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Clinical trials:
a community guide to HIV research

i-Base treatment training manual for advocates

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Contents

This booklet is one section of the i-Base training manual for advocates, available online (www.i-Base.info). Other sections include: The immune system and CD4 count; Virology, HIV and viral load; Introduction to ARVs; Side effects of ARVs; OIs and co-infections; HIV and pregnancy; Drug users and ARVs and Learning resources: science support modules.

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Introduction to this resource

This booklet is one chapter from the i-Base advocacy manual which is available free online:

www.i-Base.info

The format is very simple.

It is written by and for people who do not have a formal scientific background or medical training.

Even if you are not very academic, and this training is difficult, you can still be a very effective advocate and activist. This training will help you understand the background to treatment issues.

The training material has been written in a way that makes it easier for you to then explain the information again to other people who do not have a medical background.

As community advocates and trainers, it is important to understand and explain things that people may not have a great interested in at first, and explain them in a way that makes the new information relevant to them getting better care.

Most people don't want to know about science - they just want to get on with their lives.

You will need to explain, however, the science behind how things work. It means getting people to believe in things that they can't see with their own eyes, and getting them to trust in these things.

We can't see a virus, or a CD4 cell or any of the things that are tested in blood with the naked eye. We can't see whether one pill or another will work better or at all.

However, understanding a little about how treatment works can empower people to have more control over their treatment choices.

This course is written by treatment advocates who have had no formal medical training and who are mostly HIV-positive. We have tried to remember the biggest surprises that we found as we developed our own treatment knowledge.

Sometimes it's the surprises that keep you learning – because they show how things can in reality be very different to how you imagined them.

Hopefully, some of these will be helpful in developing your own treatment interest – once you start, you realise there is always more to learn.

8.1 Introduction

Section 8 of the i-Base manual provides information about clinical trials and research.

- It provides a key grounding for advocates interested in this subject.
- It also includes information about how research is presented and how to analyse and interpret trial results.

Community involvement in HIV research is important. Advocates have always argued for active patient and community representation and involvement at all stages of our health care, including research.

This includes being involved on the type of research and the design of trials. It helps make sure that:

- Trials are run properly
- All patients receive at least the current standard-of-care treatment
- We are able to follow both enrolment and how the trial is run
- We are able to monitor and follow early results
- As patients and advocates we have a good idea on how latest treatment advances may affect the standard of care in the future.

This will make sure that patients are treated at the current standard of care throughout the whole duration of the study, and that, if appropriate, the study is changed as new information becomes available.

Even after a study design is finalised, it will often take a year or longer before any patients are enrolled, and then several years for the study to run. Trials therefore need to be designed based on what we expect the standard of care to be for the duration of the study.

Most advocates will need training and support to be actively involved, if they are not just included to show good clinical practice, or to get a grant approved.

This involves us learning about the work and the responsibilities of being involved in research.

8.2 Aims for this section

After reading section 8, you should have an understanding of:

- How trials are designed to produce reliable and accurate information
- Why research is needed to inform treatment choices
- The basic concepts used in trials
- The main types of trials and quality of different types of studies
- Advantages and disadvantages of different studies
- Common features of all studies
- Informed consent and patient care
- Interpreting study results
- The different roles advocates can take

8.3 Why trials are important

Modern medicine is often called 'evidence-based medicine'. This is because it is based on treatments or strategies that have been **proven** to show an advantage compared to other approaches.

Well-designed research can produce detailed results, that could be repeated in similar trials.

Without trial results, treatment decisions would only be based on a mixture of:

- guesswork or intuition
- on the hope that a treatment works
- on untypical results, or
- on commercial marketing.

Hard evidence is needed to know how to improve care.

Trials can show which drugs are better than others. For example, the higher risk of side effects when using d4T compared to tenofovir in first-line therapy.

Research can show which strategies are better than others. For example, that combinations that include three drugs to treat HIV are better that combinations with two drugs.

8.4 Developing a new treatment: Phase I, II, III and IV studies

When a new drug is being developed, there are four main 'phases' of clinical research in humans. These studies are run in order - you have to start with Phase I, then II etc.

Pre-clinical research is a term used to describe earlier studies, including test-tube and animal studies, that are carried out before a drug enters human trials.

Phase I studies

Phase I studies are the first human studies.

This includes single-dose studies that are often called Phase Ia trials. A small group of patients (5-10) will take one single dose and be carefully monitored. 1-2 patients will usually get a placebo.

Short-term multi-dose studies, perhaps for 1-2 weeks, are called Phase Ib. This is where a slightly larger group (perhaps 10-20 patients) will take multiple doses and be carefully followed.

These studies are usually in 'healthy volunteers' - ie for an HIV drug, the first people to take it are HIV-negative.

Phase II studies

Phase II studies are usually the first study to look at whether the investigational compound is actually active. They are run in HIV-positve people.

These can last one day, a week or two or several months. Phase IIa studies usually enrol 20-50 people.

Phase IIb studies also look at different doses of a drug - called 'dose-finding' studies. In which case they may enrol 200-300 people.

Phase III studies

Phase III studies are the large trials that are used by regulatory agencies like the EMEA in Europe or the FDA in the U.S. to decide whether a drug will be approved.

For an HIV drug this is usually 1,000 - 2,000 patients.

If the same people from the Phase II study, continue to be followed in the Phase III study, the study is sometimes called Phase II/III.

If one study leads into another study, it is called a 'roll-over' study.

8.5 Hypotheses and endpoints

Phase IV studies

Phase IV studies are usually referred to as 'post-marketing' studies.

They involve longer follow-up of patients looking at side effects and other safety concerns. Sometimes a rare side effect, or a side effect that takes years to develop, may not be seen in a Phase III or earlier study.

Phase IV studies are usually recommended by a regulatory agencies at the same time that a drug is approved.

Although, in the past, the European regulatory agency had very little power to make sure companies followed through on these commitments, recent legislation has strengthened their authority.

Phase IV studies are now compulsory and the EMEA can withdraw a medication if safety commitments are not followed.

Several key concepts are important in research.

Trial question - the hypothesis

This is the idea or theory that the trial aims to either prove or disprove.

Every trial or study needs to start with a question. For example:

- Is something happening? ie does smoking/diet/exercise affect health? or Do our bones get more brittle as we age?
- Can doing something improve health?
- Is one treatment better than (or as good as) another?

Primary endpoint

The primary endpoint is the main way that the results of a trial will be assessed. It should be decided in the study design before any patients are enrolled.

A primary endpoint decides what level of evidence or results will be accepted to prove or disprove the study question. The choice of endpoints can determine whether the final results are going to be useful.

For example, with a new drug, the primary endpoint is often the percentage of people who have an

undetectable viral load at a certain point. This could be 8 weeks for an early effect or 48 weeks for a longer effect.

But it could also be the average drop in viral load or the average increase in CD4 count; or a direct measure of health in how many people see improved or reduced health.

Secondary endpoints

Secondary endpoints can look at everything else.

- Safety of a drug, side effects
- Impact on CD4 count
- Impact on quality of life
- Cost-effectiveness of treatment and many other factors

Community involvement in trial design can help ensure that important secondary endpoints are included when the study is first planned.

8.6 Main types of trial design

There are three main ways to categorise research. Each type of study has specific advantages and disadvantages They each provide different types of information.

Observational vs experimental (or interventional)

An observational study either looks for evidence that something has happened, or follows people to see whether something happens. The trial does not involve a specific intervention other than normal standard care.

Examples of an observational study include looking at:

- How many people have lipodystrophy at one time, or
- How many people develop lipodystrophy over time

An experimental (or interventional) study is where something specific is done in the study - ie using a treatment, strategy, or other intervention, that is recorded and analysed.

Examples of an experimental study include:

- Comparing whether switching one drug for another improves diarrhoea or another side effect

- Seeing whether diet or exercise can improve fat accumulation

Cross-sectional vs longitudinal

A cross-sectional study collects information at one point in time.

Examples of a cross-sectional study include:

- Looking at a group of patients to see how many people have osteoporosis (bone disease), or
- Finding out what percentage of HIV-positive patients are smokers

A longitudinal study follows individuals to see how things change over time.

Examples of a longitudinal study include:

- Following a group of patients to see how many develop lipodystrophy
- Following a group of patients to see whether an intervention to quit smoking could reduce the percentage of patients at risk of heart disease

Retrospective vs prospective

A retrospective study looks backwards in time.

Examples of a retrospective study include:

- Analysing a database to find out what percentage of patients failed their first combination, or
- Looking at medical records to see whether a recently reported side effect occured in other patients

A prospective study decides on what is going to be studied and then follows people over time to see what happens.

Examples of a prospective study include:

- Comparing a new HIV drug to an existing drug, or
- Following a group of patients to see whether heart disease is linked to HIV treatment

In describing a study one of each of these three terms should be included, for example:

- An observational, longitudinal, prospective study
- An interventional, longitudinal, prospective study

etc...

8.7 Randomised, double-blind, placebo-controlled trials

The most reliable evidence - often referred to as the 'gold standard' - comes from 'prospective randomised, double-blind, placebo-controlled study.

Randomisation

Randomising patients in a study is the best proven way to allow for the fact that some things in a trial - and in life - can happen by chance.

Patients in a study are often randomised when two or more groups are studied.

Randomisation is designed to balance factors in each group that could affect the study results. This includes known factors, such as sex, smoking status or social differences, and unknown factors such as genetic differences that we may not know anything about.

Randomising people, if done correctly, and especially with larger groups, should normally result in an approximate balance of all these factors.

This is a very difficult concept, but it is one of the most important things to understand.

Randomisation also stops bias and confounding.

For example, it prevents a doctor putting patients who are most ill and in need of treatment into the group that receives an active drug rather than a placebo (dummy pill). If this happened, although this may sound more 'fair', the two groups would be different at the start, so you couldn't compare the results accurately at the end.

Clinical research, by definition, involves different people getting different treatment. Often the people to get first access to a treatment in a trial, may not get the best results compared to people who use the drug after it is approved.

This is a balance of advantages and disadvantages. Disadvantages for the first people using drugs may mean they do not use the best dose, or that they risk resistance if other newer drugs aren't allowed in the study. The advantages may be that despite these problems, the drugs have still been life-saving, and the person is still alive to benefit from the next drugs in the pipeline.

Randomisation has to be done in a way that doesn't select a certain group over another.

The most common example for randomising a patient to one of two groups is to toss a coin for each patient - heads they join one group and tails they join the other.

This is because tossing a coin is random and can't be predicted.

Over time, the more a coin is tossed, the more likely that approximately 50% will be heads and 50% will be tails.

An example of bad randomisation would be assigning patients who come to clinic on a Monday to one group and patients who come on a Tuesday to another. In this example, people who come on Mondays may be different from people who come on a Tuesday, for social reasons. They may be more organised, or less likely to have a hangover from the weekend! This could represent important differences between the two groups - ie alcohol use - and this could affect the study results.

Study results always should include the characteristics of the people being studied. Sometimes, even with randomisation, you may see that one group may have different characteristics.

When this happens it can sometimes be adjusted for in the final analysis, and it needs to be considered when interpreting the study results.

Blind and double-blind studies

Blinding (sometimes called 'masking') is the term to describe a doctor, patient or researcher not knowing which study group a patient has been assigned to.

A blinded study is where the patient doesn't know which group they are in, or which treatment they are getting.

A double-blinded study is where neither the doctor nor the patient know which group the patient is in.

Blinding prevents different care or treatment being given based on the personal beliefs of either the doctor or patient.

An example of why blinding is important is that if someone know they are getting an active drug, both doctors and patients may be more likely to report side effects.

It could also affect how often a patient takes the treatment.

Placebo

A placebo is the term for a dummy drug, ie something that looks, smells and tastes like the compound or intervention that is being studied, but which has no active ingredient.

Using a placebo helps find out whether the active drug is really active. It also helps interpret side effects.

If 10% of people in the active drug group report having a headache and 2% of people in the placebo group report a headache, then it is reasonable to think that the active drug can cause headaches.

If 10% of the placebo group also reported a headache, then it is reasonable to think that the active drug doesn't cause a headache.

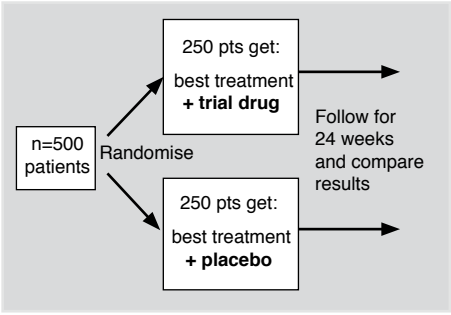
An example of why placebo studies are still important was shown in the development of capravirine (an NNRTI). In a Phase IIb study people using capravirie plus a background combination did no better than people using the same regimen plus a placebo.

This stopped further development of the study drug. It protected other patients being put at risk from using an ineffective treatment in later trials.

Control group

A control group refers to a group of patients in a study, that any intervention group is compared to. This helps to show that the intervention actually caused what was seen and that it wouldn't have happened anyway.

One common type of control group is to use a placebo.



In the example above, all patients get the best treatment with or without the new drug.

If, for example, this is a new HIV drug and the best treatment already includes 3 active drugs, then it could be difficult to see any difference between the new drug and the placebo, because both groups will already do very well.