AFROCAB / LA CAB

Why some studies finish early?
Expert planning is often wrong.

ZOOM
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Background examples

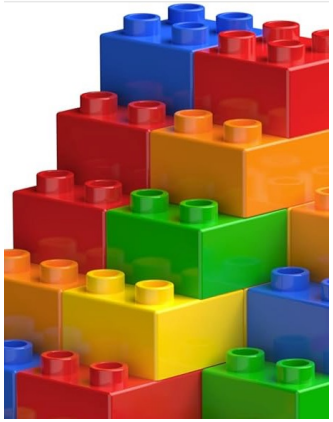
Unethical studies that caused harm?

- ***Any study*** with less than standard of care.
- Bad enrolment criteria: if your CD4 is very low and you need active ART.
- Bad ethics: study of two different fillers for facial lipoatrophy, giving one filler into each cheek.
- Bad science: transplanting fat from a buffalo hump into sunken cheeks.
- Already knowing outcome: AMP bNAbs studies?

Main study question

- Every research study has to start with a question (or hypothesis) – ie:
  - Do bNAbs work as PrEP?
  - Is is better to start ART early?
- This involves how to prove this idea. Ie what measured results would prove this. What is the comparison or control group.
- This definition is called the **primary endpoint**.

Powering the study?



- The next step is to define every detail of the study.
- This is called **powering the study** so the results cant be by chance ($p<0.05$)
- How to define the final result?
- How many people will be needed?
- How long will the study need to last?
- How different to the results in each arm need to be?
- Experts use current knowledge to predict likely results – but experts can get this wrong.

1. Can bNAbs work as PrEP?

VRC01 AMP studies

bNAbs for prevention in Southern Africa: experts knew this wouldn't work before it even started.

https://i-base.info/htb/39977

Two large randomised studies: bNAb infusion every two months.

CONs: bNAb monotherapy. Old bNAb. No baseline sensitivity testing. No oral PrEP. Based on sub-type B. Didn't work overall.

??? - Ethics for participants who expected it might work.

PROs: High retention and adherence, worked in subset of people who were sensitive, proof of concept.

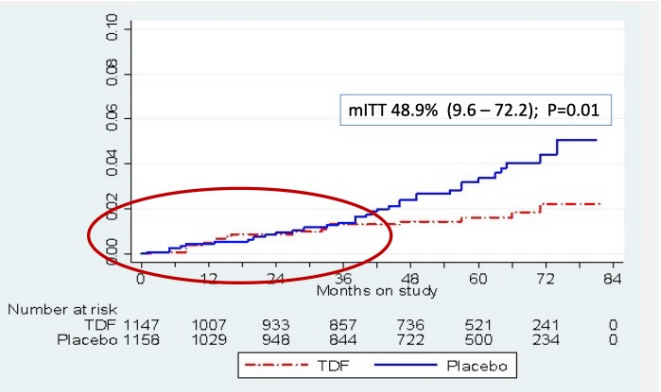
Corey L et al. NEJM, 2021.

2. Bangkok tenofovir study

Still the only oral PrEP study for people who inject drugs, 2005 – 2012.

https://i-base.info/htb/22005

- Delayed by activists for several years because the it didn't include access to ART for people who became HIV+
- No difference vs placebo for first three years – participants at very low risk.
- 2400 HIV– adults followed for 5 years.
- 17 vs 33 became HIV positive.



Choopanya K et al. Lancet 2013

3. Is is better to start ART early?

START study: When to start ART?

Large international randomised study (n=4600, in 35 countries): early (CD4 >500) vs late (CD4 = 350).

Worry about side effects and drug resistance?

Study closed early after DSBM review.

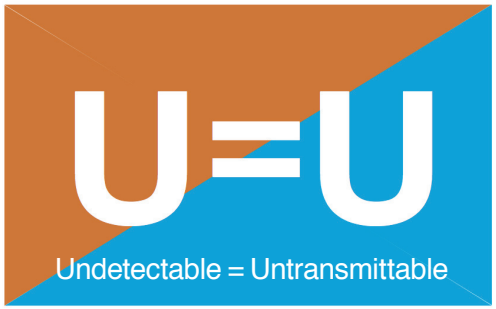
Even at high CD4 ART is better. Everyone offered immediate ART.

WHO guidelines changed within a month.

DSMB = Data and Safety Monitoring Board

Lundgren J et al. NEJM, 2015.

4. Does ART prevent transmission?



HPTN-052 study

Large intl randomised study - 1700 couples.

Q: Will early vs late ART (CD4 >350 vs 250) reduce HIV transmissions?

Experts thought that ART would only reduce transmission by about 30-50% *(definitely not U=U).*

DSMB closed study after 2 years (expected 5-6 years).

N=27 vs 1 new transmissions – ART reduced by 96%.

DSMB = Data and Safety Monitoring Board

Cohen M et al. NEJM, 2011.

5. Does TDF/FTC work as oral PrEP?

UK PROUD study in 545 gay and bisexual men.

Immediate PrEP vs deferred for 12 months.

Not powered to show efficacy.

BUT stopped early after DSBM review:

PrEP was 86% better than placebo.

3 vs 19 people became HIV+ nearly while waiting for PrEP.

Experts thought HIV rate was 3% when it was really 9%.

People were at a much higher risk = earlier answer.

DSMB = Data and Safety Monitoring Board

McCormack S et al. Lancet, 2015.

6. Is it ok to take a treatment break?

SMART study

Another large randomised study.

N=4500 people: continuous ART vs breaks in treatment (to reduce side effects of early HIV meds).

Closed by DSMB after 2 years – vs 7 years planned.

Experts were wrong. SMART showed untreated HIV caused what were thought to be side effects.

ART was much safer than people realised.

DSMB = Data and Safety Monitoring Board

El-Sadr W et al. NEJM, 2006.

Summary

- Good research studies are always better than expert opinion when people think they already know the answer.
- Keep an open mind that experts can make mistakes when planning studies.
- Independent DSMBs can stop studies early after the question is answered – limits further harm.

Thanks

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