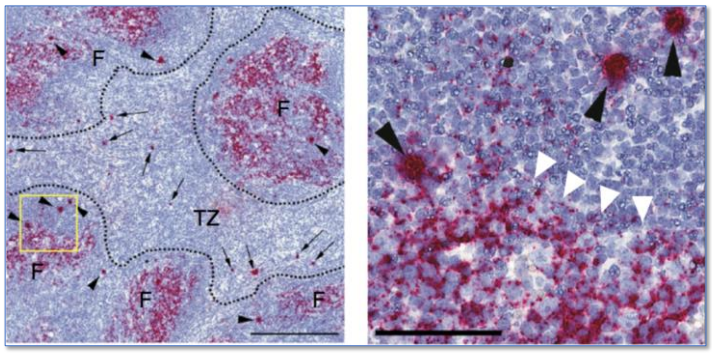
B cell follicles – a sanctuary for HIV

Red = SIV RNA

Black arrows = RNA+ lymphoid cells outside follicles

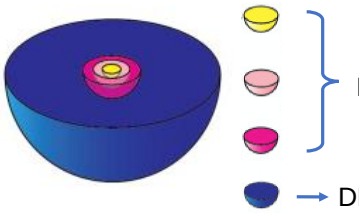
Black arrowheads = RNA+ lymphoid cells in B cell follicles

White arrowheads = extracellular follicular dendritic cell–bound virus within follicles



Fukazawa, Nat Med, 2015

Intact versus defective virus



INTACT ~ 60 / million resting CD4+ T-cells

DEFECTIVE > 80%, Contains deletions, mutations

Frequencies of infected resting CD4+ T cells

- Yellow = size of the latent reservoir measured by viral outgrowth assay
- Magenta and Pink = frequency of cells with intact proviruses
  - Potential reservoir size if intact non-induced proviruses can be induced in vivo
- Blue = cells with HIV DNA

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Ho, Cell, 2013

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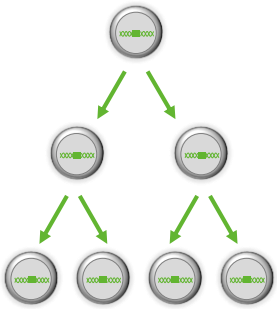
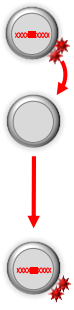
Clonal expansion versus residual replication

Proliferation of latently infected cells



Residual viral replication (productive infection)



Finzi Science 1997; Palmer PNAS 2008; Chomont Nat Med 2009; Fletcher PNAS 2014, Maldarelli Science 2014, Rasmussen Lancet HIV 2019

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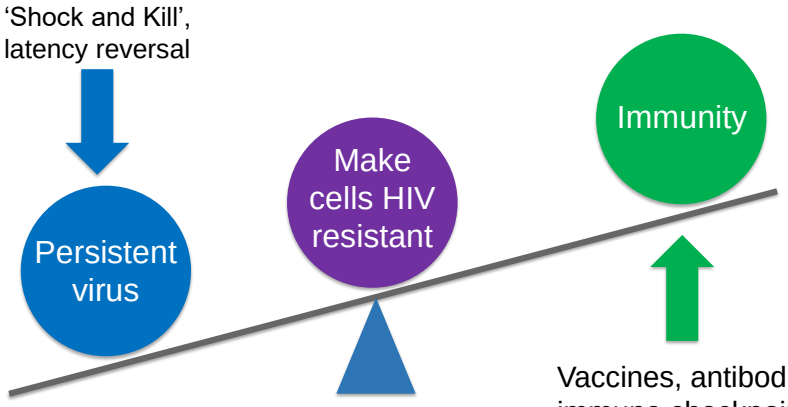
Current approaches to HIV cure/remission



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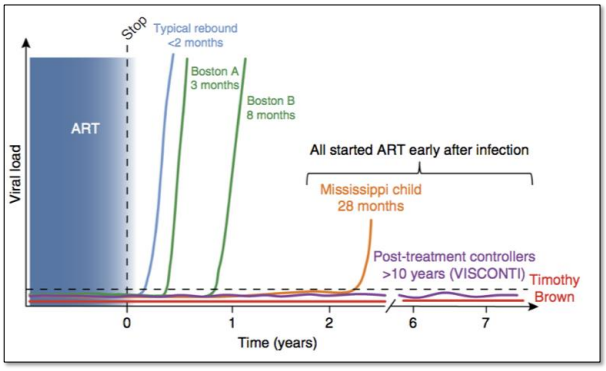
Transient or sustained remission off ART



288 day remission (Mayo)[2]

- allo-HSCT for B-ALL from CCR5 wild type donor
- ATI 2 years post HSCT
- Mild (grade 1) GVHD
- < 1% chimerism
- Asymptomatic viral rebound at day 288 and re-suppressed within 4 weeks

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1 Deeks, Nat Med 2016. 2 Cummins, PLoS Med, 2017

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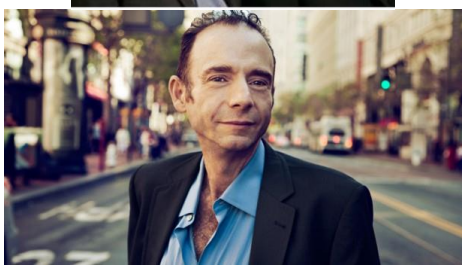
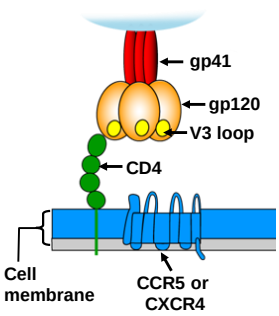
Timothy Brown



CCR5 as target for HIV remission

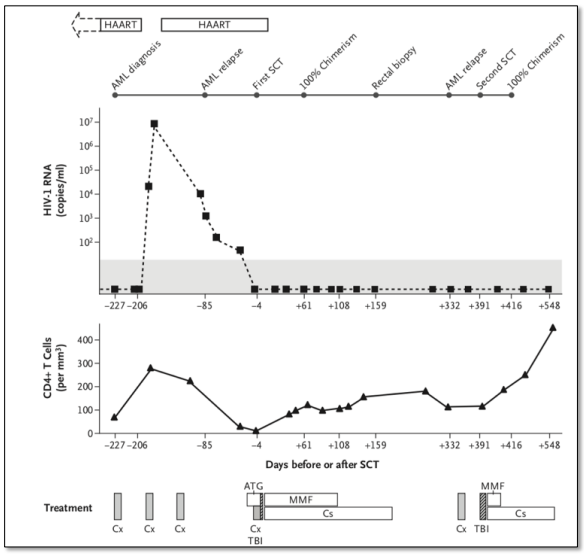


- Δ32 is a 32 base pair deletion in CCR5 preventing expression
- 1% of Europeans are Δ32 homozygous and are resistant to R5 HIV

Adapted from Doms R. Genes Dev. 2000

Timothy Brown - Berlin patient

- Initially reported when 20 months post HSCT and off ART with no viral rebound
- Now 12 years off ART
- On one pill a day PrEP



Hutter NEJM 2009


The New York Times

H.I.V. Is Reported Cured in a Second Patient, a Milestone in the Global AIDS Epidemic


BBC Sign in

NEWS

Health

UK patient 'free' of HIV after stem cell treatment


CNN Health » Food | Fitness | Wellness | Parenting | Live Longer International Edition +

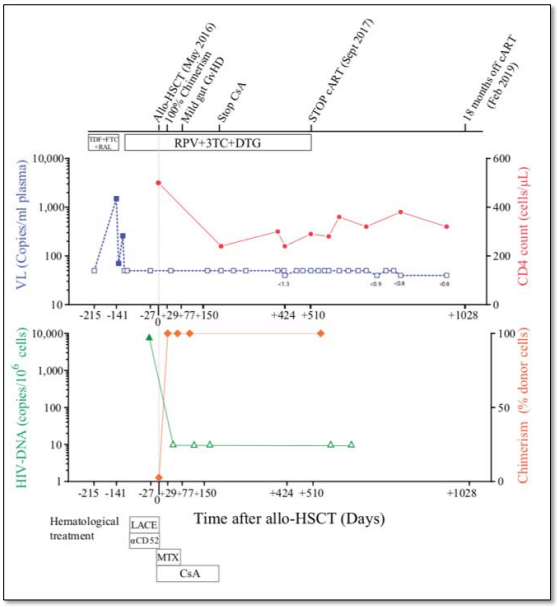
Two men might be second and third to be cured of HIV


abcNEWS VIDEO LIVE SHOWS LOG IN

The 'London Patient' goes into HIV remission: Here's what that means for HIV treatment

London patient

- Male (? age), HIV Dx 2003
- TDF/FTC/EFV 2012
- Hodgkin's Lymphoma 12/2012
- Progressed post chemotherapy
- Donor: Unrelated 9/10 HLA match, Homozygous for the CCR5 delta 32 mutation
- Conditioning: chemotherapy (LACE) and alemtuzumab (anti-CD52). No irradiation
- Discharged Day +31
- Day +77: Grade 1 GVHD



Gupta, Nature 2019

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London patient

- 100% donor chimerism from day 30
- Genotype changed from CCR5 wildtype before transplant, to CCR5 Δ32/Δ32 after transplant

- Patient cells post transplant could not be infected by R5 virus
- Patient cells from pre-transplant R5 only

- HIV not detectable in blood pre and post* ART interruption
- Loss of antibody response to HIV

*3 x VOA, 3 DNA PCR assays [1/8 replicate low +ve on one assay]

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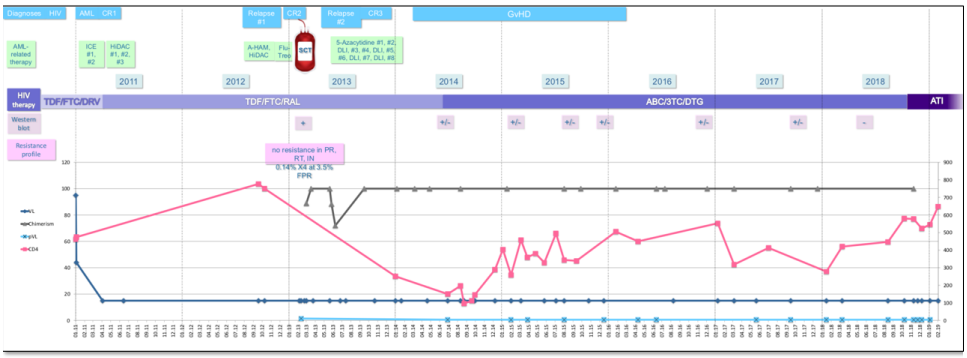
Significance

- Tim Brown was not an anomaly
- Significance of CCR5 disruption for cure strategies
  - E.g. Gene editing to remove CCR5 from T-cells,[1] but only ~ 10% of persisting CD4+ T-cells are CCR5 modified
- Continue to pursue CCR5 negative donors for PLHIV requiring HSCT
- However, these therapies are not to treat HIV but to treat aggressive cancer

Dusseldorf patient

- 49 yo male. Diagnosed with AML 2011. HSCT 2/2013
- Transplant donor: 10/10 HLA match, homozygous for the CCR5 Δ32 mutation
- Conditioning: fludarabine and treosulfan. No irradiation
- Post HSCT: Relapse 6/2013 → 8 courses of 5-azacytidine and 4 donor lymphocyte infusions → remission
- 3/2014: Grade 1 graft versus host disease

Dusseldorf patient



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Dusseldorf patient

- 100% donor chimerism
- HIV not detectable in blood and tissues[1]
- Loss of antibody response to HIV
- Patient cells from **pre-**transplant considered genotypically and phenotypically R5 expressing
- Predicted R5 tropic based on sequence data (Sanger)[2]

1 Blood (PCR, VOA, mVOA) and tissues (GIT x 4, bone marrow, lymph node) post HSCT(multiple PCR assays [1/4 replicate low +ve on one assay for ileum])

2 Next Gen sequencing 0.14% X4 at 3.5% FPR (False positive rate) → an extremely small number of reads for a very small part of the virus sequenced (V3 loop) identified as X4

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Compare the 3 cases

	London patient	Dusseldorf patient	Berlin patient
Underlying condition	Hodgkin's Lymphoma	AML	AML
HSCT, donor CCR5 Δ32/Δ32	Once	Once	Twice
Conditioning	reduced intensity: anti–CD52 (alemtuzumab)	reduced intensity: fludarabine/ treosulfan	Total body irradiation (twice)
GvH disease	Grade 1	Grade 1	Grade 1
Chimerism post HSCT	100%	100%	100%
ART post-transplant	16 months	66 months	None
Time with HIV remission	18 months	3 months	12 years

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Broadly Neutralising Antibodies

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Broadly Neutralizing Antibodies (bNAbs)

- Derived from a people that develop potent cross-neutralizing antibodies to many different HIV strains
  - International HIV Controller study[1]
- Bind HIV envelope protein expressed on HIV or the surface of infected cells
  - Neutralise free virus → can't go on to infect other cells
  - Clear infected cells → Fc receptor-dependent mechanisms (binding to Fc receptors on cytotoxic / phagocytic cells) e.g. ADCC, facilitate antigen presentation
- Can be produced in larger quantities with new Ab cloning techniques

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1 Pereyra, Science, 2010

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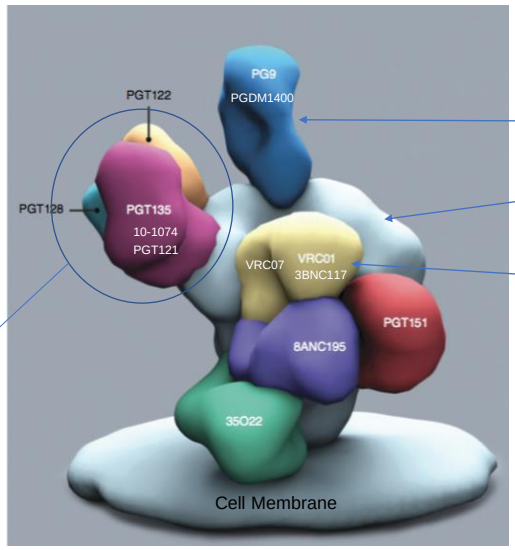
Broadly Neutralizing Abs (antigen-binding fragments) bound to the HIV Envelope trimer



High Mannose Patch / V3 loop / N332 Glycan Supersite

Adapted from Burton Nat Immunol 2015

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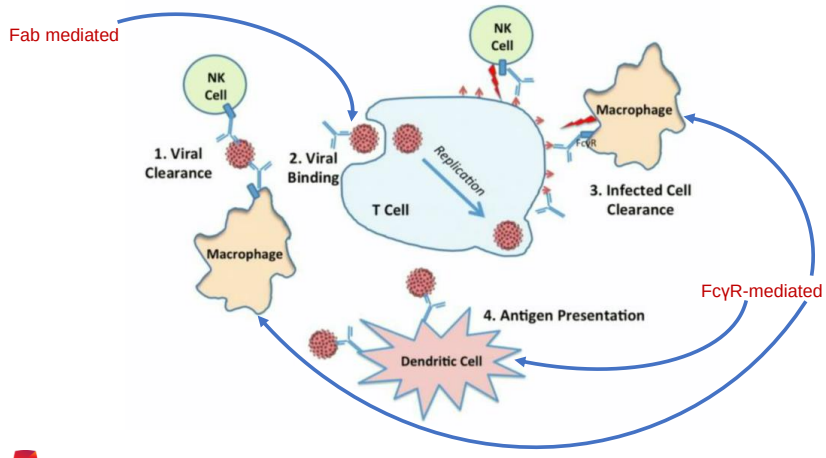
How do bNAbs work?



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Adapted from Nussenzweig CROI 2017

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Combinations of Broadly Neutralizing Antibody when interrupting ART

ARTICLE

https://doi.org/10.1038/s41586-018-0531-2

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]*

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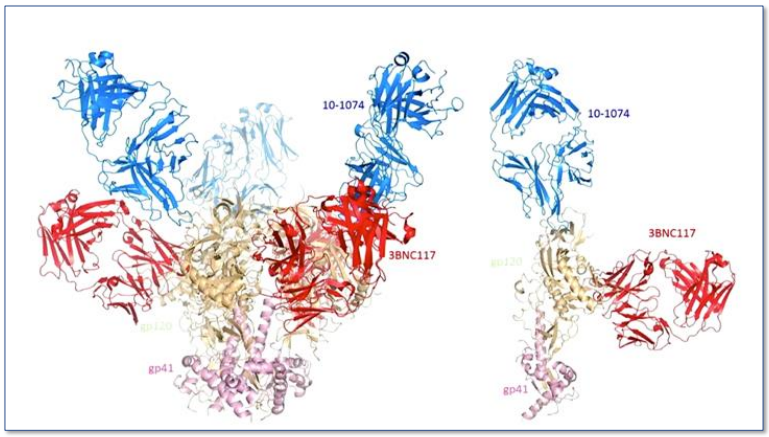
3BNC117 + 10-1074 target non-overlapping sites on HIV (CD4 binding site and V3 loop)



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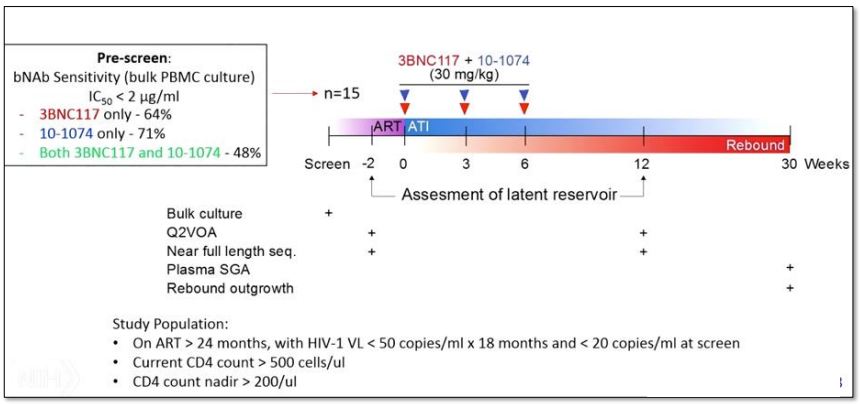
Design: 3BNC117 + 10-1074 with ART interruption



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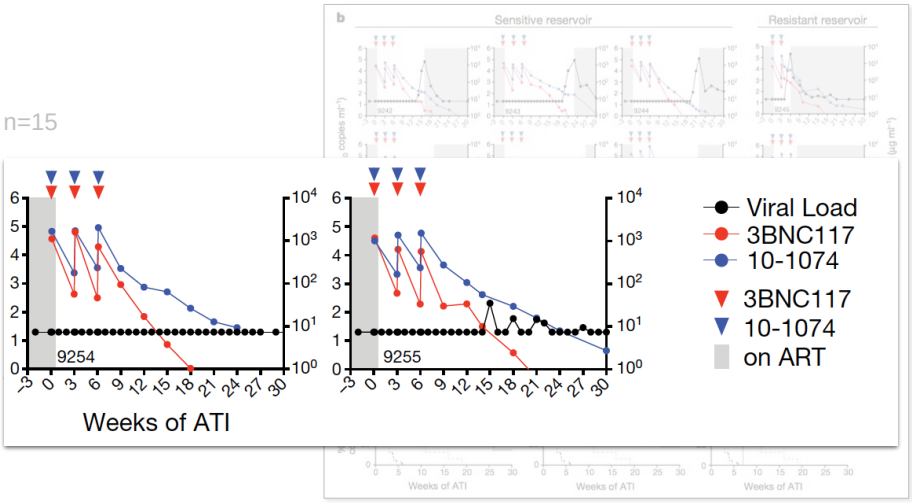
n=15



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Mendoza, Nature, 2018

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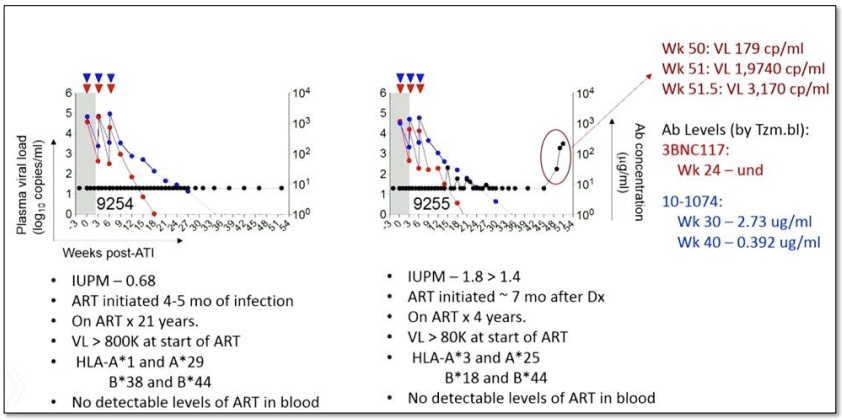
Of 2 controllers: one rebounded at 1 year, the other remains suppressed



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The person controlling virus started ART early
HLA types are not that of elite controllers

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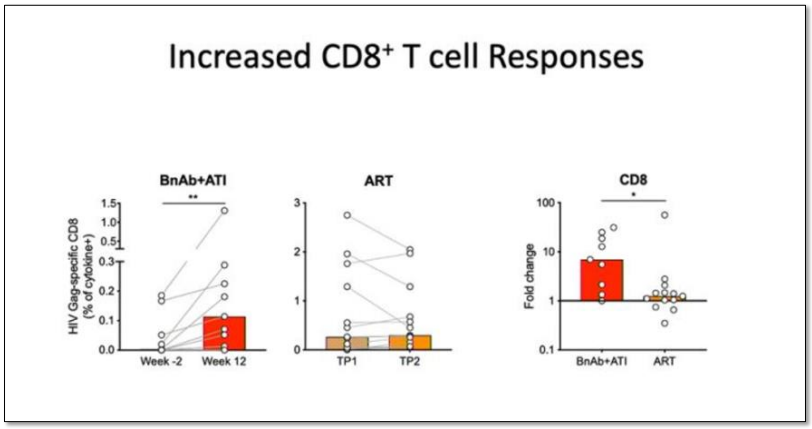
Increased HIV-specific immune responses in those receiving bNAbs even when virally suppressed

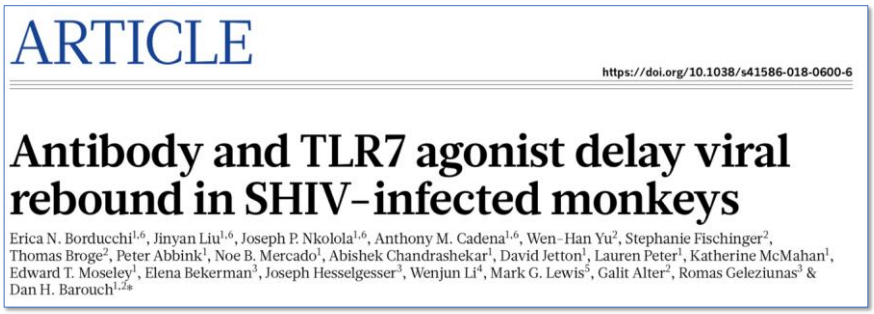


Nussenzweig, CROI plenary 2019

Combination intervention to increase HIV-specific immune responses

PGT-121 (another bNAb) and TLR7 agonist

Combining broadly Neutralizing Antibody with another immunomodulator (TLR7 agonist) in a monkey model



ARTICLE

https://doi.org/10.1038/s41586-018-0600-6

Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys

Erica N. Borducchi[1,6], Jinyan Liu[1,6], Joseph P. Nkolola[1,6], Anthony M. Cadena[1,6], Wen-Han Yu[2], Stephanie Fischinger[2], Thomas Broge[2], Peter Abbink[1], Noe B. Mercado[1], Abishek Chandrashekar[1], David Jetton[1], Lauren Peter[1], Katherine McMahan[1], Edward T. Moseley[1], Elena Bekerman[3], Joseph Hesselgesser[3], Wenjun Li[4], Mark G. Lewis[5], Galit Alter[2], Romas Geleziunas[3] & Dan H. Barouch[1,2]*

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Combinations to increase HIV-specific immune responses in the setting of ART treated suppression

- bNAb effector functions → potentially clear HIV infected T-cells and increase antigen presentation and therefore increase HIV-specific cytotoxic T-cell responses
- TLR-7 agonists
  - Activate dendritic cells to produce IFN-α and other cytokines
  - Cause activation of NK cells and cross-priming of cytotoxic T-cells
  - Therefore impact innate and adaptive immune responses
- Can a bNAb with a additional immune stimulant (TLR7 agonist) target the HIV reservoir and lead to viral control off ART

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Study Drugs

- TLR7 agonist GS-9620 (Vesatolimod)
  - NCT02858401 - Dose escalation study in suppressed patients looking for change in HIV RNA from baseline.
    - Completed March 2019, to be presented IAS 2019
  - NCT03060447 – Placebo controlled ATI study in people whose pre-ART viral load was < 5000 c/mL. GS-9620 pre and post ATI

- PGT-121
  - NCT03205917 – Phase 1 study alone and in combination with another bNAb (PGDM1400) in uninfected and infected viremic people
  - NCT02960581 (IAVI T001) – Phase 1 study in uninfected, and infected viremic and aviremic people. Partially presented at CROI 2019

- Both being developed by Gilead and in trials alone for PLHIV

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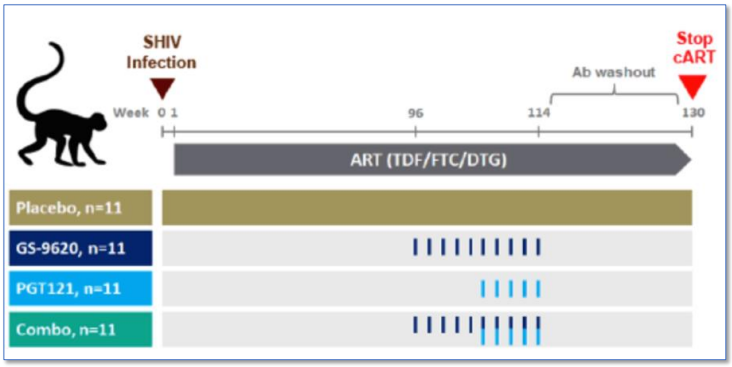
Methods

- SHIV infected (IR) then start ART (TDF/FTC/DTG) 1 week later and suppressed for 96 weeks
- 4 groups of 11 → Placebo, bNAb, TLR7, bNAb + TLR7



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Results

- Study designed for bNAb and TLR7 to be cleared from animals before interrupting ART → determine if these interventions could impact the reservoir without direct antiviral activity
- Blood and biopsy samples - showed there was no bNAb more than 10 weeks before stopping ART
- Showed that no HIV specific CD8 T-cell responses in blood or lymph node before interrupting
- Undetectable HIV DNA in lymph nodes in combination group

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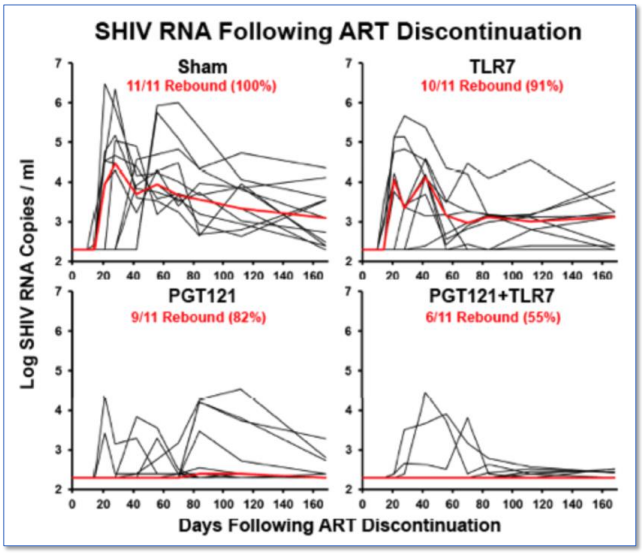

- 5 in combination arm didn't rebound for over 168 days
- Also lower peak and setpoint VLs in those that rebounded

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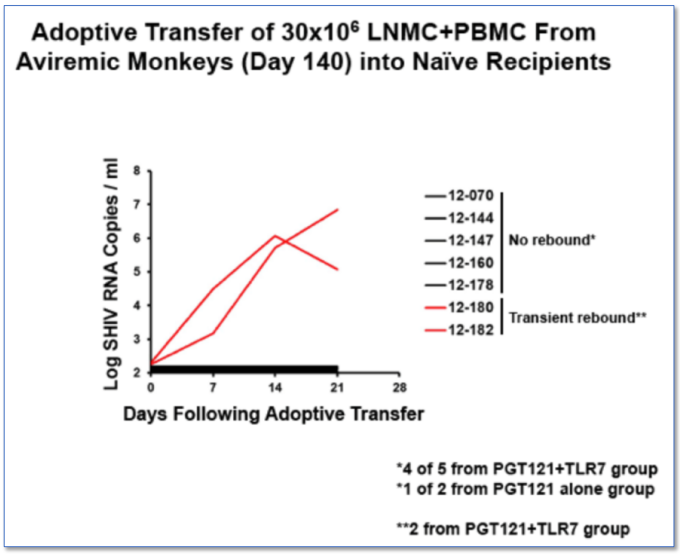
No infection of uninfected monkeys with adoptive transfer



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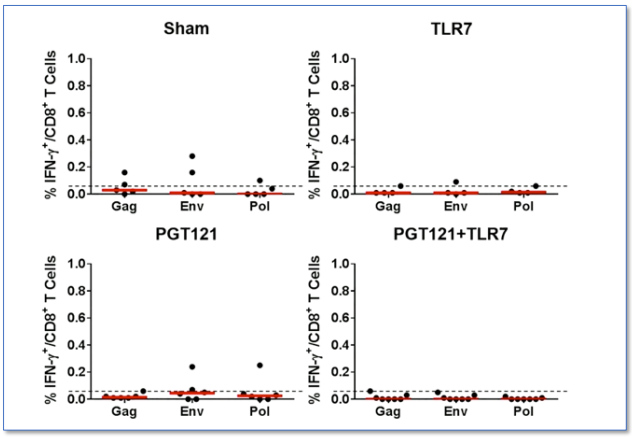
No vaccinal effect (↑ CD8 T-cell responses) – so briefly exposed to HIV and such prolonged suppression on ART



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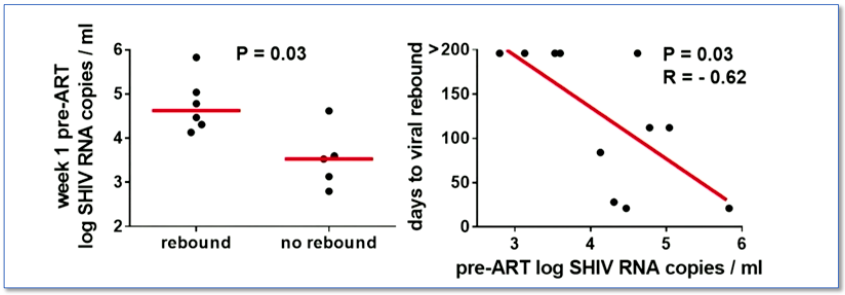
Animals that don't rebound had the lowest viral loads at week 1 (3 years prior)



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Conclusions

- Combination of PGT-121 and GS9620 had 5-fold delay in time to viral rebound and no viral rebound in 5 of 11 monkeys
- No residual PGT-121 to explain delay in rebound
- Mechanism unclear
  - May involve activation of infected CD4+ T-cells by GS-9620 and enhanced clearance by PGT-121
- No 'vaccinal effect'
- bNAb + immune stimulant may target reservoir

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Combination Therapies with TLR7 Agonists

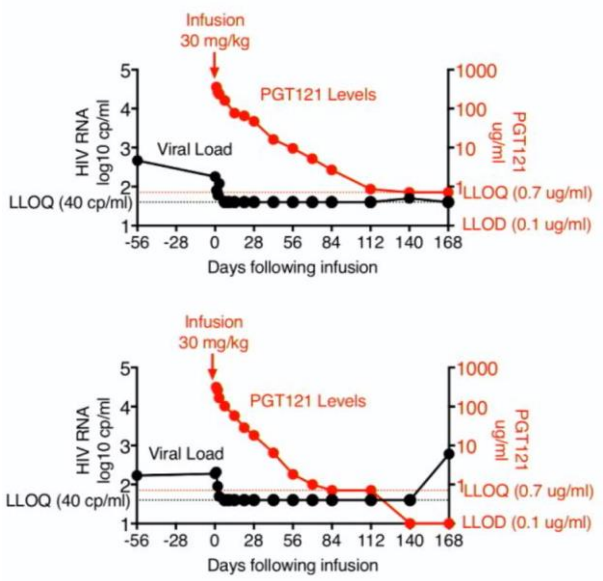
- PGT121. Engineered Fc receptor further and now called GS-9722 → completed dose escalation study in healthy volunteers. Planning for a study in HIV +ve in 2019
- Planning to combine a therapeutic vaccine and a TLR7 agonist in 2019 (sourcing a vaccine from external partners → Hookipa who have a CMV vaccine in arenavirus vector → working to develop a therapeutic vaccine with same arenavirus vector)
- Planning to combine bNAb GS-9722 with TLR7 agonist
- Developing a second bNAb

The same bNAb now in PLHIV

Part	Group	mAb	Dose (mg/kg)	Route	HIV	ART	Viral Load (Log_{10} cp/ml)	PGT121 / Placebo (N)	Enrolled
1	1	PGT121	3	IV	No	-	-	4 / 1	✓
		PGT121	10	IV	No	-	-	4 / 1	✓
		PGT121	30	IV	No	-	-	4 / 1	✓
		PGT121	3	SC	No	-	-	4 / 1	✓
	2	PGT121	3	IV	Yes	Yes	<1.7	4 / 1	✓
		PGT121	10	IV	Yes	Yes	<1.7	4 / 1	✓
		PGT121	30	IV	Yes	Yes	<1.7	4 / 1	✓
2	3	PGT121	30	IV	Yes	No	3.3 – 5	9 / -	✓
		PGT121	30	IV	Yes	No	2 – 3.3	6 / -	4 (6)
	Total							43 / 7	48 (50)

- Single infusion PGT-121 at different doses
- Safe. 5/9 people with viral load 3.3- 5 log_{10} c/mL (high viral load) had 1.7 log_{10} drop in viral load

2 people off ART with low viral load had suppression > 6 months



Combination intervention - ‘Kick and Kill”

HIV therapeutic vaccine and Latency reversal

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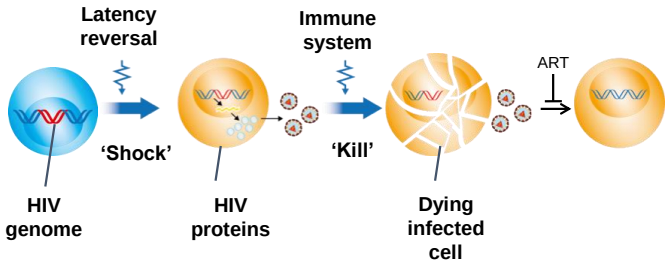
RIVER study

- **Treated Primary HIV infection**:
  - lowest reservoirs, preserved immune responses
- **The Kick:**
  - HDAC inhibitor Vorinostat
- **The Kill:**
  - ChAdV63.HIVconsv and MVA.HIVconsv*
- **Design:**
  - Randomised control comparison with ART alone
- **Primary endpoint:**
  - Total HIV DNA in peripheral blood CD4+ T-cells at weeks 16 & 18 post randomisation

*Letourneau S Plos One 2007



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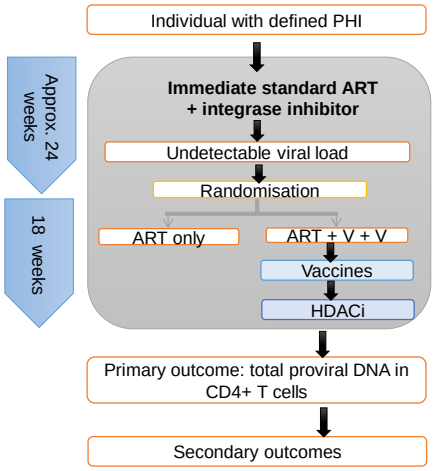
RIVER - Study design



Vaccination:
Prime
ChAdV63.HIVconsv at randomisation
Boost MVA.HIVconsv week 8 post-randomisation

Vorinostat
400mg od every 72 hours* total 10 doses

*Archin et al J Clin Invest 2017 Aug 1;127(8):3126-3135.

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Description of participants at randomisation

	ART only N = 30	ART + V + V N = 30	Total n = 60
Age (years)	31 (30,38)	35 (28,44)	32 (29,40)
Gender	30 (100%) male	30 (100%) male	60 (100%) male
Route of transmission MSM MSW Other	 26 (87%) 1 (3%) 3 (10%)	 29 (97%) 1 (3%) 0	 55 (92%) 2 (3%) 3 (5%)
CD4 count (cells/mm^3)	694 (561, 844)	710 (579, 759)	708 (568, 788)
HIV Viral Load (copies/mL) <50 50 - <200	 29(97%) 1 (3%)	 30 (100%) 0	 59 (98%) 1 (2%)
Weeks since PHI diagnosis to randomisation	28 (27,41)	28 (27,34)	28 (27,36)

Note: Numbers are N (%) or median (IQR)

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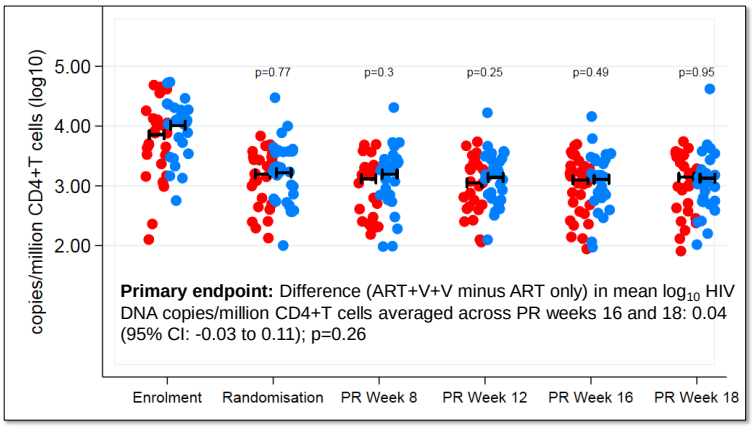
No effect (difference in HIV DNA) of intervention



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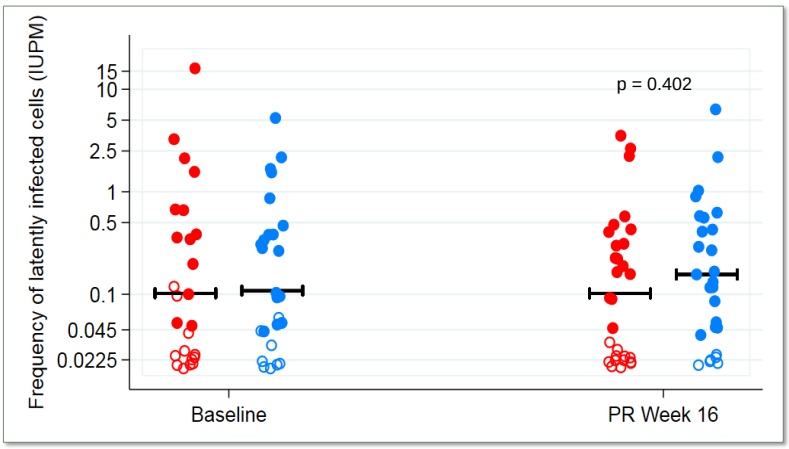
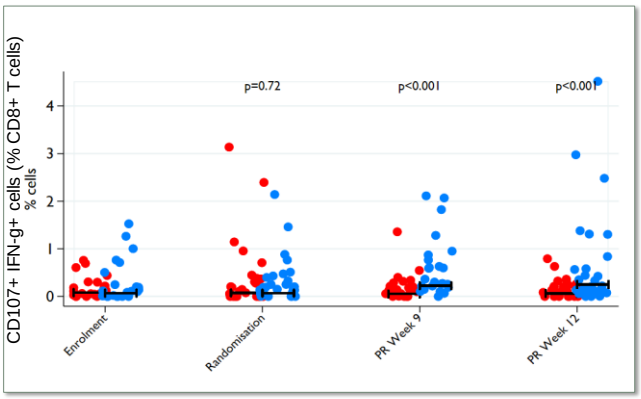
No effect by different measure of the HIV reservoir (Viral outgrowth assay)



ART only ART +V+V

ART + V + V boosts HIV-specific CD8+ T cells



p-values: rank tests for difference between groups per time-point

ART only ART +V+V

Summary

- This approach to “kick and kill” did not lead to a reduction of the HIV reservoir over ART alone, as measured by total HIV DNA, 1 year after PHI
- Interventions were safe
- ART + V + V stimulated HIV-specific CD4 and CD8 T-cell responses
- Highlights importance of a control arm for this endpoint. Definitive result
- ? latency reversing agent not potent enough
- ? epitopes in the vaccine constructs were not the correct ones to recognize latently infected cells.

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Post Treatment Control

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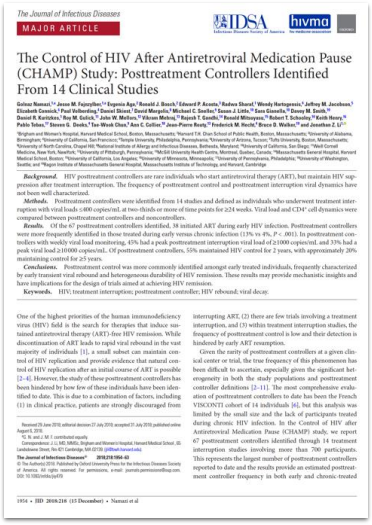
Higher frequency of post treatment control with early ART

- Post treatment control identified from 14 studies incl ATI
- 67 PTCs identified
- 38 started ART during early HIV infection
- PTC more frequently identified in those starting ART during early vs chronic infection (13% vs 4%, P<0.001)



The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA hivma

The Control of HIV After Antiretroviral Medication Pause (CHAMP) Study: Posttreatment Controllers Identified From 14 Clinical Studies

Golnoz Namazi,[1,a] Jesse M. Fajnzylber,[1,a] Evgenia Aga,[2] Ronald J. Bosch,[2] Edward P. Acosta,[3] Radwa Sharaf,[1] Wendy Hartogensis,[4] Jeffrey M. Jacobson,[5] Elizabeth Connick,[6] Paul Volberding,[7] Daniel Skiest,[8] David Margolis,[9] Michael C. Sneller,[1] Susan J. Little,[10] Sara Gianella,[10] Davey M. Smith,[10] Daniel R. Kuritzkes,[1] Roy M. Gulick,[11] John W. Mellors,[11] Vikram Mehraj,[12] Rajesh T. Gandhi,[13] Ronald Mitsuyasu,[14] Robert T. Schooley,[15] Keith Henry,[16] Pablo Tebas,[17] Steven G. Deeks,[4] Tae-Wook Chun,[2] Ann C. Collier,[18] Jean-Pierre Routy,[19] Frederick M. Hecht,[4] Bruce D. Walker,[20] and Jonathan Z. Li[1,21]

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Background. HIV posttreatment controllers are rare individuals who start antiretroviral therapy (ART), but maintain HIV suppression after treatment interruption. The frequency of posttreatment control and posttreatment interruption viral dynamics have not been well characterized.

Methods. Posttreatment controllers were identified from 14 studies and defined as individuals who underwent treatment interruption with viral loads ≤400 copies/mL at two-thirds or more of time points for ≥24 weeks. Viral load and CD4+ cell dynamics were compared between posttreatment controllers and noncontrollers.

Results. Of the 67 posttreatment controllers identified, 38 initiated ART during early HIV infection. Posttreatment controllers were more frequently identified in those treated during early versus chronic infection (13% vs 4%, P < .001). In posttreatment controllers with weekly viral load monitoring, 45% had a peak posttreatment interruption viral load of ≥10 000 copies/mL and 33% had a peak viral load ≥10 000 copies/mL. Of posttreatment controllers, 55% maintained HIV control for 2 years, with approximately 20% maintaining control for ≥5 years.

Conclusions. Posttreatment control was more commonly identified amongst early treated individuals, frequently characterized by early transient viral rebound and heterogeneous durability of HIV remission. These results may provide mechanistic insights and have implications for the design of trials aimed at achieving HIV remission.

Keywords. HIV; treatment interruption; posttreatment controller; HIV rebound; viral decay;

One of the highest priorities of the human immunodeficiency virus (HIV) field is the search for therapies that induce sustained antiretroviral therapy (ART)-free HIV remission. While discontinuation of ART leads to rapid viral rebound in the vast majority of individuals [1], a small subset can maintain control of HIV replication and provide evidence that natural control of HIV replication after an initial course of ART is possible [2–4]. However, the study of these posttreatment controllers has been hindered by how few of these individuals have been identified to date. This is due to a combination of factors, including (1) in clinical practice, patients are strongly discouraged from interrupting ART, (2) there are few trials involving a treatment interruption, and (3) within treatment interruption studies, the frequency of posttreatment control is low and their detection is hindered by early ART resumption.

Given the rarity of posttreatment controllers at a given clinical center or trial, the true frequency of this phenomenon has been difficult to ascertain, especially given the significant heterogeneity in both the study populations and posttreatment controller definitions [2–11]. The most comprehensive evaluation of posttreatment controllers to date has been the French VISCONTI cohort of 14 individuals [6], but this analysis was limited by the small size and the lack of participants treated during chronic HIV infection. In the Control of HIV after Antiretroviral Medication Pause (CHAMP) study, we report 67 posttreatment controllers identified through 14 treatment interruption studies involving more than 700 participants. This represents the largest number of posttreatment controllers reported to date and the results provide an estimated posttreatment controller frequency in both early and chronic-treated

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Namazi JID 2018

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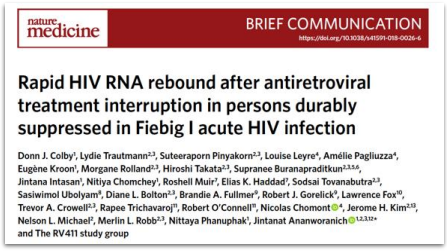
Virus rebound despite starting ART in Fiebig I



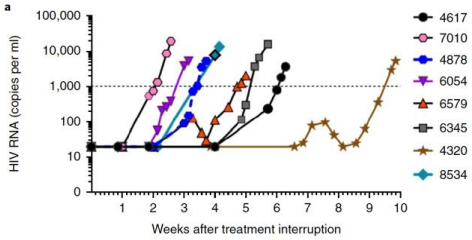
nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-018-0026-6

Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection

Donn J. Colby[1], Lydie Trautmann[2,3], Suteeraporn Pinyakorn[2,3], Louise Leyre[4], Amélie Pagliuzza[4], Eugène Kroon[1], Morgane Rolland[2,3], Hiroshi Takata[2,3], Supranee Buranapraditkun[2,3,5,6], Jintana Intasan[1], Nitiya Chomchey[1], Roshell Muir[7], Elias K. Haddad[7], Sodsai Tovanabutra[2,3], Sasiwimol Ubolyam[8], Diane L. Bolton[2,3], Brandie A. Fullmer[9], Robert J. Gorelick[9], Lawrence Fox[10], Trevor A. Crowell[2,3], Rapee Trichavaroj[11], Robert O'Connell[11], Nicolas Chomont[4], Jerome H. Kim[2,12], Nelson L. Michael[2], Merlin L. Robb[2,3], Nittaya Phanuphak[1], Jintanat Ananworanich[1,2,3,12*] and The RV411 study group



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Colby Nature Med 2018

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Additional Slides

Vedolizumab

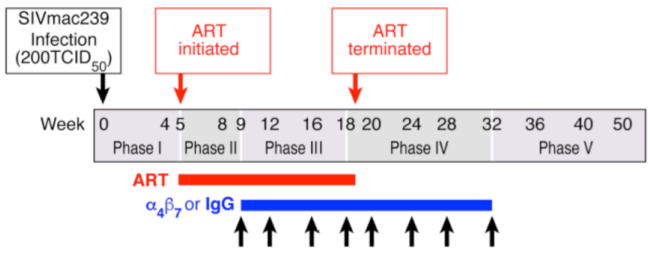
Anti-α4β7 monclonal antibody in macaques

- Pathway CD4+ T cells use to traffic into GIT is an interaction between integrin α4β7 on CD4+ T cells, with MaDCAM-1 on GIT venules
- CD4+ T cells expressing high levels of α4β7 preferentially targeted by HIV
- Monoclonal antibody against α4β7 integrin shown to decrease risk of HIV acquisition in macaques

Byrareddy, Science, 2016

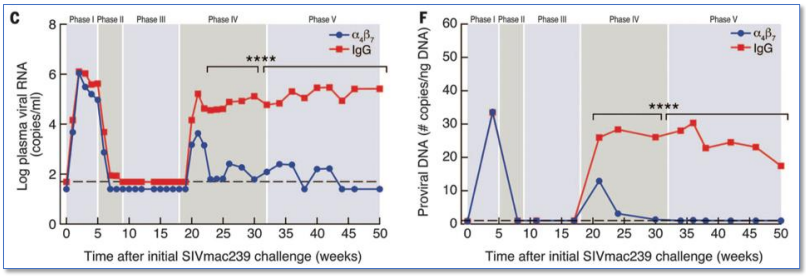
Anti-α4β7 mAb in macaques

- 18 rhesus macaques infected with SIV



Byrareddy Science 2016

Anti-α4β7 mAb in macaques



7 control animals
8 monkeys who received anti-α4β7 achieved virologic control up to 23 months post interrupting ART

- 3 additional monkeys developed antibodies against anti-α4β7 and excluded

Anti-α4β7 mAb in macaques

- ART + α4β7 mAb → prolonged virologic control and restoration of CD4+ T cells
  - Mechanism - ? HIV takes up and expresses α4β7 on virion after initial round of T-cell infection and replication. Subsequent α4β7 expressing virions are bound by the monoclonal Ab[1]
- Control persisted long after a4b7 mAb treatment was terminated
- Improvement in some T-cell subsets / changes in anti-HIV Ab response / increased NK cells / Reduced damage to GIT

Strategy post the 2016 paper

- Replicate the macaque study at NIH
- Human study

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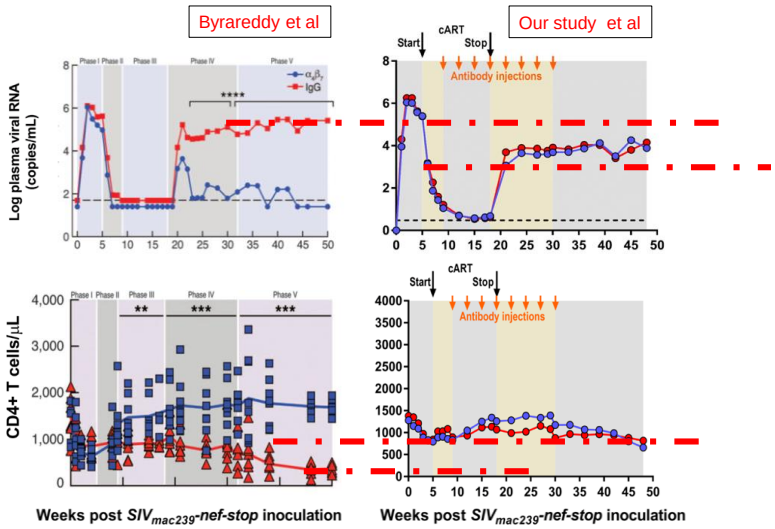
2 "identical" macaque studies

Difference not explained by viral stock, lot of antibody used or developing anti-drug antibodies.

Genetic or other differences in the macaques or other factors, including differences in virus/host balance related to differential kinetics and pathway of Nef-STOP repair, may have contributed to the differences



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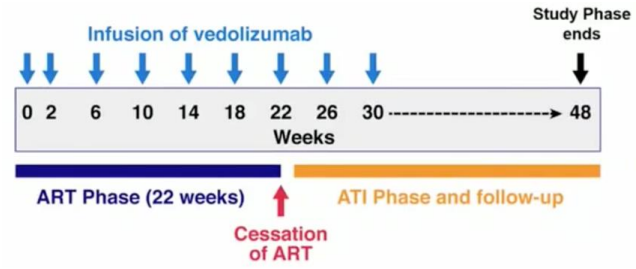
Human study

- Open label, single arm
- N=18
- CD4 > 450, virological suppression for > 2 years
- Restart criteria
  - VL > 1000 c/mL for > 4 weeks
  - 30% drop in CD4 or CD4 < 350
  - OI



Compared study patients to placebo group of a therapeutic vaccine RCT

? Why different to the first monkey study
→ Different Fc portion of Abs
→ Different host
→ Different restart criteria