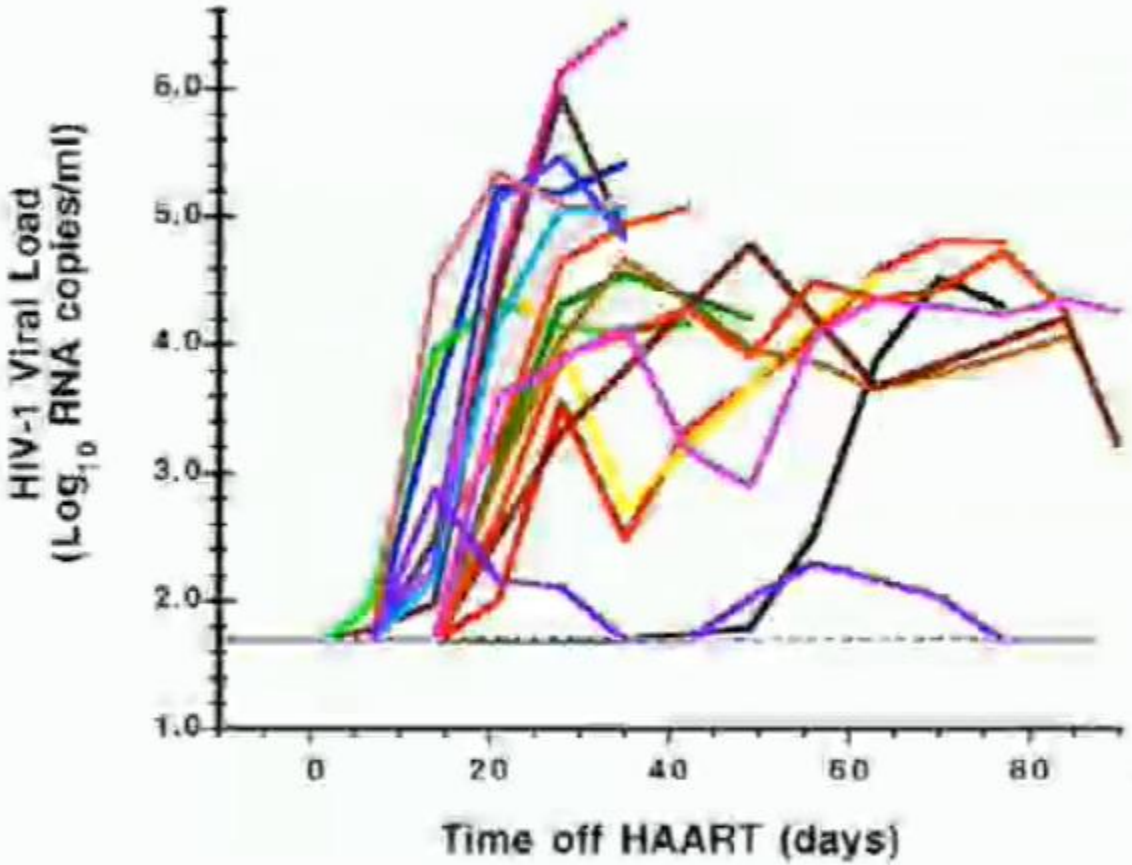
The persistent latent reservoir



Despite suppressive ART, virus rebounds after treatment interruption revealing persistent reservoir

- Latent reservoir was revealed early, but many fundamental properties remain unknown.
- Definition: replication-competent HIV provirus integrated into long-lived, quiescent cells that persist despite suppressive ART.
- Cell types:
  - Resting memory CD4 T cells
    - Central memory, Tfh, Treg, Th1, HIV-specific
  - Macrophage lineages, others
- Anatomic distribution
  - Lymph tissues
  - CNS: astrocytes and macroglia

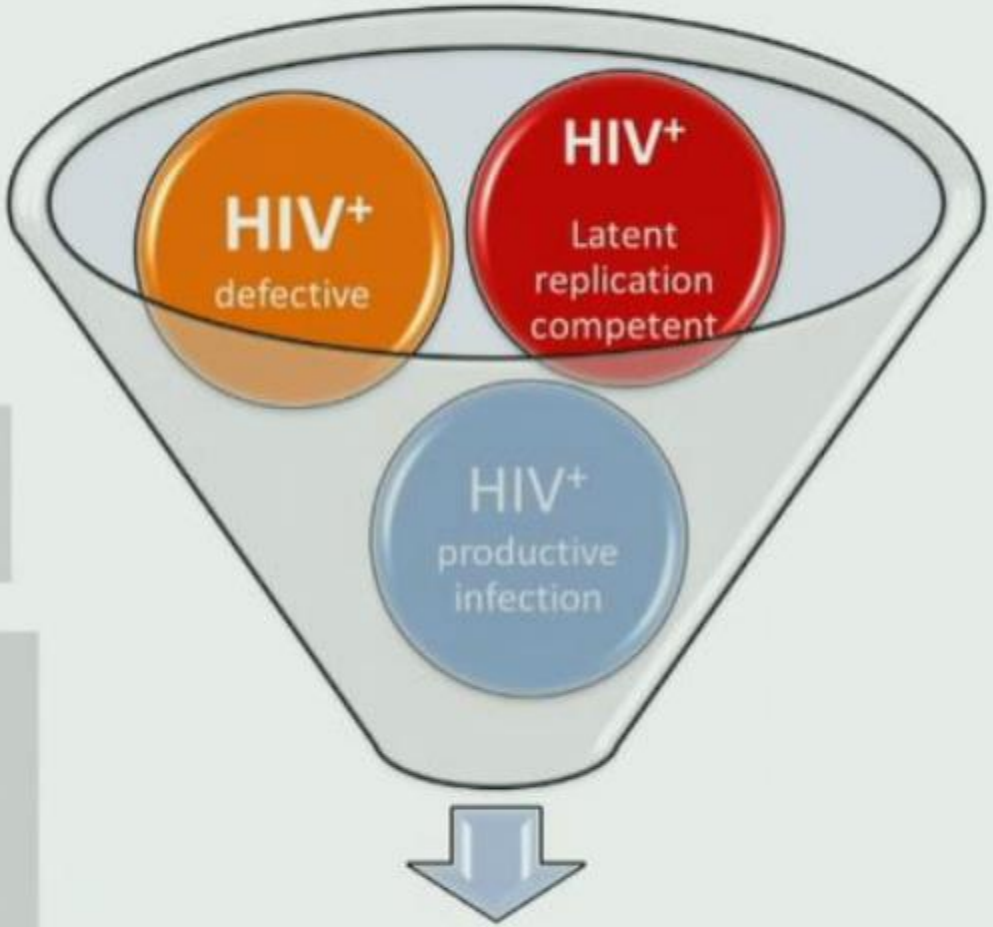
Davey R T et al. PNAS 1999;96:15109-15114

The HIV-1 reservoir - an enigma

The simple fact:
HIV-1 provirus integrates into the host cells.
Latently infected cells persist and necessitate a life long treatment.

The obvious:
Eliminate the latent reservoir to cure HIV-1

The challenge:
Size - how big is the reservoir?
Access – how can we reach the reservoir?
Eradication – how can we eliminate the reservoir?



The cellular HIV-reservoir

CD4+ T cells

T_{CM}

T_{TM}

T_N

T_{EM}

T_{SCM}

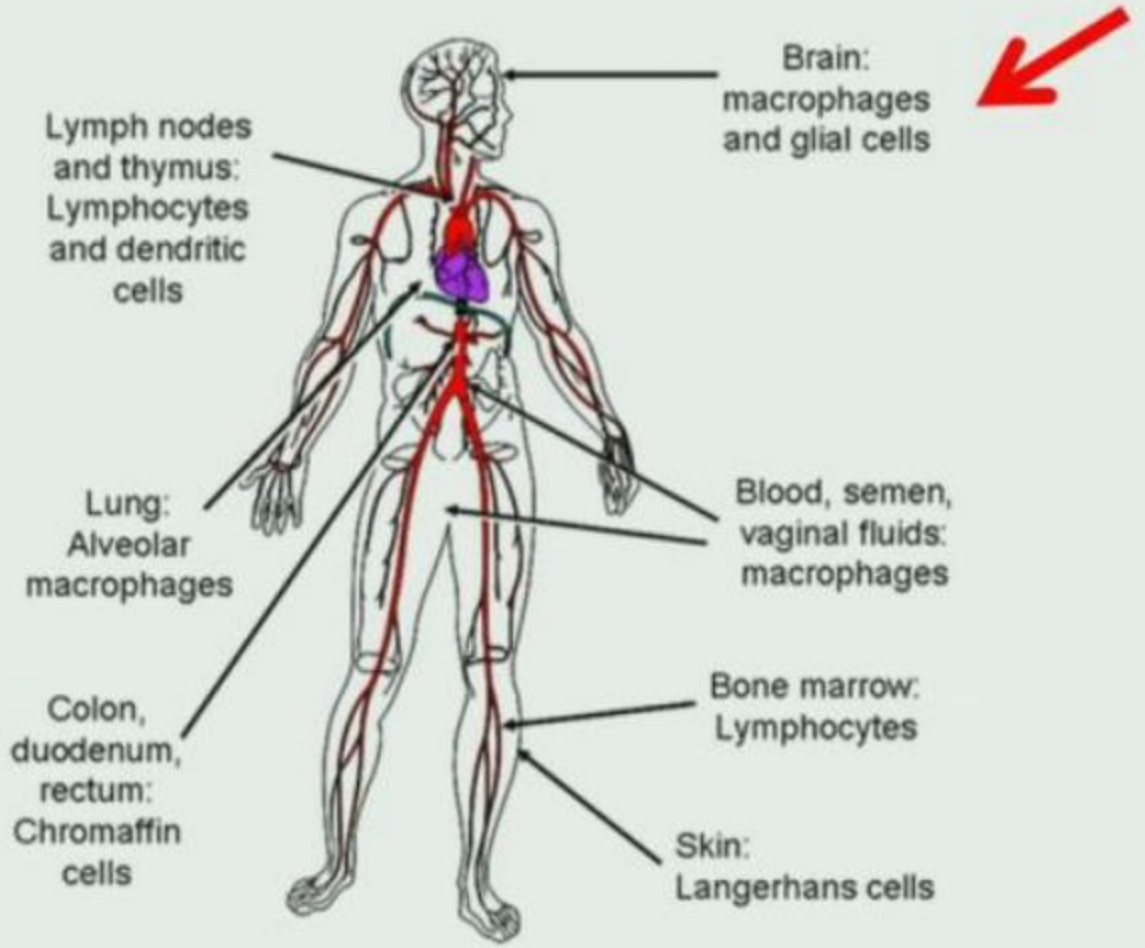
Monocytes/ Macrophages

Others?

DCs
NK cells
Renal EC
Mucosal EC
Mastocytes
Astrocytes
Microglia
Skin Fibroblasts
Stem cells

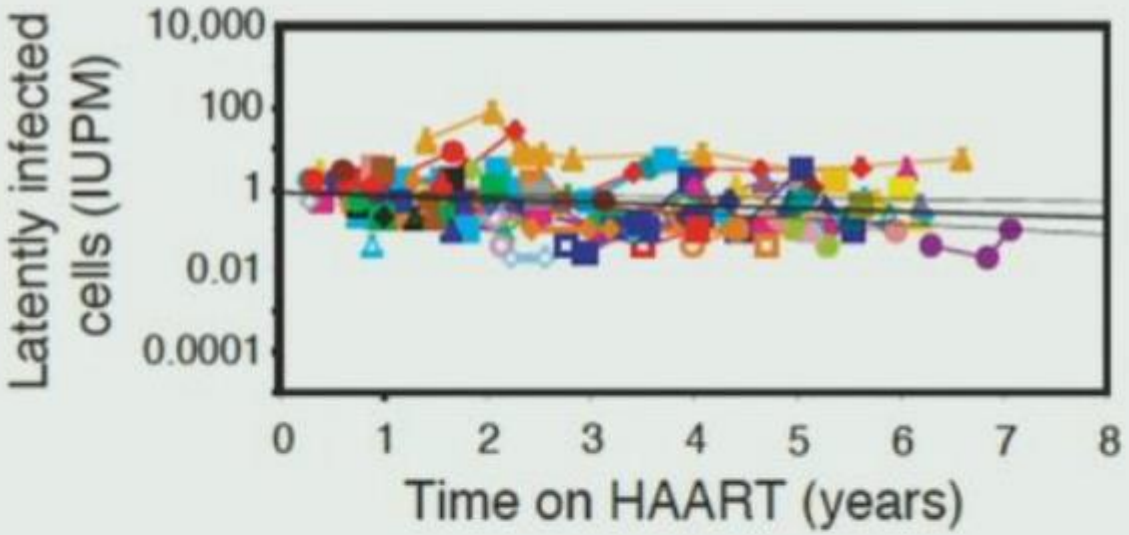
Chomont et al, Nat Med, 2009, and many others

Anatomical Sites of the HIV Reservoir



Adapted from Microbiology and Immunology online, R. Hunt, 2013

Very slow decay of the latent reservoir confirmed



The viral outgrowth assay measures

$t_{1/2}$ = 44 months

- It would take 60 years to eradicate a low reservoir estimate of 10^5cells!

Siliciano et al, Nature Medicine, 2003

Why do we not see more decay?

«Con» low level replication

1. Lack of evolution in viruses isolated from latent reservoir, in lymph nodes after two years of suppressive ART and from PBMCs

   (Günthard, J Virol, 1999/JID, 2001, Nettles, JAMA 2005)

2. Absence of evolution of rebounding virus on ART and after treatment interruption

   (Joos, PNAS, 2008, Kearny, Plos Path 2014)

«Con» low level replication

4. ART intensification mostly lacks effect on latent reservoir (Dinoso, PNAS, 2009, McMahon, CID, 2010, Gandhi; JAIDS, 2012, Rusconi PlosOne, 2013, Hunt, Blood, 2013, Markowitz, JAIDS, 2014, Ananworanich, J Viral Erad, 2015 and more)
5. Replenishment of latent reservoir by clonal expansion (Bailey J Virol, 2006, Wagner J Virol, 2013, Wagner et al, Maldarelli et al, Science, 2014)
6. Clonal expansion mostly due to cells carrying defective virus (Cohn et al, Cell, 2015)
7. Absence of «break through» emergence of resistance at the population level (Scherrer et al, CID, 2016)

Purging the latent reservoir

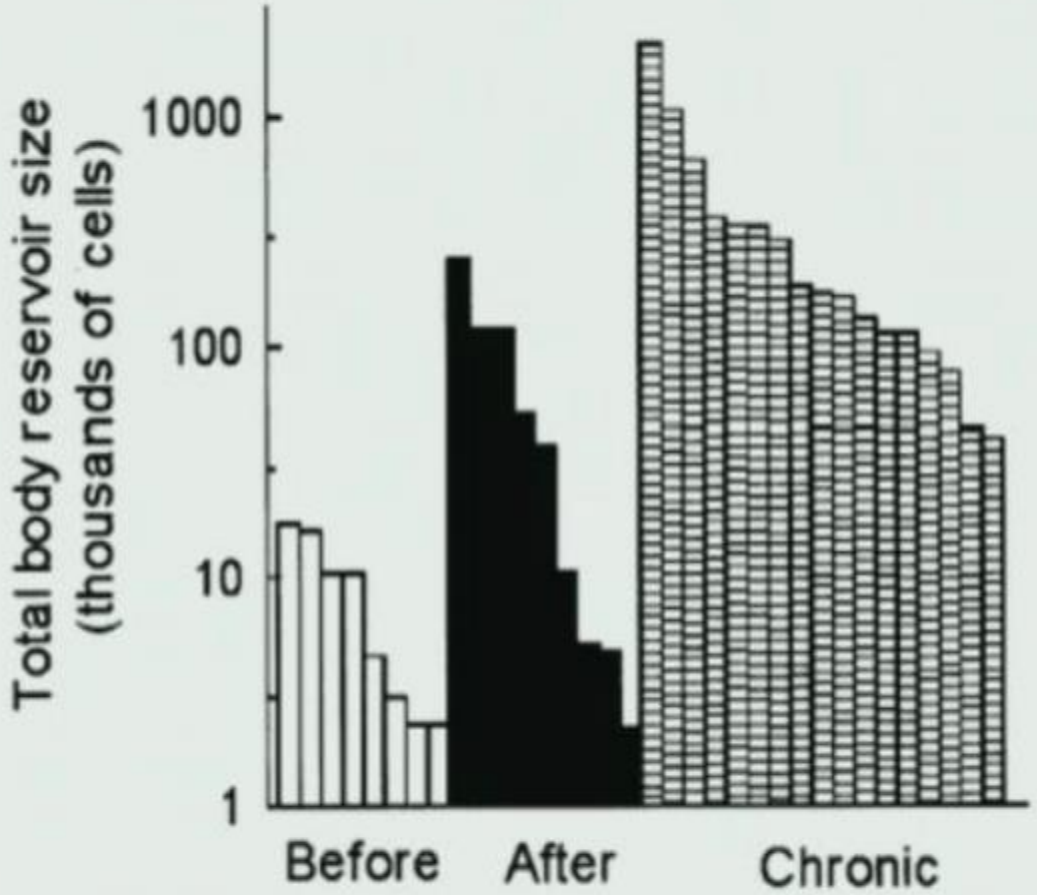
CONCISE COMMUNICATION

Immuno-activation with anti-CD3 and recombinant human IL-2 in HIV-1-infected patients on potent antiretroviral therapy

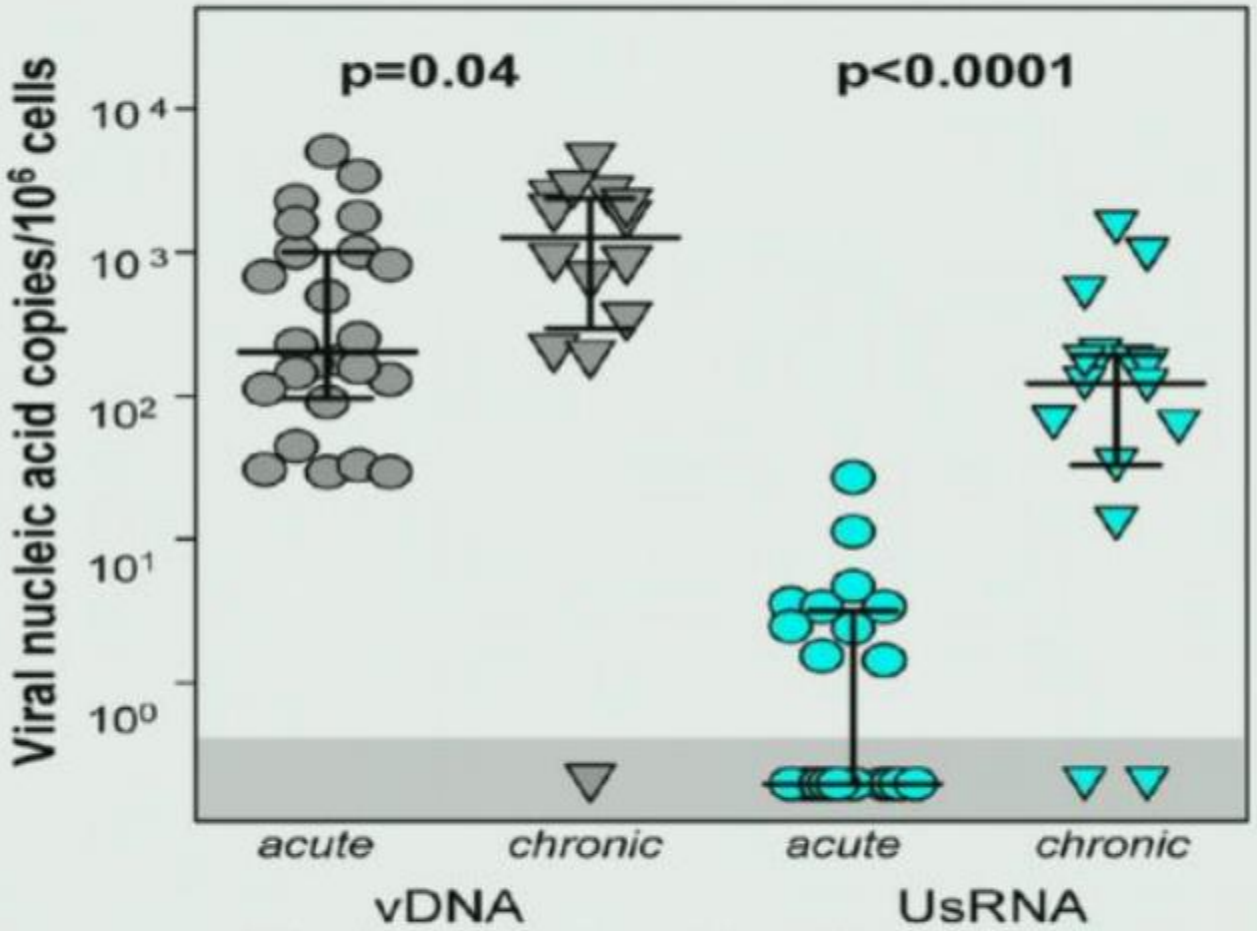
Jan M. Prins[a*], Suzanne Jurriaans[c*], Rieneke M.E. van Praag[a], Hetty Blaak[e], Ronald van Rij[e], Peter Th.A. Schellekens[b], Ineke J.M. ten Berge[b], Si-La Yong[b], Cecil H. Fox[f], Marijke T.L. Roos[e], Frank de Wolf[c], Jaap Goudsmit[c], Hanneke Schuitemaker[e] and Joep M.A. Lange[ad]

AIDS, 1999

Early ART reduces the reservoir size



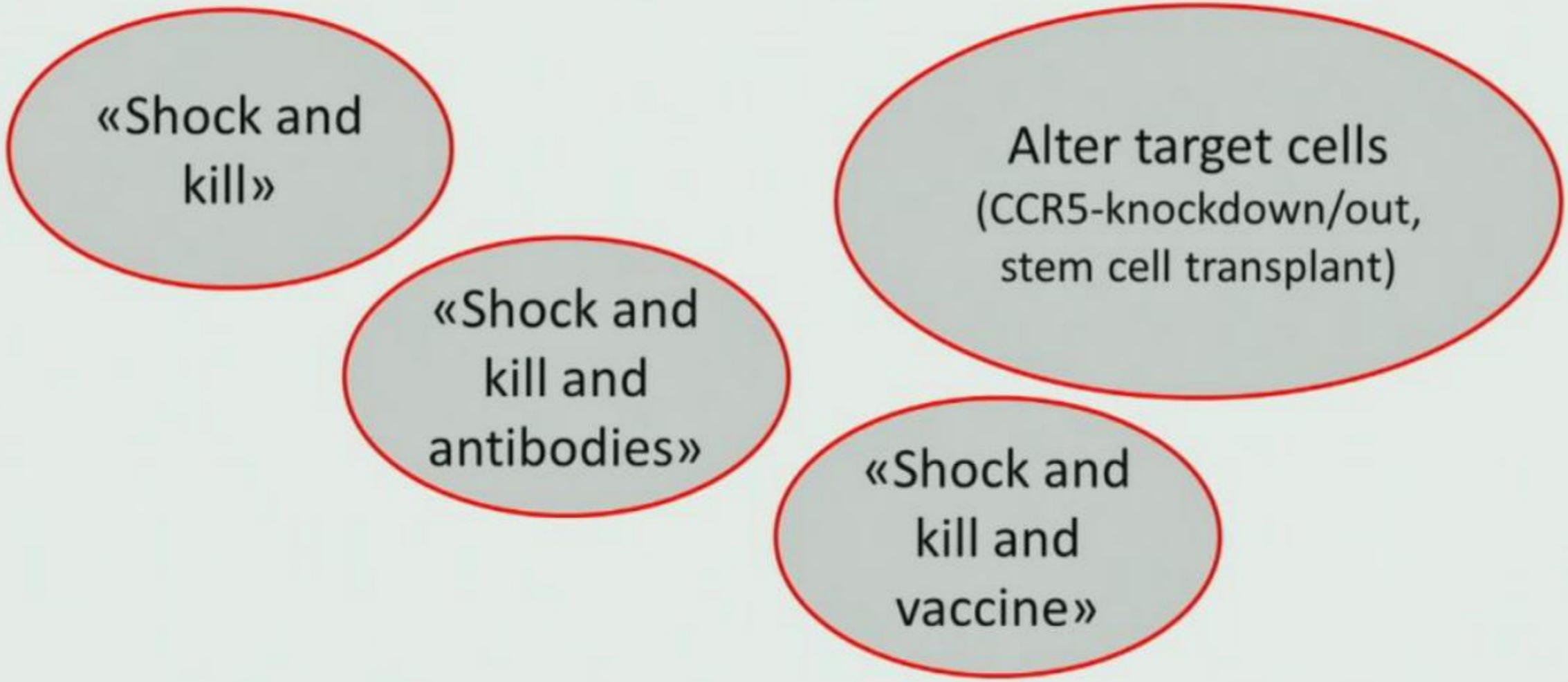
Strain et al, JID, 2005



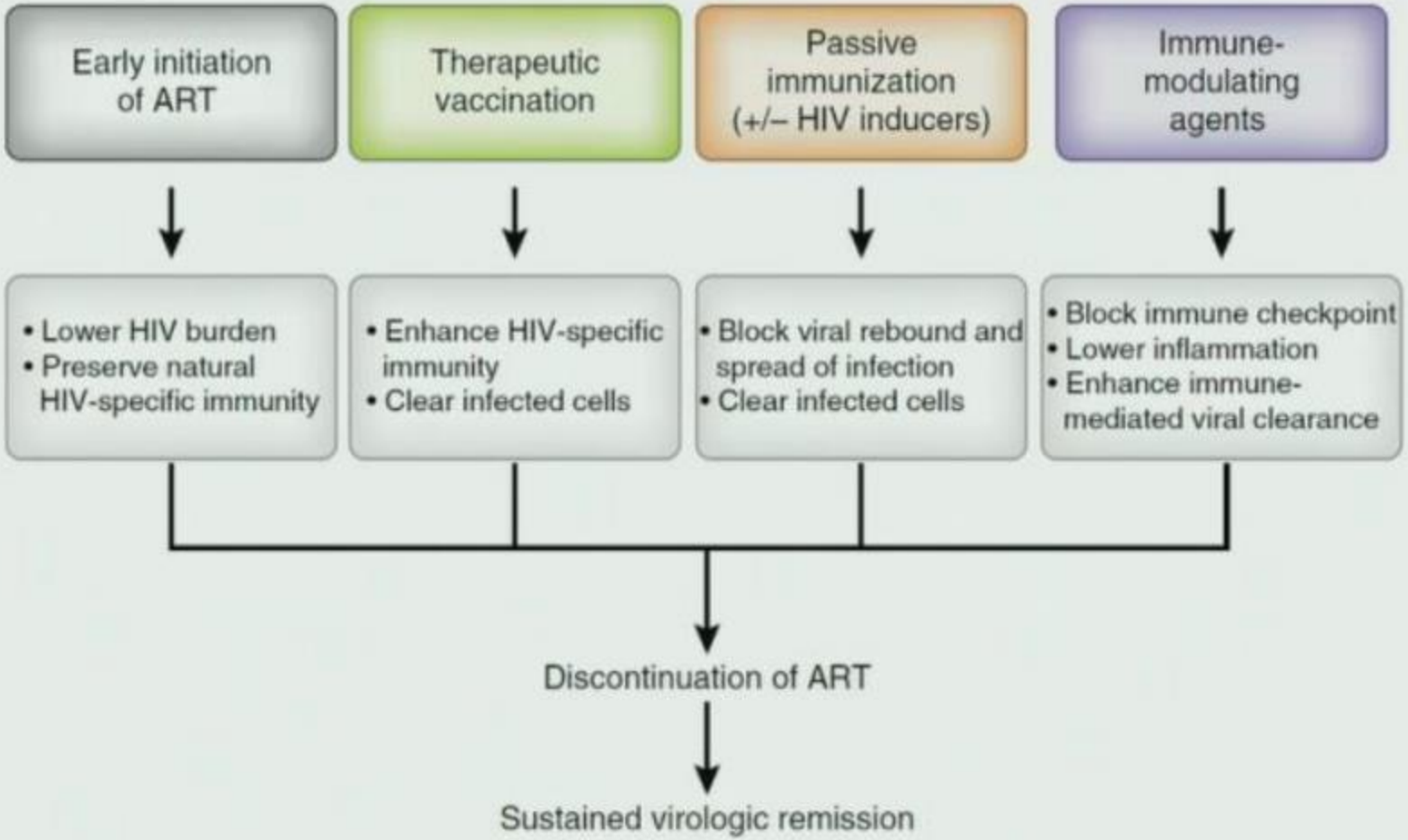
Schmid et al, Plos One, 2010

Archin, PNAS, 2012, Josefsson, PNAS, 2013, Williams, Elife, 2014

Strategies that are explored



Shock and kill strategies: Reducing the latent reservoir



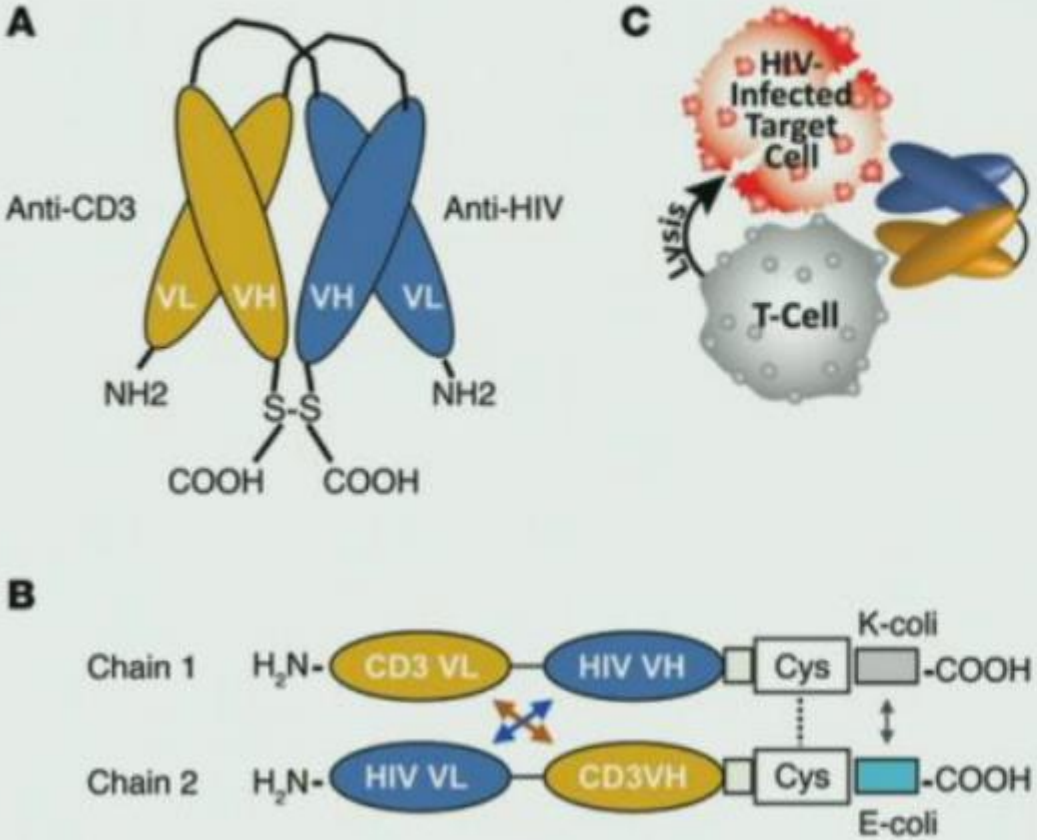
Chun et al, Nature Immunology, 2015

Low *In Vivo* Effect of Latency Reversing Agents

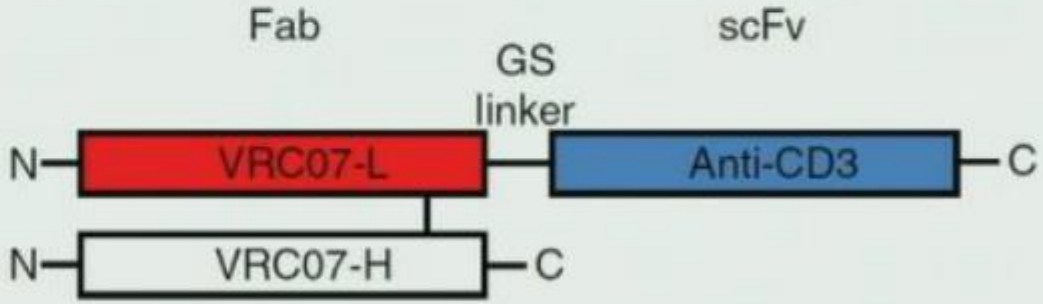
	Drug Dosing (doses)	HIV-1 Transcription (fold > baseline)	Plasma HIV-1	Post Dosing Viral Effect	T cell Activation	Reservoir Size	Refs
Vorinostat							
Archin *et al.* (2012)	400 mg (1)	4.8	No change	ND[c]	ND	ND	[14]
Elliott *et al.* (2014)	400 mg daily (14)	2.7	No change	Yes	No change	No change	[18]
Archin *et al.* (2014)	400 mg TIW[c] (22)	1.3	No change	ND	ND	No change	[15]
Panobinostat							
Rasmussen *et al.* (2014)	20 mg TIW (12)	2.9	Increased[a]	Yes	Increased	No change	[17]
Romidepsin							
Sogaard *et al.* (2015)	5 mg/m^2 (3)	3.8	Increased	No	Increased	No change	[19]
Disulfiram							
Spivak *et al.* (2014)	500 mg daily (14)	ND	Increased[b]	Yes	ND	No change	[16]
Elliot *et al.* (2015)	Dose escalation (3)	~2	Increased	Yes	ND	ND	[20]

Rasmussen et al, Trends in Microbiology, 2016

Bispecific antibodies: anti-HIV combined with anti-CD3



Sung et al, JCI, 2015,



Pegu et al, Nat communications, 2015

Altering target cells (CCR5 coreceptor)

1. **Extracellular blocking** of CCR5

2. **CCR5 knockdown**: Posttranscriptional downregulation by RNA interference mediated gene silencing

3. **CCR5 knockout**: Permanent disruption of the CCR5 gene (zink-finger nucleases, CRISPR/CAS)

Reviewed in: Allers, Curr Opinion in Virology, 2015

Conclusions and Thoughts

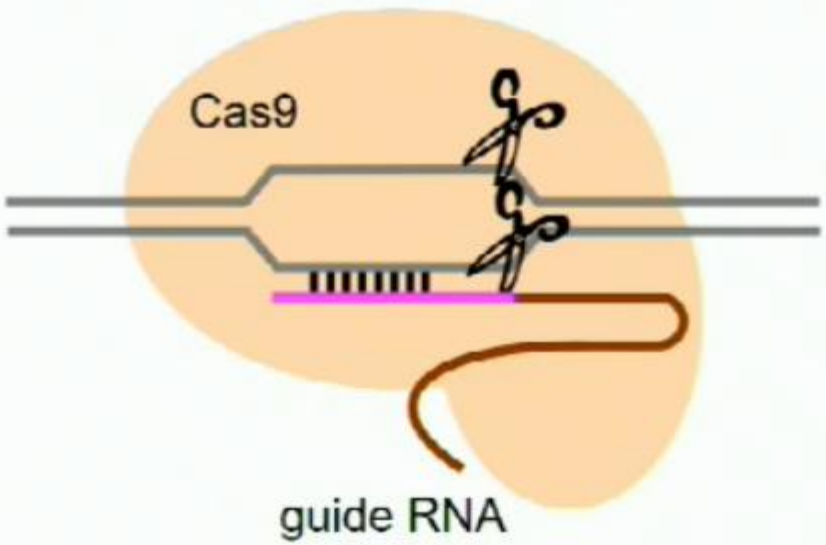
- **The HIV latent reservoir needs to be purged (how best?)**
- **Size of the reservoir is still unclear (difficulties of measuring remain)**
- **The debate continues since 1997: Is there or is there not low level replication on cART?**
- **Low level replication under cART would jeopardize «shock and kill» approaches**
- **Currently only possibility to reduce the latent reservoir is «early cART»**

Huldrych F. Günthard, MD

Genome editing tools recognize specific DNA sequences

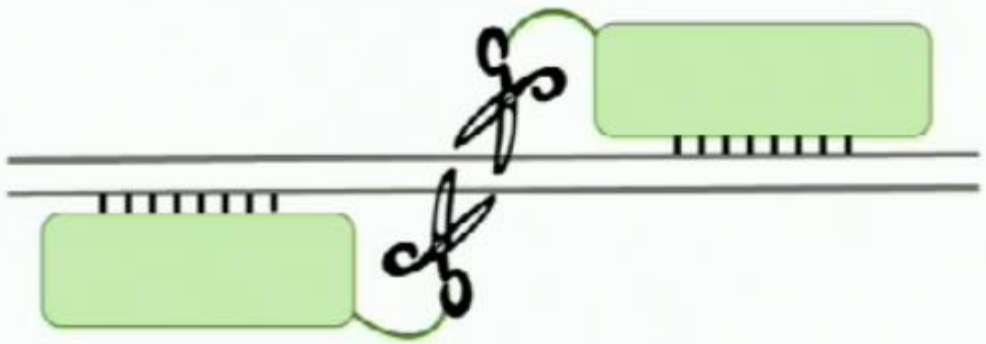
CRISPR/Cas9

- CRISPR is a homologous guide RNA
- Cas9 is a nuclease



Zinc finger nucleases / TALENs

- DNA-binding peptide arrays
- Linked to FokI nuclease



24 EX VIVO AND IN VIVO EDITING OF THE SIV GENOME IN NONHUMAN PRIMATES BY CRISPR-CAS9

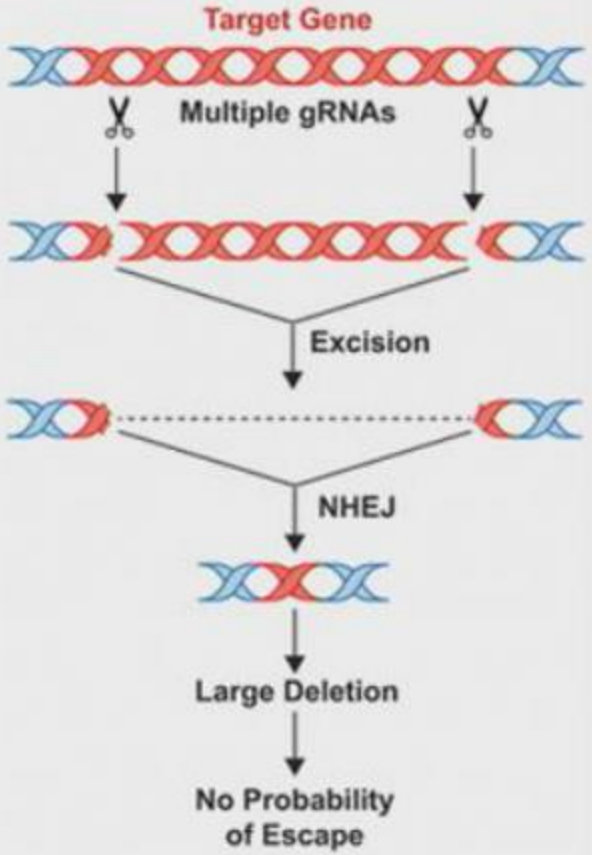
Tricia H. Burdo[1], Pietro Mancuso[1], Rafal Kaminski[1], Jennifer Gordon[1], Binhua Ling[2], Andrew MacLean[2], Kamel Khalili[1]

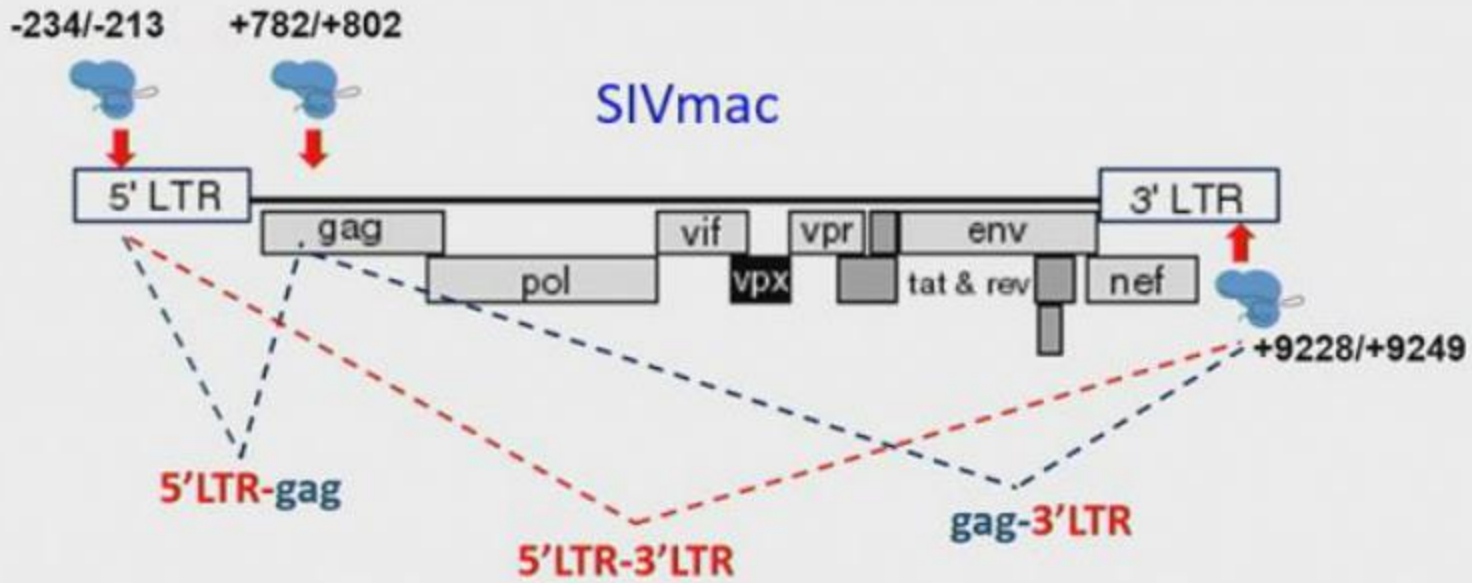
[1]*Temple University, Philadelphia, PA, USA,* [2]*Tulane National Primate Research Center, Covington, LA, USA*

Background: Antiretroviral therapy (ART) has increased survival, but is a non-curative approach as replication competent proviral DNA, with high risk for reactivation upon ART cessation, remains. As such, HIV is now a chronic disease with a broad range of co-morbidities and drug toxicity. Curative strategies to eradicate the infected cells or viral genome without further treatment are vital. Here, we develop and test the ability of the CRISPR-Cas9 gene editing method for elimination of the SIV viral genome in rhesus macaques.

Conclusion: We demonstrated, for the first time, high specificity and efficacy of the CRISPR technology for targeting SIV proviral LTR and Gag regions, which led to both ex vivo and in vivo editing of SIV DNA. These observations support the potential use of CRISPR/Cas9 technology as a curative strategy that warrants further investigation.

Targeting LTRs and gag of the SIV genome with CRISPR/Cas9 multiplex gRNAs



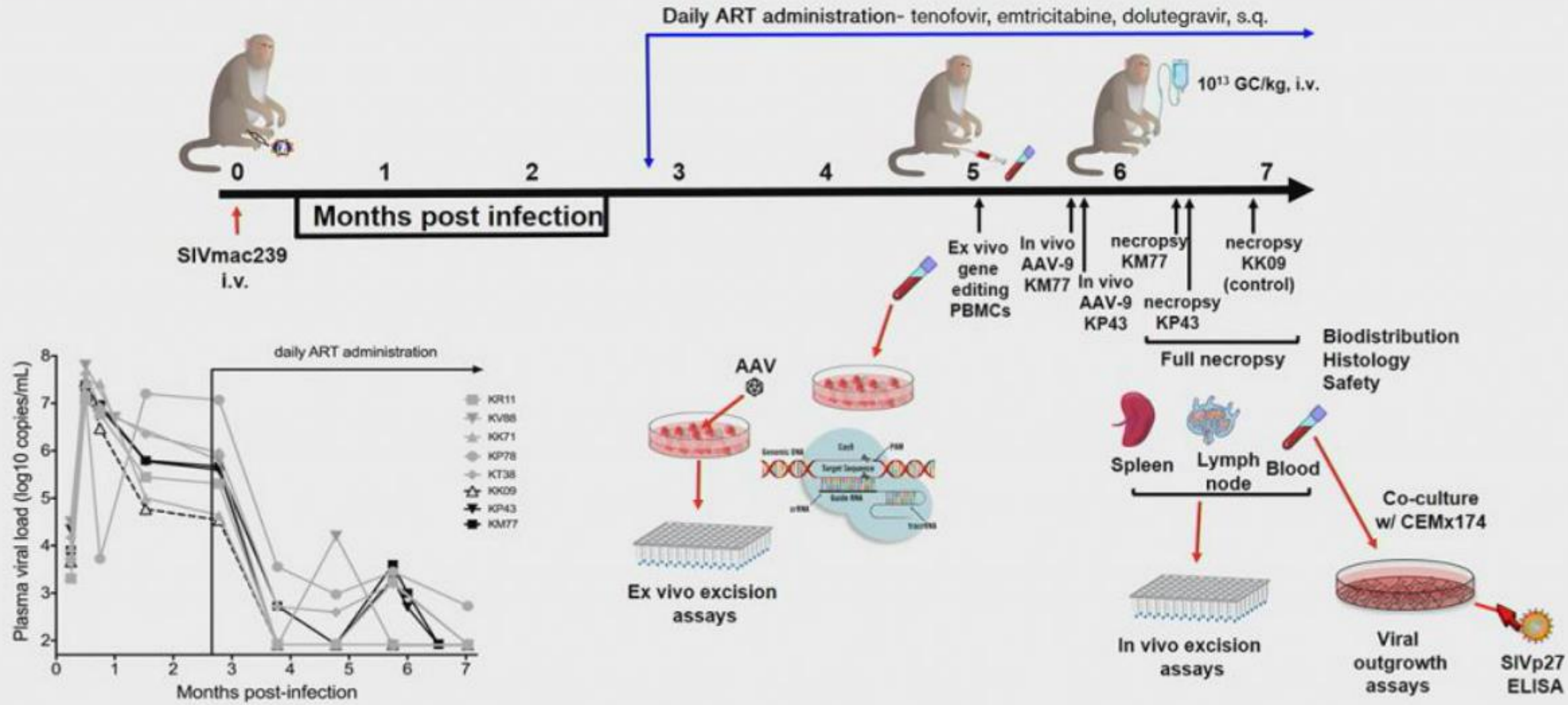


LTR gRNA/PAM- AGGCATATGTTAGATACCCAGAAGAGT

Gag gRNA/PAM- GCGTCATCTGGTGCATTCACGCAGAAG

White MK et al 2016
PLos Pathogens 12(12): e1005953.

Non-human primate experimental design



Conclusions

1. Design and confirmation of an all-in-one AAV delivery vector for targeting LTRs and gag of the SIV genome with CRISPR/Cas9 multiplex gRNAs
2. Cleavage of the SIVmac239 DNA by AAV9/CRISPR-Cas9 *in vitro*
3. Cleavage of SIV DNA and verification of Cas9 mRNA and gRNA expression in *ex vivo* treated rhesus PBMCs
4. Cleavage of SIV viral DNA in blood after *in vivo* AAV-9-CRISPR treated NHPs
5. Lack of viral outgrowth from PBMCs from NHPs after gene editing
6. Widespread biodistribution of Cas9 DNA in tissues- confirmed by ddPCR and DNAScope
7. Confirmed viral excision in tissues (spleen, lung and lymph nodes) after *in vivo* gene editing

25 **DELAYED VIRAL REBOUND DURING ATI AFTER INFUSION OF CCR5 ZFN-TREATED CD4 T CELLS**

Pablo Tebas[1], Julie Jadlowsky[1], Pamela Shaw[1], Gary Lee[2], Dale Ando[2], Sukyung Kim[1], SoeYu Naing[1], Simon Lacey[1], Bruce L. Levine[1], Don L. Siegel[1], Carl H. June[1], James L. Riley[1]

26 **MULTIDOSE IV ROMIDEPSIN: NO INCREASED HIV-1 EXPRESSION IN PERSONS ON ART, ACTG A5315**

Deborah McMahon[1], Lu Zheng[2], Joshua C. Cyktor[1], Evgenia Aga[2], Bernard J. Macatangay[1], Catherine Godfrey[3], Michael Para[4], Ronald T. Mitsuyasu[5], Joseph Hesselgesser[6], Curtis Dobrowolski[7], Jonathan Karn[7], Edward P. Acosta[8], Rajesh T. Gandhi[9], John W. Mellors[1], for the A5315 Team

27 **PEMBROLIZUMAB INDUCES HIV LATENCY REVERSAL IN HIV+ INDIVIDUALS ON ART WITH CANCER**

Thomas S. Uldrick[1], Steven Fling[1], Scott V. Adams[1], Ajantha Solomon[2], Priscila H. Gonçalves[3], Nicolas Chomont[4], Rob Gorelick[5], Jeffrey D. Lifson[5], Robert Yarchoan[6], Martin "Mac" A. Cheever[1], Frank Maldarelli[7], Steven G. Deeks[8], Sharon R. Lewin[2], for the DARE and CITN-12 Study Teams

29LB **SUSTAINED HIV-1 REMISSION FOLLOWING HOMOZYGOUS CCR5 DELTA32 ALLOGENIC HSCT**

Ravindra K. Gupta[1], Sultan Abduljawad[1], Laura McCoy[1], H P. Mok[2], Dimitra Peppa[1], Helen Lee[2], Eleni Nastouli[3], Jonathan Lambert[3], Matthew Pace[4], John Frater[4], Andrew Lever[2], Simon Edwards[5], Eduardo Olavarria[6], Ian Gabriel[6], for the CHERUB and ICISTEM Study Groups

110 SILENCING OF RETROVIRAL GENE EXPRESSION BY THE HUSH COMPLEX

Stephen P. Goff, *Columbia University Medical Center, New York, NY, USA*

Retroviral DNAs are transcriptionally silenced in a number of settings and in specific cell types, an important mechanism for the inhibition of virus replication. The HUSH complex (containing the three subunits TASOR/FAM208A, MPP8, and periphilin) was originally identified as required for the maintenance of silencing of transfected DNAs integrated into heterochromatic regions of vertebrate genomes. HUSH binds to histone H3K9me3 marks, and brings the histone methyltransferase SETDB1/ESET to sustain and likely spread this H3K9me3 silencing modification along chromatin. HUSH was found to be important for the silencing of those retroviral DNAs that have integrated into heterochromatin. This position-dependent silencing by HUSH is distinct from the more universal silencing of retroviral DNAs in embryonic stem cells, mediated by zinc finger proteins tethering TRIM28/Kap1 to specific sequence elements of the viral DNA. We have recently found that the HUSH complex is also involved in the silencing of unintegrated viral DNAs of many retroviruses in virtually all cell types. HUSH is recruited to unintegrated DNA of the mouse leukemia viruses by NP220, a large DNA-binding protein with preference for oligo(C) sequences. This silencing, involving both SETDB1/ESET and histone deacetylases (HDACs), is relieved upon integration of the DNA into euchromatic regions of permissive cell types. NP220 and HUSH thereby act to inhibit early viral gene expression and the overall rate of virus replication. The Vpx and Vpr proteins of HIV-2 and various strains of the simian immunodeficiency replication. Vpx can also induce expression of HIV-1 proviruses in various models of latency, suggesting that HUSH may help maintain repression of silent proviruses in the latent reservoir.

Cervical Cancer in HIV infected women in Johannesburg, South Africa

- Cervical Cancer rates in a HIV treatment clinic ranged from 615/100,000 (before screening programs) to 260/100,000 (from 2009 after screening). Overall rate is 506/100,000. [1]
- Treating cervical HSIL prevents invasive cervical cancer. However:
  - Up to 50% of women living with HIV have persistent of recurrent HSIL after LEEP[2]
  - Randomized controlled study of LEEP vs cryo for treatment of cryo-eligible HSIL in South African women living with HIV found persistent/recurrent HSIL in 18.5% and 27.2% respectively[3]

Poor HSIL treatment outcomes compromise the effectiveness of cervical cancer control programs. The additional follow-up and repeated treatments represents a challenge for programs with limited resources and capacity.

1) Rohner E etal IJC 2017
2) Adam etal BMC Cancer 2008
3) Smith J etal AJOG 2017

Cindy Firnhaber
University of Colorado Medical Center
Aurora, CO, USA

Baseline Characteristics

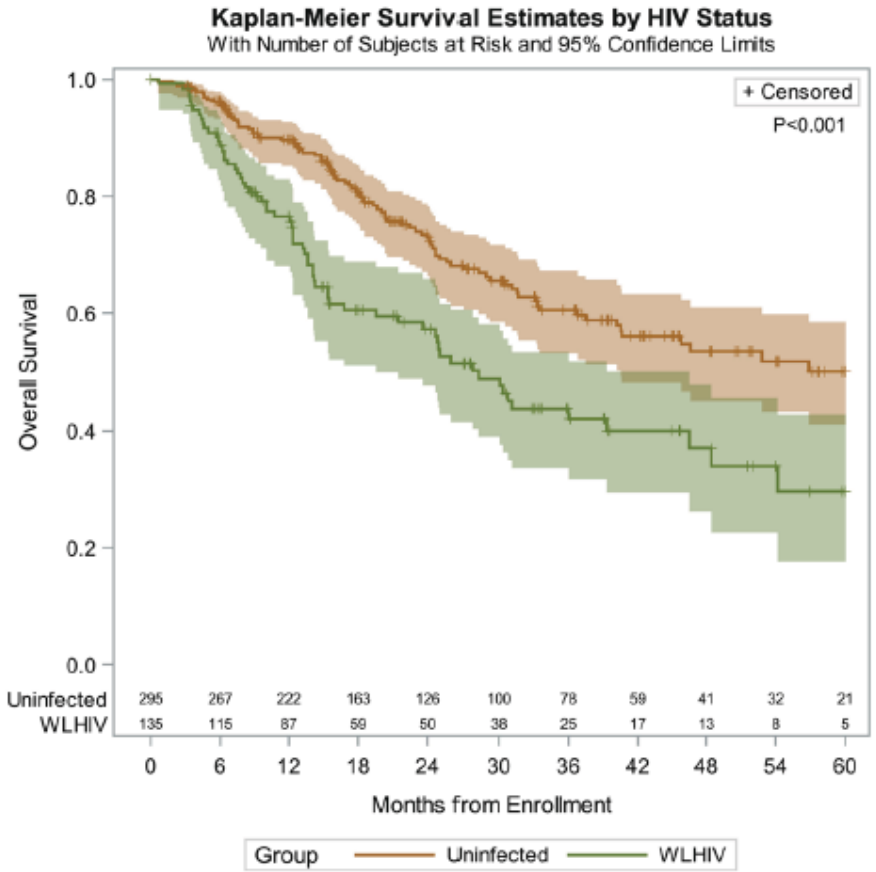
Characteristic	qHPV (n=90)	Placebo (n=90)	Total (n=180)
HSIL/ASC-H cytology prior to entry	86 (95.6%)	83 (92.2%)	169 (93.4%)
Cervical Histology prior to entry			
CIN 2	41 (46%)	46 (51%)	87 (48%)
CIN 3	49 (54%)	44 (49%)	93 (52%)
Black African	90 (100%)	86 (96%)	176 (98%)
Current tobacco use	3 (3%)	5 (6%)	8 (4%)
Plasma HIV-1 RNA			
<200 copies/ml	77 (95%)	76 (93%)	153 (94%)
Missing	9	8	17
Age, Median (IQR)	40 (35, 47)	39 (35, 44)	39 (35, 46)
CD4 count, Median (IQR)	511 (300, 689)	483 (337, 745)	489 (302, 724)
Nadir CD4, Median (IQR)	125 (61, 200)	108 (50, 200)	116 (50, 200)

Primary Endpoint

Endpoint	qHPV (n=87)	Placebo (n=87)	RR, 95% CI
Primary endpoint Cytologic or histologic HSIL	46 (52.9%)	39 (44.8%)	1.2 (.87-1.6), P=.29
Histologic HSIL CIN 2 or CIN 3	28 (32%)	27 (31%)	1.04 (.67-1.6), P=.8
CIN 3	9 (10%)	11 (13%)	.82 (.36-1.9), P=.64

16 HIV IS ASSOCIATED WITH DECREASED BREAST CANCER SURVIVAL: A PROSPECTIVE COHORT STUDY

Katrin S. Sadigh[1], Ryan M. Hodgeman[2], Neo Tapela[3], Isaac Nkele[2], Memory Bvochora-Nsingo[4], Sebathu Chiyapo[4], Tlotlo B. Ralefala[3], Jason A. Efstathiou[5], Oaitse John[2], Galaletsang Motswetla[2], Surbhi Grover[6], Jerry Younger[5], Mompati O. Mmalane[2], Shahin Lockman[7], Scott Dryden-Peterson[7]



Results: A total of 430 women with breast cancer with known HIV status were enrolled (4 women with unknown HIV status excluded), including 135 (31.4%) WLHIV and 295 (68.6%) uninfected women. WLHIV were younger than uninfected women, median 47.5 and 55.5 years, respectively ($p<0.001$). Among WLHIV, 110 (84%) were on ART prior to cancer diagnosis (median duration 6.8 years) and median CD4 count was 513 cells/μL. Advanced cancer stage (III/IV) was common for both WLHIV (67%) and uninfected women (66%). Immunohistochemistry results were available for 250 women (58%); 154 (62%) women were ER+ and 65 (26%) were triple-negative. Receptor status was similar by HIV status ($p=0.89$). The majority (69%) received multimodality treatment with curative intent and the proportion did not differ by HIV status ($p=0.80$). After 847 patient-years of follow-up, 156 women died, including 66 (49%) WLHIV and 90 (31%) uninfected women. Three women (0.7%) were lost to follow-up. The majority of deaths (141, 90%) were attributed to cancer and none to HIV. Two-year survival for WLHIV was lower than those without HIV, 57% and 73%, respectively (see Figure, $p<0.001$). Findings were similar in adjusted analyses with WLHIV experiencing higher mortality (hazard ratio 1.86, 95%CI 1.33 to 2.61, $p<0.001$). Cancer stage, treatment intent, and personal income less than $50/month were also inversely predictive of survival ($p<0.001$ for each).

39LB RANDOMIZED TRIAL OF RALTEGRAVIR-ART VS EFAVIRENZ-ART WHEN INITIATED DURING PREGNANCY

Mark Mirochnick[1], David E. Shapiro[2], Leavitt Morrison[2], Lisa Frenkel[3], Nahida Chakhtoura[4], George K. Siberry[5], Brookie Best[6], Maria Leticia S. Cruz[7], Blandina T. Mmbaga[8], Jose Henrique S. Pilotto[9], Avy Violari[10], Sinart Prommas[11], Esau Joao[7], for the NICHD P1081 Protocol Team

	RAL arm	EFV arm	P-value*
Delivery viral load <200 copies/mL[a]	174/183 (95%)	151/179 (84%)	<.001
Enrolled 20 to <28 weeks	85/88 (97%)	87/90 (97%)	
Enrolled 28 to <37 weeks	89/95 (94%)	64/89 (72%)	
Remained on study drug through delivery[b]	199/200 (>99%)	188/194 (97%)	.05
Rapid, sustained virologic response AND remained on study drug through delivery[c] (combines the next 3 rows)	151/162 (93%)	98/156 (63%)	<.001
Viral load ≥2.0 log decline or <200 copies/mL by wk 2	153/162 (94%)	105/156 (67%)	
Viral load <1,000 copies/mL at all time points after wk 4	144/149 (97%)	140/147 (95%)	
Remained on study drug through delivery	161/162 (99%)	151/156 (97%)	
Maternal adverse event ≥grade 3 until wk 24 after delivery[d]	61/206 (30%)	59/197 (30%)	.91
Stillbirth	3/200 (2%)	1/194 (1%)	.62
Preterm birth (<37 wks gestation)	24/195 (12%)	20/190 (11%)	.63
Infant adverse event ≥grade 3 until wk 24 after delivery[d]	50/199 (25%)	48/194 (25%)	.94

*Cochran-Mantel-Haenszel test stratified by gestational age at entry (20-<28, 28-<31, 31-<34, or 34-<37 wks), except Fisher exact test for stillbirths and preterm births.

[a]For all women with screening/entry viral load (VL) > 200 copies/mL and VL result ≤21 days pre-delivery.

[b]For all women who received at least one dose of study drug and remained on-study through delivery.

[c]Secondary composite outcome for all women in the primary virologic response and tolerability analyses with a VL result at study week 2 (day 11-17) and at least one subsequent VL result after study week 4.

[d]For all women who received at least one dose of study drug; for live-born infants delivered on-study.

49 **EXPANDING TESTING STRATEGIES IN PARIS: A FREE POSTAL COMPREHENSIVE STI TEST KIT**

Delphine Rahib[1], **Heloise M. Delagreverie**[2], Iris Bichard[3], Audrey Gabassi[2], Nicolas Guigue[2], Marie-Laure Chaix Baudier[2], Beatrice Bercot[2], Constance Delaugerre[2], Nathalie Lydié[1]

	Performed Test (%) (tested samples / total samples)	Positivity rate (%) (reactive tests / performed tests)
HIV	81%	1.3%
HCV	81%	0.5%
HBV	70%	0.3%
Syphilis	49%	1.8%
CT – Throat	100%	1.8%
CT – Anal	99%	7.2%
CT - Urine	99%	1.6%
NG –Throat	100%	8.2%
NG – Anal	99%	4.8%
NG – Urine	99%	0.6%

53LB POINT-OF-CARE VIRAL LOAD TESTING IMPROVES HIV VIRAL SUPPRESSION AND RETENTION IN CARE

Paul K. Drain[1], Jienchi Dorward[2], Lauren Violette[1], Justice Quame-Amaglo[1], Katherine Thomas[1], Natasha Samsunder[3], Hope Ngobese[3], Koleka Mlisana[3], Pravi Moodley[3], Deborah J. Donnell[1], Ruanne V. Barnabas[1], Kogieleum Naidoo[3], Salim Abdool Karim[3], Connie L. Celum[1], Nigel Garrett[3]

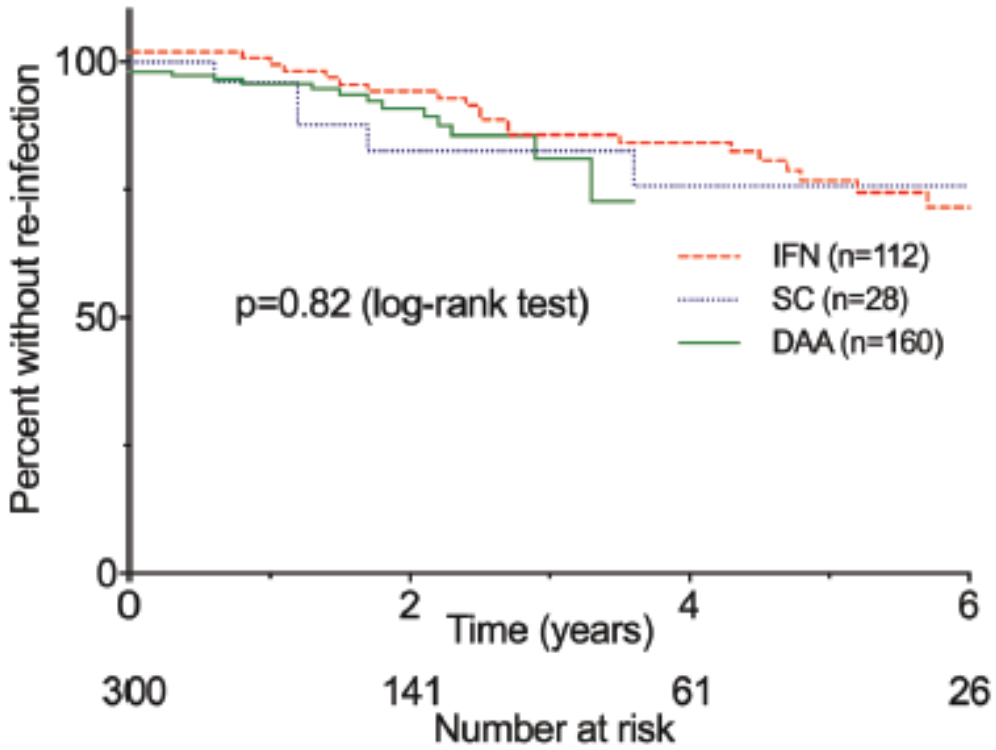
Table. Composite primary outcome and secondary endpoints in the STREAM study.

	Standard-of-Care (SOC) arm	Point-of-care viral load (VL) testing (Intervention arm)	Absolute Risk Difference [a] (Intervention - SOC) [2-sided 95% CI]	p-value [b]
Primary outcome				
VL suppression <200 copies/mL and retention in care [c]	75.9% (148/195)	89.7% (175/195)	13.9% [6.4, 21.2]	0.0004
Secondary endpoints				
VL suppression <50 copies/mL and retention in care [c]	71.3% (139/195)	85.6% (167/195)	14.4% [6.2, 22.3]	0.001
VL suppression <200 copies/mL	83.1% (162/195)	93.3% (182/195)	10.3% [3.9, 16.8]	0.003
Retention in care [c]	84.6% (165/195)	92.3% (180/195)	7.7% [1.3, 14.2]	0.03
VL suppression <200 copies/mL, among those with a 12-month VL test result	91.0% (162/178)	96.3% (182/189)	5.3% [0.2, 10.7]	0.05
VL test result communicated to participant, among those with a mid-study blood draw	74.7% (127/170)	99.5% (191/192)	24.8% [18.4, 31.8]	<0.0001
Secondary endpoints as time to event	**Median days to event [IQR]**		**Cox Hazard Ratio [2-sided 95% CI]**	**p-value**
Appropriate switch to second-line ART following virologic failure	4/9 76 [20, 134]	6/7 0.5 [0, 7]	4.7 [1.3, 17.3]	0.02
First referral into the CCMDD decentralized ART delivery program [d]	52/195 261 [231, 281]	116/195 168 [168, 175]	3.4 [2.5, 4.8]	<0.0001

a. We used Newcombe-Wilson score to calculate 2-sided 95% confidence intervals.
b. We used Fisher's exact test to calculate 2-sided p-values.
c. Retention in care was defined as collecting ART from the study clinic or a community pharmacy at 44-56 weeks after enrollment.
d. The Central Chronic Medicine Dispensing and Distribution (CCMDD) program is a decentralized ART delivery at community pharmacies.

86 **HCV REINFECTION AMONG HIV-INFECTED MSM IN NEW YORK CITY**

Jesse R. Carollo[1], Stephanie H. Factor[1], Gabriela Rodriguez-Caprio[1], Asa Radix[2], Stephen M. Dillon[3], Rona Vail[2], Krisczar J. Bungay[3], Robert Chavez[4], José Lares-Guia[5], **Daniel S. Fierer**[1], for the New York Acute Hepatitis C Surveillance Network



Conclusion: The high HCV re-infection rate in our large cohort of HIV-infected MSM in NYC was independent of whether clearance was by IFN or DAA treatments, or by SC, and comparable to Europe rates. Most re-infections occurred within the first 2 years, but infections continued to occur for more than 11 years after clearance. These data suggest that long-term surveillance is warranted for all HIV-infected MSM after clearance of HCV infection. Further, strategies to reduce HCV re-infections are needed to meet the goal of eliminating HCV in these men who are at significant risk for HCV infection.

105 USING EHR DATA TO IDENTIFY POTENTIAL PrEP CANDIDATES IN A LARGE HEALTH CARE SYSTEM

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Background: HIV preexposure prophylaxis (PrEP) prevents HIV acquisition but uptake has been limited. Electronic health record (EHR) data may help identify patients who are at high risk of HIV acquisition and could benefit from PrEP.

Methods: We developed and validated a prediction model to identify potential PrEP candidates in a cohort of members of Kaiser Permanente Northern California not diagnosed with HIV and having ≥2 years of enrollment and ≥1 outpatient visit during 2007-2017. Using EHR data on 68 demographic, clinical, and behavioral variables potentially predictive of HIV risk, we applied logistic regression and machine learning methods to predict incident HIV cases in a derivation dataset of patients entering the cohort in 2007-2014. We assessed performance of candidate models by cross-validated area under the curve (AUC, range 0-1). We evaluated how the best-performing model might perform prospectively by validating it among members entering the cohort in 2015-2017, and compared this full model with simpler models using only traditional risk factor variables (i.e., men who have sex with men [MSM] and sexually transmitted infections [STIs]).

Results: Of 3,751,740 eligible patients in 2007-2017, there were 1422 incident HIV cases. The best-performing model for predicting incident HIV was least absolute shrinkage and selection operator (Lasso), with an AUC of 0.90 in 2007-2014. The final model included 41 predictors, such as Black race, home ZIP code, urine positivity for methadone, and use of medications for erectile dysfunction. The full model performed well when validated prospectively using 2015-2017 data (AUC 0.89). Model performance remained high when excluding the MSM variable (AUC 0.87) or STI variables (AUC 0.90), but was reduced when including only MSM (AUC 0.74), STIs (AUC 0.61), or both (AUC 0.78; Figure). Patients in the top 1% of HIV risk scores included 45/68 (66%) male HIV cases but 0/13 (0%) female HIV cases among those entering the cohort in 2015-2017. Using the top 1% of risk scores to define potential PrEP candidates in 2015-2017, we identified 6076 candidates, of whom 5577 (92%) were not currently on PrEP.

Conclusion: Prediction models using EHR data can identify patients who are at high risk of HIV acquisition but not using PrEP, and should be tested as a strategy to improve PrEP use. Models using rich clinical data outperform models using only traditional risk factors. Additional EHR variables or other data are needed to identify females who may benefit from PrEP.

136 INTERFERON A2B REDUCES INDUCIBLE CD4-ASSOCIATED HIV IN ART-SUPPRESSED INDIVIDUALS

Livio Azzoni[1], Emmanouil Papasavvas[1], Jay Kostman[2], Pablo Tebas[3], Karam Mounzer[2], Ian Frank[3], Kenneth M. Lynn[3], Linden Lalley-Chareczko[2], Rui Feng[3], Scott Appel[3], Bonnie J. Howell[4], Daniel Holder[4], Shih Lin Goh[4], Guoxin Wu[4], Luis Montaner[1]

139 LONG-ACTING CABOTEGRAVIR + RILPIVIRINE AS MAINTENANCE THERAPY: ATLAS WEEK 48 RESULTS

Susan Swindells[1], Jaime-Federico Andrade-Villanueva[2], Gary J. Richmond[3], Giuliano Rizzardini[4], Axel Baumgarten[5], Maria Del Mar Masia[6], Gulam Latiff[7], Vadim Pokrovsky[8], Joseph M. Mrus[9], Jenny O. Huang[10], Krischan J. Hudson[9], David A. Margolis[9], Kimberly Smith[9], Peter E. Williams[11], William Spreen[9]

140LB LONG-ACTING CABOTEGRAVIR + RILPIVIRINE FOR HIV MAINTENANCE: FLAIR WEEK 48 RESULTS

Chloe Orkin[1], Keikawus Arasteh[2], Miguel Górgolas Hernández-Mora[3], Vadim Pokrovsky[4], Edgar T. Overton[5], Pierre-Marie Girard[6], Shinichi Oka[7], Ronald D'Amico[8], David Dorey[9], Sandy Griffith[8], David A. Margolis[8], Peter E. Williams[10], Wim Parys[10], William Spreen[8]

141 SAFETY AND PK OF SUBCUTANEOUS GS-6207, A NOVEL HIV-1 CAPSID INHIBITOR

Jennifer E. Sager, Rebecca Begley, Martin Rhee, Steve K. West, John Ling, Scott D. Schroeder, Winston C. Tse, Anita Mathias
Gilead Sciences, Inc, Foster City, CA, USA

142 A PHASE IIA STUDY OF NOVEL MATURATION INHIBITOR GSK2838232 IN HIV PATIENTS

Edwin DeJesus[1], Sara Harward[2], Roxanne C. Jewell[2], Mark Johnson[2], Etienne Dumont[3], Viviana Wilches[3], Fiona Halliday[4], Christine Talarico[2], Jerry Jeffrey[2], Kevin Gan[3], Franco B. Felizarta[5], Anita Scribner[6], Moti Ramgopal[7], Paul Benson[8], Brian A. Johns[2]

158 OBESITY: A GROWING PROBLEM IN ANTIRETROVIRAL THERAPY

John R. Koethe, *Vanderbilt University, Nashville, TN, USA*

Over the past two decades, the prevalence of obesity (i.e., body mass index ≥30kg/m^2) among persons living with HIV (PLWH) has steadily risen, which is clinically important as obesity increases the risk of diabetes, cardiovascular disease, fatty liver disease, neurocognitive impairment, and other comorbidities. Among PLWH, traditional risk factors for obesity (e.g., food insecurity, lack of readily available healthy foods, insufficient physical activity, and limited knowledge of healthy lifestyle practices) intersect with HIV-specific factors. Many PLWH experience abrupt weight gain after starting antiretroviral therapy (ART). A retrospective analysis of more than 14,000 patients starting ART found that, after three years of treatment, 22% of normal-weight individuals became overweight and 18% of overweight individuals became obese. Weight gain on ART is multifactorial and may be due, in part, to reduced inflammation and catabolism following viral suppression; increased access to health education, social support services (e.g., food assistance), smoking cessation, and treatment of depression with entry into HIV care; and effects of specific ART medications. While weight gain appears to occur with all current ART regimens, between-class and within-class differences have emerged. AIDS Clinical Trials Group (ACTG) study A5257 found a higher incidence of severe (>10%) weight gain among ART-naïve participants after starting a regimen containing the integrase strand transfer inhibitor (INSTI) raltegravir versus the protease inhibitors (PI) darunavir or atazanavir, each boosted with ritonavir. In a large retrospective analysis, ART-naïve patients starting INSTI-based regimens had higher weight gain compared to those starting non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens; among INSTIs, weight gain was greater with dolutegravir and raltegravir versus elvitegravir-containing regimens. Recent smaller analyses also report weight gain among patients with virologic suppression switched from PI- or NNRTI-containing regimens to INSTI regimens, and a minor weight increase in those switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF). In summary, weight gain is common among PLWH starting ART and may occur following regimen switches. Rigorous clinical trial data is needed to confirm findings from observational cohorts, in addition to studies of potential mechanisms linking antiretroviral agents and body weight.

Immunotherapy strategies

- **Toll-like Receptors**
- **IL-15**
- **IFN-alpha**
- **Therapeutic vaccines**
- **CAR T cells**

- ***Phase 1 clinical trials of single and combination therapies***

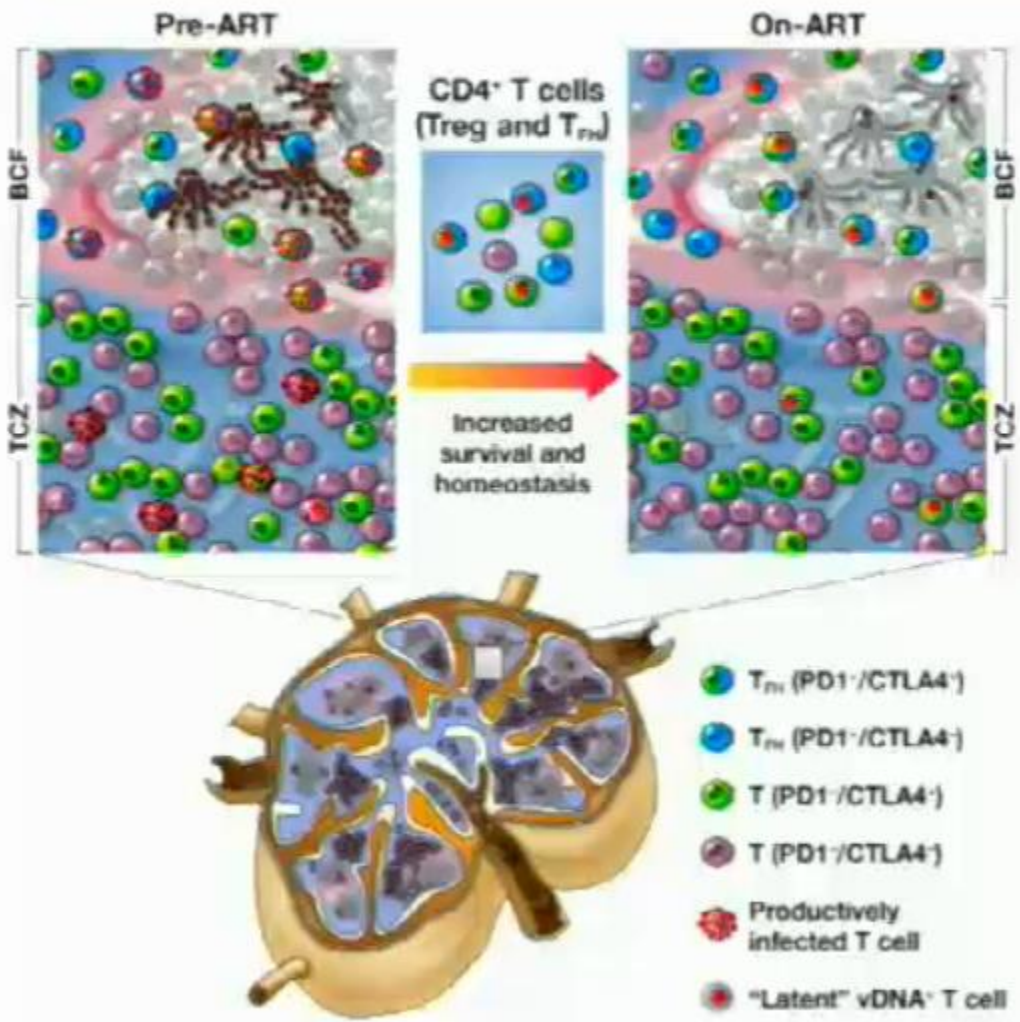
L Azzoni # 136; Thurs AM
IFN-a2a reduces inducible HIV in ART-suppressed individuals

P Tebas. #25; Tues AM
Delayed rebound with CCR5 ZFN-treated CD4 T cells

Weds & Thurs Poster sessions
*ATI trial insights
*Human trials of cure strategies
*Cure studies in animal
*Abs & CAR T cell approaches

Tsai et al., JVI 2017; Borducchi et al., Nature 2018; Watson et al., PLoS Pathogs 2018; Webb et al., Blood Adv 2018.

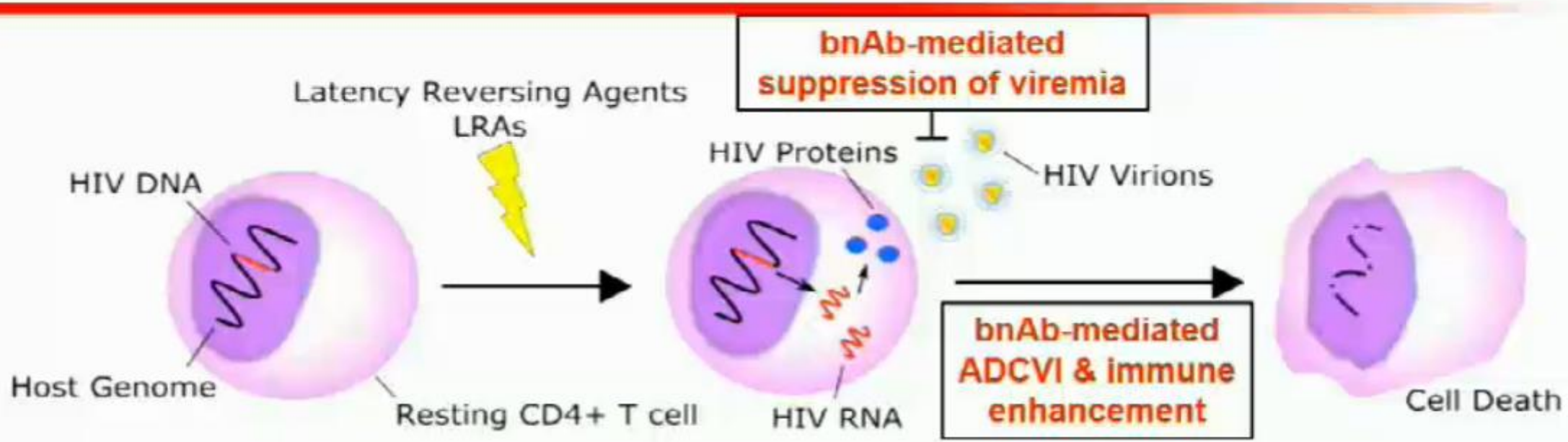
Coinhibitory receptors: PD-1 & CTLA-4



- Important regulators of cytolytic activity
- In chronic infection, markers of cellular exhaustion & immune dysfunction
- ART suppression: highly enriched for inducible HIV DNA
  - T_{FH} (PD1+): B cell follicle
  - Treg (CTLA-4+): T cell zone
- ***Targets for immunotherapy***
  - ***Reverse latency in CD4 T cells (shock)***
  - ***Enhance killing by CD8 T cells (kill)***

McGary et al., Immunity 2017; Banga et al., Nat Med 2016

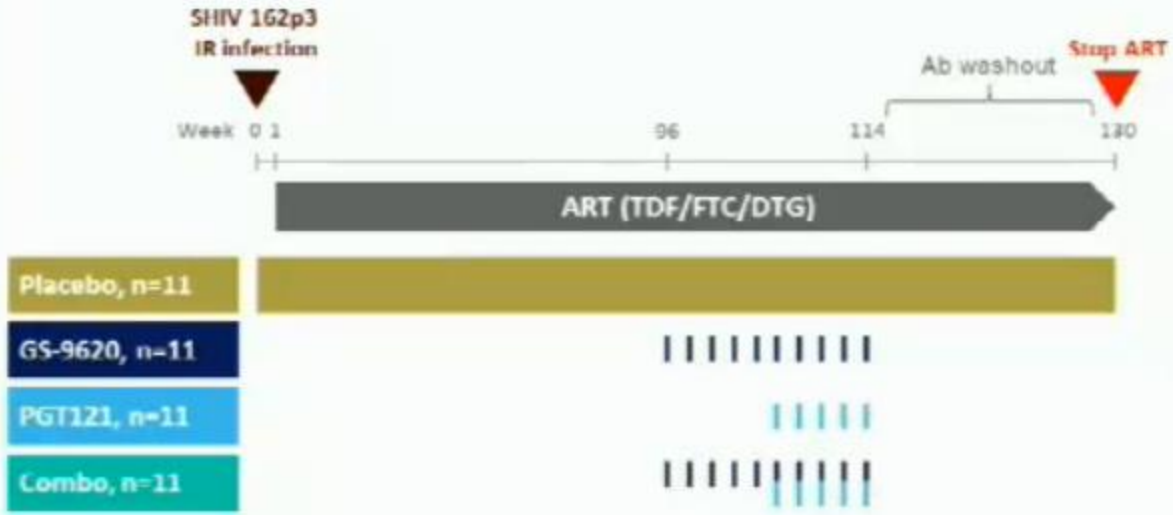
bnAbs in “Shock & Kill” cure strategy

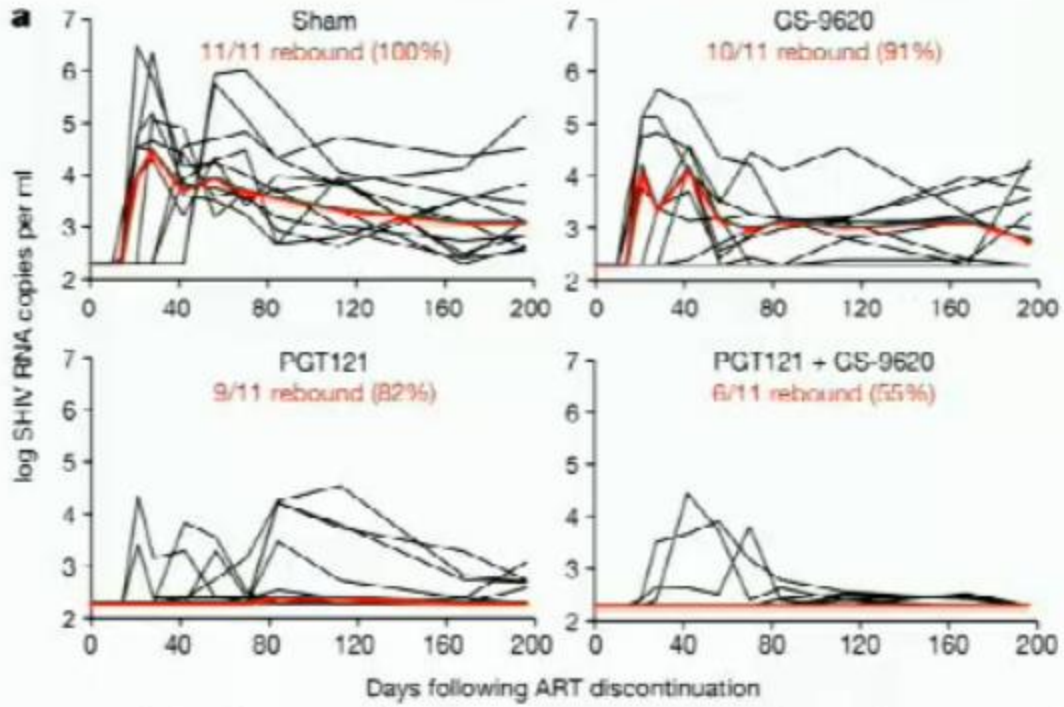


- **bnAbs would provide “Kill”:**
  - Durable, well-tolerated virus suppression
  - Clear infected cells via ADCVI and enhanced host immune function

Kim et al., Cell Host Microbe 2018

Combination therapy: bnAb + TLR7 Ag





PGT121+GS-9620 in SHIV-infected RM

- ART at 1 week post-infection, x 2 years
- PGT121 +/- TLR7 Ag, washout
- ATI

- Delayed or prevented rebound
  - 6/11 rebound combo arm
- 5 RM without rebound
  - Negative adoptive transfer
  - No rebound after CD8 depletion

Borducchi et al., Nature 2018