Do we need new drugs for treatment naïve patients?

The NIH Perspective

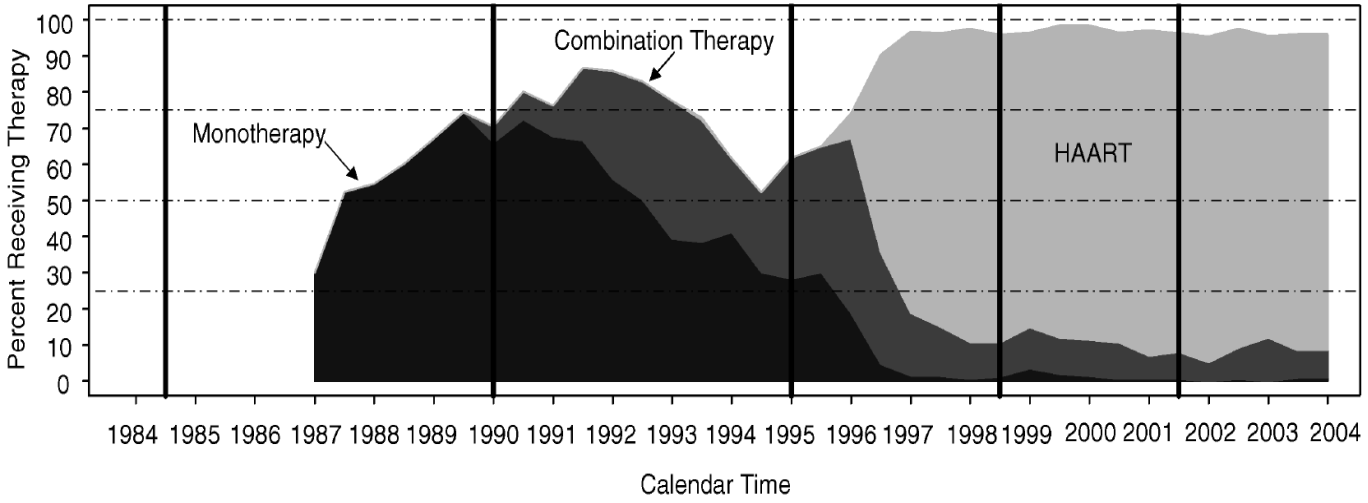
The naïve patient

- From a research perspective we have drugs that inhibit RT, PR, Entry IN
- All drugs suppress virus replication
- Combinations result in suppression of HIV replication to undetectable levels

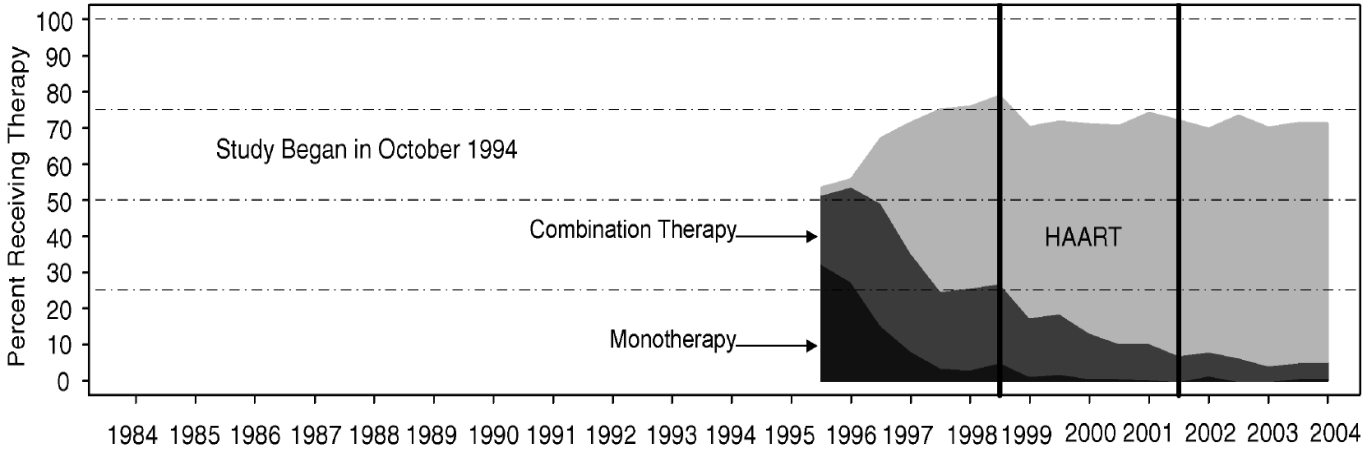
- CD4 cell numbers rebound (by and large)
- Patients can have sustained responses lasting years

Outbreaks of therapy

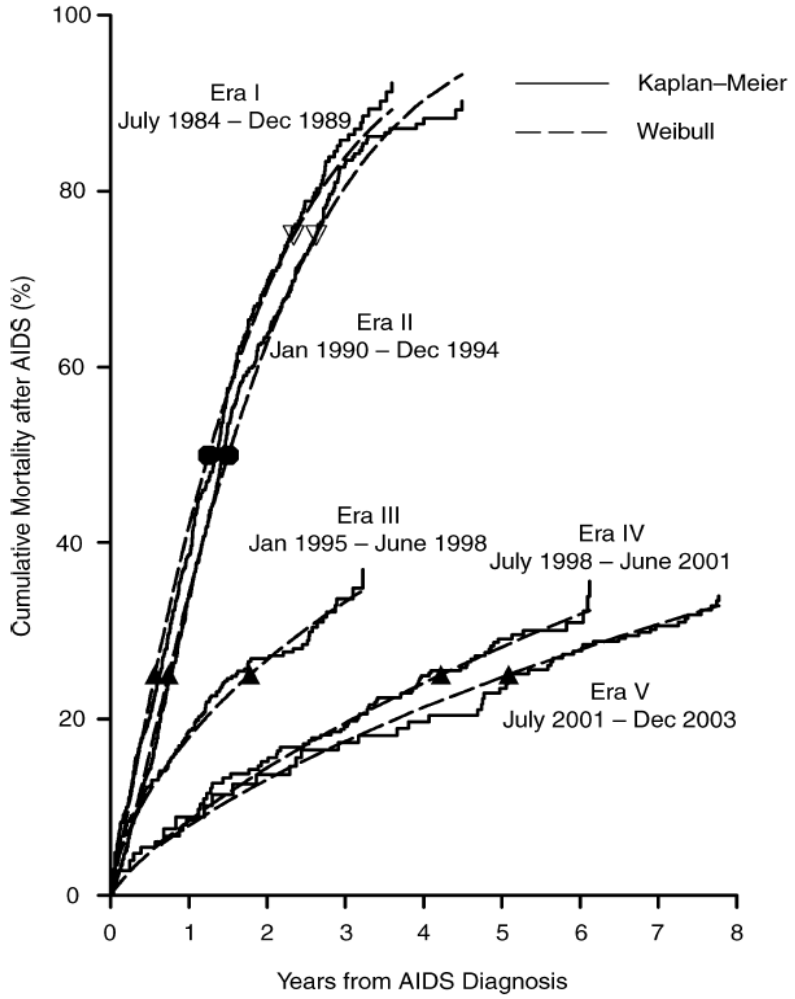
Multicenter AIDS Cohort Study

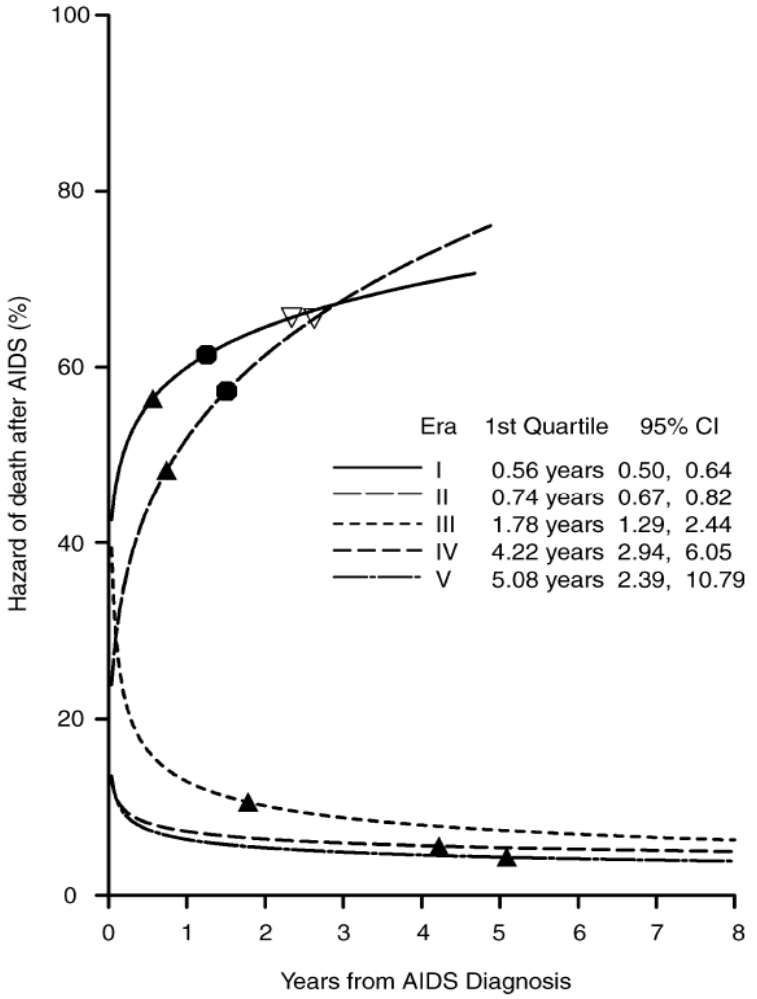


Women's Interagency HIV Study



Improvement in survival with each new era of therapy





M.F. Schneider et al. (2005) AIDS

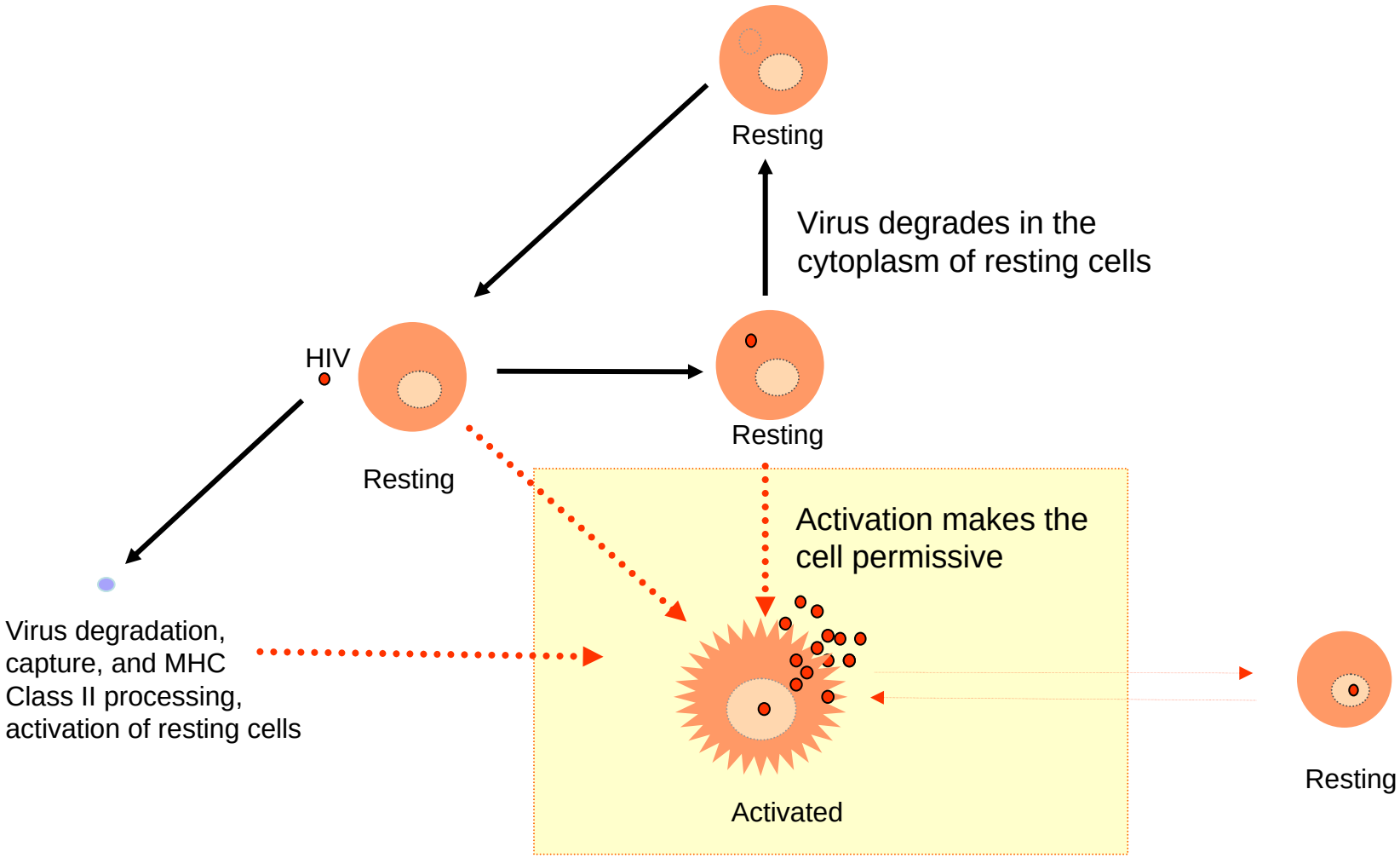
The naïve patient

- HAART is a lifelong commitment
- HAART is based upon prevention of resistance, not on pharmacologic synergy
- Different drug classes have side effects
- The rebuilt CD4 response still can’t suppress the infection
- Long term consequences of treated HIV infection continue to emerge
- From the NIH perspective there are a number of critical research questions that this population can help address

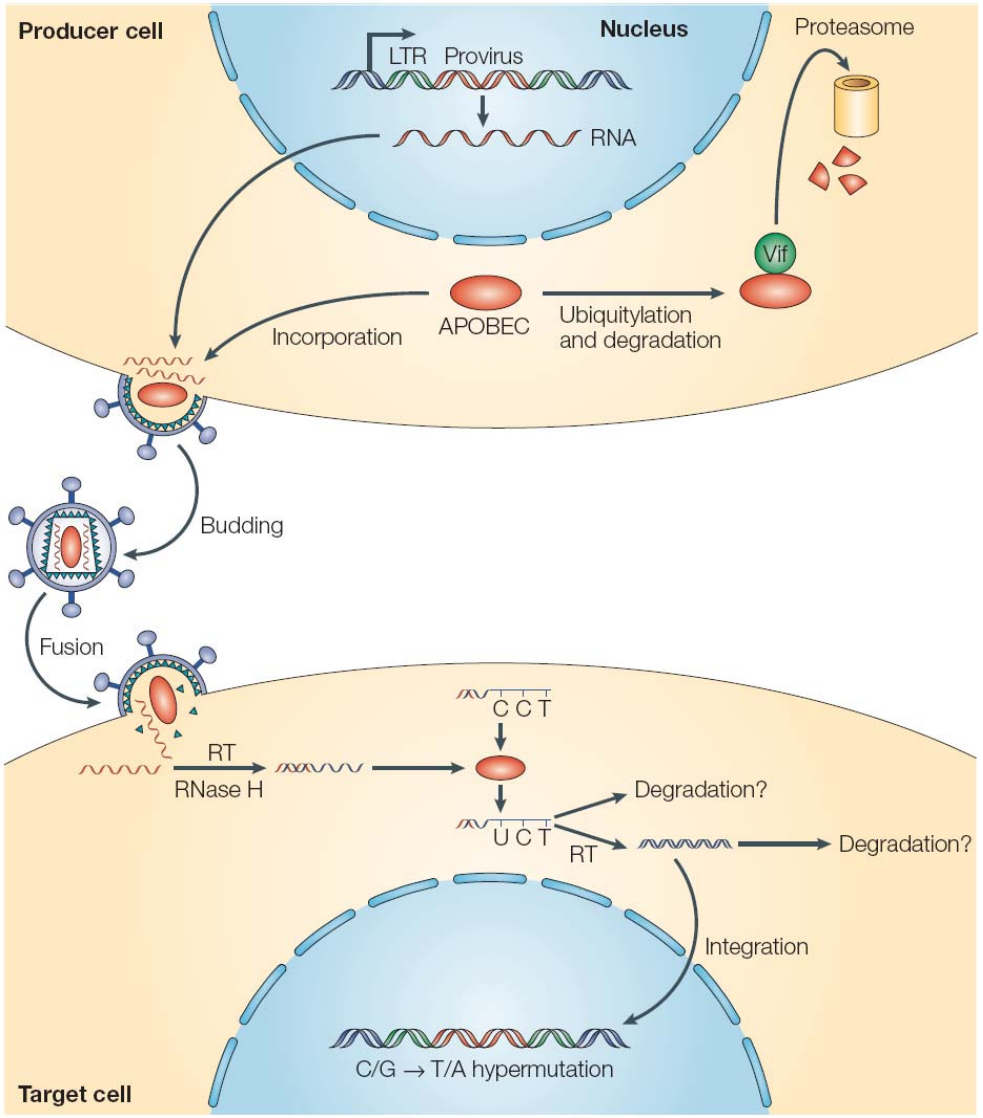
Provocative research questions

- What drives the continual, persistant viral replication?
- In HAART-treated patients does virus rebound from persistent replication, the latent reservoir, or both?
  - Bob Silicianco's data is pretty persuasive that no current regimens impact the reservoir
- Accepting the latent reservoir hypothesis, is eradication possible?
- Can we develop methods to build an immune response that creates an elite controller?

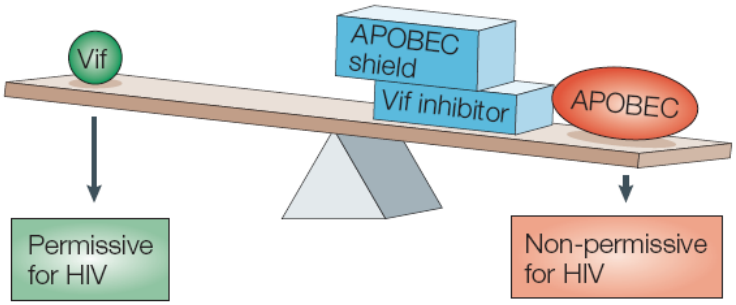
Why is there rebound -- the role of $CD4^+$ T cell activation in HIV replication



APOBEC:Vif interactions



APOBEC hypermutates as well as promotes genome destruction



Block Vif

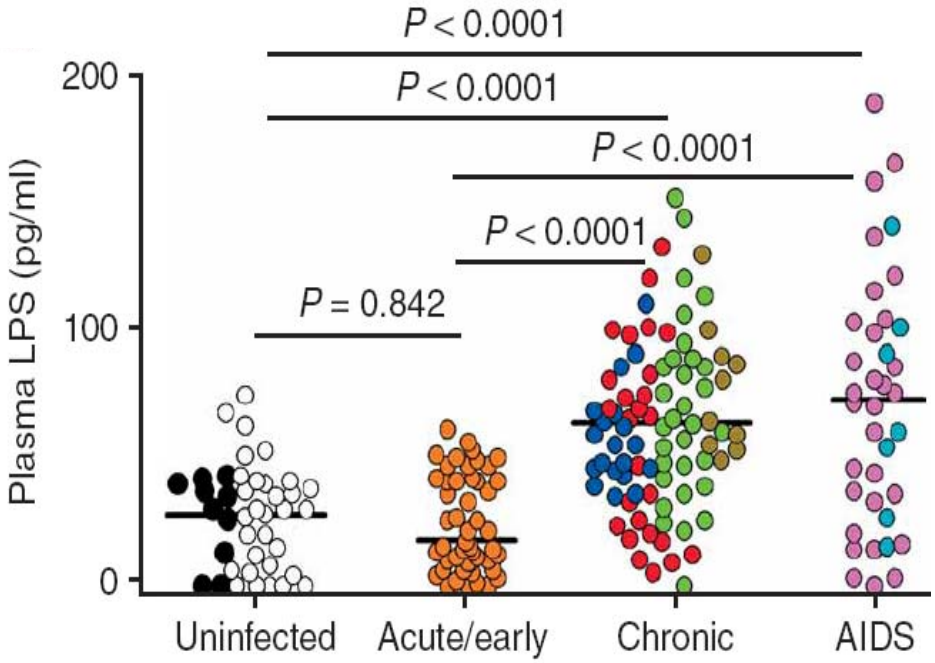
R.S. Harris and M.T. Liddament (2004) Nature Rev. Immunol.

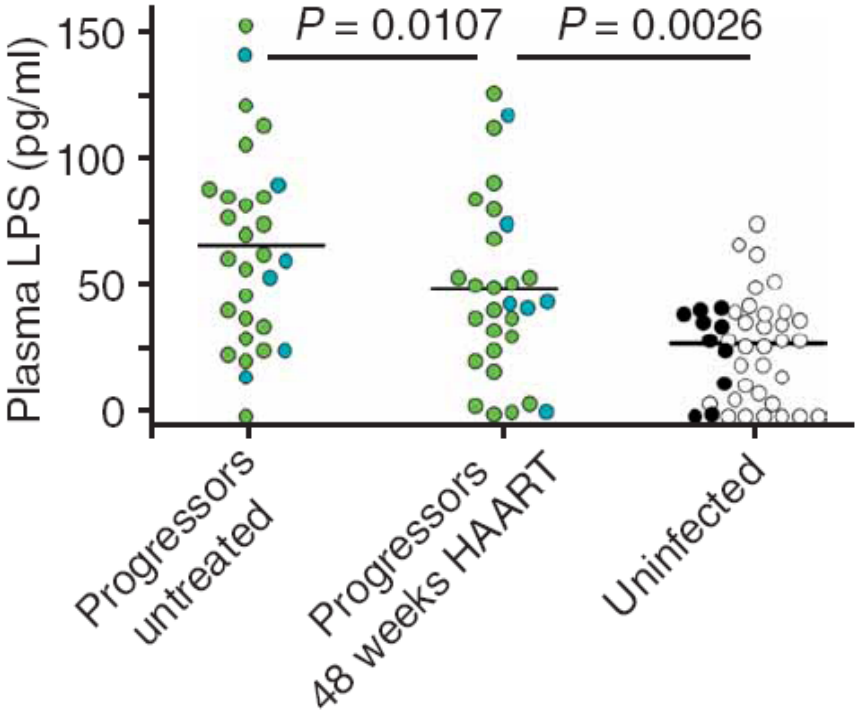
Provocative research questions

- Effects of therapy on GALT, lymph nodes and other tissues
  - What are the consequences of microbial translocation?
  - Can HAART reverse the damage to the GALT and the gut and promote immune reconstitution?

Increase in LPS with progressive disease

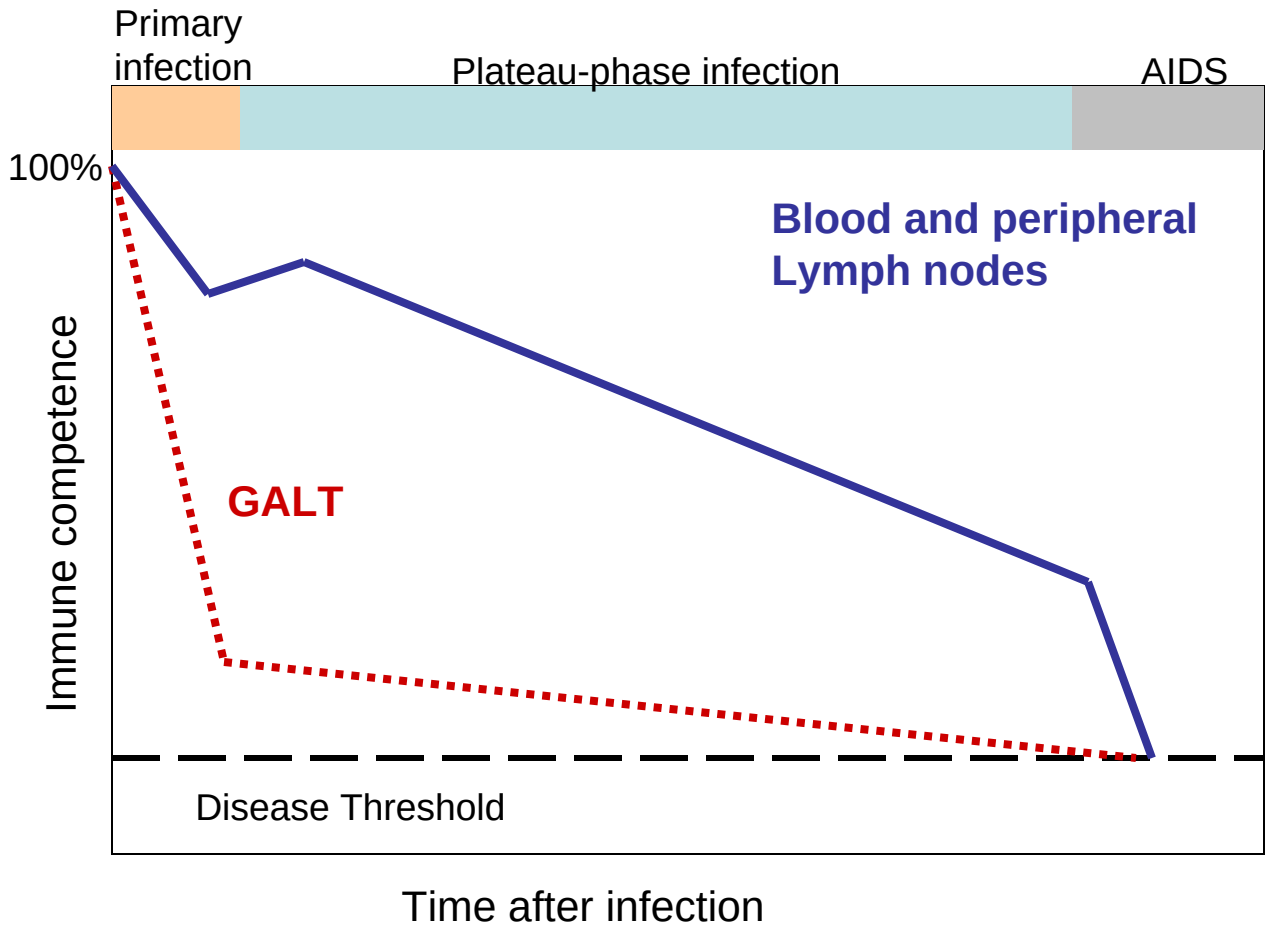
Bacterial products translocation – a cause or a consequence of disease progression?





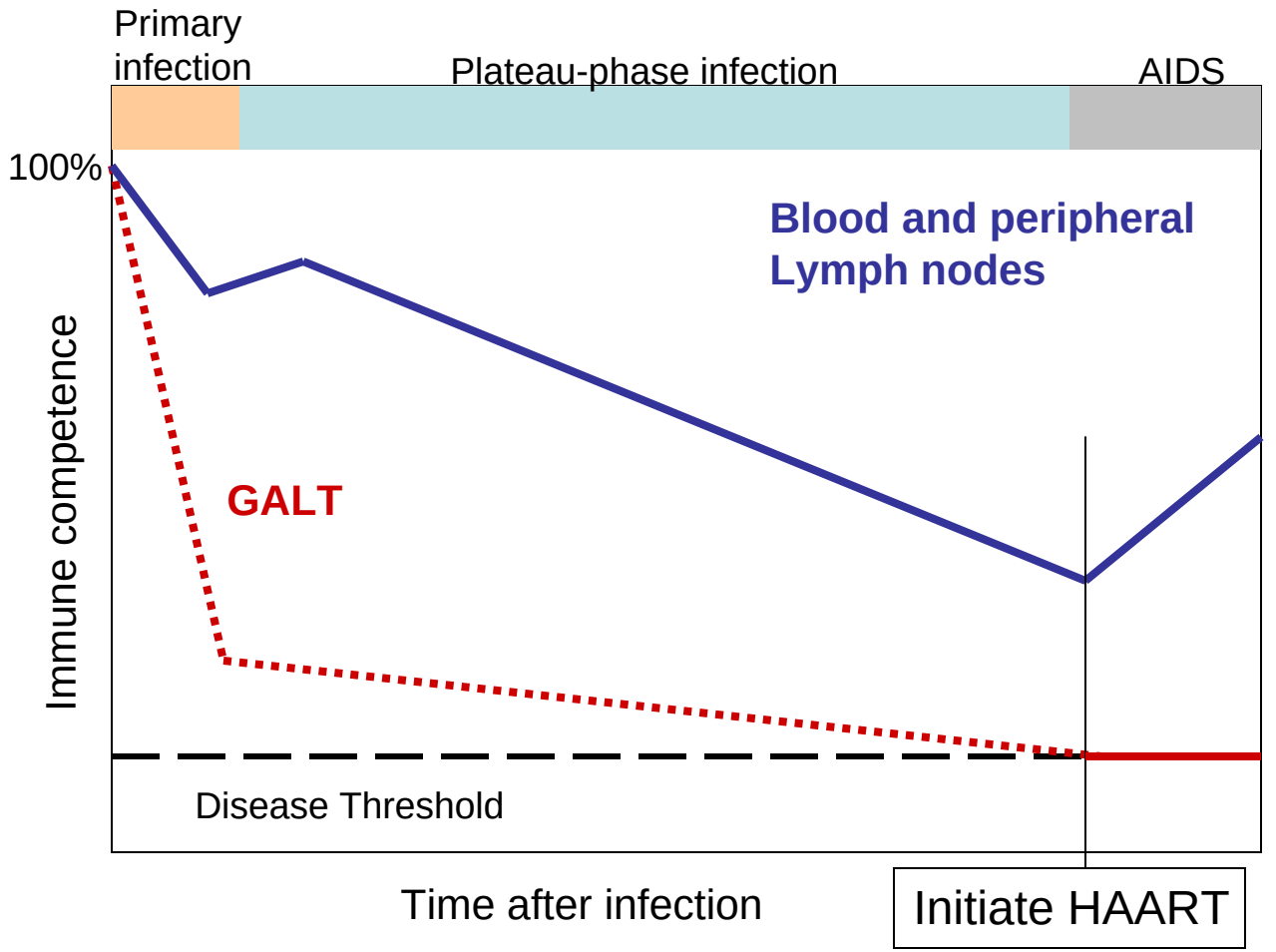
Brenchley et al. Nature Med 2006

The microenvironment matters



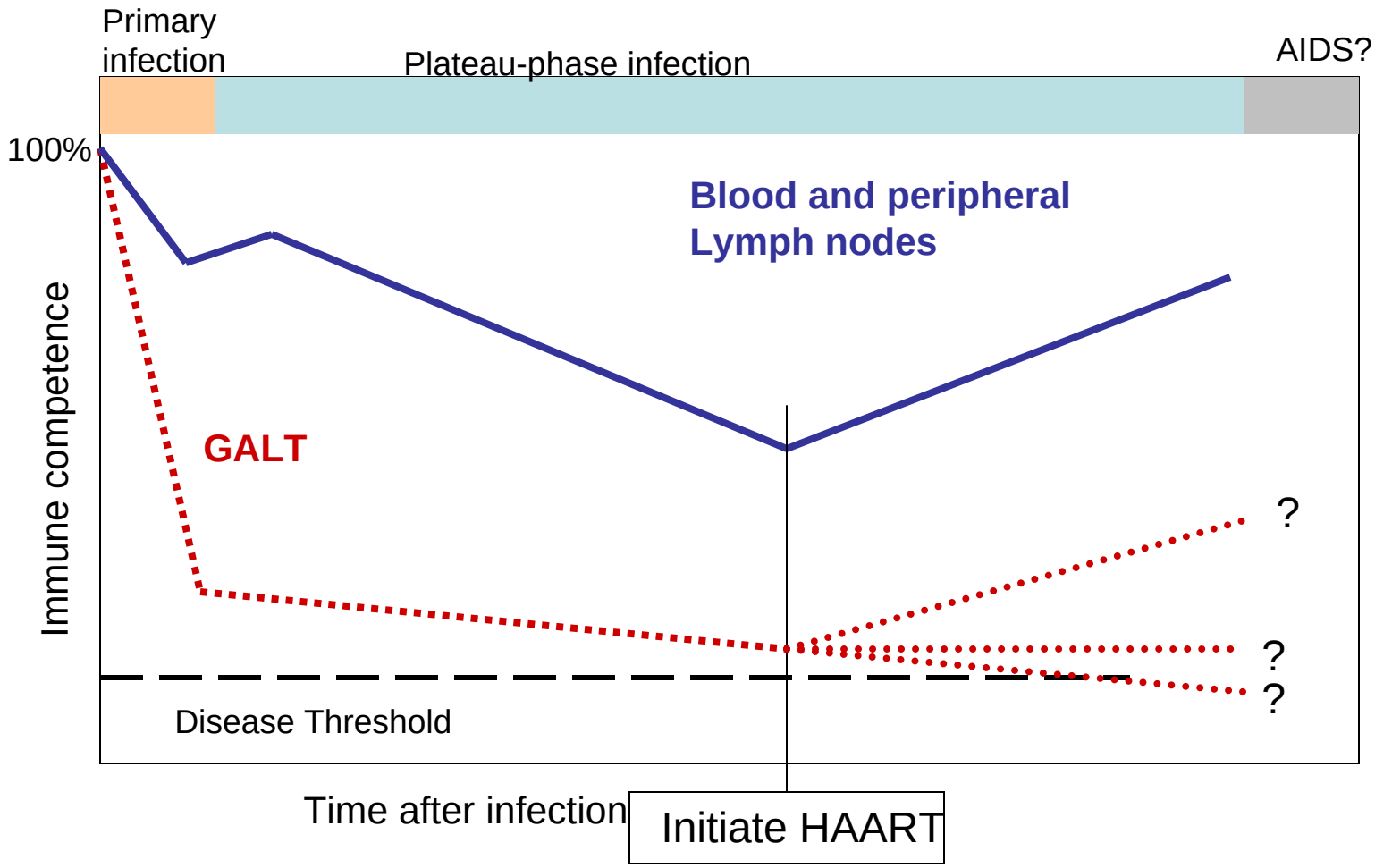
Adapted from L. J. Picker & D. I. Watkins (2005) Nature Immunology

Current therapy stabilizes GALT



Adapted from L. J. Picker & D. I. Watkins (2005) Nature Immunology

Can new approaches have a different outcome?



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