

Introduction to the science of HIV research for treatment activists



EATG STEP workshop:
25 Sept 2020

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i-Base.info

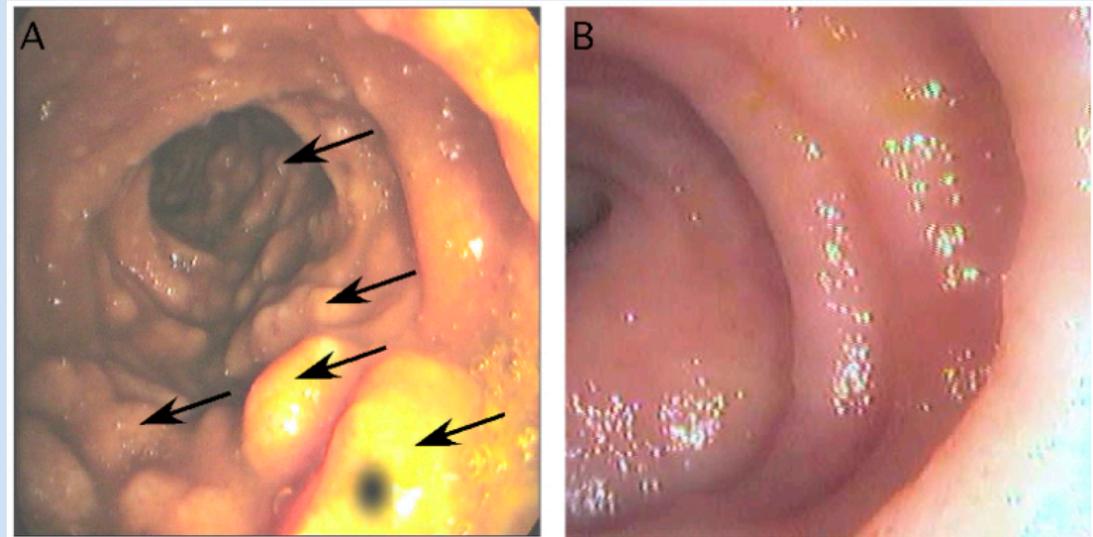


Image: (c) Brenchley et al.

Overview

- This talk will be an online discussion about scientific approach to medical research linked to HIV.
- Two hours to explore this subject – ask many questions...
- Best way to learn – *please take notes.*

Expectations

What would you like to know?

Learn one, teach one...

Treatment Action Campaign (TAC) see treatment literacy as a community process.

Learn something, pass it on.

An early UK HIV prevention equivalent was “nag one, shag one”.



Basic answers

- Science can find out whether an idea is true, or provable: facts vs opinion, fake vs real.
- If results are true – not just from luck - then repeating the study will get the same results.
- Community involvement produces better science – better questions, engagement and enrolment – faster answers.
- Community activism can reduce delays in improving care.

Use surprises

When was TDF first shown to work as PrEP?

What percentage of your CD4 cells are in blood?

How quickly does viral load drop after starting ART?

What happens to CD4 cells in the gut after HIV infection, and roughly when?

Do you know about Tuskegee?

Tsai C-C et al, Science 1995

Daily weight-based daily PMPA (tenofovir) SC for one month in 35 macaques inoculated IV with SIV (10 x 50% infectious dose): 5 arms, follow up 40-56 weeks.

Dose	Day started	n	% infected
20mg/kg	48 hrs pre	n=5	0
30mg/kg	48 hrs pre	n=10	0
30mg/kg	4 hrs post	n=5	0
30mg/kg	24 hrs post	n=5	0
Placebo	48 hrs pre	n=10	100

1. Tsai C-C et al, Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl)adenine. Science 1995. (NIH funded).

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Reactions?

How does TDF study make you feel: seven years before TDF was approved as ART.

How does that make you feel about the speed of science?

How does that make you feel about political (funding and topic) priority for HIV prevention?

- *Remember 20-year timeline for TasP and U=U?*

<2% of CD4 cells are in peripheral blood

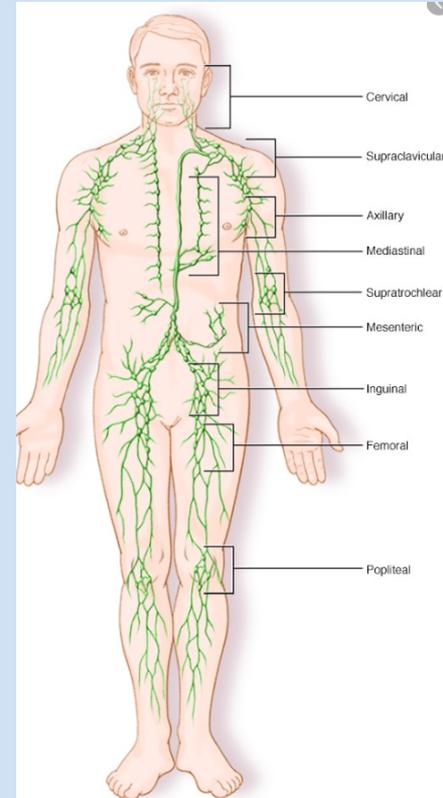
2%



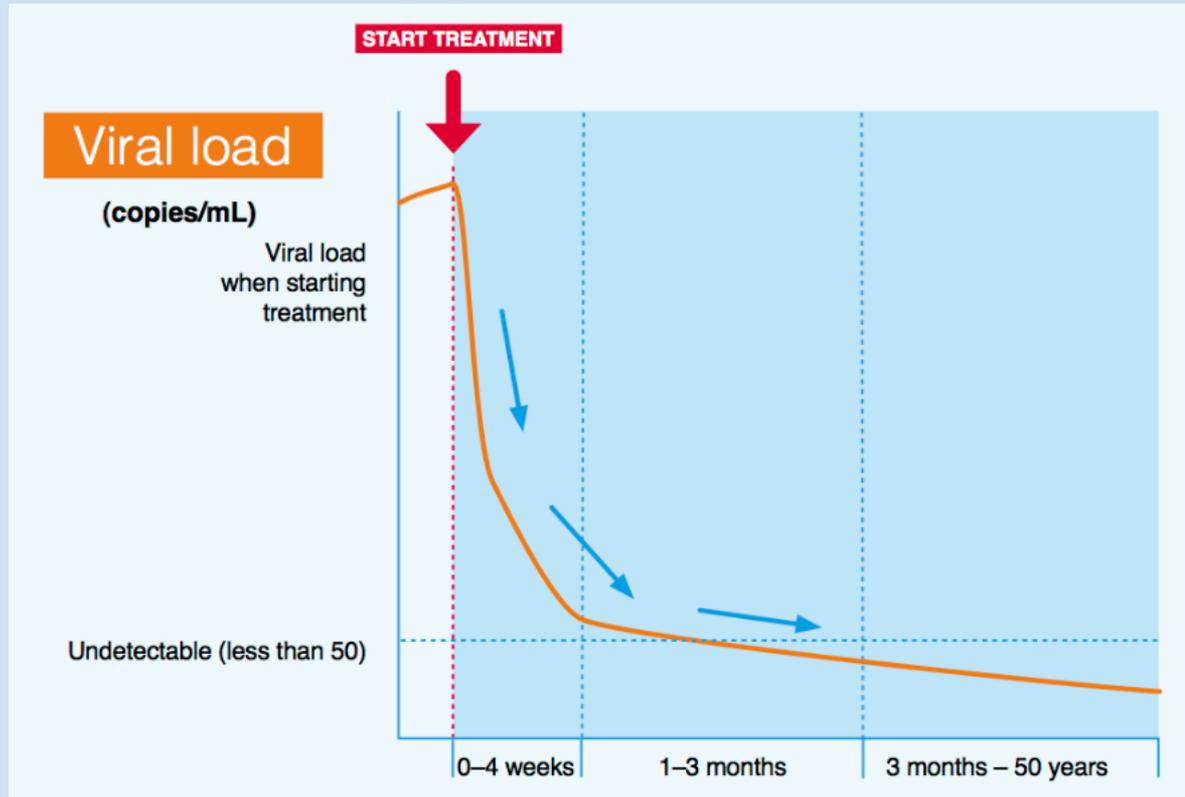
CD4 cells in the peripheral blood are a surrogate marker for immune system.

>98% of CD4 cells are in the lymph system, mainly sleeping (HIV reservoir).

98%

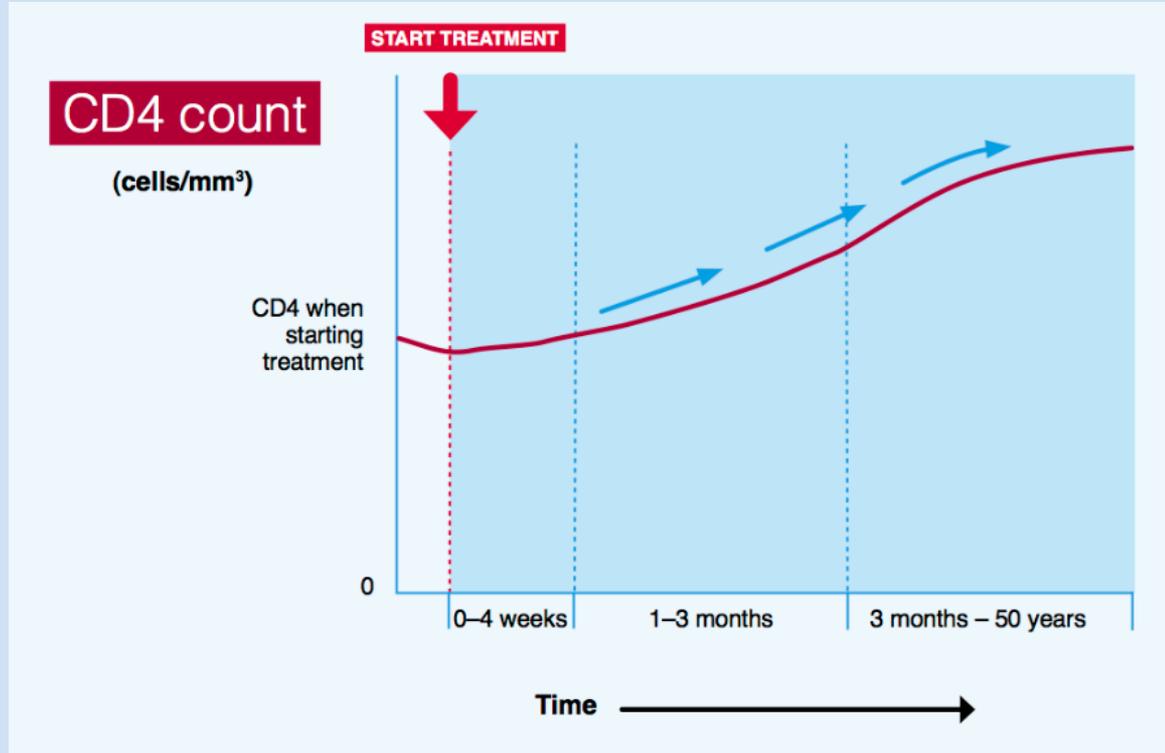


Viral load on ART



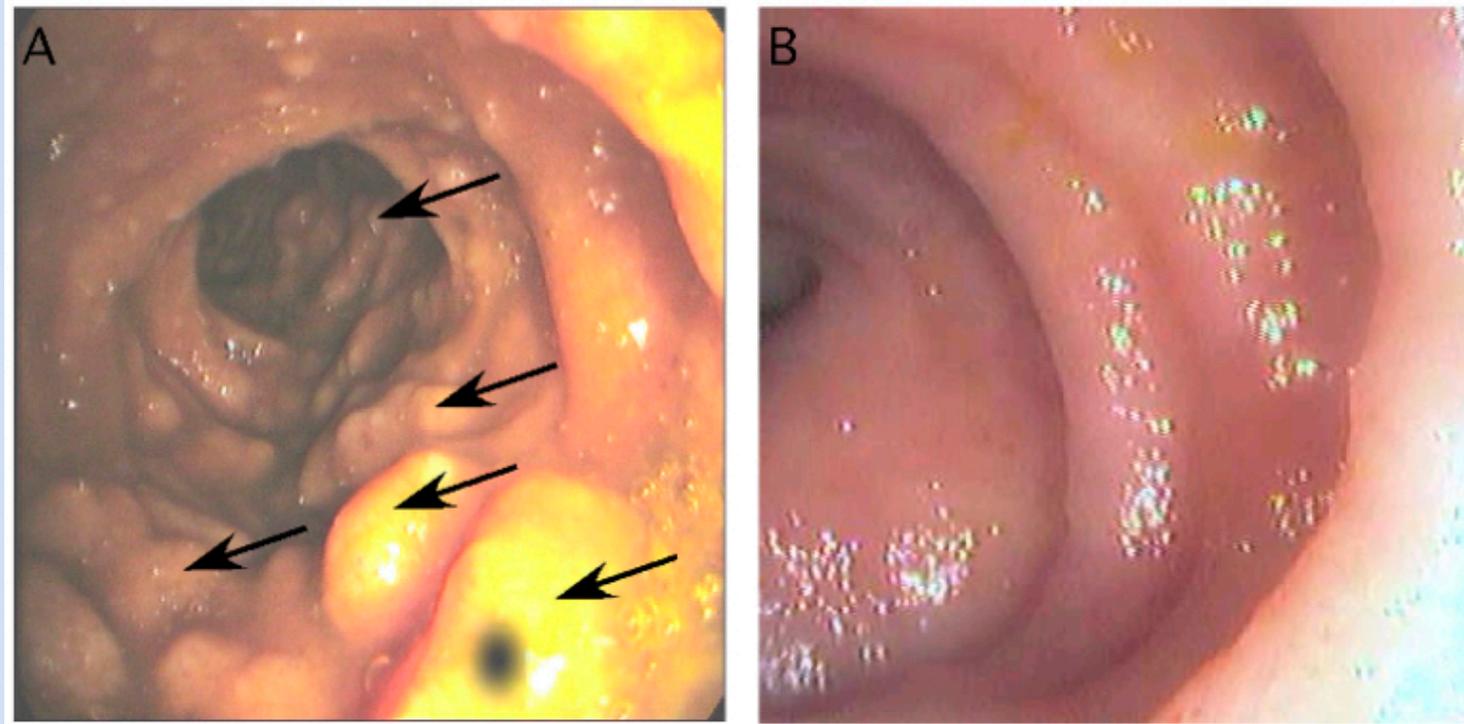
ART works from the first pill, reducing viral load the steepest within the first few days. This is from actively circulating CD4 cells. Over the next weeks and months the slope is less steep.

CD4 on ART



CD4 recover is better to be slower and steadier.

CD4 depletion in gut in acute HIV infection



JM. Brechley, Daniel Douek et al. (2004) CD4 T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract. *J Exp Med.* 200(6):749–759

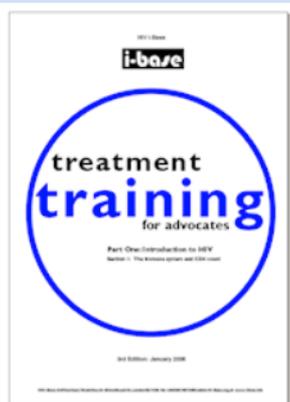
Treatment training for advocates (ttfa)

8-section treatment training for activists – January 2016

This resource contains eight modules with questions and answers.

This manual is designed for people with no previous

editions)



- 1 Immune system and CD4 count
- 2 Virology, HIV and viral load
- 3 Introduction to ART
- 4 Side effects of ARVs
- 5 Opportunistic infections (OIs) and coinfections
- 6 HIV and pregnancy
- 7 Drug users and HIV
- 8 Clinical trials and research

i-base.info/ttfa

Produced for EATG STEP programme in 2005. Russian, Spanish, Italian, Portuguese, Bulgarian.

English edition updated four times after major changes in HIV guidelines.

Treatment training for advocates

**Clinical trials: a
community guide to
HIV research (2015)**

**HIV Drug Resistance
Course (2014)**



i-base.info/ttfa

Additional sections on

- clinical trials.
- HIV drug resistance.

“Scientific method”

The scientific approach to understanding the world usually involves three stages.

1. Observe or question something.
2. Deciding on one or more hypotheses that might explain it.
3. Invent experiments to test these ideas.
4. (Getting results into practice)

Science of HIV research

- “Scientific method”.
- Study design – appropriate question.
- Statistics – define confidence in results.
- Presenting results: conferences, peer review publications, press releases.
- Conflicts of interest.

- Community involvement throughout.

Three key concepts

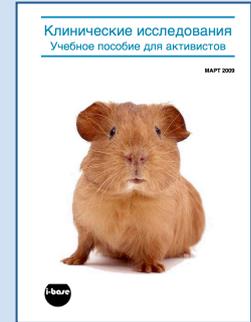
Experimental vs observational.

Prospective vs retrospective.

Longitudinal vs cross-sectional.

Evidence from different studies

- Meta-analysis of similar RCTs.
- RCT – Randomised Controlled Trial.
- Observational cohort.
- Systematic literature review, meta-analyses
- Single arm, uncontrolled studies.
- Case note reviews, case studies.
- Expert opinion.



Grading evidence

Guidelines – guide to minimum standard of care.
Grade evidence and recommendations differently:
ie US, vs WHO, vs EACS.

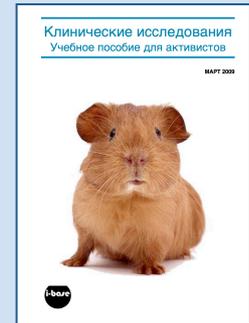
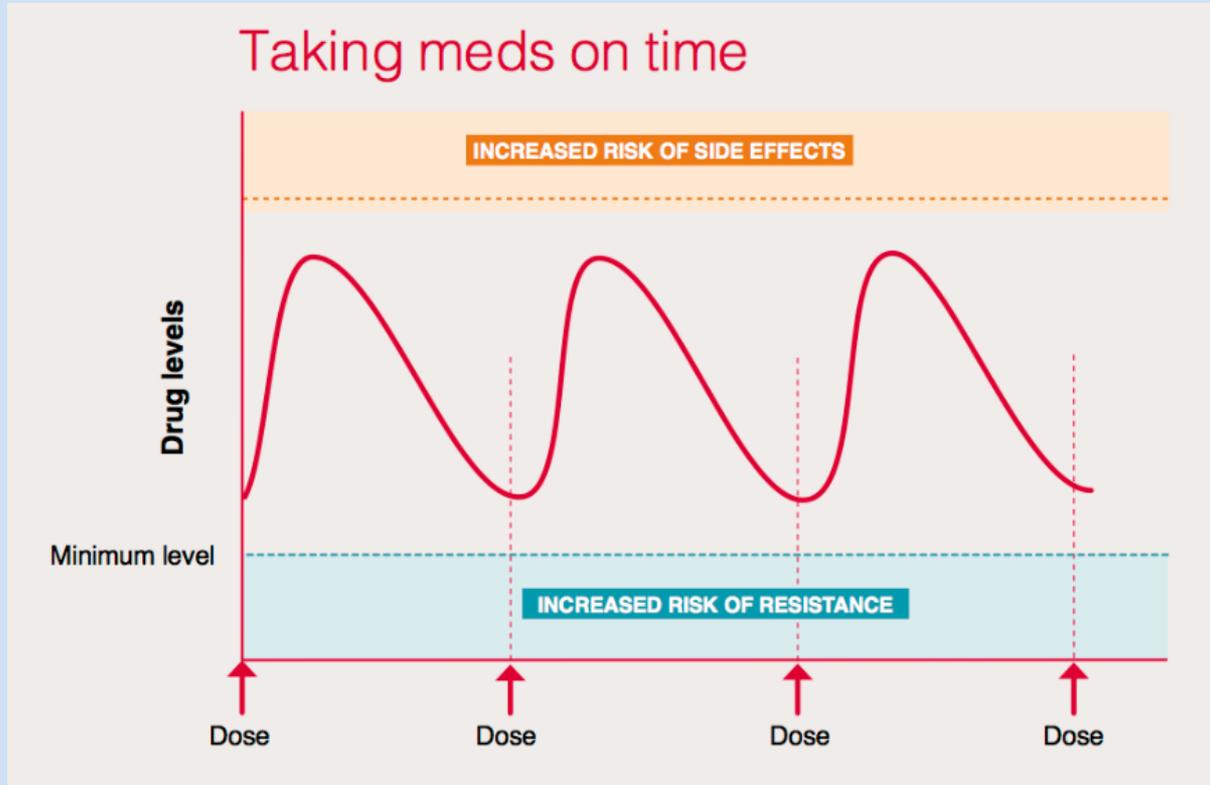


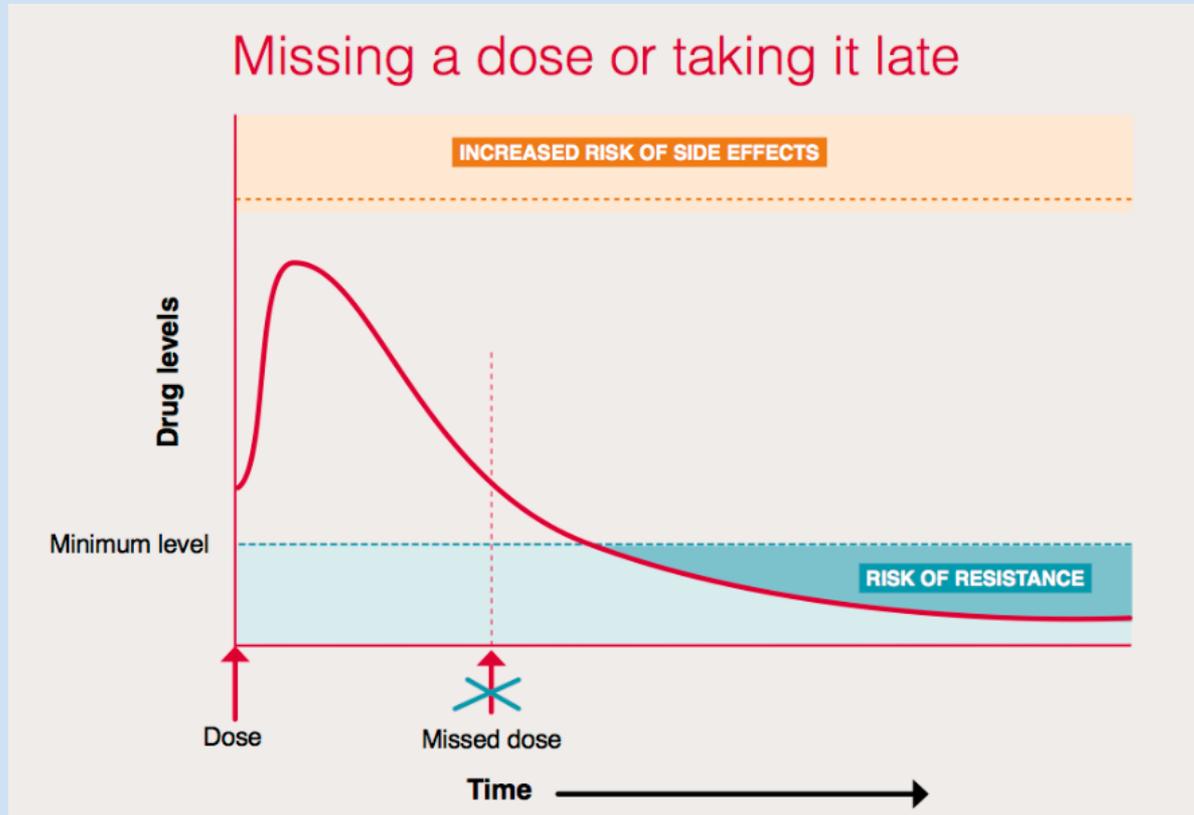
Table: Grading of recommendations and levels of evidence

Recommendation	Quality of evidence for recommendations
A: Required, should always be followed	(I) At least one randomised trial with clinical endpoints
B: Recommended, should usually be followed	(II) At least one randomised trial with surrogate markers
C: Optional	(III) Observational cohort data (IV) Expert opinion based on other evidence

Drug levels, PK, adherence



Drug levels, PK, adherence



Community involvement: ethics

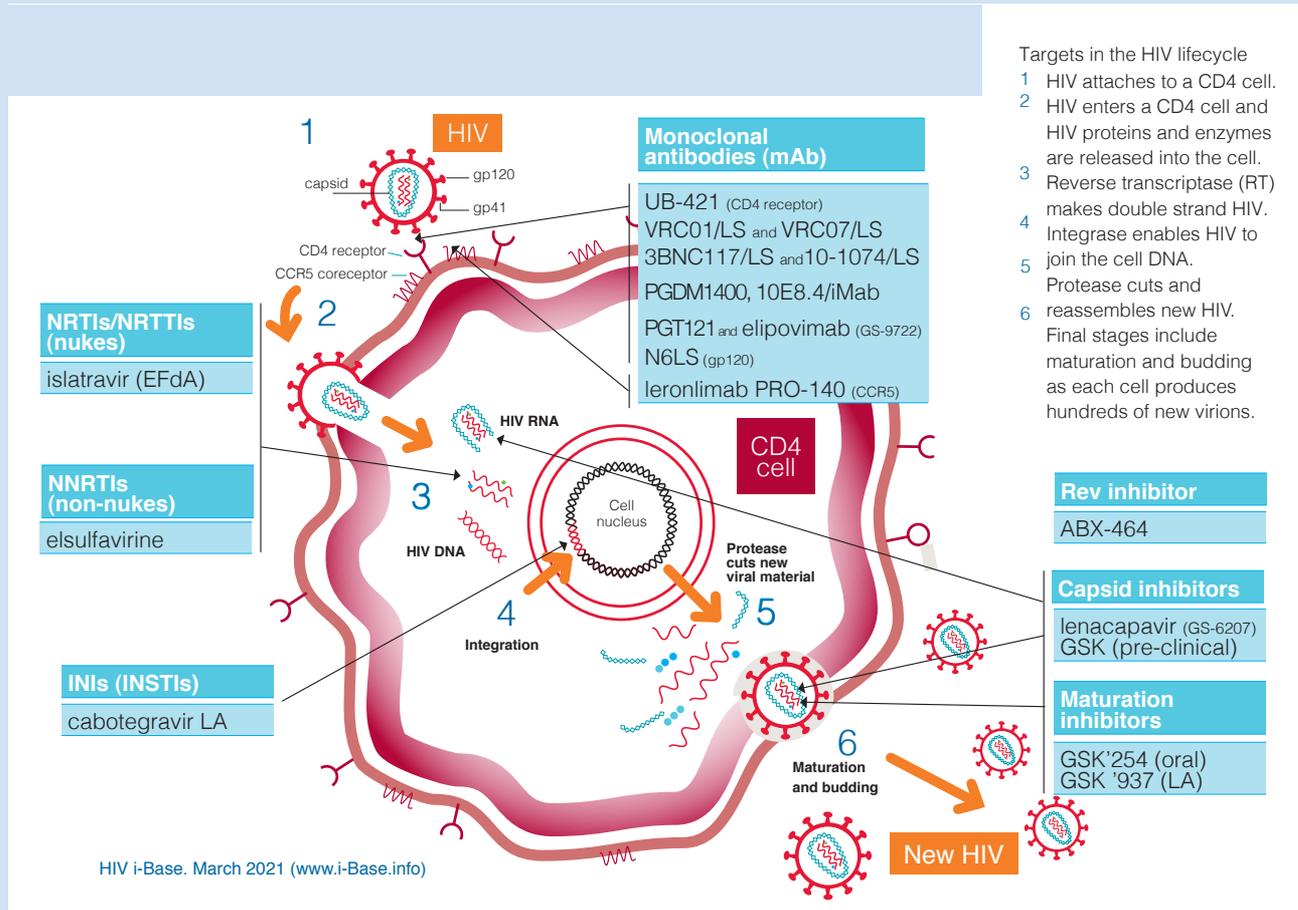
- Informed consent - voluntary.
- Risks and benefits.
- Not knowingly cause harm*.
- Genuine research questions.
- Able to benefit from results.

* Ie - Tuskegee study, 1932 – 1972. Unethical US research into syphilis that withheld treatment for decades from African-American participants.

<https://www.cdc.gov/tuskegee/timeline.htm>



HIV lifecycle: targets for pipeline drugs



Long-acting injections: CAB/RPV LA

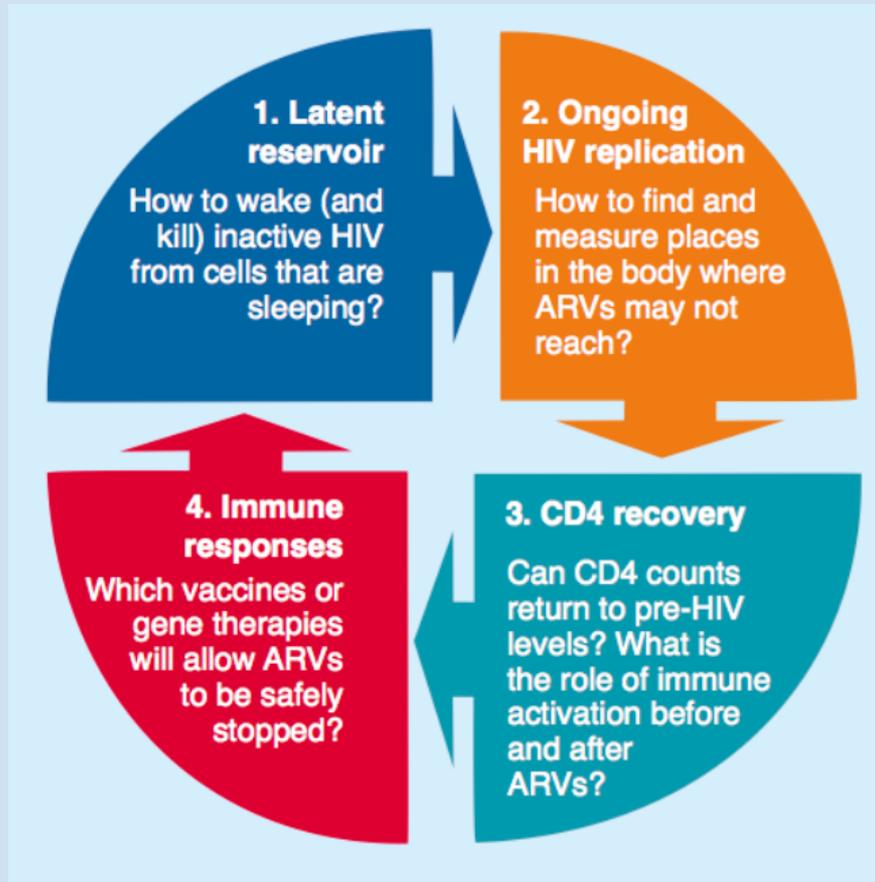
- cabotegravir/rilpivirine LA (Cabenuva).
- Phase 3 ATLAS (experienced) and FLAIR (naive) studies: monthly injections.
- April 2019 – submitted to FDA.
- July 2019 – submitted to EMA.
- December 2019 – FDA manufacturing issues.
- March 2020 – approved in Canada.
- July 2020: Resubmitted to FDA.

- Approval expected – access will depend on price.

CAB/RPV LA: 2-monthly dosing

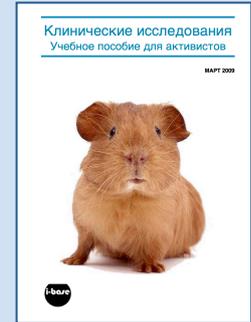
- Phase 3 ATLAS-2M (two-monthly dosing) (CROI 2020).
- RCT in 1045 treatment experienced adults.
- 10 viral failures: 8 vs 2 in 2M vs 1M .
- RPV resistance in 6/8 vs 1/2 and INSTI resistance in 5/8 vs 2/2, respectively.

The Cure puzzle



8.18 Key studies in HIV research

- First reports, AZT studies, HAART.
- Getting VL < 50 copies/mL.
- PK boosters.
- ART during pregnancy.
- Development of FDCs (Trizivir, generics, Atripla).
- SMART and START studies.
- PrEP and PARTNER studies.



Further reading

[i-base.info/
guides/art-
in-pictures](http://i-base.info/guides/art-in-pictures)

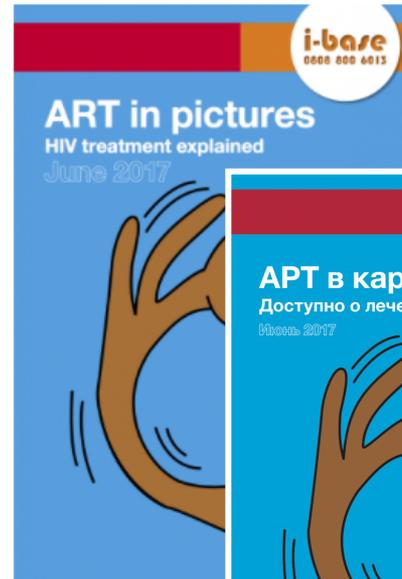
ART in pictures: HIV treatment explained

This publication explains some of the ideas and science behind HIV and treatment.

Each section includes a picture and summary notes. Additional text in each section tells a more detailed story.

The resource was developed as an advocacy course for HIV positive people

- [Order print copies](#) (free in UK)
- [Translation into Russian](#)



Conclusion

- Medical research is now highly accessible: go to the source.
- Read everything, watch everything...
- Question everything...
- Talk to everyone – activists, doctors, researchers...
- Write, report, publish etc

Thanks

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Additional slides