

## Advances Toward a Cure for HIV

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### Financial Relationships With Commercial Entities

Dr Siliciano has served on the scientific advisory board for Gilead Sciences, Inc. Her lab has received a grant from Gilead Sciences, Inc. (Updated 08/3/20)

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### Learning Objectives

After attending this presentation, learners will be able to:

- Describe basic mechanisms that allow HIV to persist despite antiretroviral therapy (ART)
- Recognize how proliferation of latently infected resting CD4+ T cells contributes to viral persistence
- Describe 1 current approach for achieving an HIV cure

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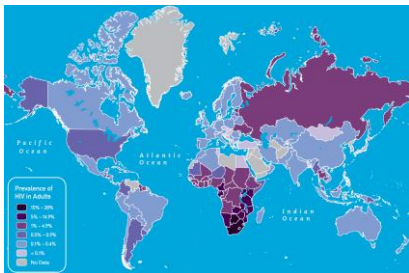
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### Magnitude of the problem



38,000,000 infected

23,000,000 on ART

3 people cured

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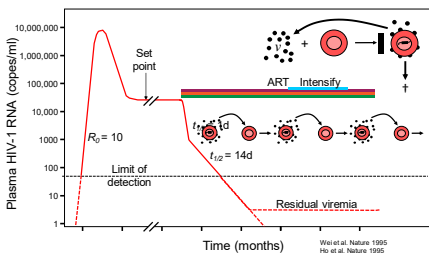
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### HIV replication dynamics



Wong et al. Nature 1995  
Ho et al. Nature 1995  
Pensiero et al. Nature 1997  
Finzi et al. Nature Med 1999  
Domestic et al. JAMA 1999  
Dirocco et al. PNAS 2009  
Bull and Rasmussen, CD4, 2010

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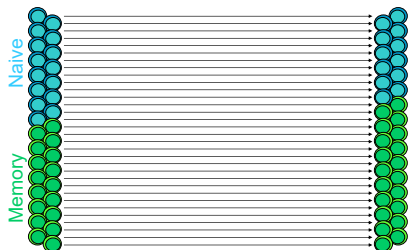
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### Physiology of resting and activated CD4+ T cells



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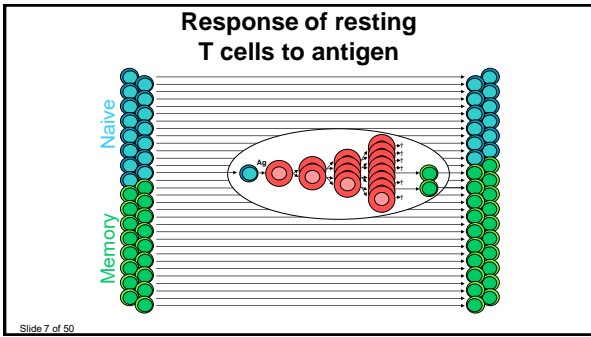
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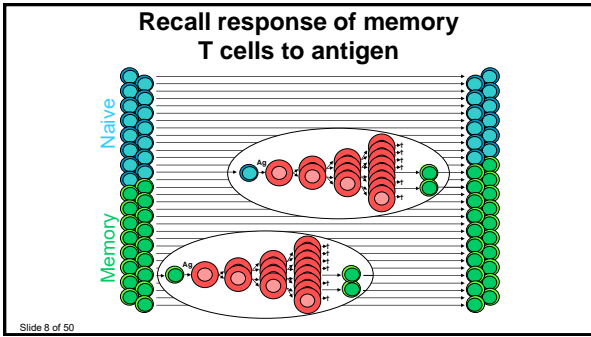
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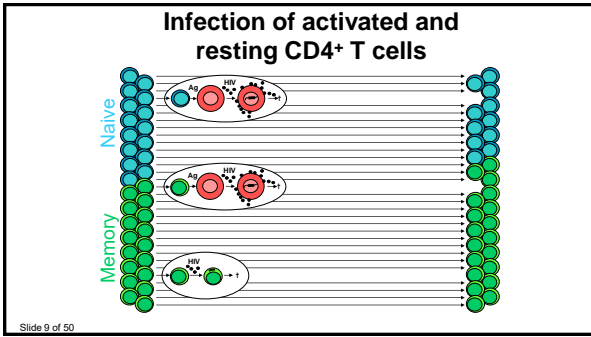
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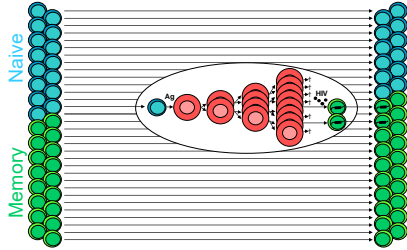
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### Establishment and maintenance of a latent reservoir



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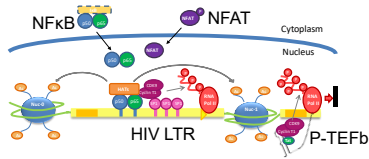
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### HIV gene expression depends on inducible host factors



Nabel and Baltimore, *Nature* 1987  
 Tong-Starksen et al, *PNAS* 1987  
 Duh et al, *PNAS* 1989  
 Kinoshita et al, *Immunity* 1997

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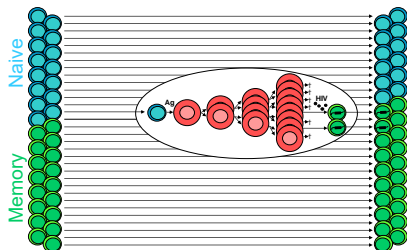
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### A stable latent reservoir for HIV



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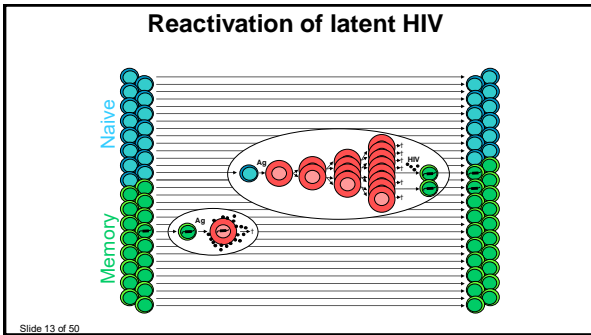
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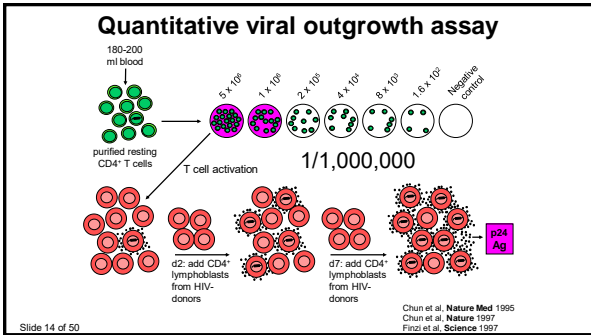
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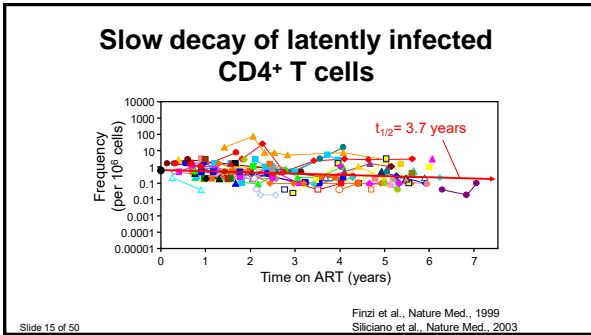
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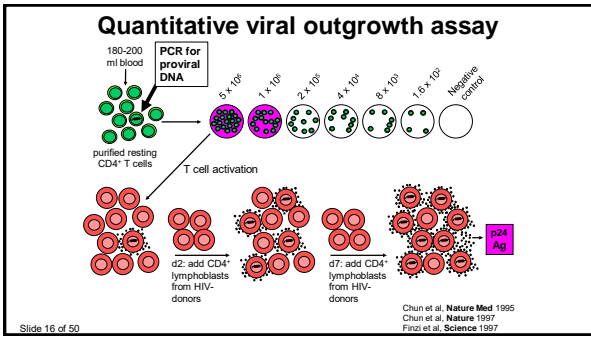
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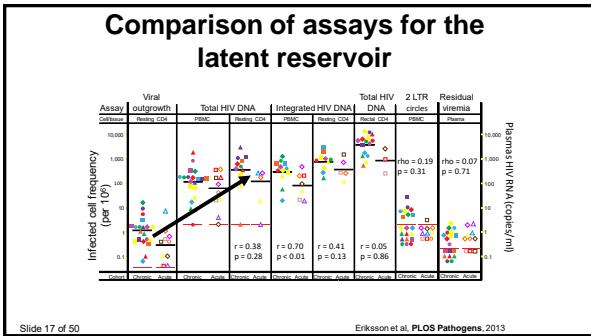
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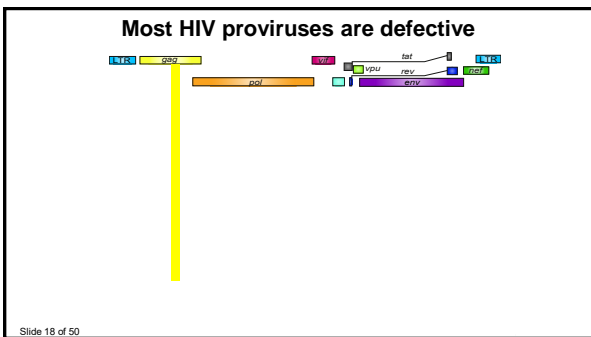
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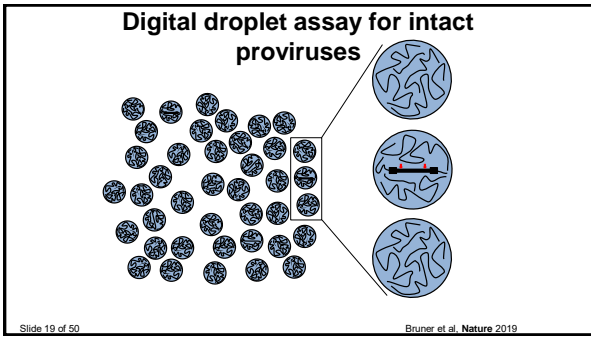
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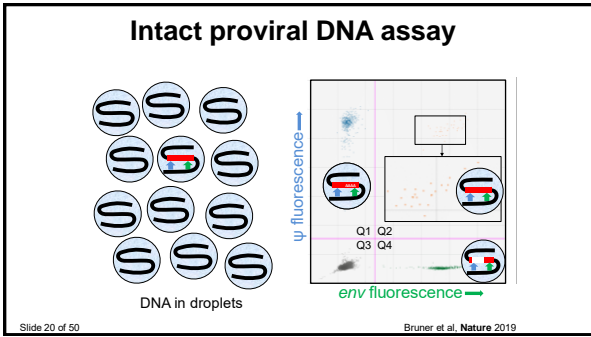
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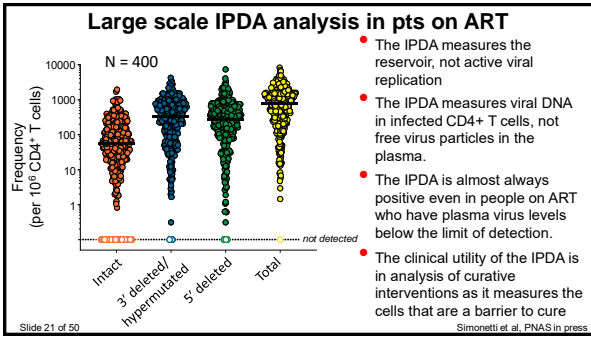
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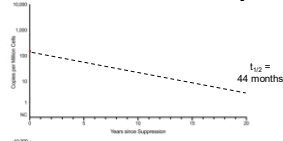
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### Intact proviruses decay more rapidly than defective proviruses



- Cells with intact proviruses decay more rapidly than cells with defective proviruses
- This may indicate some immune pressure on infected cells during ART.
- This decay is slow! In first 7 years,  $t_{1/2}$  is close to 44 months. Subsequently, even slower

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Peluso et al. JCI Insight 2020

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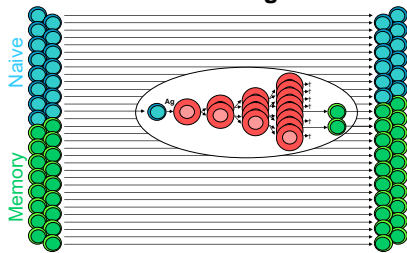
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### Response of resting T cells to antigen



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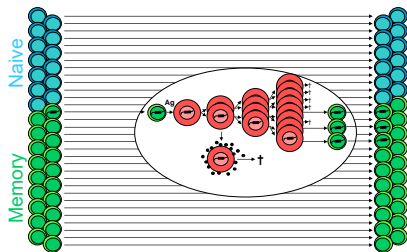
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### Infected cells can also proliferate



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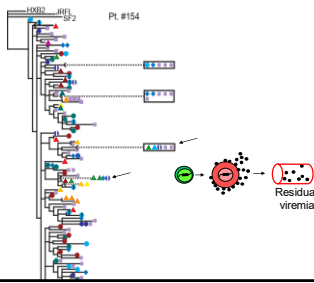
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## Proliferation of infected cells



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Tobin et al., J Virol 2005  
Bailey et al., J Virol 2006

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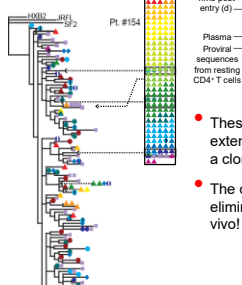
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## Clonal nature of residual viremia



- These sequences reflect extensive proliferation of a clone of infected cells
- The cells we want to eliminate can proliferate in vivo!

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Tobin et al., J Virol 2005  
Bailey et al., J Virol 2006

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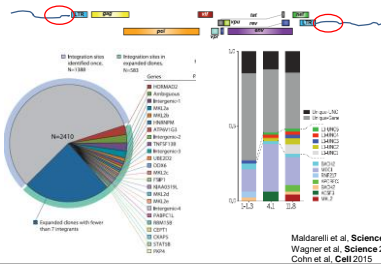
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## Clonal expansion detected by integration site analysis



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Maldarelli et al., Science 2014  
Wagner et al., Science 2014  
Cohn et al., Cell 2015

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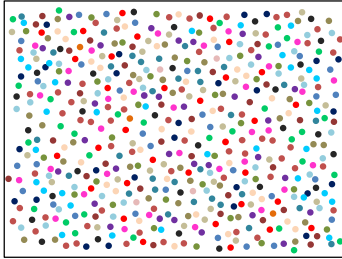
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**The latent reservoir**



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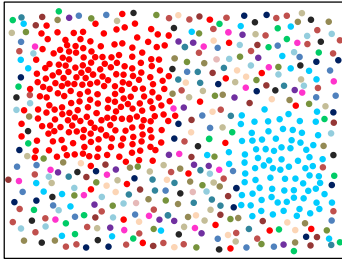
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**Clones of latently infected cells**



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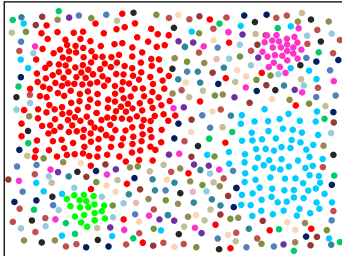
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**Clones of latently infected cells**



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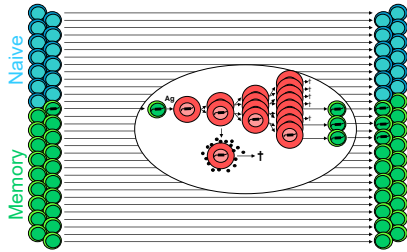
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### Infected cells can also proliferate



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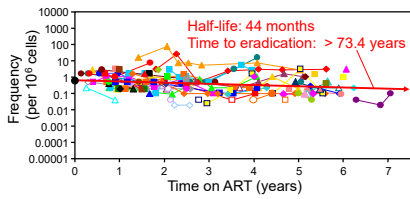
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### Slow decay of the latent reservoir in resting CD4+ T cells



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Finzi et al. *Nature Med* 1999  
J. Siliciano et al. *Nature Med* 2003

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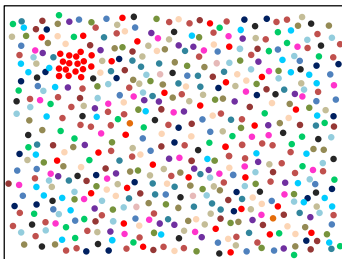
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### Clones of latently infected cells wax and wane



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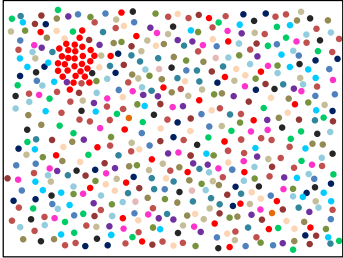
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**Clones of latently infected cells  
wax and wane**



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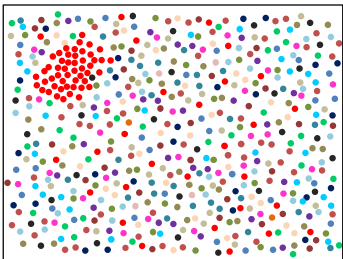
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**Clones of latently infected cells  
wax and wane**



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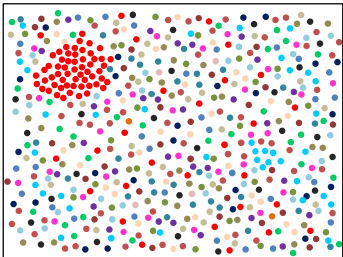
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**Clones of latently infected cells  
wax and wane**



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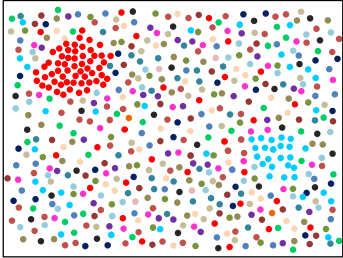
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**Clones of latently infected cells  
wax and wane**



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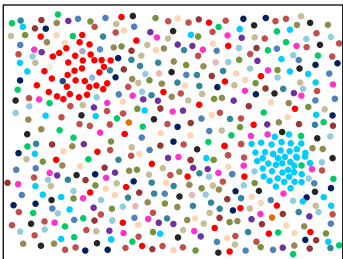
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**Clones of latently infected cells  
wax and wane**



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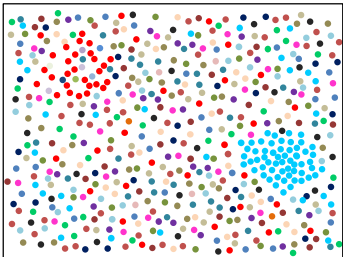
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**Clones of latently infected cells  
wax and wane**



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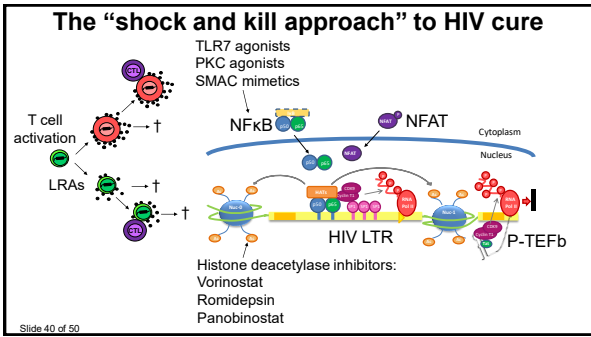
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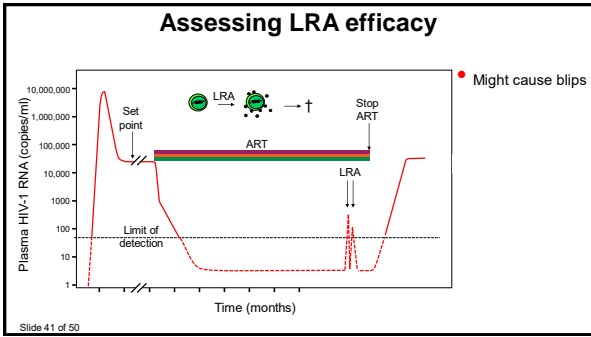
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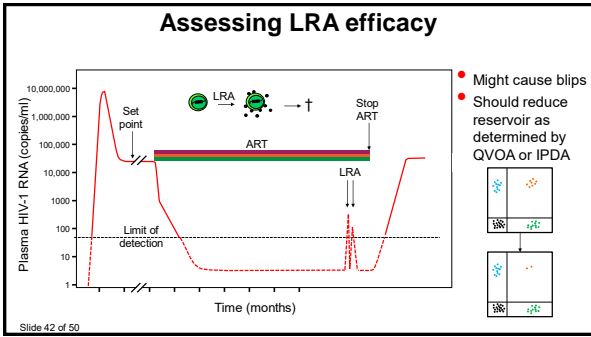
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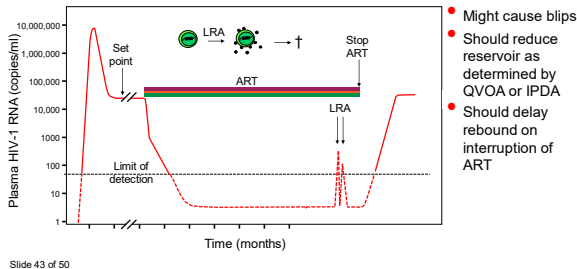
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### Assessing LRA efficacy



- Might cause blips
- Should reduce reservoir as determined by QVOA or IPDA
- Should delay rebound on interruption of ART

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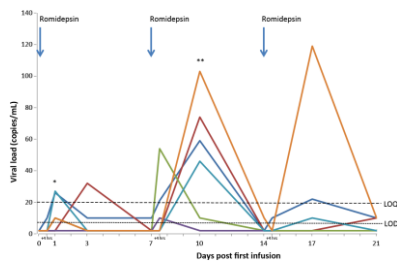
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### Clinical trial of romidepsin



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Courtesy of O. Sogaard, Aarhus University

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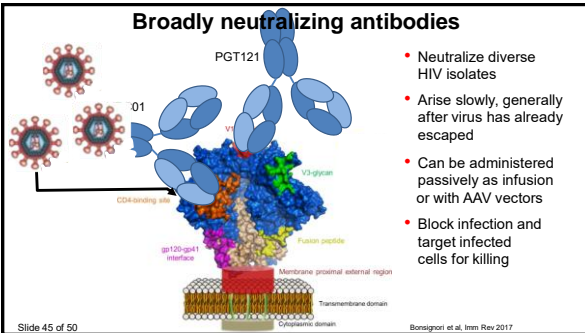
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### Broadly neutralizing antibodies



- Neutralize diverse HIV isolates
- Arise slowly, generally after virus has already escaped
- Can be administered passively as infusion or with AAV vectors
- Block infection and target infected cells for killing

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Borsignoni et al. Imm Rev 2017

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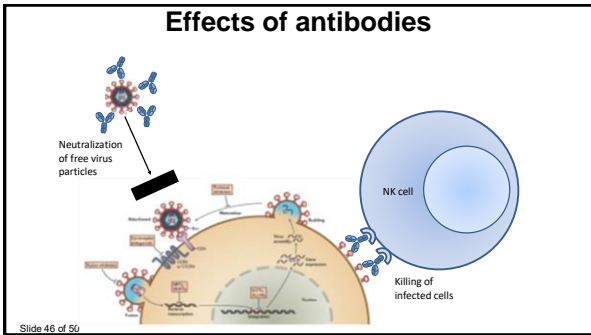
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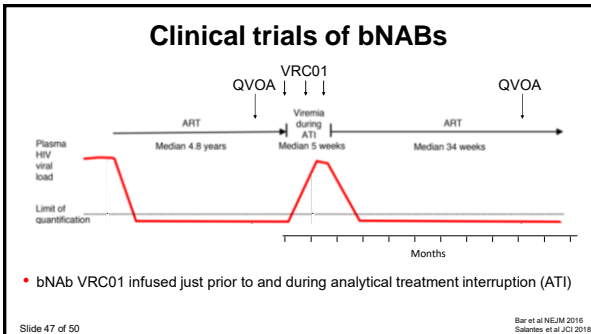
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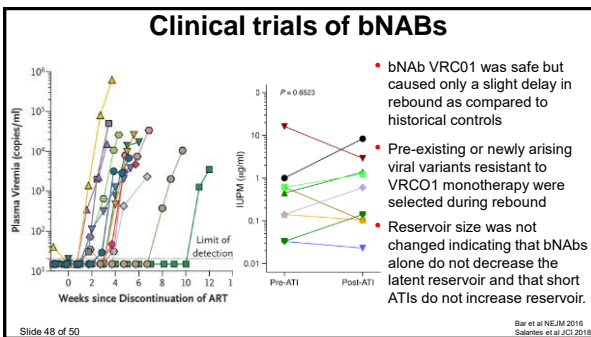
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## Conclusions

- The latent reservoir in resting CD4+ T cells is the major barrier to cure
- Accurate measurement of the reservoir is important for evaluating cure interventions and requires distinguishing intact proviruses from defective ones. This can be done with a novel assay, the IPDA.
- The reservoir is maintained by the proliferation of infected cells in response to antigens. This is a serious problem for cure efforts.
- Eliminating the reservoir through the "shock and kill" strategy will require finding better ways to turn on latent HIV and better ways to induce the killing of productively infected cells
- Broadly neutralizing antibodies are of great interest in the HIV vaccine field and may also be useful to enhance killing of infected cells.

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## Thank you

### Collaborators

Steve Deeks  
Rebecca Hoh  
Greg Laird  
Katie Bar  
Pablo Tebas

### Funding

Gilead (unrestricted research grant)  
Howard Hughes Medical Institute  
NIH: Martin Delaney Collaboratories  
Bill and Melinda Gates Foundation



Martin Delaney  
Collaboratories



Howard Hughes  
Medical Institute

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**2020** Ryan White  
HIV/AIDS Program  
CLINICAL CONFERENCE

## Question-and-Answer Session

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