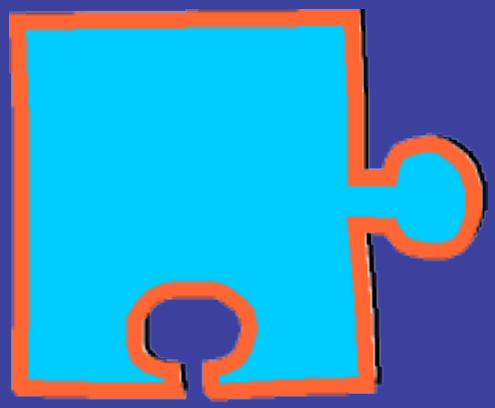
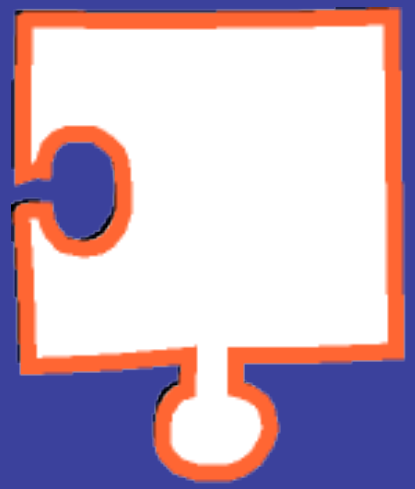
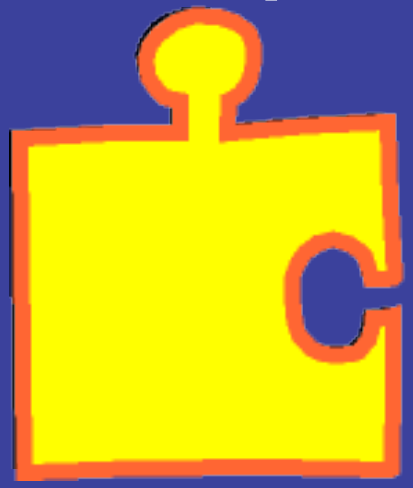
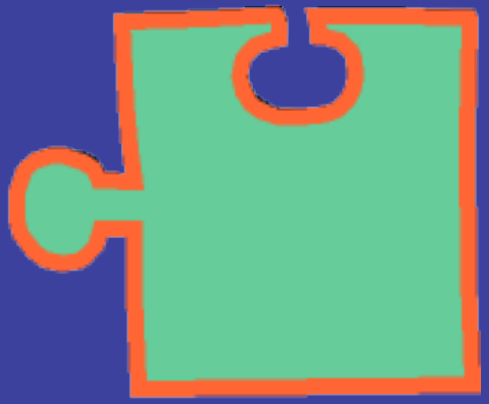




HIV cure research: pieces in the puzzle



Simon Collins
HIV i-Base



Martin Delaney collaborative research

NIAID funded programmes – also ANRS
http://www.niaid.nih.gov/topics/HIVAIDS/Research/cure/Pages/default.aspx

Defeat HIV – The Delaney Cell and Genome Engineering Initiative
http://defeathiv.org/collaboratory/

Collaboratory of AIDS Researchers for Eradication (CARE)
https://www.delaneycare.org/

DARE – The Delaney AIDS Research Enterprise

pre-reading for meeting

- New approaches in HIV eradication (John Frater)
- Sharon Lewin talk at BHIVA

  http://www.bhiva.org/121004SharonLewin.aspx
- i-Base/NAM reports
- poz.com
- IAS roadmap for a cure

  http://www.iasociety.org/Web/WebContent/File/HIV_Cure_Full_recommendations_July_2012.pdf

What is meant by ‘cure’

Sterilising cure	Functional cure
Cure	Remission (without ART)
Berlin patient (Timothy Brown + 2 others?)	Elite controllers and Tx in PHI + TI (VISCONTI cohort)
HIV eradication, no need for treatment	HIV viral control by immune system without treatment
No longer infectious (no virus but may be antibody+)	Transmission still possible / disclosure still important
Most difficult	Difficult - but less difficult...
>90% interest *	<50% interest *

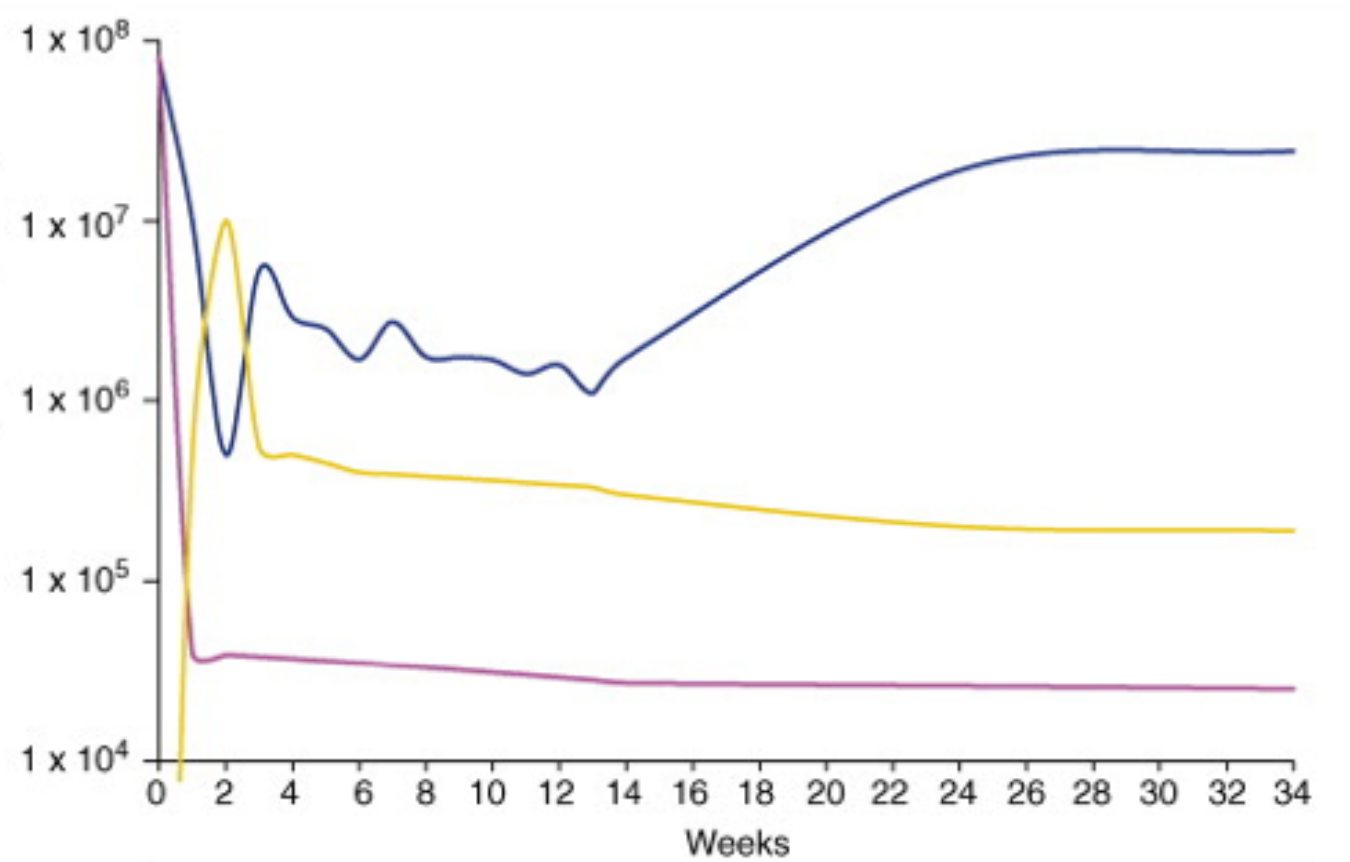
* Fred Verdult, HIV-positive survey, Towards a cure meeting, Washington 2012
http://www.iasociety.org/Default.aspx?pageId=681

HIV – early assault vs chronic infection

- HIV reaches major compartments: gut, brain, GI tract, lymph, stem cells – within weeks of infection
- Most significant assault, then slow and gradual
- Viral load when not on treatment likely to cause problems, but low-level relative impact is likely to be much smaller – ie treatment after 2 vs 3 vs 4 years has less impact than <6mo vs >6mo.

See CROI 2012: Buzon et al. (oral 151), Perelson et al (oral abstract 152)

- **Within weeks of infection, HIV reaches all major body compartments: gut, brain, GI tract, lymph**

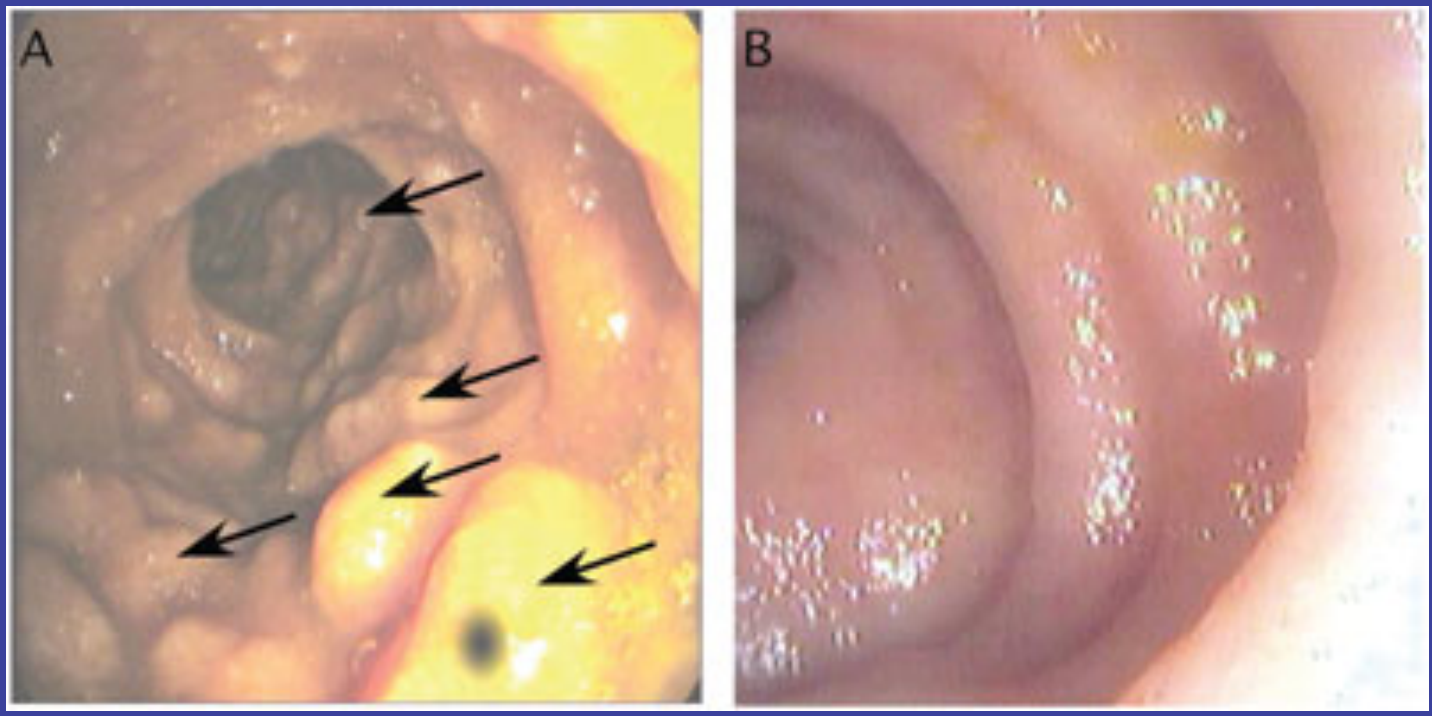


CD4 in blood

viral load

CD4 in gut

Severe depletion of CD4 cells in lamina propria in early infection (Douek et al.)



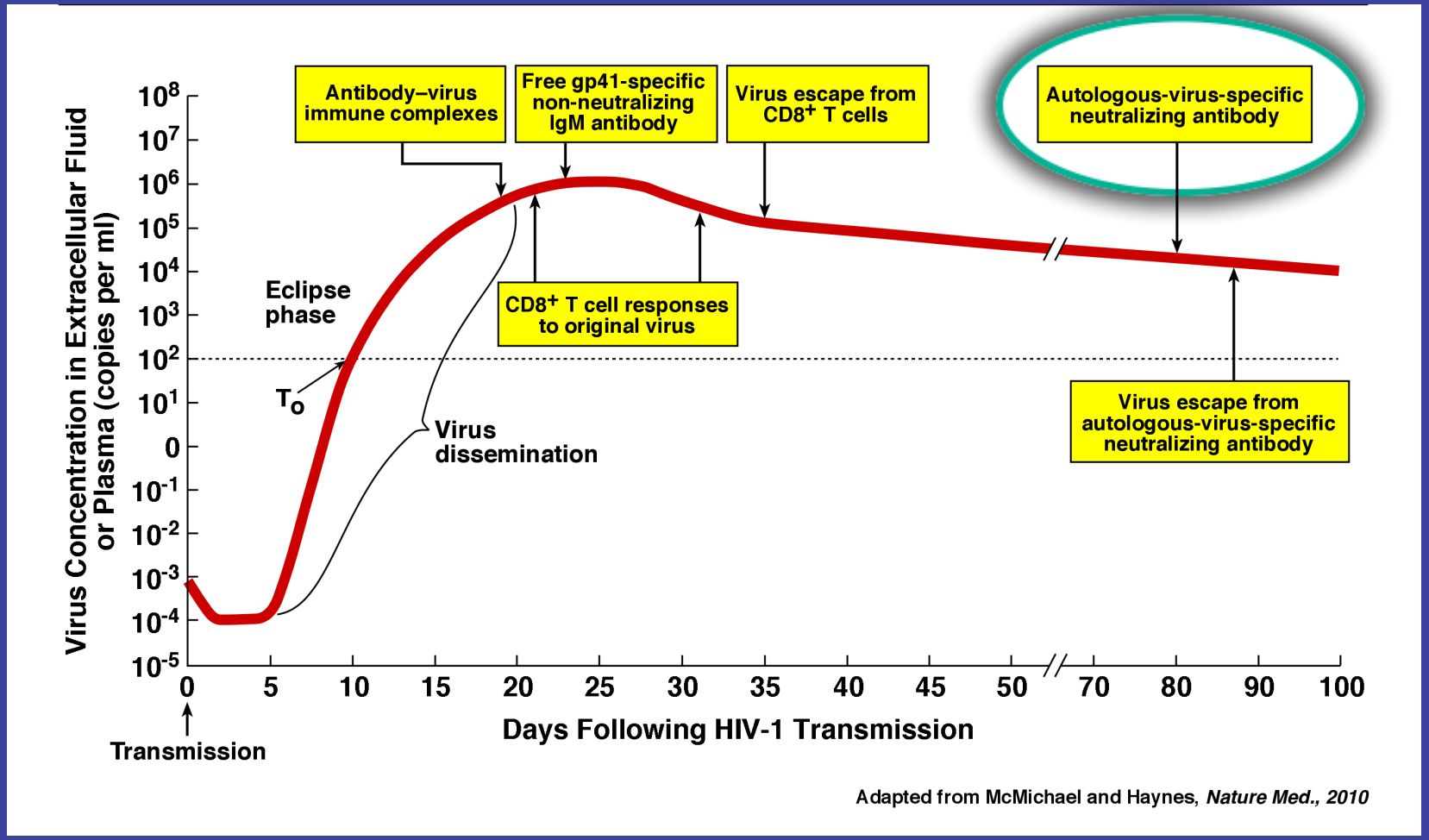
Douek D et al, Nature 466, S2–S3 (15 July 2010) doi:10.1038/nature09234

- **Implications? - microbial translocation, LPS and chronic immune inflammation**

The problem: HIV is a tricky virus

- HIV targets the immune cells that would otherwise destroy it
- It mutates, changing structure, so that any immune responses are quickly overcome ("viral escape")
- HIV infects CD4 cells than are on the pathway to becoming dormant, integrates into the cell DNA and remains archived in long-lived cells that are in this dormant stage

Immune responses to HIV



Fauci, IAS 2010

Proof-of-concept: a cure is possible

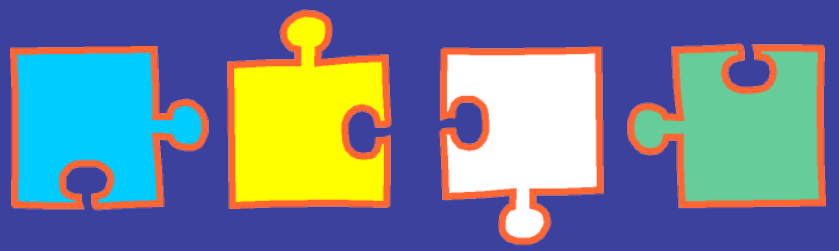
- Timothy Brown – off-treatment for 5 years with no viral load (Q - recoverable DNA?, infectious?)
- Mechanism NOT understood.

  - chemotherapy? immune suppression? whole body irradiation? CCR5-d32 donor? graft vs host disease (GVHD)? Tx interruption (ALL TWICE)

- Two stem transplant cases HIV DNA negative (at 8-17 months) but still on ART.

HIV cure research

- At least 10 years away – a vaccine may come before a cure.
- Current treatment is effective, tolerable, safe and affordable – high barriers for a cure to beat (near normal life expectancy)
- Combination approaches



- IAS Roadmap for a Cure – 7 keys areas – most unanswered questions

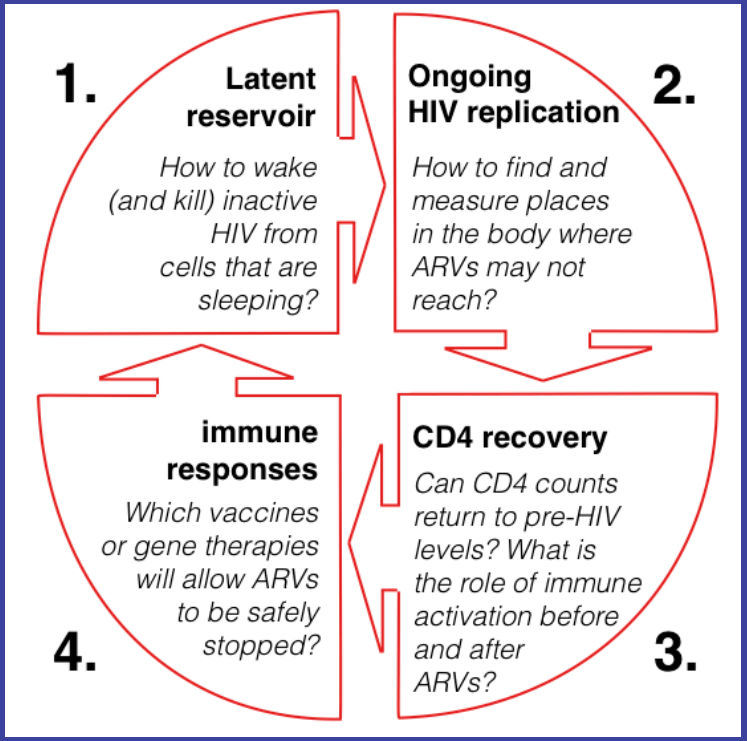
What to measure: IAS roadmap

- HIV RNA (1 c/mL), proviral DNA (total/spliced/unspliced)
- Intracellular HIV DNA, including linear, circular and integrated HIV DNA forms; cell associated RNA? LTR-circles (marker of ongoing replication)
- Replication competent? [infectious unit per million cells (IUPM)]
- Where? plasma vs lymph tissue (gut?) vs other sites?
- Sample storage, standardising tests, research vs trials

See IAS report: Roadmap for a cure

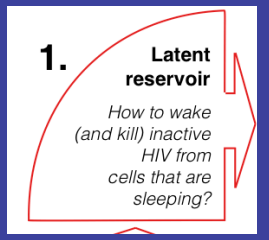
Multiple approaches: four areas

- Latent reservoir
- Ongoing replication on ART
- CD4 recovery
- Immune response

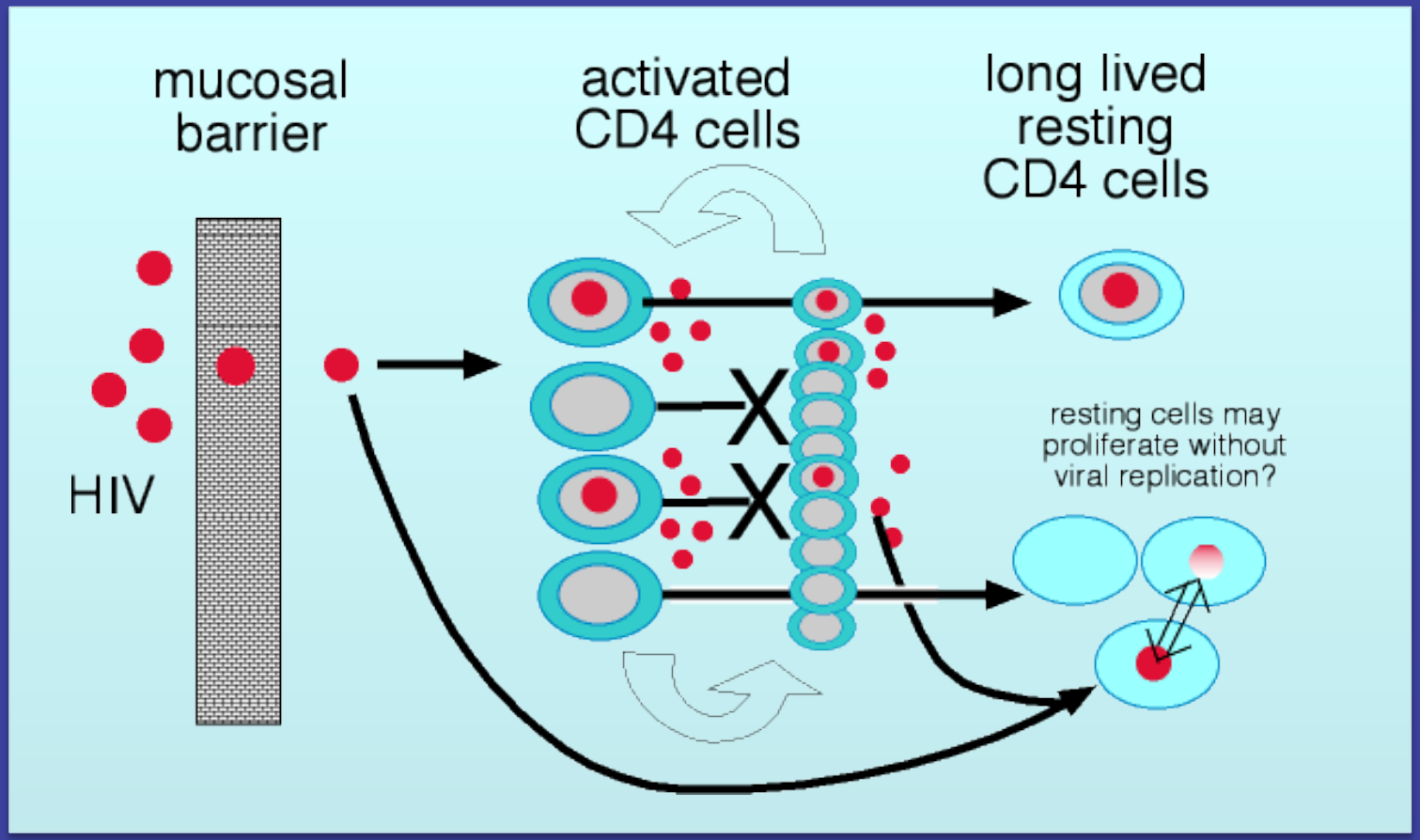


Leading researchers have different views for each area and on the relevance of each

Latently infected CD4 cells

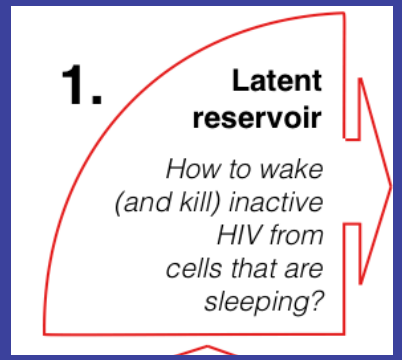


- **LATENT = SLEEPING / DORMANT / RESTING**



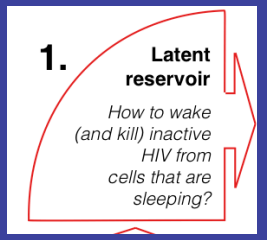
For detailed review see: Hasse AT, Nat Rev Immuno (2005)

CD4 reservoir



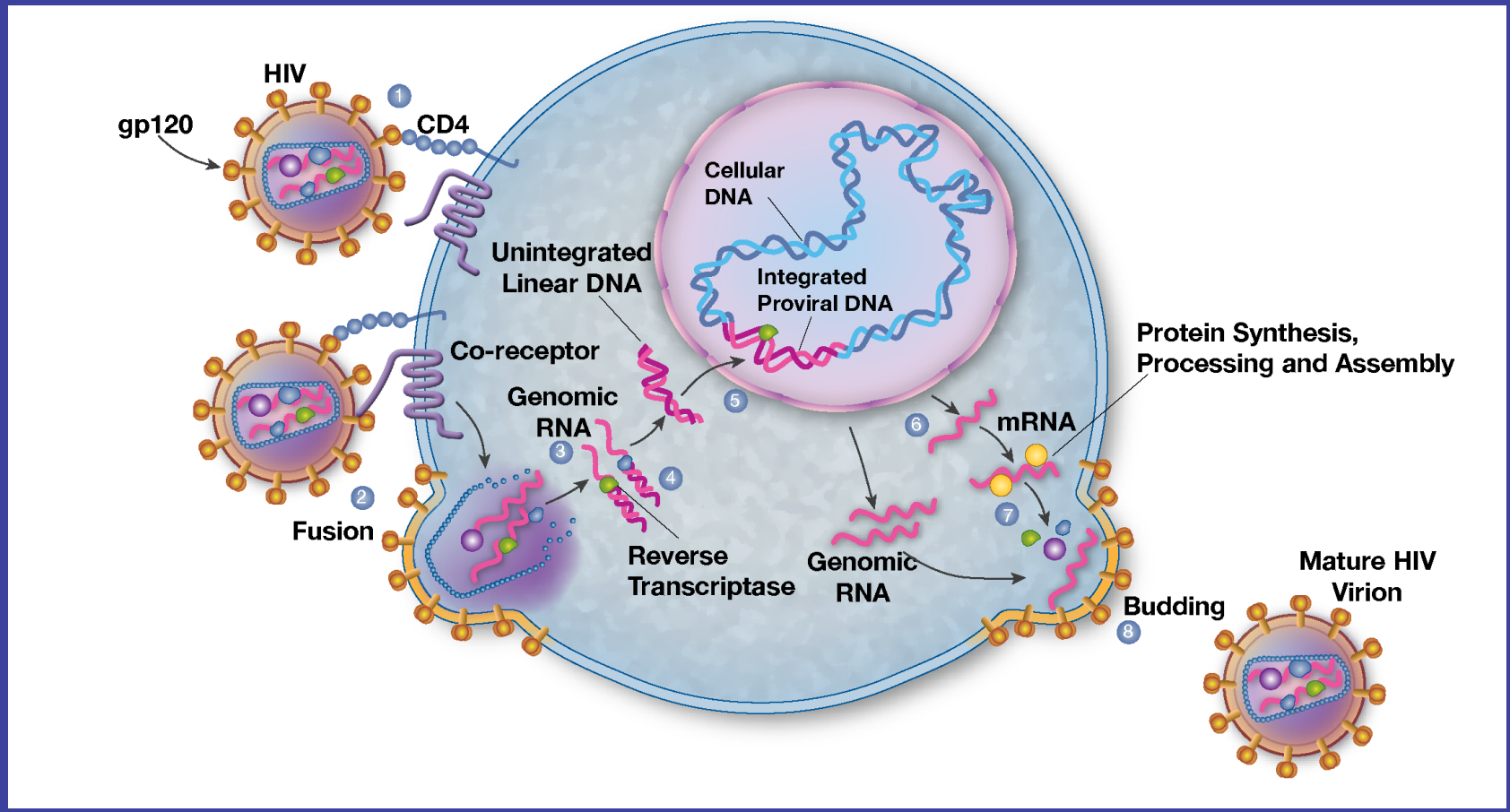
- Simple model: newly infected naive CD4 cells return to resting state (with HIV in its DNA) = natural function
- Complex model: CD4 cells can rest at any stage or their own lifecycle (in the thymus, when naive, when mature), sleep can be "from dozing to coma", infection can occur while resting (not just in active cells that then sleep).

Latently infected CD4 cells



- LATENCY is a NATURAL state for CD4 cells: they are produced in the bone marrow, mature in the thymus, primed by antigen and archived until needed. (Think of the immune system like a reference library)
- The problem is erratic waking.
- Latency maintained by active mechanisms that can be targeted by drugs that interfere with these.
- OPTIONS: Exhaust (activate), kill, silence, or replace.

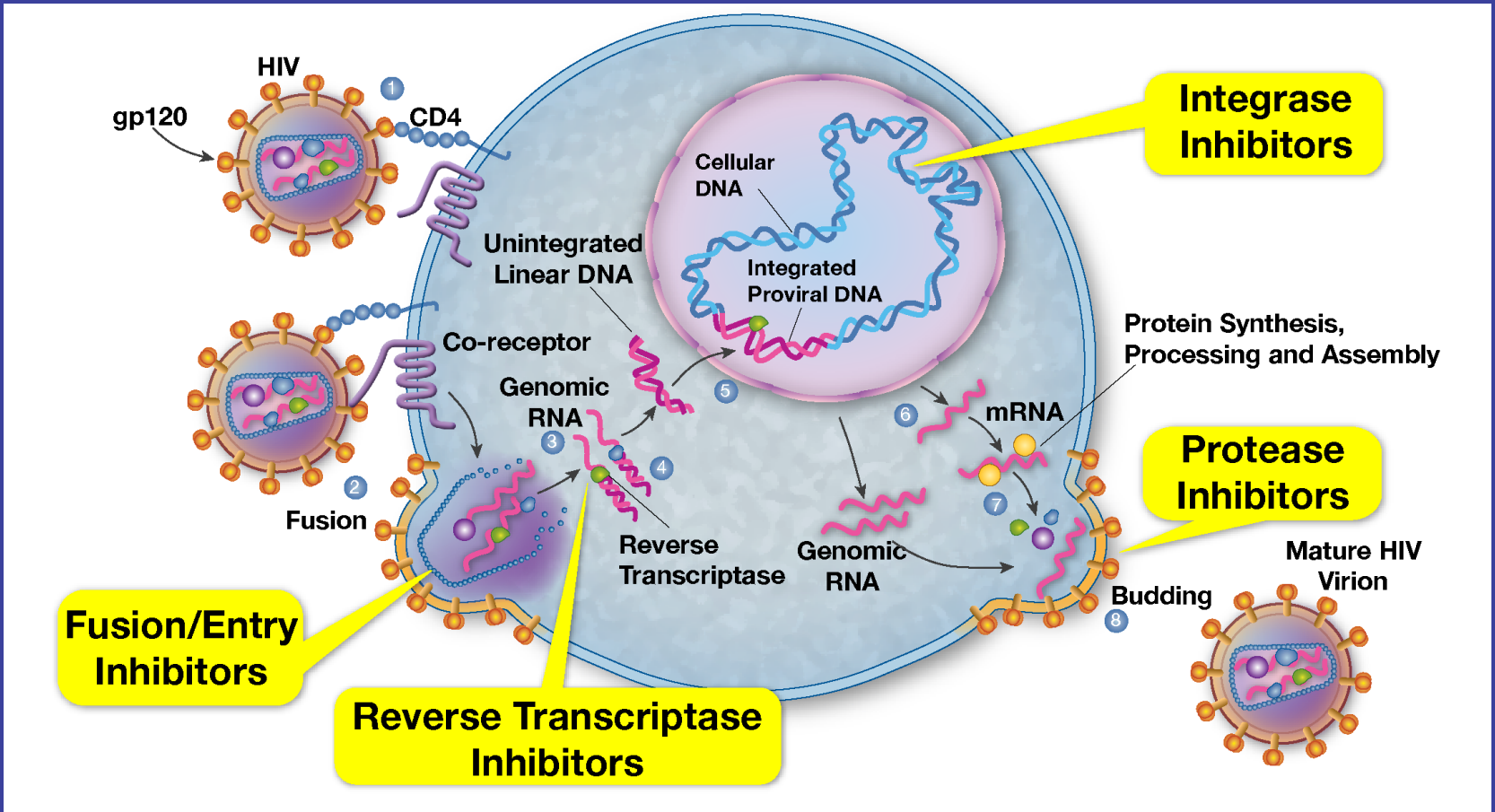
HIV lifecycle: ART targets activated cells



Fauci, IAS 2010

Resting pool is mainly of cells with integrated HIV

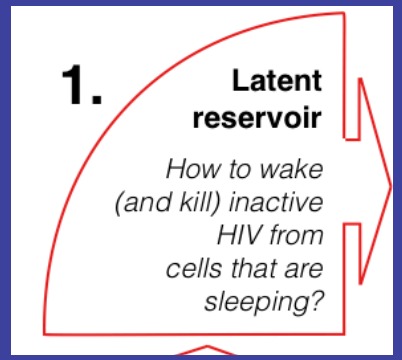
HIV lifecycle: ART targets activated cells



Fauci, IAS 2010

When resting, ART target enzymes are not active

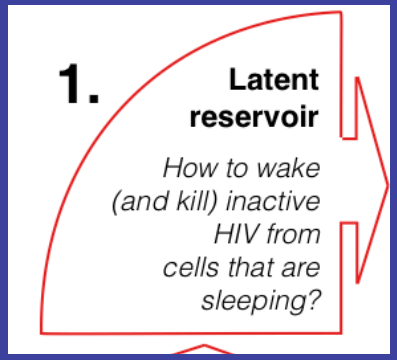
Latent reservoir: how to wake sleeping cells



- The resting CD4 reservoir is an important focus for cure research – just because it exists
- What is the size? How to measure? Where? Is it competent? This research is defining efficacy of ART and for treatment and prevention.
- Impact of ART? timing of ART? could the pool ever be eradicated? 60+ yrs or topped up? or other cellular sites?

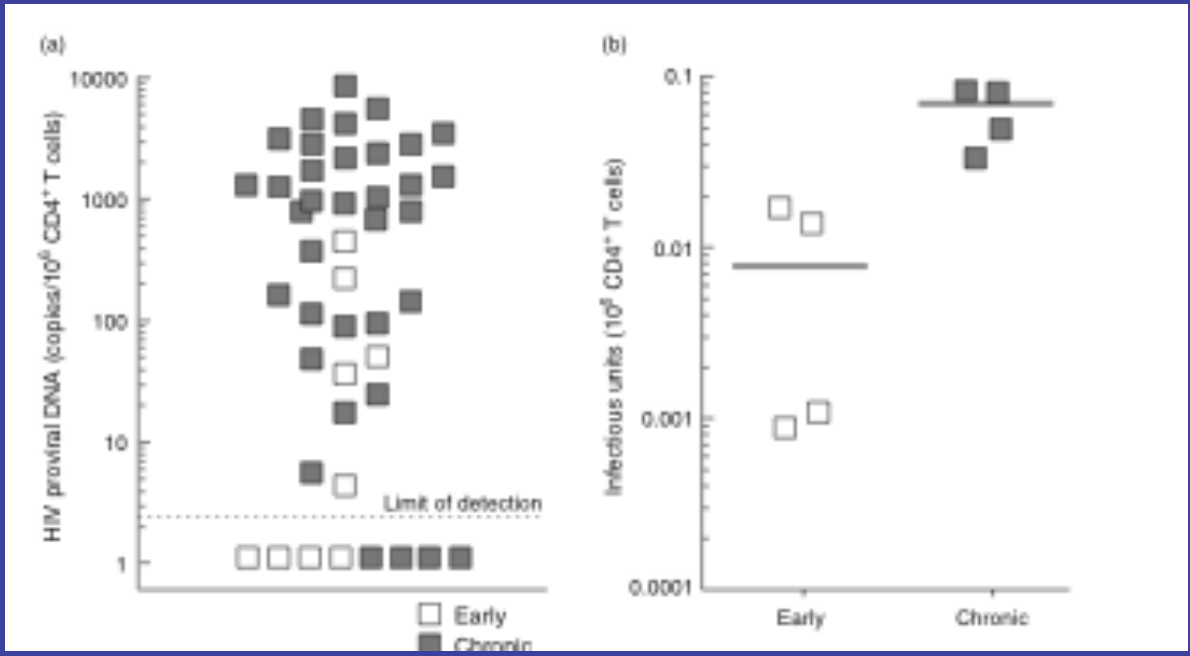
Tae-Wook Chun – AIDS, 2010

AIDS: 27 November 2010 - Volume 24 - Issue 18 - p 2803–2808 – FREE ONLINE



- **Reservoir lower in 9 pts acute (<6mo) vs 35 chronic: ~ 5 vs 950 /m cells (P<0.003).**

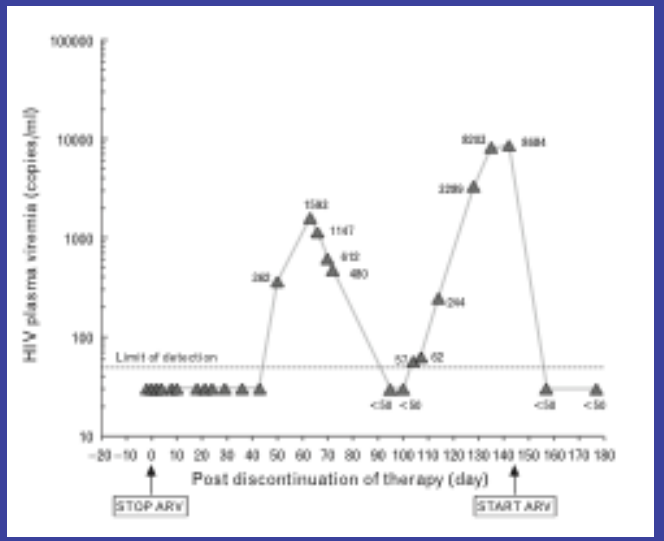
  Med 7 yr <50 c/mL (range 3-10) - NOT linear w/time?



Tae-Wook Chun – AIDS, 2010 – slide 2

AIDS: 27 November 2010 - Volume 24 - Issue 18 - p 2803–2808 – FREE ONLINE

- No proviral DNA in 4/9 (44%) acute vs 4/35 chronic (11%) – new tests, and most non-infectious.
- One man treated in acute infection for 10 years – 1.7 cells/1,000,000,000 - lowest detected.
- STI>rebound 1500 c/mL (d50)
  reduced <50 c/mL off Tx
  increased to 8600 (d143)
  restarted ART



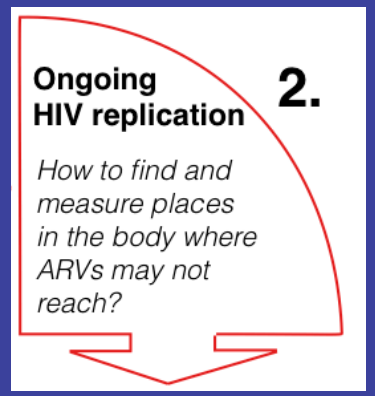
- optimistic or pessimistic? nearly vs ever?

Drugs to target latency

- Existing approved drugs may reverse CD4 latency – but not HIV specific? implications?
- HDAC inhibitors (vorinostat/SAHA – multi dose at CROI 2013), panobinostat, rhomedepsin), AMES+?
- disulfiram (anti-alcohol)
- anti PD-1

Problem: cells with activated HIV do not then die?

Ongoing replication



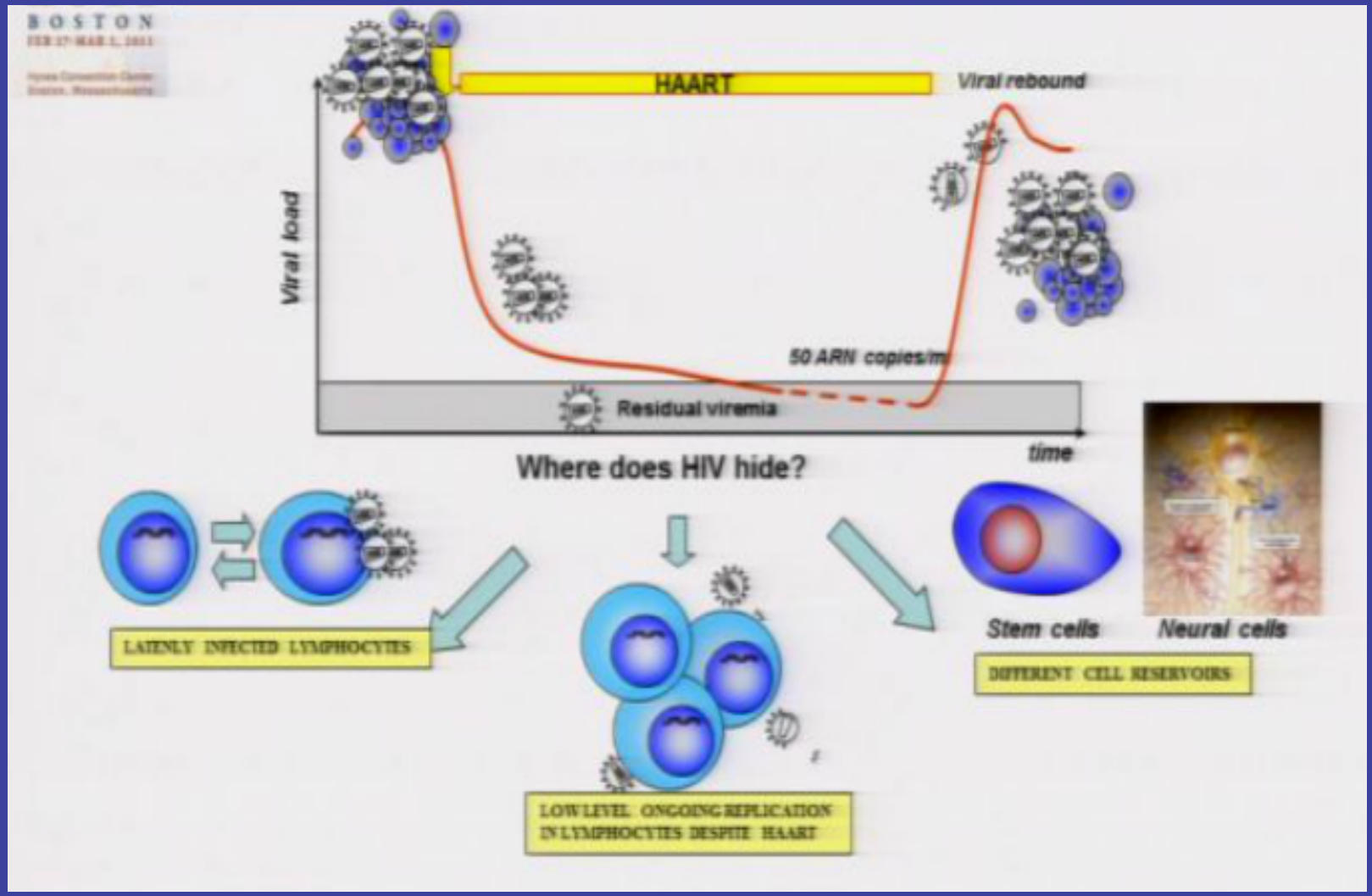
- HIV easily found: 1-5 copies/mL
- Where is source? ongoing replication vs release from resting cells vs other sites: major disagreement

  - intensification – no effect in blood – any class

  - different sites – perhaps in gut and others

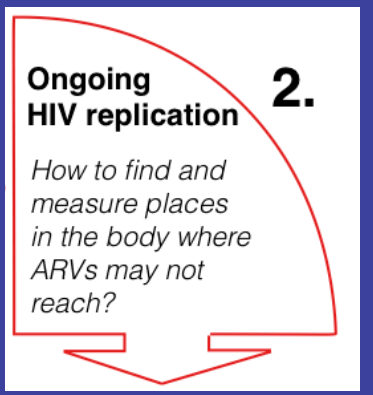
- Only clinically relevant for cure: i.e. a pool to re-establish infection. Viral evolution on ART?

Ongoing replication



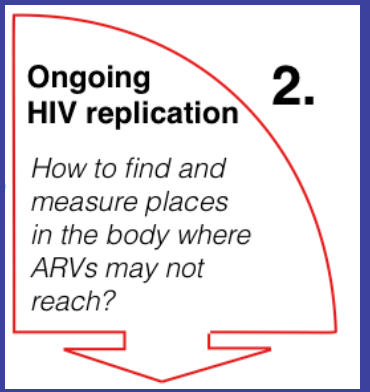
Aleami J. CROI 2011

Ongoing replication



- Current studies are focused on gut samples using integrase inhibitors, even though raltegravir studies reported no impact on viral load in plasma
- Site out of ART reach will reseed reservoir
- Treatment in primary infection – a few people suppress VL off-treatment – VISCONTI cohort – different to elite controllers

VISCONTI cohort: rare

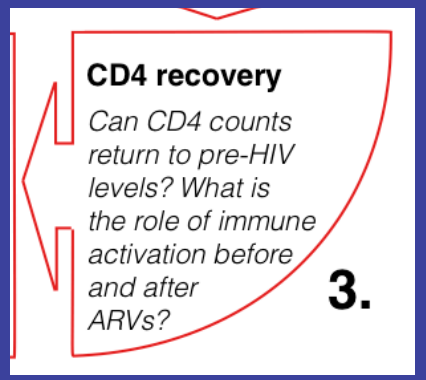


- Saez-Cirion et al, CROI 2011, abs 515
- 10/45 pts treated within 10 wks of infection
- Median 3 yrs ART (range 1-7 yrs) with VL <50 c/mL
- After interrupting treatment viral load controlled for > 5 years without treatment
- Now 12/75, distinct responses vs elite controllers

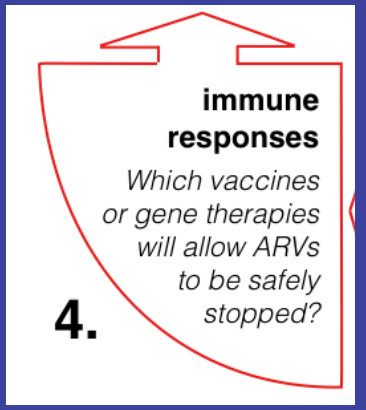
http://www.retroconference.org/2011/Abstracts/41477.htm

CD4 recovery/immune activation

- ART-based CD4 responses are strong and effective, especially with early treatment (while CD4 >350)
- Why is recovery not complete?
- How to reverse immune damage?
- Overlap with research into immune inflammation/activation before ART/on ART
- Overlap with ageing research?



Immune responses



- Immune therapy – stem cell transplant, mediated changes – harvest, modify and reinfuse CD4 cells with CCR5 deleted (Sangamo)
- In Chun paper, tiny reservoir still rebounded
- In HDAC-inhibitor studies, if CD4 cells don't die after activation, CTL-immune response needed (ie vaccine)

Ethical issues: who to treat?

- Strategy of easiest to cure vs most to lose?
- Should cure strategy focus on those who are easiest to cure? Recent infection, early treatment, highest CD4, lowest VL, longest on treatment, heterozygous for delta-32: BUT LEAST TO GAIN
- Should strategy focus on greatest need/risk? lowest CD4, fewer options, chronic infection etc
- What if a cure is only active for 50, 20, 5% pts

Ethical issues: informed consent

- Current studies will not be a cure: personal benefit is unlikely and personal risk is likely (side effects and/or treatment interruption)
- How to ensure informed consent (ie people not enrolled based on unrealistic optimism that they may be the lucky cure). How to manage treatment interruptions? Choice of safest patients?
- Acceptable risk given that life expectancy on ART?

Questions

- Current ART reduces resting pool/reservoir
- Current latency targets not HIV specific: risks from activation & one cell missed could restart infection (reinfection) – Chun et al - good or bad?
- If immune (CTL) response not produced early, why late? – currently unable to contain a tiny pool
- If CTL is answer, or gene therapy works, how important is targeting latency target

Thanks