TOWARDS A CURE:

WILL IT EVER BE TRULY ACHIEVABLE?

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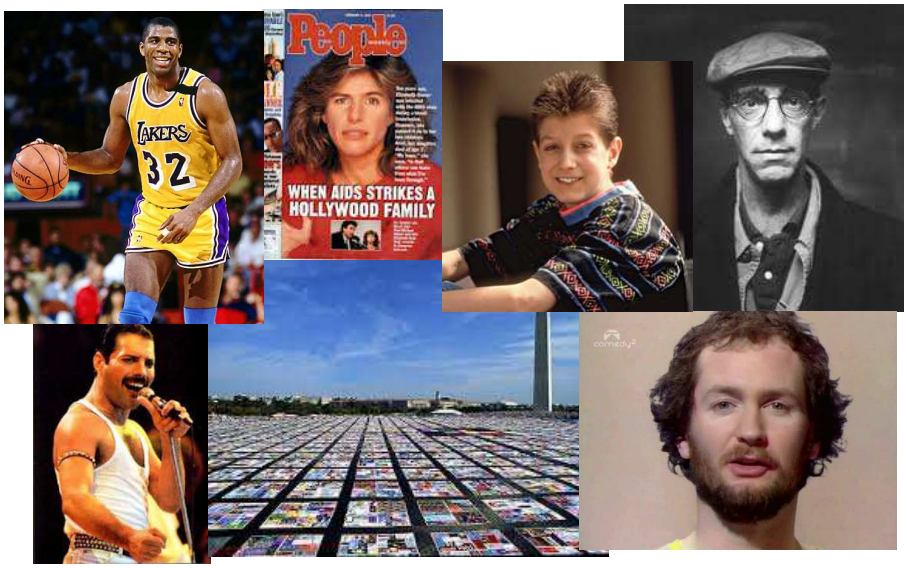
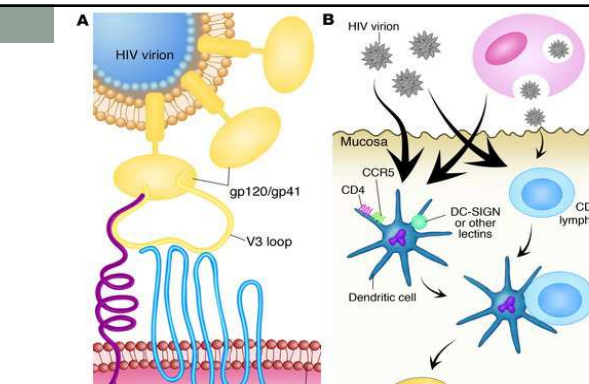
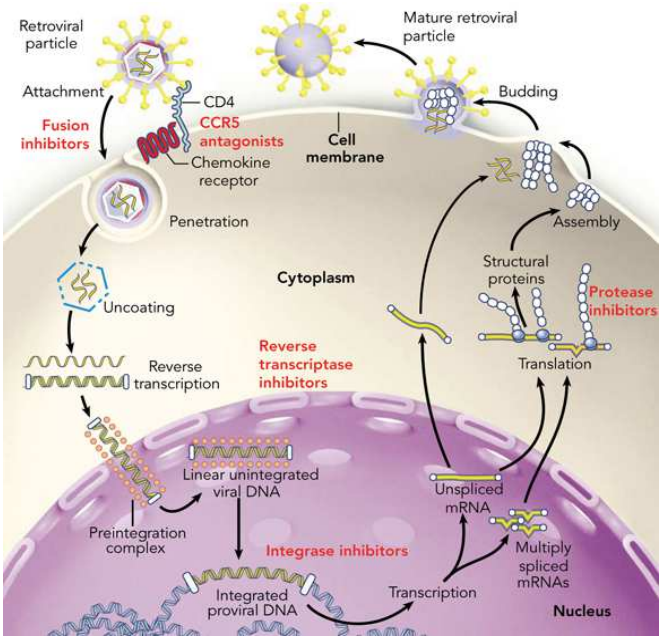
towards an HIV cure
people focused
science driven

HIV if untreated can lead to AIDS







ART works by blocking new virus production

Evolution of HIV Treatment

HOW DID WE STOP AIDS? ANTIRETROVIRAL THERAPY

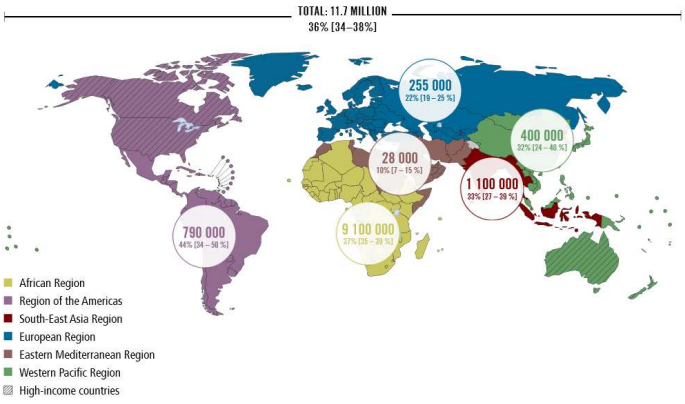
IT WORKS!!

Haitian Patient, before and after Receiving Free Treatment for HIV Infection and Tuberculosis.

The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public-private partnerships.

ART has had the most dramatic change to survival for people living with HIV

Number of people receiving ART and percentage of all people living with HIV receiving ART in low- and middle-income countries overall and by WHO region, 2013[a]



[a]Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS).

Strategic Timing of AntiRetroviral Treatment: START study

When to Start Therapy: Balance Now Favors Earlier ART

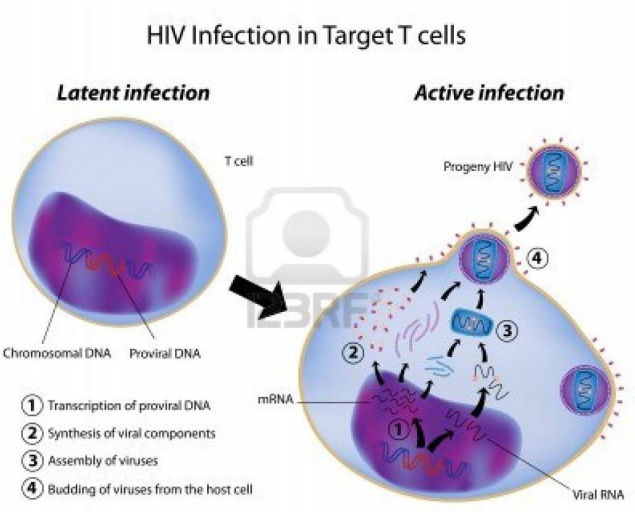
- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

- ↑ potency, durability, simplicity, safety of current regimens
- ↓ emergence of resistance
- ↓ toxicity with earlier therapy
- ↑ subsequent treatment options
- Risk of uncontrolled viremia at all CD4 levels
- ↓ transmission

Delayed ART **Early ART**

START

Why can't ART cure HIV?



How could we consider a “Cure” for HIV?

Functional cure or remission

- No viral replication off antiretroviral therapy
- There may be the occasional latently infected cells, (Detectable viral DNA) but no/little evidence of viral transcription or replication
- No risk of onward transmission
- No ongoing immunological damage

Sterilising Cure

- No latently infected cells and so no detectable virus DNA AND RNA
- No detectable viral reservoir
- No detectable viral transcription
- Timothy Brown

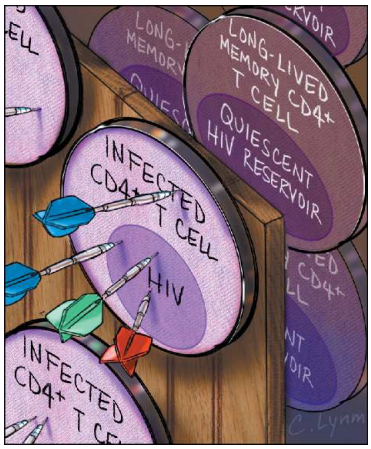
Imperial College London

The HIV reservoir

What is it? Where is it? Why is it a problem?

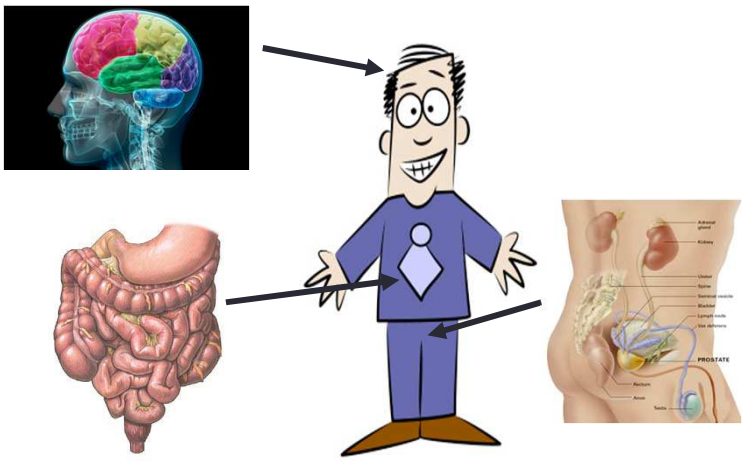
The HIV reservoir is like a needle in a haystack,
if we can’t find - is it not there?

What assays should be used to measure the reservoir/determine “cure”?

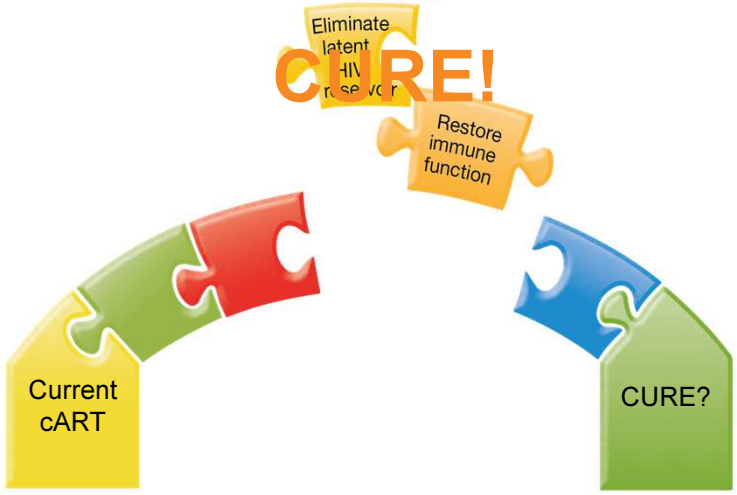


- Viral outgrowth assays?
- T-cell activation assays?
- q-PCR-based assays?

Anatomical reservoirs

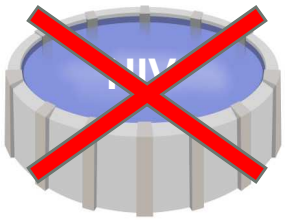


Bridging the gap from current cART to cure

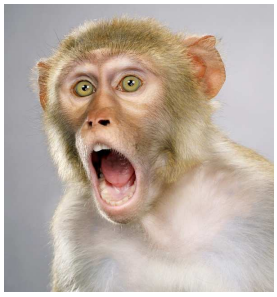


cART, combination antiretroviral therapy

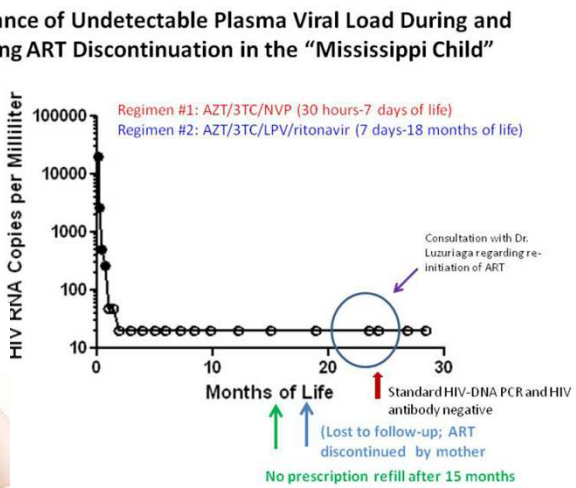
What if we give ART VERY early?



3 DAYS



Has one Baby been "cured" by early ART?



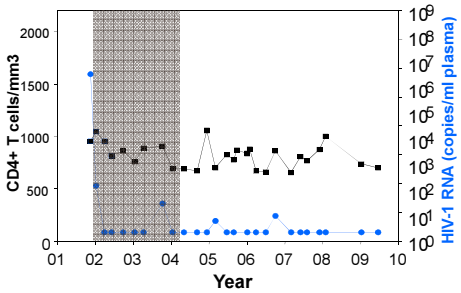
Is the baby cured?

- Unfortunately no
- Age 4 – Routine F/U
  - VL 16,750 copies/ml
  - Decreasing concentrations of CD4+
  - Detectable antibodies against HIV
- Sequencing – same strain as Mother's

Trials	VL < 50 after no ART	AHI stage	Time at ART	ART duration before interruption
VISCONTI (Hocqueloux L, 2010)	15.6%	Fiebig II to V	2.2 months from diagnosis	**5 years**
Swiss 1 (Gianella S, 2011)	9%	Fiebig I to VI	≤ 4 months from infection onset	1.5 years
Primo-SHM (Grijsen ML, 2012)	5%	70% F I to IV 30% F V-VI	2 months from diagnosis	0.5 years or 1.5 years
ANRS CO6 PRIMO (Goujard C, 2012)	11%	Fiebig I to VI	3.1 months from infection onset	1.5 years
CASCADE (Lodi S, 2012)	8.2%	Fiebig I to VI	≤ 3 months from seroconversion	1 year
Trials without post-treatment controllers SPARTAC (von Wyl V 2011; Volberding P 2009; Rosenberg ES 2010; Fidler S 2011)		Fiebig I to VI	2-6 months from diagnosis	1+ year

Functional cure: post ART controllers – The Visconti Cohort

Post-treatment controllers (PTC): infected individuals controlling HIV-1 infection after interruption of cART



14 patients

Months on cART : **36.5** (12-92)

Months post-cART: **89** (48-115)

Therapy started within 10 weeks following Primary Infection (median 39 days p.i.)

Saez-Cirion et al PLoS Path 2013

Different ideas on how to cure HIV

Inhibit residual replication
- Enhanced cART: novel drug classes/treatment intensification

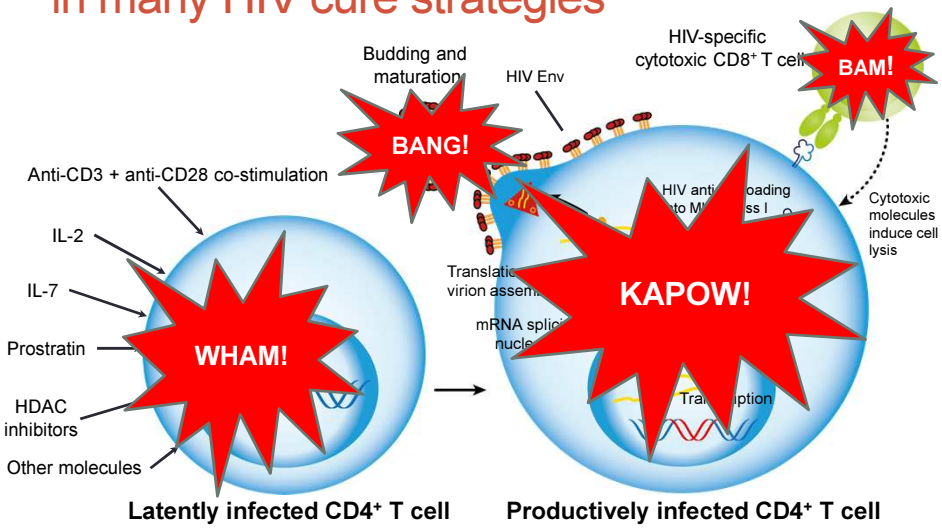
'Shock and kill'
- Induce HIV re-activation plus intensive cART*; valproic acid; vorinostat, panobinostat; disulfiram; phorbol ester derivatives; cytokines; immunotoxins

Immune stimulation
- Cytokines: IL-2, IL-7, IL-21
- Therapeutic vaccines
- Anti-PD-1, anti-PD-L-1,

Gene therapy
- Replace or silence
- CCR5 knock-down; siRNA/short hairpin RNA

*Some treatment examples are not licensed for this indication
Marsden MD & Zack JA. Future Virol 2010;1;5(1):97–109. Katlama C, et al. Lancet 2013;381(9883):2109-17.
Kent et al. Lancet Infect Dis 2013;13(7):614–21.

Activating latent virus is a necessary step in many HIV cure strategies

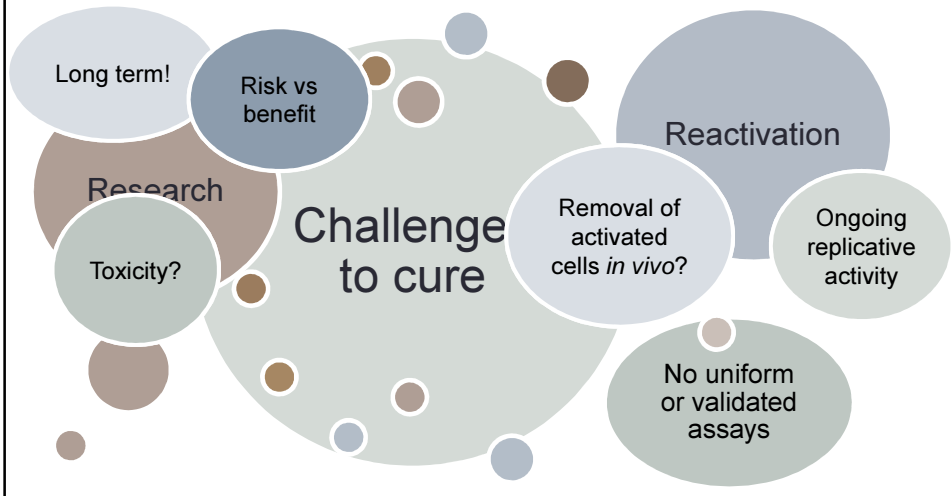


Adapted from Marsden MD & Zack JA. Future Virol 2010;5(1):97–109.

Timothy Brown/The Berlin patient: Example of a sterilizing cure?

- Treated for acute myelogenous leukemia by BMT
- Donor was homozygous for CCR5 gene deletion
- Interruption of ARVs
- No detectable HIV RNA for over 7 years

Research challenges



Rasmussen TA, et al. Hum Vaccin Immunother 2013;9(4):790–9. Katlama C, et al. Lancet 2013;381(9883):2109–17.

CHERUB

COLLABORATION HIV ERADICATION OF RESERVOIRS: UK BRC

Current and planned HIV Cure research in the UK

University College London Hospitals NHS | Guy's and St Thomas' NHS | Imperial College Healthcare NHS | Oxford Radcliffe Hospitals NHS | Cambridge University Hospitals NHS

UCL | University of Oxford | King's College London | Imperial College London | University of Cambridge

Clinical Cohorts in Development

Observational cohorts

- **ART + Chemotherapy** in HIV+ on ART
- Viral reservoir characterization SPARTAC study
- **CHERUB-yc :** HIV research in young people and children with perinatally acquired HIV
- **HEATHER:**
  - A: Prospective cohort of ART treated PHI
  - B: Suppressed since HIV seroconversion on ART for > 2 years

Intervention trials

- ART in PHI +/- IVIG
- River Study

RIVER
Research In Viral Eradication of HIV Reservoirs

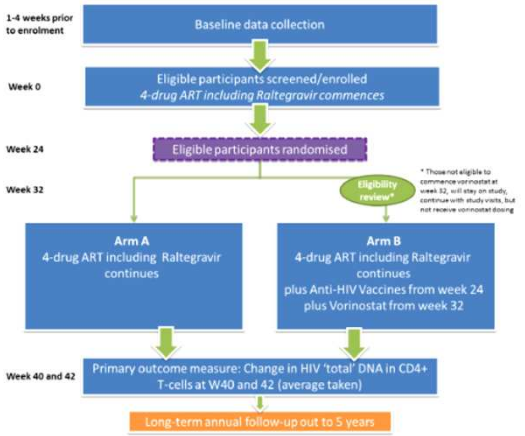
- Two-arm (proof of concept) randomised phase II trial
- ARM A (Control):
  - 4-drug cART including Raltegravir
- ARM 2:
  - 4-drug cART including Raltegravir plus ChAd prime and MVA boost vaccines; followed by a 28-day course of vorinostat (10 doses in total)

- **Dr. Sarah Fidler**
  - **Chief Investigator**
    - **Imperial College London, HIV Clinical Trials Unit**

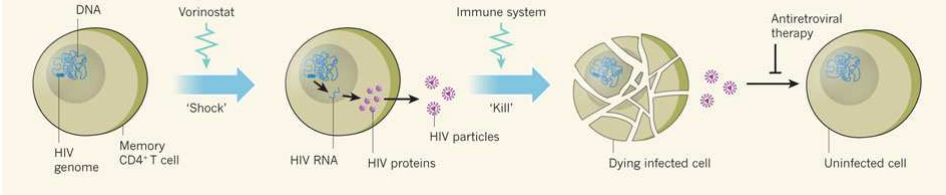
RIVER
Research In Viral Eradication of HIV Reservoirs

TRIAL SCHEMA

Figure 1 Trial Entry, Randomisation and Treatment



RIVER
Research In Viral Eradication of HIV Reservoirs



Conclusions towards a cure for HIV

towards an HIV cure
people focused science driven

- ARV during acute HIV infection (AHI)
- Post treatment controllers (PTC) = >3 yrs treatment during AHI
- Predictors for PTC
  - short interval from HIV onset to ARV initiation
  - long duration of ARV
  - low HIV DNA and high CD4+ counts prior to interruption
- Combined interventions of ARV + therapeutic HIV vaccines + reservoir activators (+ early ARV at AHI)

Summary

- New ideas to cure HIV
- *Will it work on a global scale?*
- *Will people get re-infected?*
- *How toxic are the drugs?*
- *How much will this cost?*

Ethics of cure research

- **Social/ethical implications of HIV cure research**
  - *Patient conceptions of "cure"*
  - *What is the duration of "cure"?*
  - *Concerns or issues of beneficence/justice*
  - *Therapeutic misconception*

Thank You

- Dr. Sarah Fidler and Dr. John Thornhill
- Kristin Kuldanek and Kanta Mahay
- NHIVNA & European HIV Nursing Network
- Clinical Trials Participants
- …and you.

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