Science & research

Simon Collins
HIV i-Base

i) why we need evidence and not just expert opinion

ii) trial design and research

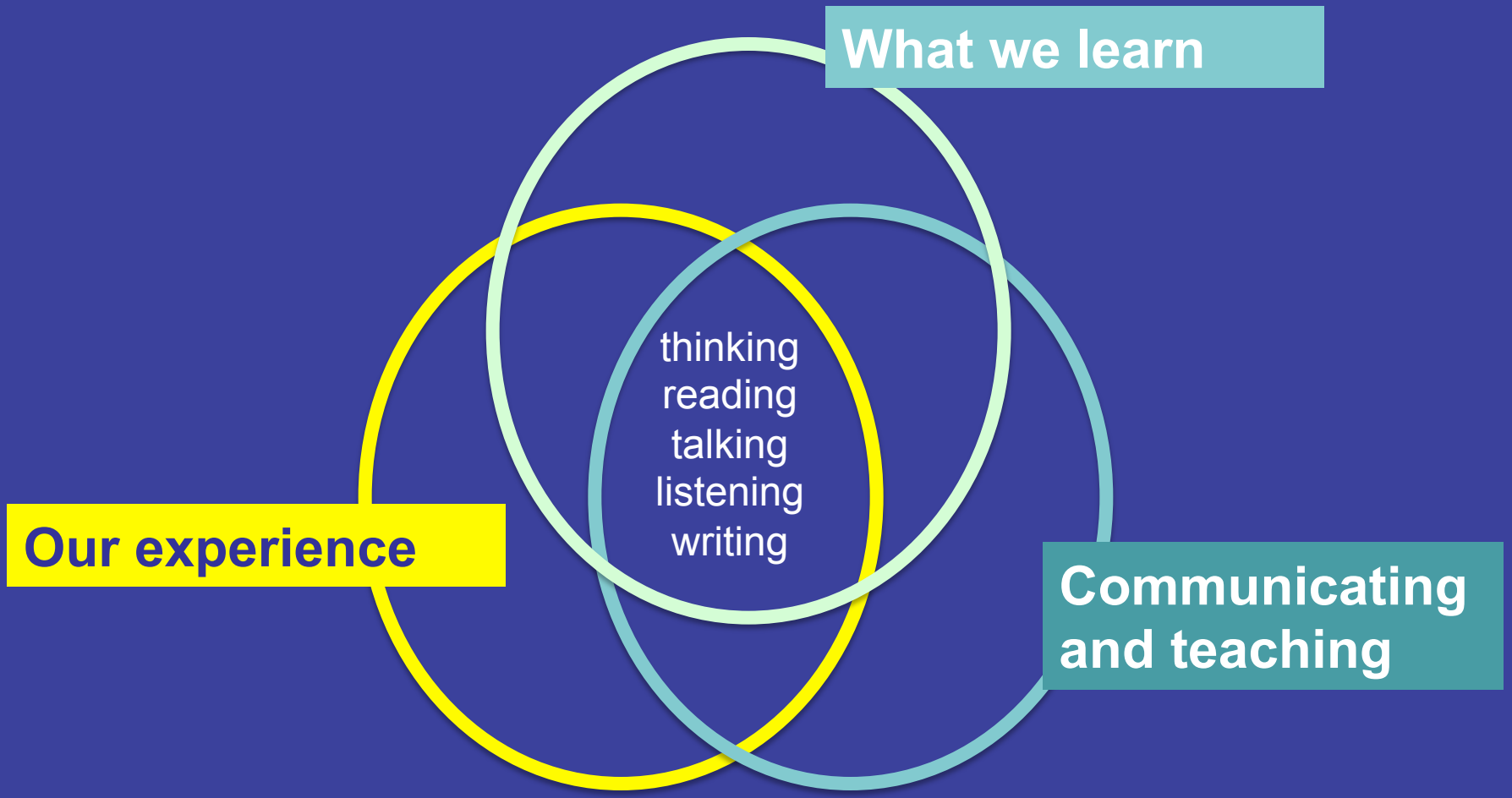
Activist training

- The CAB is a treatment activist network. Our focus is on science and research because healthcare in the UK is based on "evidence-based medicine"
- Understanding the basics of research is essential if we are to explain this to others
- This is the start of a learning experience that can develop over many years

Activism vs advocacy

- Some CAB members identify primarily as either activists or advocates
- Activism is an approach where you decide that things could be better than they are. And then doing something to make things change. Lots of people are activists with giving themselves this title.
- Advocacy is specific to helping another individual to get better care.

Activist training: skills and practice



Introduction

- Please write notes
- Keep a glossary of new terms and words
- The training will include new tools to understand and explain research
- Please report at least one session each for the report
- Please ask questions
- Please provide feedback

Results are repeatable and generalisable

Research study

n = 500

Population results

n = 500,000

Research needs to be designed so that there is confidence in the results to use them on a population level…

Key: n = number

Clinical evidence

- Studies can prove a theory, disprove a theory or need further studies to answer the question
- By definition a study can be repeated something is true
- Research involves extending results from a small to a large group of people
- Relatively recent – mainstream since 1950

Types of research.1

Different types of study have advantages and disadvantages ***depending on the study question***.

1) Prospective or retrospective:
   Looking forward or backwards?
2) Observational or experimental:
   Just observing or experimenting?
3) Cross-sectional or longitudinal:
   Single timepoint or following over time?

Types of research.2

Different types of study also provide different levels of evidence:

- Randomised, controlled trial (RCT) - double-blinded, clinical vs surrogate endpoints
- Cohort studies
- Cross-sectional study
- Case-control study
- Systematic literature review / meta-analyses
- Case report / case review
- Expert opinion

Clinical research

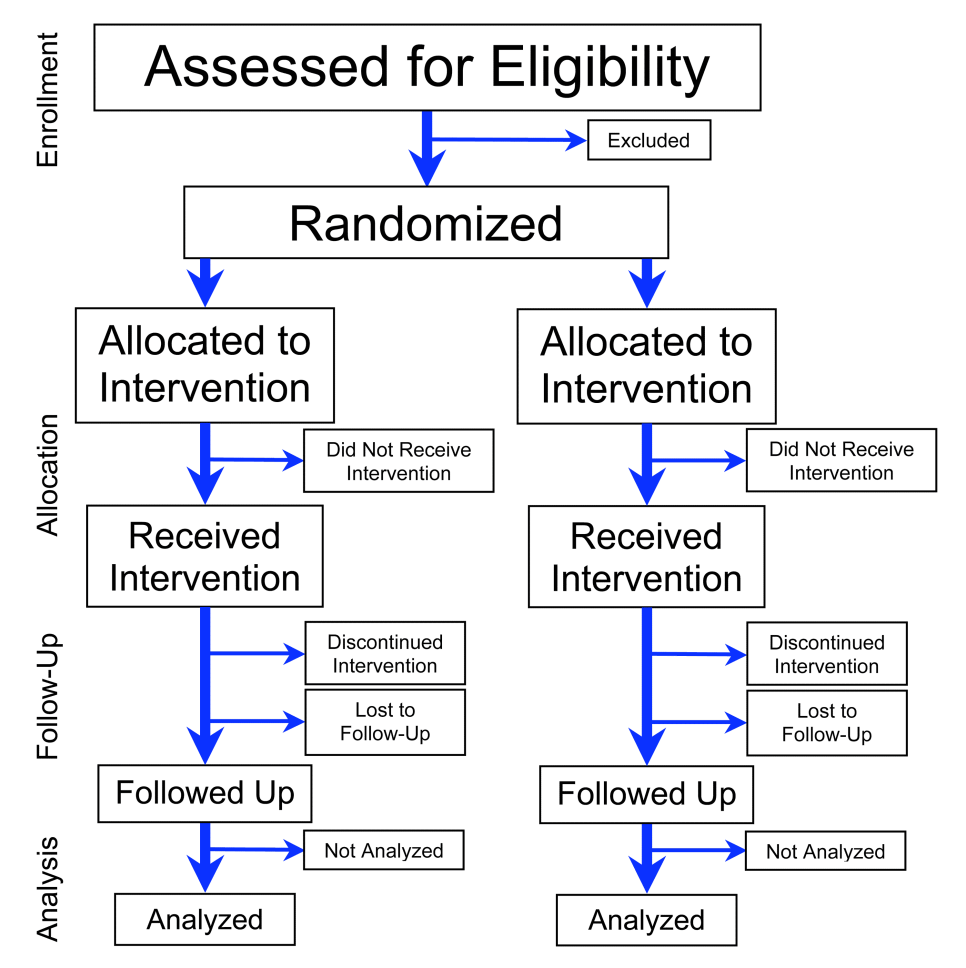
- Every study starts with an idea – sometimes called a theory or question or hypothesis
  Write down three study questions
- Different types of studies produce different types of results
  Write down three types of studies
- Every study tells a story – we need to understand the story first before we can explain it to anyone else
  List three recent health studies

Study format

- Title – summary of research (impartial, not showing results?)
- Background – why the study is important
- Methods – outline of what will be done
- Results – outcome – what was observed
- Discussion – implications, strengths and weaknesses of the study
- Conclusion – summary of what was proven or not.

Read everything by asking questions

Randomised clinical trial - RCT



* http://en.wikipedia.org/wiki/Randomized_controlled_trial

Clinical evidence – examples

- Citrus fruit and scurvy *
- Streptomycin for TB *
- START – Using ART when CD4 is >500 vs 350 cells/mm3
- PARTNER – what is the risk of transmission when viral load is <50 c/mL

* http://en.wikipedia.org/wiki/Randomized_controlled_trial

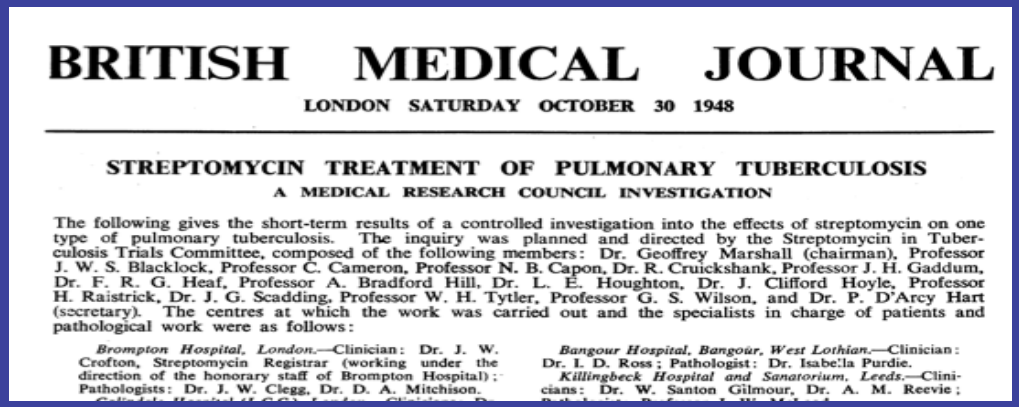
James Lind - Scurvy

Background: Sailors health at sea
Methods: N=12 scorbutic sailors into six groups of two.
•They all received the same diet, plus:

Group 1 - a quart of cider daily,
Group 2 - twenty-five drops of elixir of vitriol (sulfuric acid),
Group 3 - six spoon of vinegar,
Group 4 – 0.5 pints of seawater,
Group 5 - two oranges and one lemon
Group 6 - a spicy paste plus a drink of barley water.

Results
•The treatment of group five stopped after six days when they ran out of fruit, but by that time one sailor was fit for duty while the other had almost recovered. Apart from that, only group one also showed some effect of its treatment.
Conclusion - ??
•http://en.wikipedia.org/wiki/James_Lind

Streptomycin – BMJ 1948



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie;

Background: TB – no available treatment

Methods: N=107 - randomised to streptomcin (n=55) - 0.5 mg IM, every 6 hours for 4 months vs control (n=52). Not aware of study.

Results: 7% (n=4) vs 27% (n= 14) deaths within 6 months – statistically significant – less than 1% likelihood it could happen by chance; and 51% (n=28) vs 8% (n=4) improved (<0.001% by chance); esp in most sick.

Conclusion - ??

- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2091872/

Research example (Streptomycin – BMJ 1948)

Background: What was the study question?

Methods:
- What type of experiment was designed to answer the question?
- How? With what? Measuring what?

Results:
- Who were studied – what type of people?
- What was observed? – were there differences between people?
- Were results significant?

Discussion
- What else was important? Were there risks? What other studies are needed? What can we interpret?

Conclusion
- Was the question answered? How can the results be used?

Evidence vs opinion

- Evidence-based medicine was only recently formalised - since 1988
- Balance of the risks vs benefits of any intervention based on available evidence
- Categorise evidence based on the quality of the study
- Formalised in guidelines – often one category for the quality of the study and another for the strength of the recommendation

START study

- Balance of the risks vs benefits of starting treatment at CD4 >500 vs 350 cells/mm3
- Flow chart – study design
- What are the primary and secondary objectives?
- Any surprises?

PARTNER study

- Quantify the risk of HIV transmission when HIV positive partner in on treatment
- Flow chart – study design
- What are the primary and secondary objectives?
- Any surprises?

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START Study

http://insight.ccbr.umn.edu/

VERY EXCITING – >4000 people with CD4 counts above 500 randomised to early vs late

PARTNER Study

http://www.partnerstudy.eu/

VERY EXCITING – follows pos/neg couples for HIV transmissions when VL is undetectable

Thanks

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TasP: available evidence

Table 1. HIV transmission in serodiscordant couples on ART and PY of follow-up of condom-less sex

Reference	Type of study	Setting	VL lower limit of detection, copies/ml	Transmissions on ART, *n*	Estimated HIV transmission per 100 PY (95% CI)	Proportion of couples having condom-less sex, %	Follow-up index case on ART and having condom-less sex, PY
Cohen, *et al.* [1]	Randomized controlled trial	Heterosexual couples; 13 sites in 9 countries	<400	1	0.1 (0.0, 0.4)	7	63.4
Attia, *et al.* [6]	Systematic review and meta-analysis	Two cohort studies including serodiscordant heterosexual couples on ART with VL<400 copies/ml [7,8]	<400	0	0 (0, 1.27)	25	218.25
Donnell, *et al.* [3]	Observational cohort	Heterosexual couples; 14 sites in 7 African countries	240	1[a]	0·37 (0·09, 2·04)	7	19.1
Reynolds, *et al.* [9]	Observational cohort	Heterosexual couples; Rakai Study, Uganda	<400	0	0 (0, 5.98)	46	28.9

[a]Genetically linked HIV-1 transmission. ART, antiretroviral therapy; PY, person-years; VL, viral load.

Rodger et al. Antiviral Therapy 2013; 18:285–287

TasP: available evidence

Study (n = couples)	No of trans-missions	Rate per 100 PYFU (95%CI)	% couples no condoms	F/U time with risk (years)
HPTN-052 (n=1763)	1	0.1 (0.0, 0.4)	7	63.4
Meta-analysis (n=93+393)	0	0 (0, 1.27)	25	218.25
Partners (n=3381)	1	0.37 (0.09, 2.04)	7	19.1
Rakai (n=32)	0	0 (0, 5.98)	46	28.9

Adapted from Rodger et al. Antiviral Therapy 2013; 18:285–287