Towards a Functional HIV Cure

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HIV Cure: A formidable task

HIV Cure terms

HIV Sterilizing cure: No detectable viral remnants

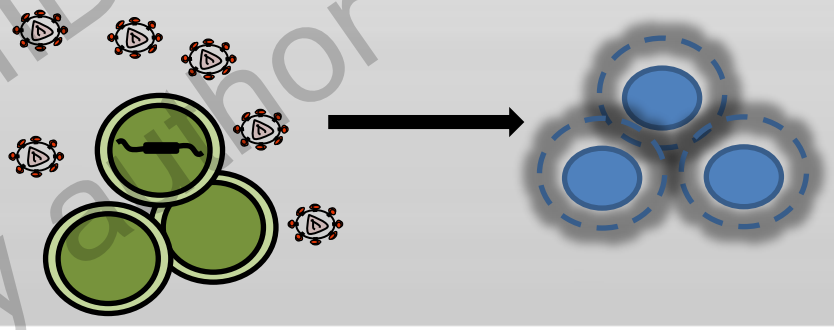
Intermediate: No replicating virus but detectable viral remnants

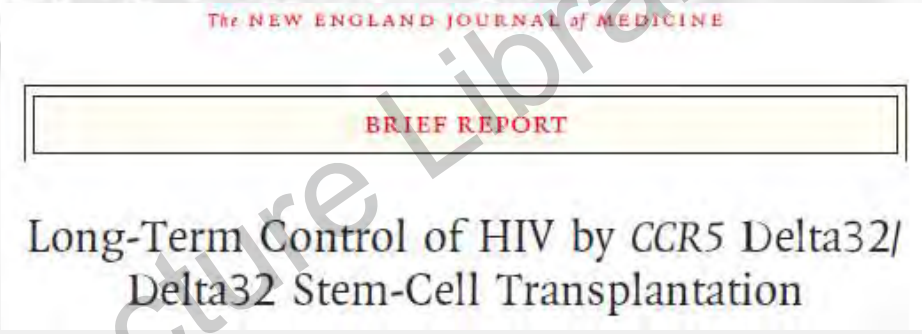
HIV Functional cure: Detectable virus replication but no disease

HIV Cure

The Berlin Patient

- 1995: HIV diagnosis
- 1996: Initiated cART
- 2006: Acute myeloid leukemia
  - Non-responsive to chemotherapy
- 2007: Relapse of leukemia
  - Bone marrow transplantation
  - Idea: Donor with homozygous deletion in the CCR5 gene
- Stopped cART in February 2007 with no re-emergence of HIV since





Hütter *et al*, NEJM 2009

HIV Cure Inspiration

…The Impossible – Made Possible…

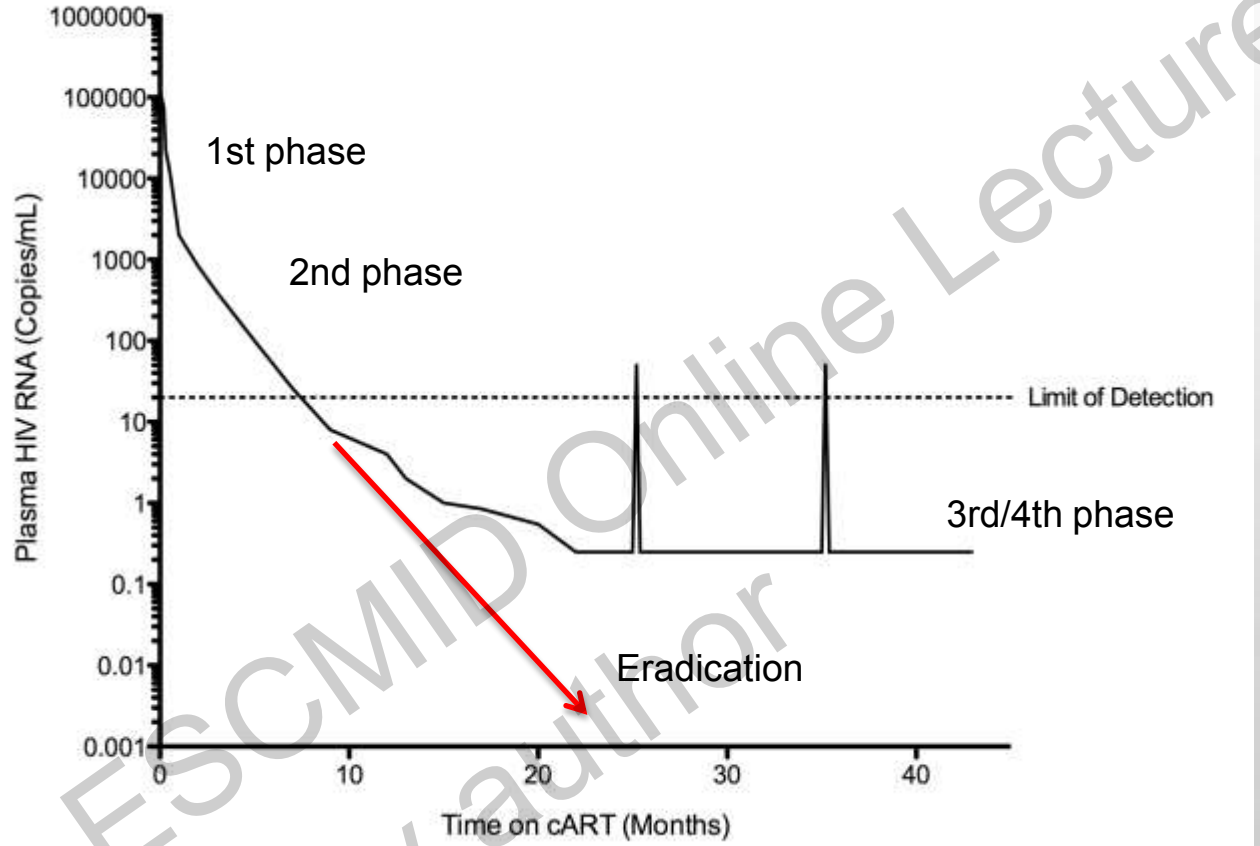
HIV Cure Research

What are the obstacles?

What are the strategies pursued?

Obstacles to HIV Cure

The dynamics of viral persistence on cART



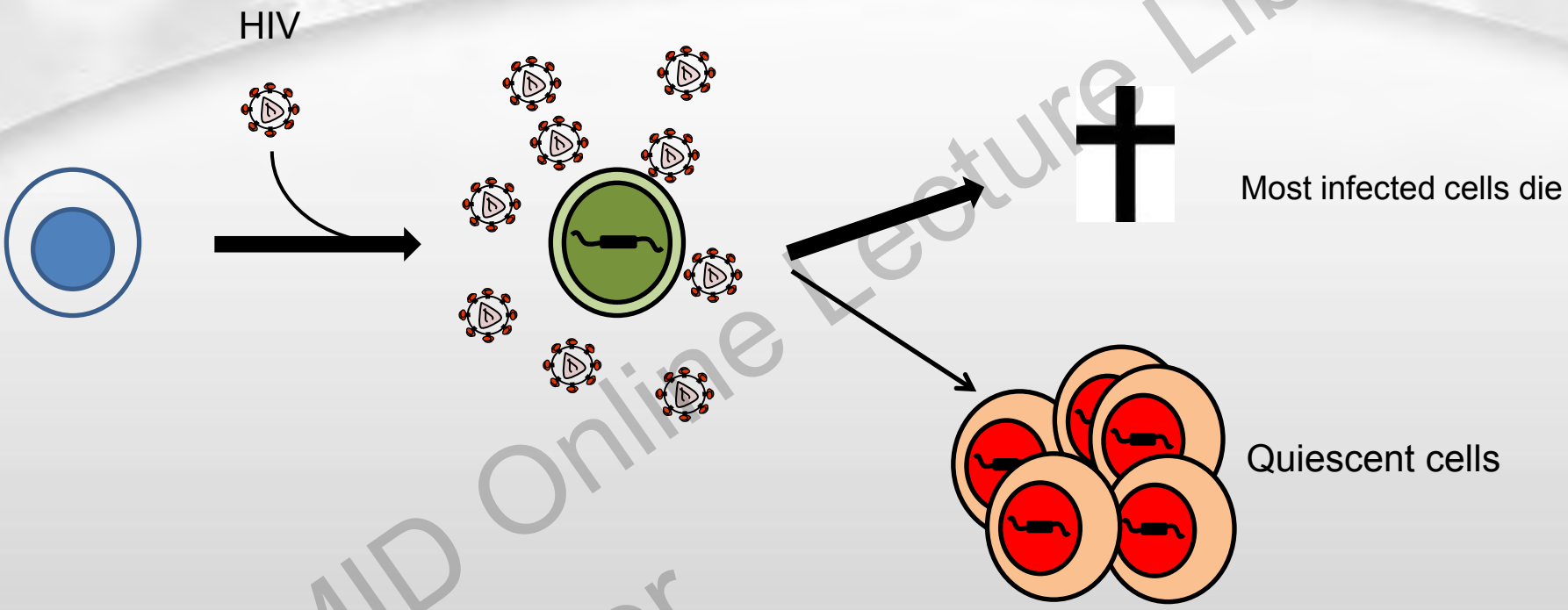
Finzi *et al* Science 1997

Chun *et al* PNAS 1997

Finzi *et al* Nature Medicine 1999

Palmer *et al* PNAS 2008

The Latent Infection



Understanding the biology of CD4 T cell homeostasis

Wagner *et al* CROI 2014

Lichterfeld *et al* CROI 2014

Buzon *et al* Nat Med 2014

HIV Cure Strategies

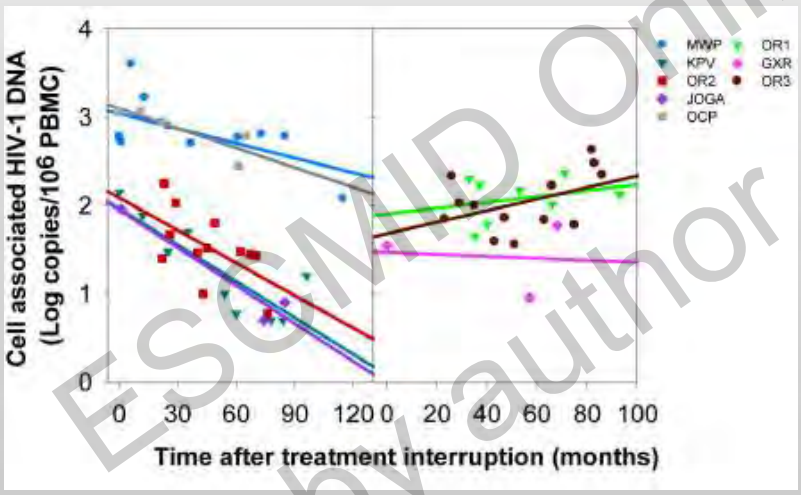
- **Eliminate residual viral replication**
  - cART Intensification studies, early treatment initiation
- **Host gene editing approaches**
  - CCR5 knock-out studies
- **Reactivate latent viral expression**
  - HDAC inhibitors, PKC activators
- **Enhance immunity**
  - Innate immunity (e.g. IFN-a treatment)
  - Adaptive immunity (e.g. Therapeutic HIV vaccination)

HIV Cure strategies

- **Eliminate residual viral replication**
  - cART Intensification studies
  - Most studies show no effect on residual replication

Gandhi *et al* PLOS Med 2010
Buzon *et al* Nat Med 2010
Vallejo *et al* AIDS 2012

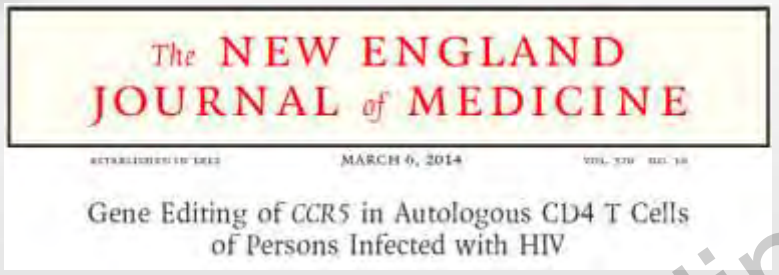
- **Post treatment controllers**
  - Identification of patients controlling HIV upon cART cessation
  - Initiation of cART close to seroconversion

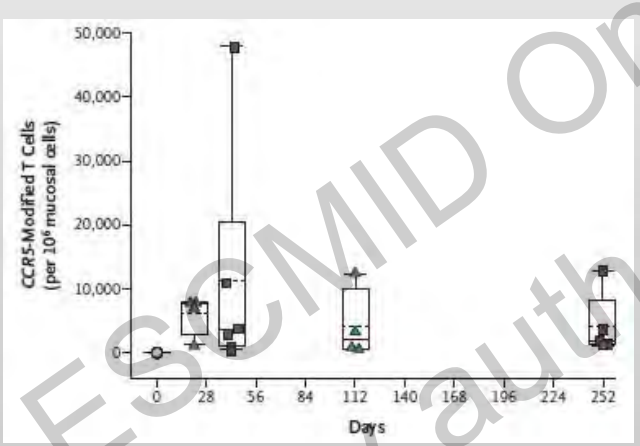


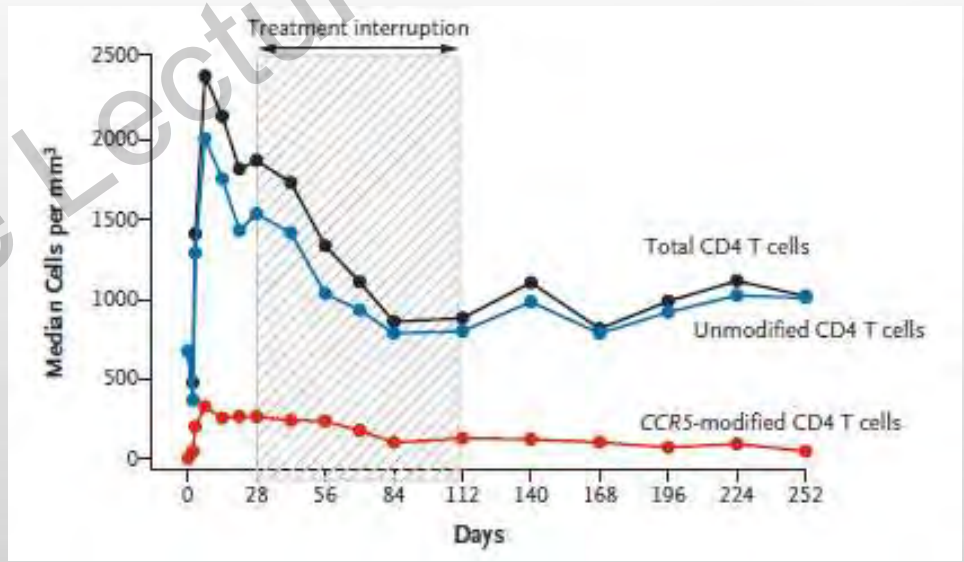
Lodi *et al* Arch Intern Med 2012
Saez-Ciron *et al* PLOS Path 2013
Stöhr *et al* PLOS One 2013

HIV Cure strategies

- **Host gene editing approaches**
  - Zinc-finger nucleases CCR5 knock-out studies







Tebas *et al* NEJM 2014

HIV Cure strategies

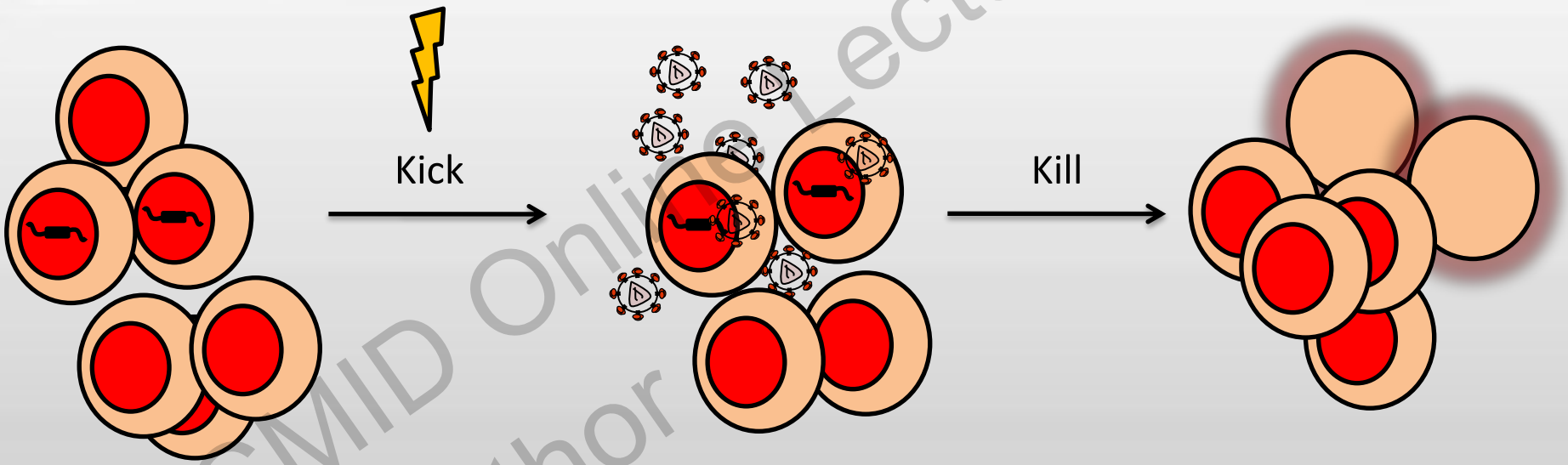
- **Host gene editing approaches**
  - Second Zinc Finger nuclease (CCR5 targeting) study
  - Prior Conditioning with Cytoxan increase gene therapy modified CD4 T cells
  - Generally 1-2 log reduction in peak viremia

Blick *et al* CROI 2014

- **Gene silencing and endogenous HIV inhibitor**
  - Lentiviral vector delivering gene knock-down of CCR5 and membrane located HIV fusion inhibitor
  - Clinical trial in Hematopoietic progenitor stem cells

HIV Cure strategies

- **Reactivate latent viral expression**
  - HDAC inhibitors, PKC activators

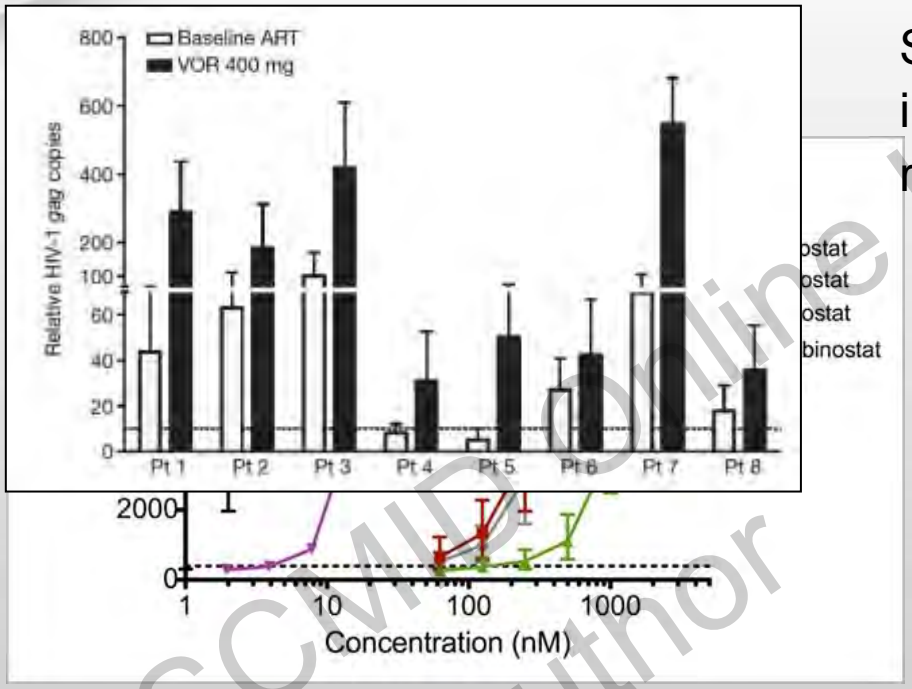


Kick and Kill strategy

Deeks *S.* Nature 2012

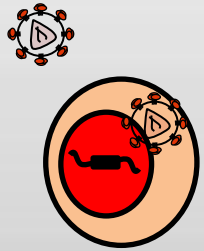
HDAC Inhibitors in HIV

Owing to their impact on chromatin condensation and viral transcription, HDACi are currently investigated for their ability to reactivate HIV-1 expression



Single dose vorinostat led to a 4.8-fold increase in cell-associated HIV RNA in resting CD4+ T cells

We identified panobinostat as highly potent with regard to reactivation of latent HIV



Archin *et al*, Nature 2012

Lewin *et al* CROI 2013

Rasmussen *et al* HVIT 2013

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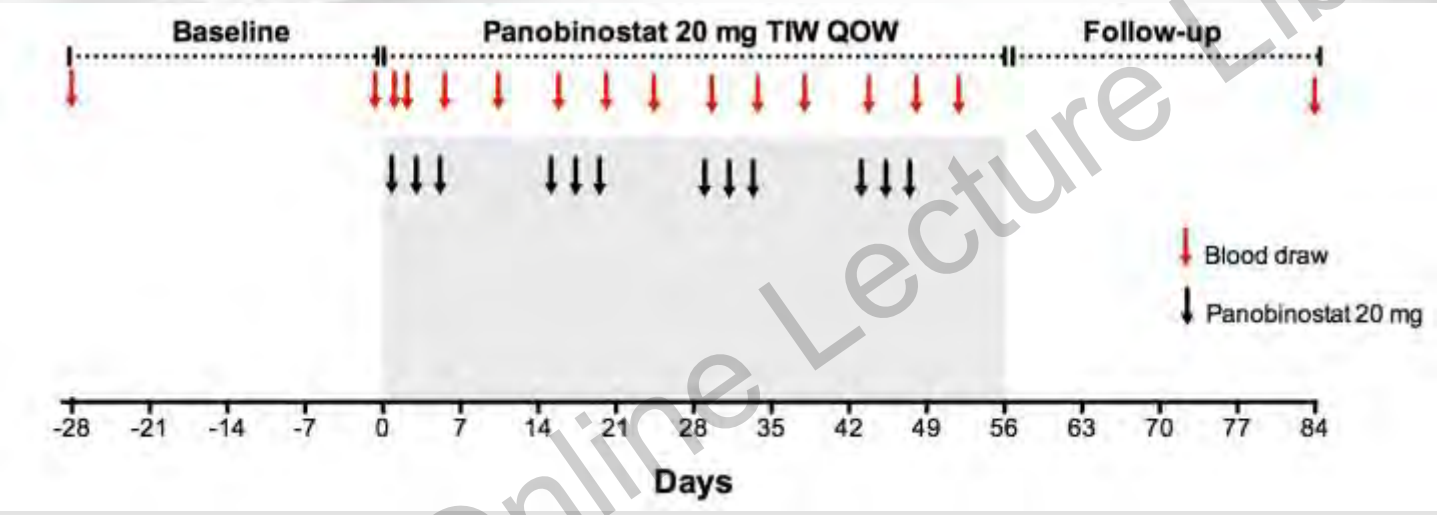
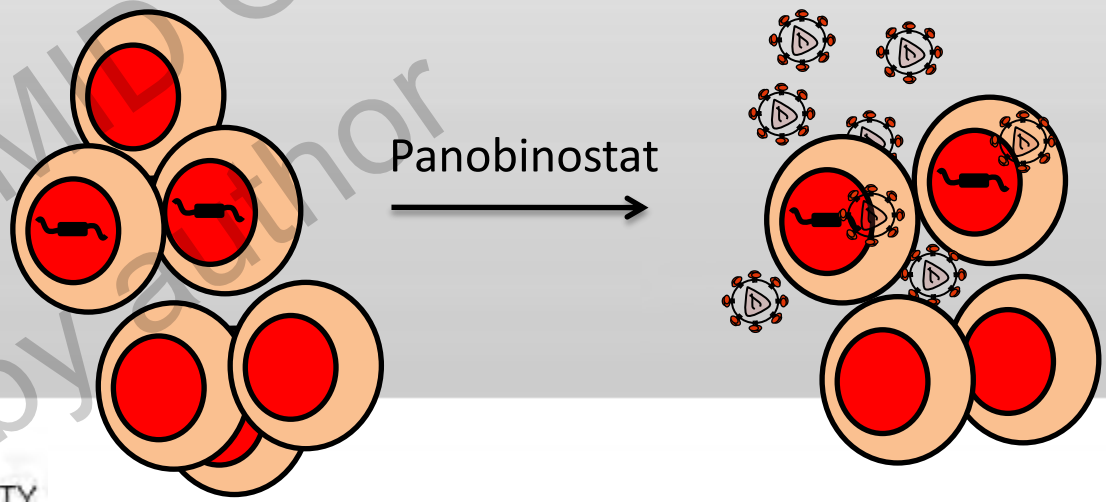
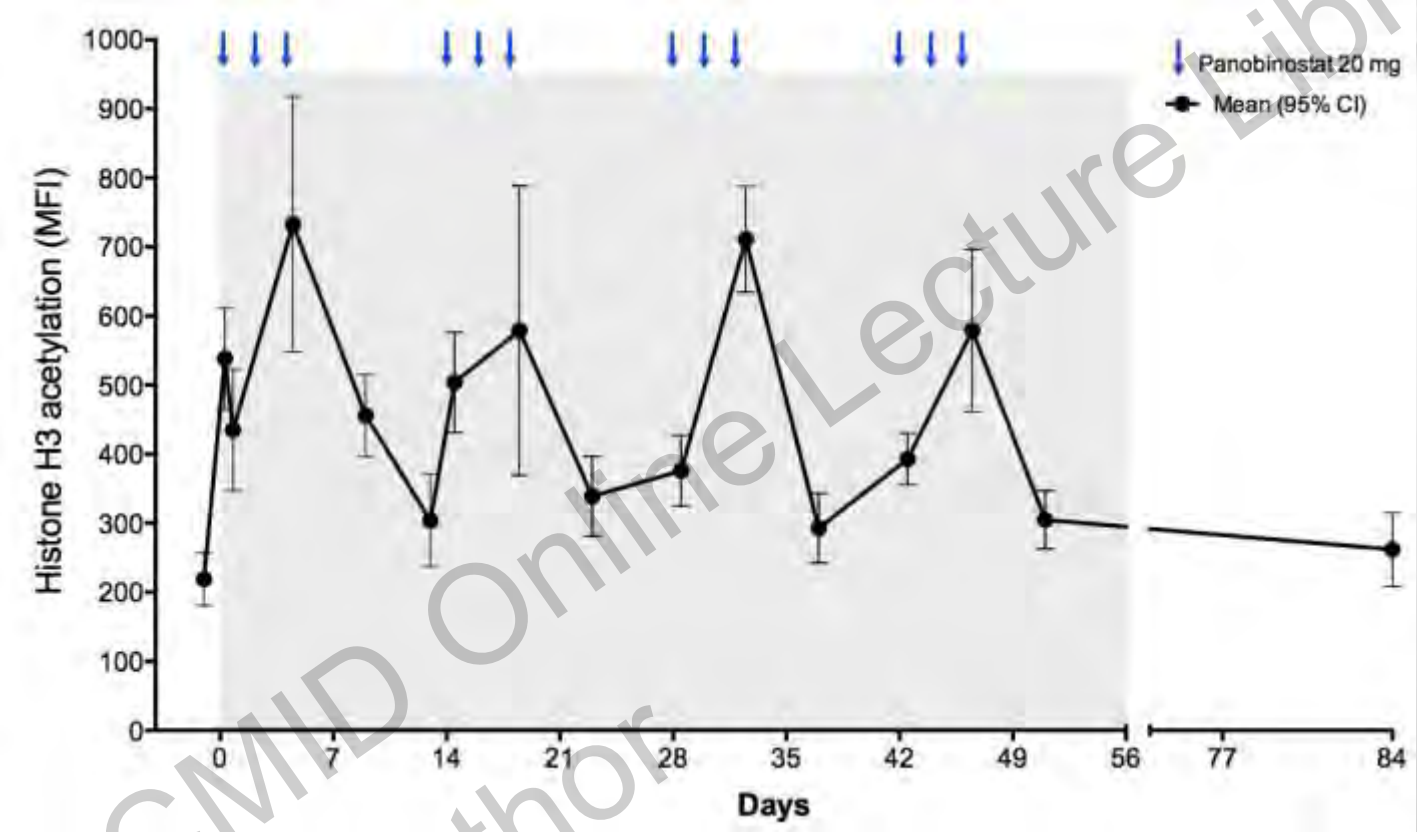
Research for the future

Panobinostat Study Design



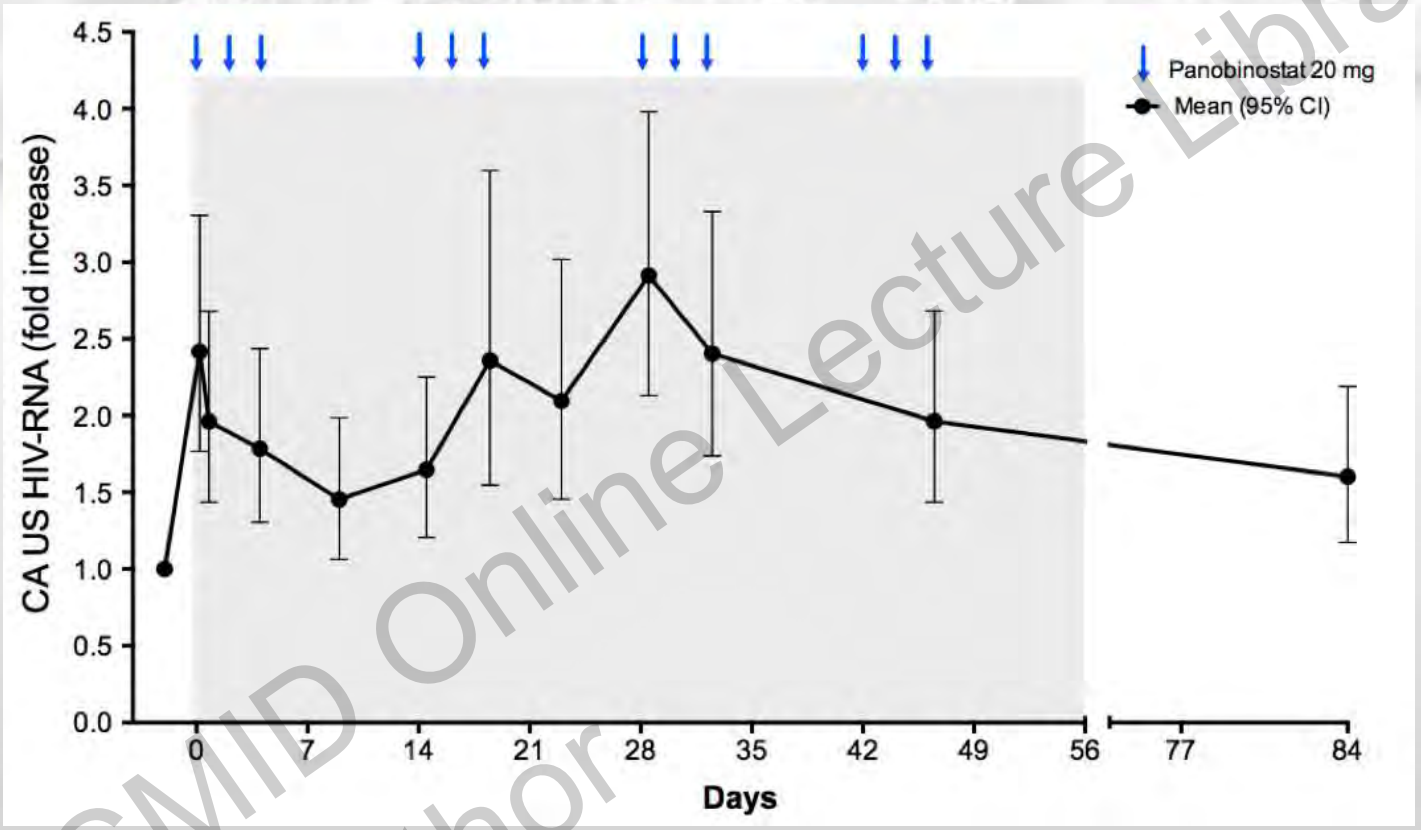


Histone acetylation



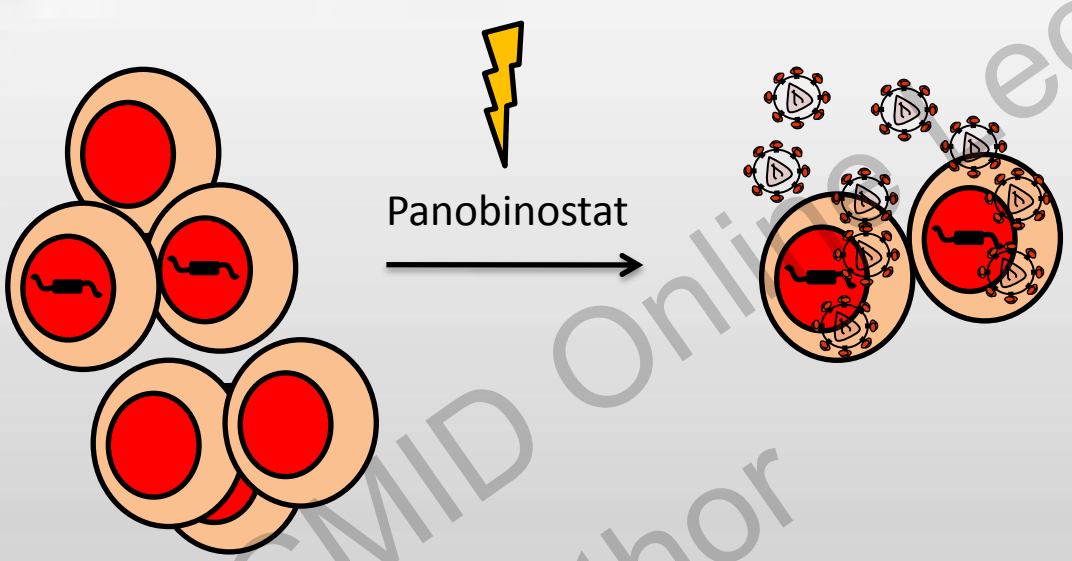
- Increase in histone H3 acetylation 2 hours after receiving first dose of panobinostat
- **Increases and decreases in histone acetylation correspond to the cyclic dosing pattern**

Cell-associated HIV RNA in CD4+ T cells

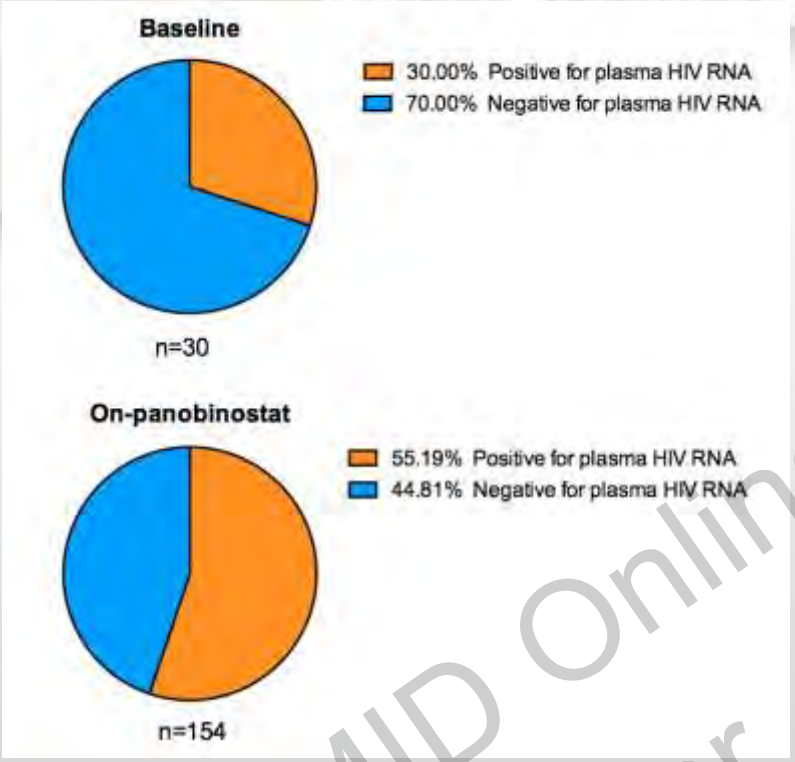


- A highly statistically significant increase over time (repeated measurement ANOVA; P<0.0001)
- Median maximal increase of 3.5 (range 2.1–14.4)

Viral reactivation



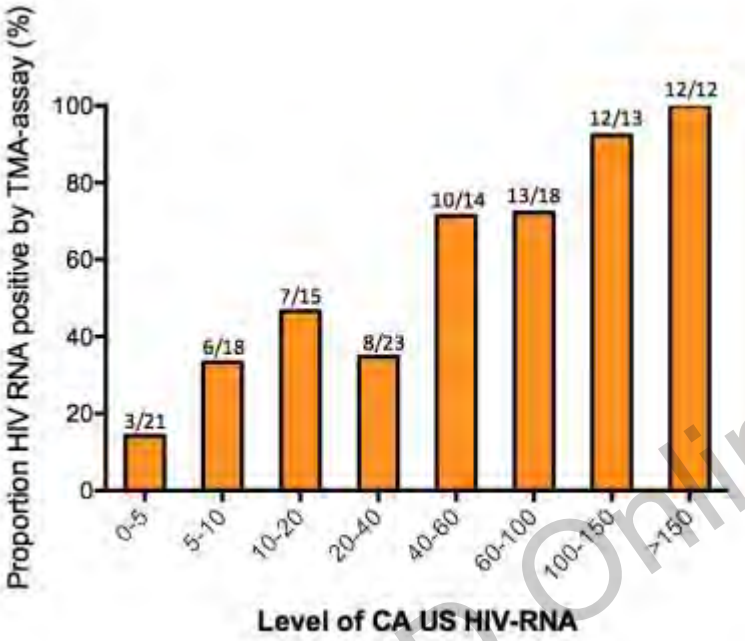
Viral particle release

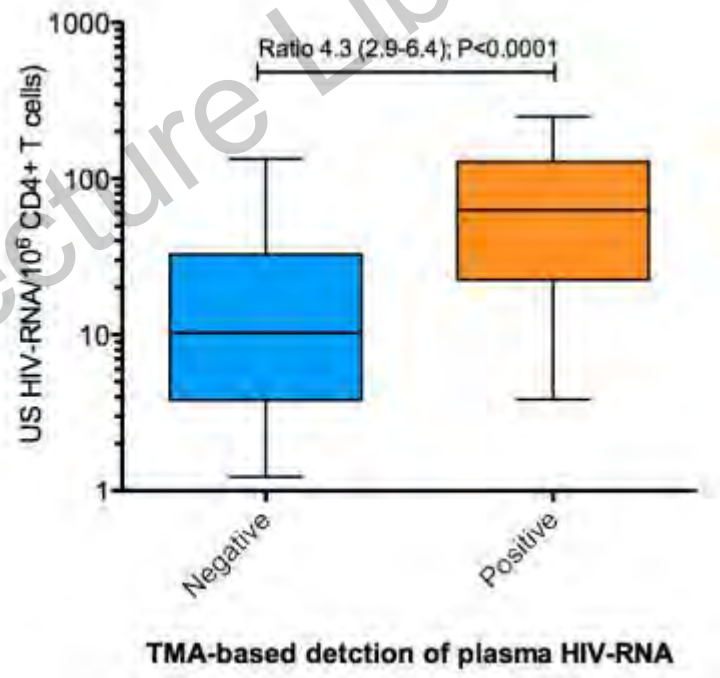


Viral particle release determined by the qualitative NAT screening system (PROCLEIX ULTRIO Plus, Genprobe)

- Logistic model with a random effect for each patient to allow for correlations due to repeated binary observations
- Odds ratio **10.5 (95% CI 2.2;50.3)** for positive test on-treatment

Low level viremia

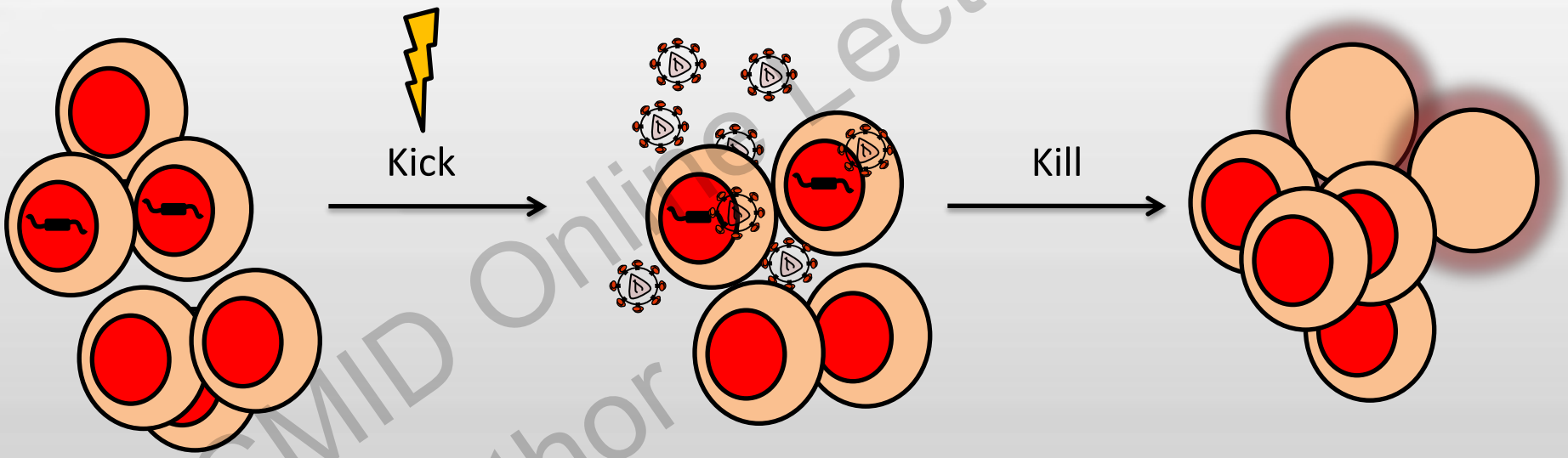




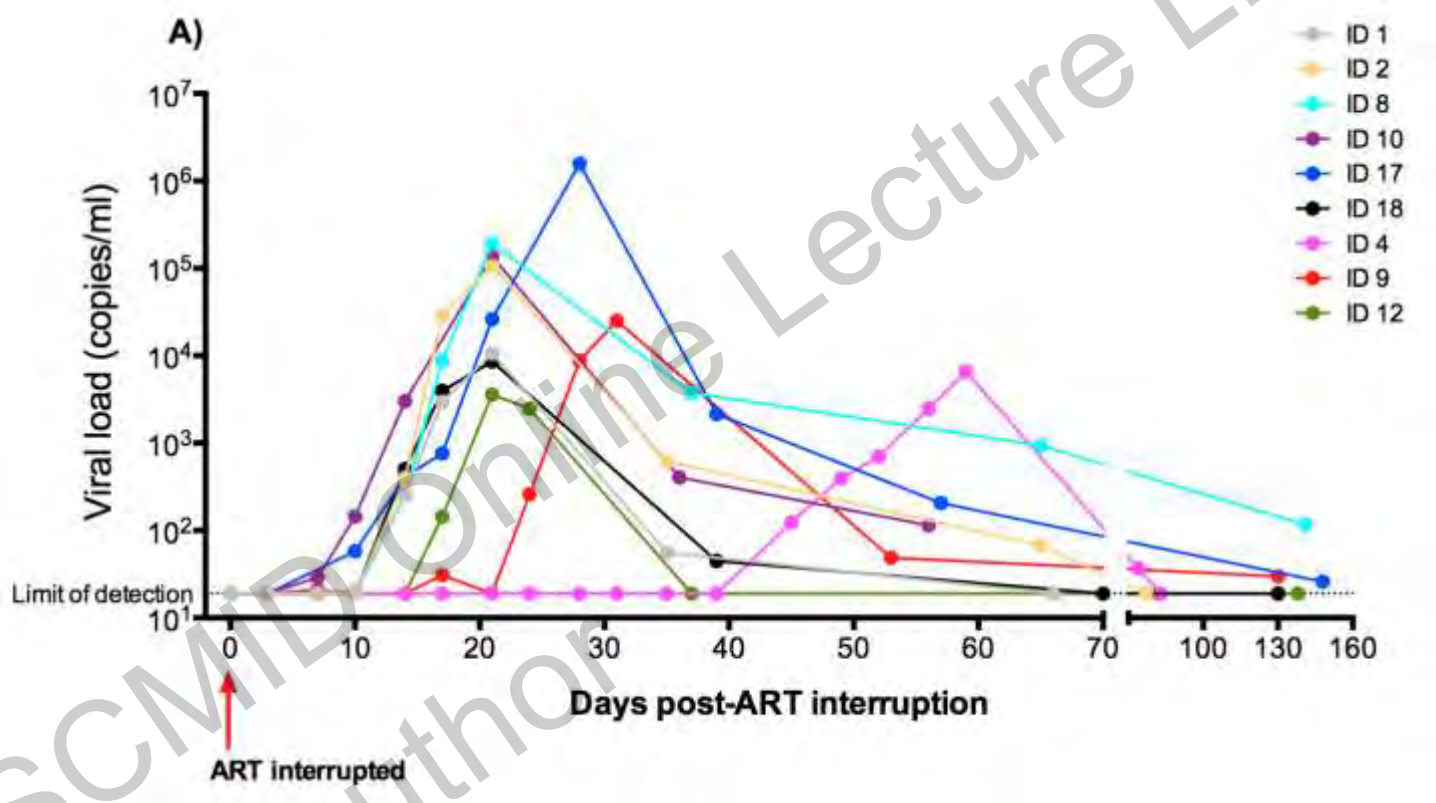
- Levels of cellular HIV RNA **4.3-fold higher** in plasma HIV-positive vs HIV- negative samples
- The proportion of plasma samples positive for HIV-RNA increases with increase in cellular HIV-RNA in paired samples

Panobinostat provided the kick to reactivate HIV

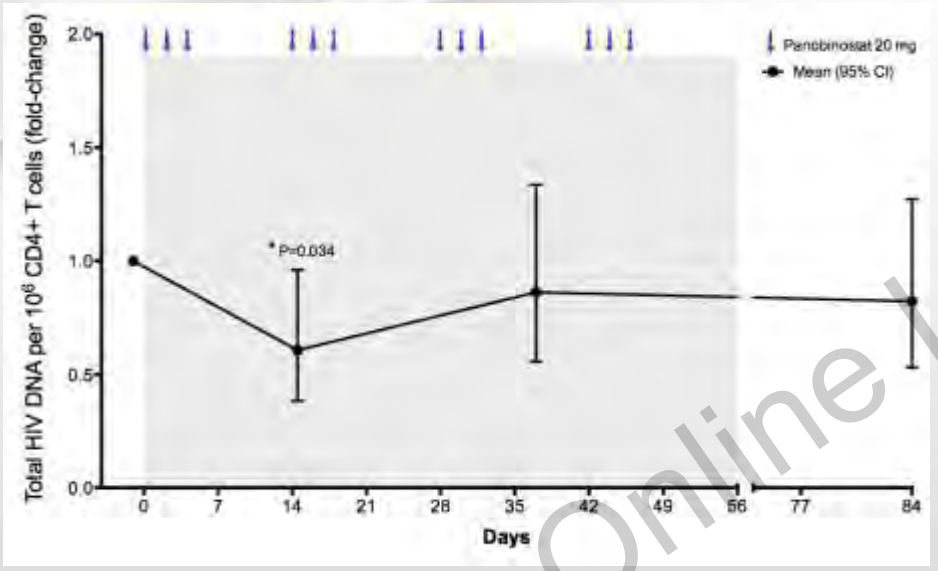
…but did it impact the reservoir?

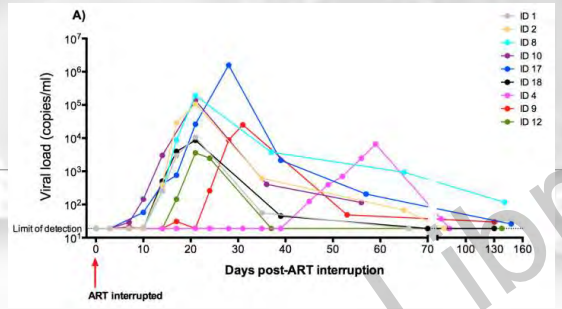


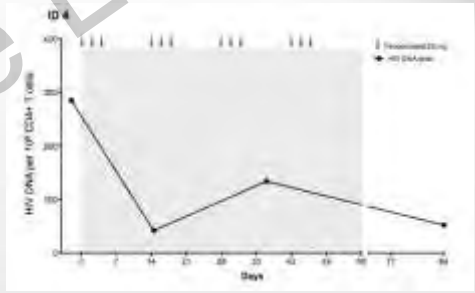
Analytic treatment interruption

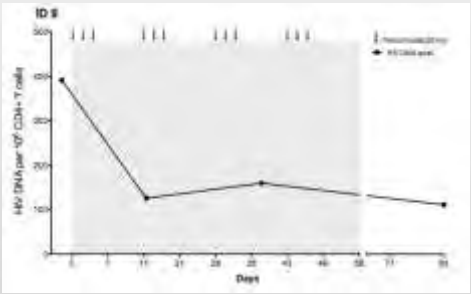


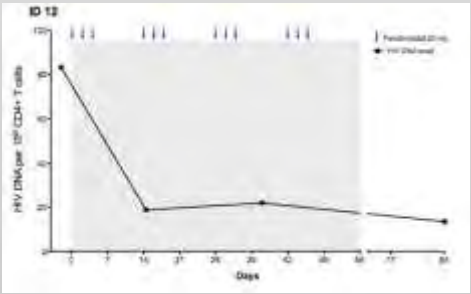
HIV Reservoir





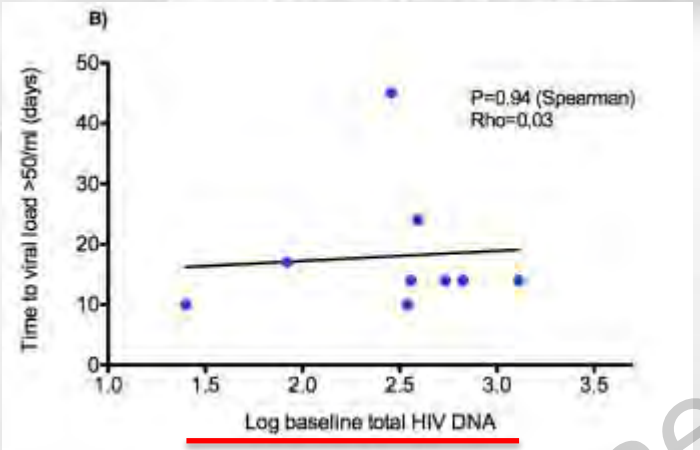


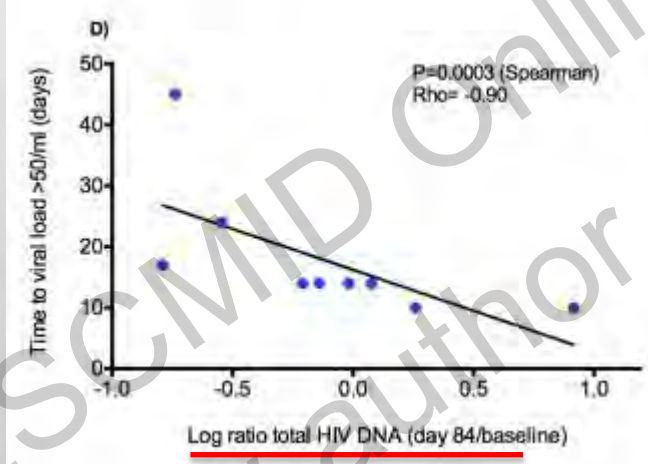


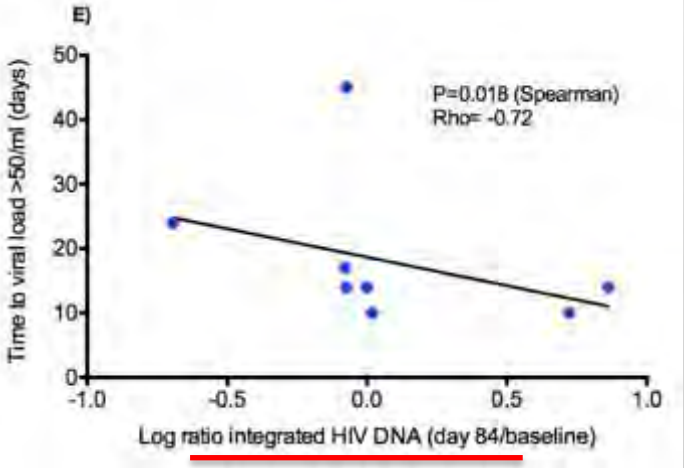


- Decrease from baseline to day 14
- Cohort wide no decline in total HIV DNA from baseline to day 84 (4 weeks post treatment)

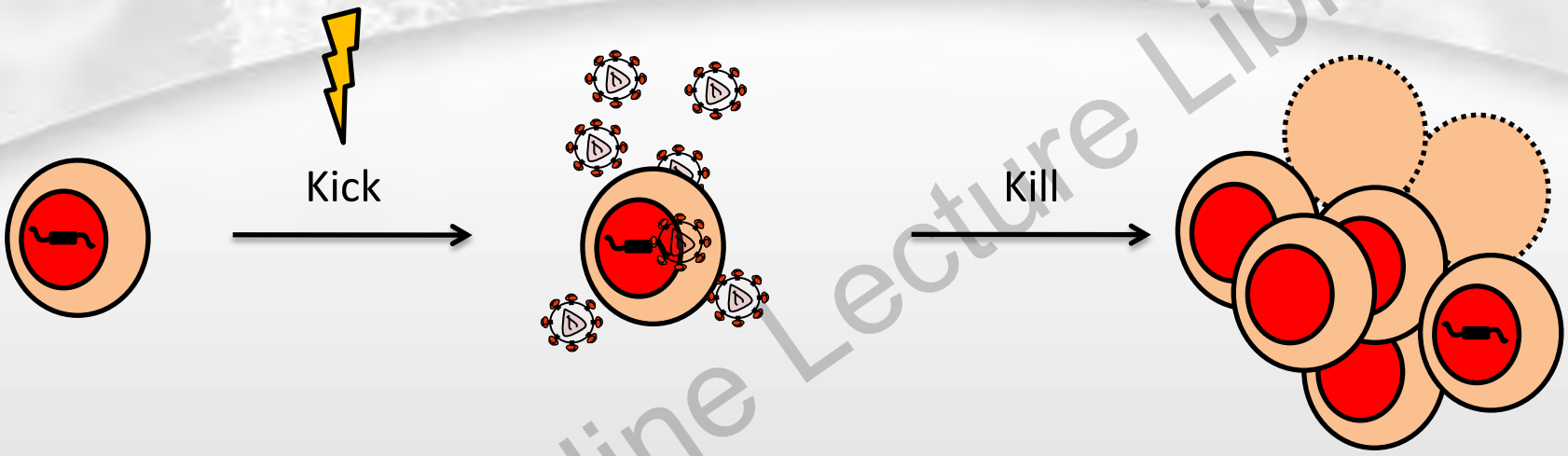
Impact on Rebound?







Conclusion



- Panobinostat can provide the kick to reactivate HIV
- Impact on the reservoir is associated with time to rebound
- Ongoing work to decipher the immune parameters

HIV Cure strategies

- **Eliminate residual viral replication**
  - HAART Intensification studies, early treatment initiation
- **Host gene editing approaches**
  - CCR5 knock-out studies, Integrated provirus targeting
- **Reactivate latent viral expression**
  - HDAC inhibitors, PKC activators
- **Enhance immunity**
  - Innate immunity ex IFN-a treatment
  - Adaptive immunity ex Therapeutic HIV vaccination

HIV Immunotherapy

- IFN-α therapy

Azzoni *et al*, JID 2013

- Therapeutic vaccination
  - Generally has led to ~0.5- 1 log decrease setpoint viral load
  - CMV-based vector vaccine in pre-clinical development
  - Combination strategies with latency reversing agents to demask the latent virus

Hansen *et al* Nature 2013

Garcia et al Sci Transl Med 2013

Pollard *et al*, Lancet ID 2014

HIV Cure "Boston Patients"

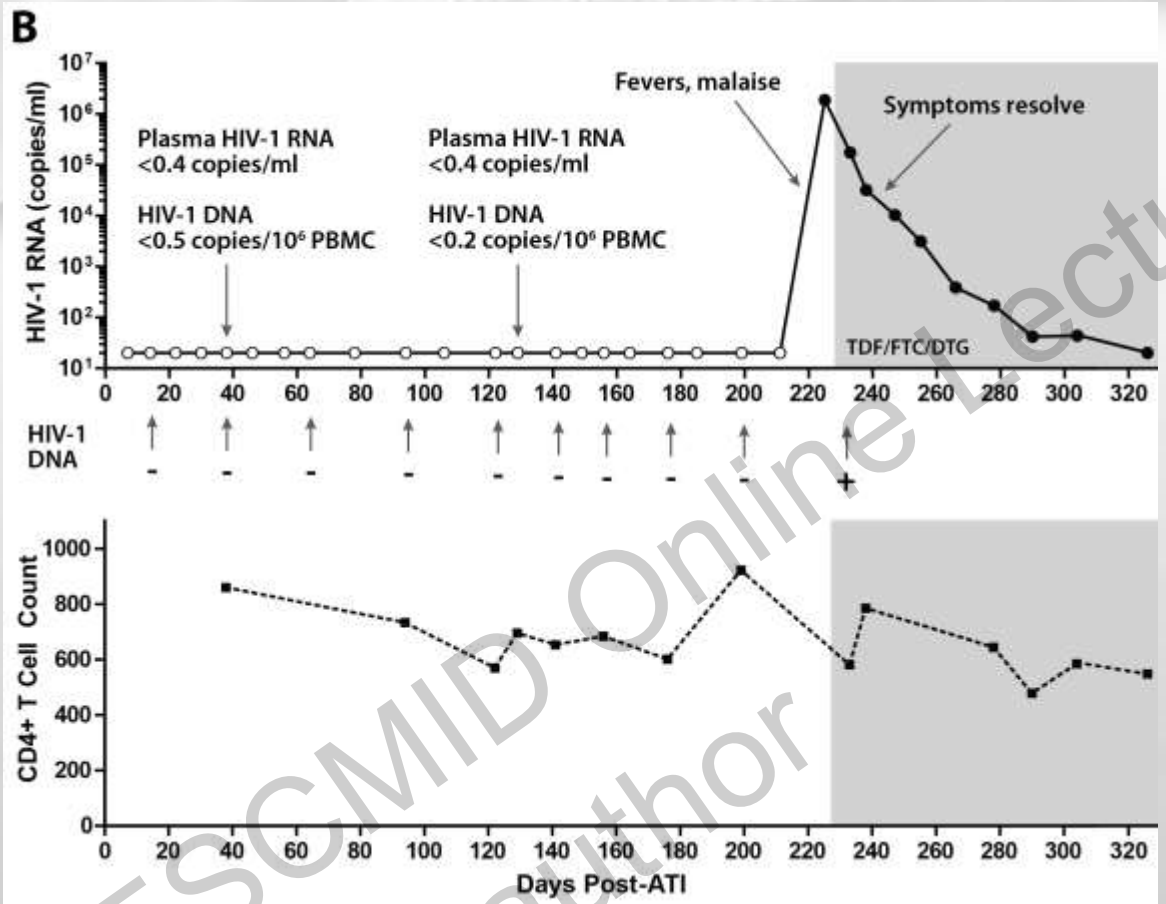
	Patient A	Patient B
CCR5 genotype	Δ32 Heterozygote	Δ32 Heterozygote
Pre-transplant HIV DNA	144 copies/mio PBMC	96 copies/mio PBMC
Allogeneic transplant	CCR5 wildtype	CCR5 wildtype
cART post transplant	4.5 years	2.8 years
Chimerism	<0.001% host PBMC	<0.001% host PBMC
Post transplant HIV detection	Negative	Negative

Tested resting CD4 T cells from > 150 mio PBMCs for replicational competent virus and HIV DNA

Henrich *et al*, JID 2013

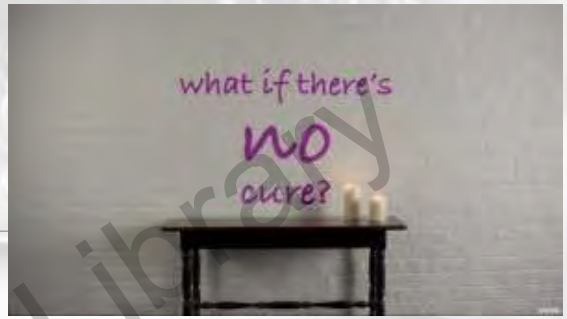
Henrich *et al* CROI 2014

HIV Cure "Boston Patients"



Data Courtesy from Timothy Henrich

Conclusions



An HIV Cure is a formidable goal

- The Post-Treatment Controllers tell us that viral control upon cART cessation is possible
- Novel gene editing / therapy technologies are moving fast into clinical trials. Combination with hematopoietic stem cell modulation is next vital step
- Latency reversing agents has been identified that “kick” the virus out of latency
- We need effective modalities to enhance the viral killing

Collaborators

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The Danish Council for Strategic Research

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