

# hiv treatment update

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Gus Cairns

## in this issue

“Just give me the figures.” Ever said that to a doctor who’s pussyfooting around how serious some illness is? If you’re lucky enough never to have been in that position, you may, if you have HIV, have said it when they tell you your CD4 count is ‘fine’. And we bet you’ve said it to a garage mechanic; or a plumber; or an insurance salesman.

This HTU is all about the figures. We can get through a lot of life operating on hunches, rules-of-thumb, maybe spiritual guidance. But for really important decisions, it helps to know how likely something is; how long it will last; what it will cost. Figures sharpen the world, bringing into focus things that seem blurry.

But to use them you have to read them right. Caroline Sabin’s beginners’ guide to interpreting drug trials shows that things are not always as reported. Newspapers love miracle cures and wonder drugs, and HIV research has had a history of false dawns and disappointments. Last month, for instance, the media was getting very excited about bananas and reporting that a substance found in everyone’s favourite phallic fruit worked better against HIV than two current drugs.

What researchers had actually found was that, in test tube trials, the banana compound was better able to prevent HIV from entering cells than two drugs – maraviroc and T20 – that also blocked entry, and might make a suitable candidate for inclusion in an experimental microbicide. Not a pill. But all the newspapers heard was “better than”, and they ran with it.

Of course, it works the other way too. For years, evidence has been slowly accumulating that, on the whole, it’s better to be on HIV drugs than not. From the SMART trial onwards at least, virtually all studies comparing people on HIV treatment to people off it show a lower mortality in people on the pills.

The effect this has had on mortality is impressive, so much so that you sometimes hear that “there’s no reason why someone diagnosed with HIV today can’t have a normal lifespan”. People hear this and then understandably get very cross when they apply for, let’s say, life insurance and get turned down, or priced out.

Despite there being more options for HIV-positive people than there were (see page 4), insurance underwriters are hard-nosed businesspeople making broad-based decisions about risk and, as the piece on life expectancy (page 14) describes, there is not a single, simple answer to this question in the case of HIV.

What studies actually show is that for *some* people, in *some* settings, life expectancy with HIV is *approaching* normality. For a lot of the rest of us, it still prunes off at least as many years as smoking 20 cigarettes a day would.

Sharpening the focus on the data doesn’t always bring reassurance. Sometimes it brings an exact appreciation of the work we have left to do to conquer this virus.



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# securing your future

*Emma Lunn* looks at insurance for people with HIV.

Over the past 20 years the outlook for people with HIV has changed. Improvements in medication and the introduction of highly active antiretroviral therapy (HAART) mean that people diagnosed HIV positive can expect to live longer than they might have expected to back in the 1980s.

This is good news, but it means that HIV-positive people need to think about their financial situation, not just on a day-to-day basis but in the longer-term too.

## Life

Life insurance (or 'assurance') is a policy that pays out a lump sum when the policyholder dies. The aim is to prevent the dead person's partner or family from struggling financially. The 'sum assured' is the amount of cover you have or the amount the policy will pay out when you die.

When you take out a life insurance policy you will pay a regular premium, usually monthly. How much this is depends on several factors including how much cover you want, how long you want it for, your gender, occupation, health and medical history.

Most people only consider life insurance if they are married or in a civil partnership, or have children or other responsibilities such as a joint mortgage with someone else. The idea is the payout will support your partner or family financially if you die at a time when they are relying on your salary. It could be used to cover things such as mortgage repayments, replace the deceased person's salary, or to pay childcare or education expenses.

In the past it was impossible to get life insurance if you had tested positive for HIV as insurers simply deemed the risk of a policyholder dying too high. However, in 2005 the Association of British Insurers (ABI) set up the ABI

Expert Working Group on HIV and Insurance to tackle these issues. The group, which was composed of clinicians, HIV interest groups and insurers, worked to ensure that the insurance industry treated the subject of HIV risk with sensitivity and fairness. It also looked at HIV statistics and claims data and researched ways that life insurance could be offered to people with HIV.<sup>1,2</sup>

Since then treatment and knowledge of HIV has improved and so has the attitude of the insurance industry, albeit slowly.

The introduction of highly active antiretroviral therapy (HAART) over the past few years has prolonged the lives of many people who are infected with HIV (see *How long have I got, doc?* on page 14). Meanwhile insurance companies, underwriters and intermediaries have worked together to design specialist life insurance policies for people who have tested HIV-positive.

## Life insurance and gay men

In the past it was not just having HIV that prevented some people from finding life cover. Life insurers asked applicants if they were gay and some sent gay men for HIV testing. Regardless of the result, gay men were often charged 'loaded' premiums (i.e. they were more expensive).

Since 2005 there have been significant changes to the way gay men are treated by insurance companies. The ABI HIV and Insurance guidelines removed the so-called 'gay questions' from application forms and started to underwrite policies on the basis of sexual behaviour instead of a person's sexuality.

Further to this, it is no longer acceptable to ask if an applicant is gay and insurers will not ask questions about your sexuality. Even if you inadvertently disclose such information, it will not be used in assessing your

application and gay men will not be asked to take an HIV test simply because of their sexuality.

Neither can insurers make assumptions about an applicant's sexuality from the details of his or her living arrangements, occupation or medical history. Instead, they must assess each applicant on a case-by-case basis, using the best available relevant evidence.

Insurers can now ask applicants, regardless of their sexuality, only a general HIV-risk question, such as: "Within the past five years, have you been exposed to the risk of HIV infection?" Insurers sometimes include examples of increased risk of HIV in their question: "This can be caught through unsafe sex, injecting drug use, or blood transfusions or surgery undertaken outside the EU."

If the answer is 'yes', insurers may require an HIV test before granting life cover. However, applicants will not be penalised by insurers simply on the basis of having taken an HIV test in the past, and do not need to declare negative HIV test results.

## Life insurance and immigrants

Not being born in the UK or not having citizenship does not in itself preclude you from getting life insurance, but almost all insurers ask separately about travel and residence abroad. The ABI's agreed form of question in this case is to ask people whether they have lived, worked or travelled abroad in the last five years or intend to in the near future.

If someone has lived or worked for any length of time in a country with high HIV prevalence they will be asked to take an HIV test as a condition of obtaining life cover. 'High prevalence' has no numerical definition but is likely to mean east, south and west Africa, parts of the former Soviet Union and some



countries in Latin America and the Caribbean. If you test HIV-positive, or disclose positive status, your position is the same as anyone else in the UK.

#### **Non-disclosure**

In insurance terms 'non-disclosure' is basically lying on your application form. This includes both making false statements and, just as importantly, omitting information that would affect your eligibility for cover. Each year hundreds of insurance claims are turned down for non-disclosure, even if the claim was unrelated to the condition concerned, and often because the applicant has

inadvertently missed out information they might not have thought relevant.

For this reason you need to answer all the questions in the application carefully, accurately and to the best of your knowledge and belief.

On all applications for life insurance, critical illness cover and income protection insurance, you will be asked if you have tested positive for HIV. If the answer is 'yes', you must say so. The wording that appears on application forms is:

"Have you ever tested positive for HIV, hepatitis B or C, or are you awaiting the results of such a test? If the result is negative, the fact of having an HIV test will not, of itself, have any effect on your acceptance terms for insurance."

If you have HIV and omit the truth about your HIV status it could result in your policy not paying out when you die and your dependents being left without financial help.

People who have a pre-existing medical condition may find their life insurance premium is 'loaded'. This means it's

more expensive than a standard premium to reflect the extra risk to the insurer. And some pre-existing conditions – including HIV – will mean an applicant is rejected by some or most insurance companies.

### Specialist policies

Essentially an HIV-positive person will still be turned down for life insurance by most mainstream life insurers. However there are currently two specialist policies for people with HIV, but applicants will have to meet certain criteria to be accepted.

#### PruProtect

In April 2009 the Prudential extended its existing PruProtect life cover product to include people living with HIV. The product provides up to £250,000 life cover over a maximum period of ten years.

Applicants need to meet the following qualifying criteria:

- Aged between 25 and 50.
- Have not contracted HIV from intravenous drug use.
- Must be receiving highly active antiretroviral therapy (HAART) in the UK, have commenced treatment in the past five years and have been receiving treatment for at least six months.
- Treatment should result in an increased CD4 cell count, and viral load should be suppressed to near undetectable level.
- Must be hepatitis B and C negative.

Experts say the main drawback to the policy is that it only covers a limited range of people living with HIV, but the aim is to broaden the qualifying criteria to cover more people as time progresses. Cover is only available through UK brokers and intermediaries so applicants need to obtain advice before submitting their application.

Premiums are underwritten on individual circumstances and will generally be higher than traditional life insurance policies. For example, in one known case an applicant was charged

£68.79 a month for £100,000 worth of cover compared to £6.16 on a standard premium.

For more information, see [www.pruprotect.co.uk](http://www.pruprotect.co.uk).

#### Pulse

Pulse has a product specifically designed for individuals who are HIV-positive, but do not have AIDS. This product, the 'Harbour' policy, provides a modest amount of life cover for death from natural causes only – up to £10,000 – with a substantial amount of personal accident cover, up to £200,000, as well. The advantage of this cover is that it can be obtained without medical evidence and can therefore be put in place quickly.

However experts say the product is little more than an accident policy with £10,000 life insurance bolted on and applicants can expect to pay up to 30 times the normal premium for the cover provided by the policy.

For more information, see [www.pulse-insurance.co.uk](http://www.pulse-insurance.co.uk).

Both the PruProtect and Pulse products are offered by a number of different brokers and financial advisers.

### Life insurance policies taken out before an HIV-positive diagnosis

Some people will have taken out a life insurance policy at a time before they tested positive for HIV. In this situation it is not necessary to inform the insurer that your health status has changed and even if you do, they cannot change the policy retrospectively, nor increase your premiums.

In the event of your death, through HIV, AIDS or any related illness, the life insurance policy would pay out as normal unless the policy specifically says that HIV diagnosis invalidates it.

Anyone who took out a life insurance policy before a positive HIV diagnosis should think very carefully – and seek professional advice – before they cash it in or surrender it. Once you have been diagnosed with HIV it becomes very difficult, and more expensive, to obtain life cover so if you have an existing policy it's generally a good idea to hang on to it.

Private medical insurance, critical illness cover, income protection and accident, sickness & unemployment (ASU) cover are other types of insurance against health-related problems. Unfortunately these are not available to people with HIV at present. If you are diagnosed after taking out one of these types of insurance, it should still provide cover in the case of illness – but again, check your policy carefully in case there is a clause withdrawing cover in the case of HIV diagnosis.

### Employee benefits

Many employers offer life insurance, a company pension, private medical insurance or other protection policies as an employee benefit.

This can create a tricky issue for someone who is HIV-positive as they may not want to tell their employer about their health status, but know that a positive diagnosis excludes them from most protection policies. In this situation it is advisable to request to see the application form. If the employer has a group policy, in some cases there won't be any questions about pre-existing conditions.

However, if there are questions about pre-existing conditions then it's advisable to go back to your employer and simply state that you have a pre-existing medical condition that you know will exclude you from the cover. You're under no obligation to say what the condition is.

### Mortgages

A mortgage is a loan to buy your home. You borrow money and pay it back with interest over a period of time (the 'mortgage term') that you agree with the lender – usually a bank or building society. The loan is secured against your home so if for any reason you can't repay it, the bank or building society can sell your home to get back its money.

You *can* get a mortgage if you have HIV (though not an endowment mortgage – see below). Fundamentally, mortgages are underwritten based on your financial situation rather than health status.

How much you can borrow depends on your personal circumstances, such as your income, your outgoings and

whether you're buying alone or with a partner. There are two main ways to repay your mortgage:

- **Repayment** – your monthly payment is split between paying off the loan and paying off the interest you owe on the loan.
- **Interest-only** – your monthly payment pays only the interest charges on your loan, and you must arrange some other way to repay the loan.

Health is not part of the underwriting process for a mortgage. Instead mortgage companies look to assess affordability and check there is adequate security (i.e. your home is worth the amount of the loan). So they will check out things like your income, employment situation and credit history.

The main problem you'll have with mortgages if you are HIV-positive is getting life insurance to cover the loan.

Life insurance is not a requirement for mortgages in general, but you may find that mortgage lenders try to sell you a life insurance policy alongside the mortgage. You could be frank or you could say you have a pre-existing medical condition their insurance would not cover: there are many medical conditions that preclude life cover. In the unlikely event they ask you what it is, you do not have to tell them.

Alternatively you could say you prefer to make your own arrangements, or that you intend to shop around.

### Endowment mortgages

Endowment mortgages were popular in the 1980s and '90s but are not offered now. With an endowment mortgage, you do not repay any of the capital you borrow during the term of the loan. Instead, your monthly payments are made up of interest on your mortgage loan and the premium for the endowment. The endowment policy should grow to produce a lump sum large enough to repay the loan in full at the end of the pre-agreed period, normally 25 years. Within the package you also pay for life insurance, which will repay the loan if you die.

In some cases an endowment will have been taken out before a positive HIV diagnosis. In this situation the same rules apply as to other life insurance policies: once the policy has been taken out and underwritten based on the information available at the time, the policy still stands unless there is an HIV-specific exception. If you have an existing policy it's generally a good idea to hang on to it, so you should think very carefully – and seek professional advice – before you cash it in or surrender it.

### Who to get advice from

Anyone looking for a mortgage should consider using a mortgage broker or independent financial adviser. This will mean you get access to a wide variety of mortgage products on the market, not just those offered by a particular bank or building society.

Mortgage brokers won't ask you questions about your health when you apply for a mortgage but they will ask you questions about your job, income and credit history. They might try to sell you life insurance, or other types of protection policy, alongside the mortgage, but the same rules apply as to lenders in general: you're under no obligation to take out insurance.

Some people may be eligible for shared-ownership or key-worker schemes, or council right-to-buy schemes. Although mortgages for these schemes may be structured in a different way to standard mortgages, they are still underwritten based on your financial situation rather than health status, so an HIV-positive status is not an issue. However some shared ownership schemes may require life insurance to be taken out to protect the loan.

### What to do if your income drops because of ill-health

If you don't have any protection for your mortgage such as income protection or accident, sickness & unemployment cover (ASU), you might struggle to repay your mortgage if your income drops due to ill-health or unemployment. There are several things you can do to prepare for or deal with this situation.

- **Self-insurance:** This is when you save for a rainy day. It takes time to build up a substantial sum so the sooner

you start the better. Cash ISAs provide tax-free interest on savings and other savings and investment vehicles can deliver decent returns.

- **Flexible mortgages:** Flexible mortgages allow overpayments and subsequent underpayments. Therefore you could overpay when things are going well and underpay or take a payment holiday if your income drops.
- **Interest-only:** If you are on a repayment mortgage you can save money each month by switching to an interest-only mortgage. It's best to only do this as a short-term measure though as otherwise you will still owe the outstanding capital when you get to the end of the mortgage term.
- **Rent-a-Room:** If you have a spare room in your property the government's Rent-a-Room scheme allows you to earn up to £4250 tax-free each year from taking in a lodger. ■

### For more information

In most cases concerning insurance products it's a good idea to get advice from an independent financial adviser (IFA) with experience in this area.

Personal recommendation is a good way to find an IFA, but you should check their authority with the Financial Services Authority (0300 500 5000 or at [www.fsa.gov.uk/register/home.do](http://www.fsa.gov.uk/register/home.do)). Otherwise, there are professional organisations whose members will meet certain criteria: The Personal Finance Society ([www.thepfs.org](http://www.thepfs.org)) or the Institute of Financial Planning ([www.financialplanning.org.uk](http://www.financialplanning.org.uk)).

### Compass Mortgage and Insurance Services

[www.compassindependent.co.uk](http://www.compassindependent.co.uk)  
0845 474 3075

### Isis Financial Planners

[www.isis-financial-planners.co.uk](http://www.isis-financial-planners.co.uk)  
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# making sense of randomised trials

Want to know more about cutting edge treatment news but feeling blinded by science? *Caroline Sabin*, Professor of Medical Statistics and Epidemiology at University College London, describes how clinical trials are constructed and analysed to ensure they provide a fair and unbiased result and offers some guidance on how to interpret the statistics.

Randomised controlled trials (RCTs) are of fundamental importance when judging the value of a new treatment or strategy.

There are two main reasons for this. Firstly, trials include a control group (or 'arm'). This group is made up of people who will take the standard treatment, or none if there is no standard care, instead of the new treatment. This means the investigators can evaluate any additional health gains associated with the new treatment, over and above any that would have been expected anyway.

Secondly, treatments in an RCT are allocated to individuals in a random manner. This means that the characteristics of the people receiving each treatment should be similar at the start of the trial, so if there are any differences in outcomes at the end of the trial, it can be assumed that these are due to the treatment itself.

Often a placebo (dummy) treatment is used to 'blind' the trial. The aim of this is so the patient (in a 'single-blinded' trial) or, as is more often the case, the patient and the clinical team (in a 'double-blinded' trial) do not know which treatment they are receiving. This is important so that patients are not treated in a different way, or report symptoms selectively, because they know which treatments they are on.

To really benefit from these features, data from RCTs has to be examined carefully to distinguish genuine findings from ones that mean nothing, and to identify possible causes of bias.

## Randomisation

**Randomisation** means that a particular treatment is allocated to a participant in a trial on the basis of chance alone. As a result, the 'baseline characteristics' of

people in each arm of the trial should be broadly similar.

Thus the first important analysis to be performed in any trial is a simple comparison of the key demographic and clinical characteristics of the individuals in each arm of the trial at baseline (before starting the new treatment or strategy).

We sometimes perform **hypothesis tests** to investigate whether any of the differences between the groups are **statistically significant** or not. These tests usually start with an assumption that any difference between the groups is due to chance alone: this is referred to as the **null hypothesis**. If the differences witnessed are then bigger than would be expected by chance, the differences are said to be **statistically significant** (see glossary).

Hypothesis testing of the people taking part in the trial (the 'trial population') is vital in *non-randomised* trials, such as an observational survey of patient outcomes in a 'real-world' setting. In an RCT, however, we know that randomisation should mean that any differences seen are due to chance only. The statistical methods used to analyse the outcomes of RCTs make an allowance for these chance differences, and so in general we don't need to worry about them. However, if there are any substantial differences in the baseline characteristics of those receiving the different treatments, we may have to allow for this in any analysis.

## Endpoints

Trial **endpoints** are outcomes that capture the effects of the new treatment. It is generally recommended that investigators should identify a single **primary endpoint** which best reflects how well the treatment works. Any major

decisions about how good it is will be based on this endpoint.

Deciding what the primary endpoint will be will also be used to decide how many participants will be needed to be randomised to each arm: for instance you'll need fewer participants if your endpoint is the number who achieve an undetectable viral load (a common event) than the number who die (hopefully a rare one).

The trial will also have several **secondary endpoints**, chosen to capture other important aspects of treatment effect and safety, which will be used to provide supportive evidence when decisions are made about the future use of the new treatment.

In the HIV setting, the choice of a trial endpoint is not always straightforward. Endpoints may be **binary** (i.e. ones with a yes/no response, such as whether the viral load is above or below 50 copies/ml at week 48), **continuous**, such as the CD4 count, or **time-to-event** (endpoints that measure the time taken for an event – such as viral load suppression – to occur).

However, as well as potent antiviral and immunological activity, HIV drugs should ideally also have minimal potential for the development of resistance, be associated with as few toxicities as possible and should have minimal impact on quality of life. Choosing a single endpoint to capture these aspects is often problematic.

For this reason, there has been a move towards the use of **composite endpoints** in trials. These consider a range of outcomes, with an individual meeting the criteria for the composite endpoint as soon as s/he meets the criteria for any one component of the endpoint.

## Analysing the endpoints; how to read trial results

Assuming that there are no large imbalances in baseline characteristics, endpoints can be compared across the treatment arms using simple tests such as the **Chi-squared test** or a **t-test** (see glossary). The outcome of these methods is a value known as the **p-value**, which allows investigators to judge whether their findings are likely to be real or due to chance.

However, in an RCT, this information on its own is not sufficient – we also need to estimate the size of the **treatment effect** (how much *additional* benefit has been gained through the use of the new treatment?) and calculate its **confidence interval** (how *precise* is our estimate of the effect?).

As an example, look at the box here. We have a trial with two treatment arms – regimen A (the investigational regimen) and regimen B (standard care). Our **primary endpoint** is the proportion of patients with a viral load below 50 copies/ml at 48 weeks. The box shows the outcome in each arm of the trial: 85% with a viral load under 50 copies/ml in arm A and 77.4% in arm B.

The **p-value** in this table (which equals 0.007) is less than 0.05 (the usual threshold that we use to indicate statistical significance). This means that there's only a 0.7% probability that this sort of difference could have arisen by chance and is not a real effect.

The **treatment effect** is 7.6% (85.0% minus 77.4%). This means that for every 100 patients treated with regimen A, we would expect that an additional 7.6 patients would attain virological suppression, compared to the number we would have expected had they all been treated with regimen B.

The **confidence interval** for this effect tells us that this true benefit could be as small as 2.3% or as large as 12.8%.

We can now use this information to consider the benefits of the new regimen in light of any disadvantages (e.g. an increased cost or worse toxicity profile).

Our **secondary endpoint** is the CD4 count and here we would also want to see what, if any, additional improvement is provided by the new regimen over and above standard care.

In the example, it can be seen that regimen A is associated with only an additional 6 cells/mm<sup>3</sup> gain in CD4 count over the 48-week period compared to regimen B. This is of borderline significance: the *p*-value is 0.05, indicating that had we conducted 100 such trials, and there really had been no difference between the drugs, then we would have seen a difference of this size or greater in five of them. You'll notice also that the confidence interval *crosses* (i.e. *includes*) zero – the true additional 'benefit' provided by the new drug could be as great as plus 12.1 cells/mm<sup>3</sup> or as small as minus 0.06 cells/mm<sup>3</sup> (i.e. a very small detrimental effect on the CD4 count).

### Outcomes from an RCT in which individuals are randomised to one of two treatment arms

	Treatment arm		<b>p-value</b>	<b>Treatment effect</b> (A – B); (95% <b>Confidence interval</b> )
	Regimen A Investigational drug	Regimen B Standard care		
Number (N) of individuals randomised	413	421		
<b>Primary endpoint</b> N (%) with viral load <u>below</u> 50 copies/ml at 48 weeks	351 (85.0%)	326 (77.4%)	0.007	<b>Treatment effect</b> 7.6% <b>Confidence interval</b> 2.3% to 12.8%
<b>Secondary endpoint</b> Mean change in CD4 cell count (cells/mm <sup>3</sup> ) from baseline to week 48	63	57	0.05	<b>Treatment effect</b> +6 <b>Confidence interval</b> -0.06 to +12.1



For example, the time-to-loss-of virological-response (TLOVR) algorithm generates a composite endpoint, which incorporates components relating to confirmed virological failure, early drop-out from the trial, switching to a new treatment and the development or worsening of illness.

Analysing a composite endpoint takes a lot of care. Take a situation, for instance, where overall there is no difference in TLOVR between arms but, while the new treatment is more effective than the old one, it also causes more drop-outs due to mild but bothersome side-effects. How much weight do you give to each component?

### Confounders

A major benefit of randomisation is that it minimises the possibility that **confounding** may be present.

Confounding is encountered frequently in observational studies and occurs because the characteristics of individuals receiving one regimen are different to those of individuals receiving another.

This means that if outcomes differ between the groups, it is difficult to know whether this is a result of the different treatments, or the different characteristics. Similarly, if outcomes turn out to be the same, we may fail to detect a true difference.

The lack of confounding in most RCTs means that it is acceptable to present simple comparisons of the outcomes in the different treatment arms. If, however, the characteristics of people recruited to the different treatment arms in a trial are substantially different, and any of these characteristics could also impact on outcomes, then investigators may need to perform an **adjusted** analysis. In adjusted analyses, we try to control for (weed out) the other factors. We usually use **regression**, a mathematical technique that allows us to gauge the degree of influence one or more factors have on an outcome.

### False positives and negatives

When we perform any statistical comparison on a dataset, there is always the possibility that we may get the wrong answer. This doesn't mean that our sums are wrong: it means that the

result of the hypothesis test fails to reflect the true situation.

Statistical errors are of two types. Firstly, we may find a significant difference in outcome that is simply a chance finding (a **false-positive** signal): this is called a **type 1 error**. The threshold usually set for statistical significance means that false-positive signals *will* occur, on average, in one of every 20 tests performed. What seems significant may not always be so.

Secondly, we may fail to detect an important effect of the new treatment: this is a **false-negative** result and is called a **type 2 error**. The most common reason for this is that the trial did not recruit sufficient numbers of individuals. This will mean that the confidence intervals are too large for findings, even if they are real, to be statistically significant. It's like trying to see details in an out-of-focus photograph.

### Dealing with missing people and data

Ideally all people recruited into an RCT will be able to continue their participation until the end of the trial, but there will nearly always be some individuals who drop out of the trial prior to the planned completion date. Such patients are said to have been '**lost to follow-up**' (LTFU). Others may have to switch treatments halfway through the trial and others may discontinue treatment totally. The way these so-called **protocol deviations** are dealt with in the analysis is highly influential.

One school of thought takes the pragmatic view that in practice there will always be people who do not return for care or who have to switch their prescribed treatments. An **intent-to-treat** (ITT) analysis includes people who drop-out or switch, as they are retained in the treatment arms to which they were randomised, regardless of their actual treatment usage.

This approach is preferred for several statistical reasons, in particular because it provides a better estimate of the treatment's effect in a real-life setting in which some people are bound not to take the treatment as allocated.

Opponents of this approach argue that by incorporating treatment switches in this way, the measured effect of the treatment is less than its true effect because of the inclusion of people who did not take it properly. They argue that the best estimate of the treatment's true potential value can only be estimated in those people who actually took the treatment as prescribed. Such an **on-treatment** (OT) analysis only includes individuals who continue to take the treatment that is randomly allocated to them, exactly as prescribed.

An OT analysis may certainly appear to provide a better idea of how well the treatment works under ideal conditions. But people who switch treatments are often the very ones for whom the treatment is not so suitable, because of tolerability/toxicity problems, because they find it difficult to adhere to, or simply because they don't feel it's working. So OT analyses generally give overly optimistic estimates of the true treatment effect.

For this reason, this approach is not recommended for **superiority** trials – those designed to show that one drug/regimen is better than another. **Non-inferiority** trials, which are designed to show that a new treatment is the same as, or not substantially worse than, standard care require a different analytical approach; for these trials, OT analyses may also be recommended. Clinicians do want to know how well the treatment is likely to perform in the real world, but may also want to know how well they could get it to perform if factors preventing it being taken properly could be modified.

### Summary

RCTs provide the most robust form of evidence when judging whether a new treatment is likely to be more effective than existing treatments. As such, they are often heavily cited and – rightly – form the basis of many treatment guidelines. However, it is important that those reviewing trial results should be aware of the specific issues that may arise with RCTs, and take these into account. Forewarned is forearmed: next time you read a report on a treatment trial, look carefully at the results. ■

## Glossary

### Adjusted analysis

An analysis of the trial data that controls for factors other than the treatment that could have influenced the outcome.

### Bias

When the estimate from a study differs systematically from the true state of affairs.

### Binary endpoint

An endpoint in a trial where there is only one of two options (e.g. yes/no, viral load under or over 50 copies/ml).

### Chi-squared test

A statistical test used when comparing two proportions (e.g. percentages with viral load below 50 copies/ml).

### Composite endpoint

An endpoint in a trial that includes several component parts; an individual is deemed to have met the criteria for the composite endpoint as soon as they meet the criteria for at least one of the components.

### Confidence interval

A range of values that gives us an indication of how precise our estimate is: it gives us a range of plausible values for the true treatment effect based on the results of the trial. If the confidence interval is wide, our estimate is imprecise.

### Confounding

Often occurs in observational studies, when the characteristics of individuals treated with one regimen differ from those treated with another regimen; can lead to biased estimates of the treatment effect.

### Continuous endpoint

An endpoint in a trial that captures a measurement which can have any value in a range, e.g. CD4 count.

### Hypothesis test

Any statistical test that aims to assess whether the differences observed are likely to have occurred by chance.

### Mean

A measure of the 'average' value, used for continuous measurements that follow a symmetric (normal) distribution. The sum of all the values observed divided by the number of values measured.

### Median

A measure of the 'average' value, used for continuous measurements that do not follow a symmetric (normal) distribution, which is often the case for biological measures. The central value in a data set, with an equal number of values on either side. The median is also less influenced by 'outliers' the few people with very high or very low values.

### Null hypothesis

Our starting point for any hypothesis test, which assumes no effect.

### Primary endpoint

A single endpoint in an RCT which most accurately reflects the beneficial effects of treatment.

### *p*-value

The result of any statistical test which allows us to judge whether the results are likely to be due to chance or not. It is a probability and so must fall between 0 and 1; the closer the *p*-value is to 0, the stronger the evidence provided by the trial. A *p*-value of 0.05 or below is the usual one chosen as the threshold for statistical significance – see below.

### Randomisation

A process by which treatments are allocated to patients in a trial on the basis of chance alone.

### Range

The spread of values, from the smallest to the largest. The **inter-quartile range** (IQR) only includes the middle 50% of values and measures the degree of spread of the most common values.

### Regression

A mathematical model that allows us to measure the degree to which one or more factors influence an outcome.

### Secondary endpoint

Endpoints in a trial that provide supportive evidence to the primary endpoint.

### Standard deviation

Provides a measure of the spread of values.

### Statistical significance

The point at which we conclude that any differences seen are unlikely to have occurred by chance. The cut-off used most often is 0.05 – this means that the probability that the difference seen is a chance finding is less than one in 20.

### Time-to-event endpoint

An endpoint in a trial that measures the time taken for the individual to reach some event (e.g. clinical progression, virological suppression).

### Treatment effect

A measure of the additional benefit provided by the new treatment, over and above that which would have been expected by chance or using standard care.

### *t*-test

A statistical test used to compare two means (e.g. the mean CD4 counts of those in the treatment and control arms).

# news in brief



## Health

### HIV hospitalisation hasn't declined

A study<sup>1</sup> of people with HIV in the US Department of Veterans Affairs, the nation's largest HIV healthcare provider, has found in the era of effective HIV therapy a third of patients are still being hospitalised, and that this rate has not changed over time.

Investigators monitored trends in hospitalisations for 2429 patients between 1999 and 2007. A total of 822 patients were hospitalised at least once. There was no change in the overall rate of hospitalisations – 13.7% – during the study. The mean duration of hospitalisation (six days) was also unchanged.

The patients had a mean age of 37 and had been living with HIV for seven years. Those admitted to hospital had a mean age of 41 years, increasing from 39 to 43 years.

Mean CD4 cell count through the study period was 554 cells/mm<sup>3</sup>; CD4 cell count at the time of hospitalisation rose from 409 to 466 cells/mm<sup>3</sup>. Sixty-two per cent (70% of those admitted to hospital) were taking HIV drugs and 52% had a viral load below 400 copies/ml.

Gastrointestinal illnesses (including liver disease) were the most common cause of hospitalisation (2.4% per year), followed by surgery, bacterial infections, respiratory disease and cardiovascular disease. One per cent of patients had admissions for AIDS-defining conditions, which formed 8% of all admissions, and this did not change over time.

Hospitalisation for liver disease increased by 71%; the proportion of patients hospitalised who had hepatitis C increased from 8% to 14%, and having hepatitis C increased the risk by 46%.

Hospitalisation for cancers increased by 50% and for cardiovascular disease by 24% but admissions for neurological disease fell by 25%.

Patients with a current CD4 cell count above 350 cells/mm<sup>3</sup> had a significantly reduced risk of admission to hospital.

“Hospitalisations continue to occur at high rates among HIV-infected persons,” comment the investigators, adding that “HAART used by treatment guidelines seems to be protective of hospitalisations due to non-AIDS-related causes.”

## Viral load

### Viral loads linked in transmission pairs

A study<sup>1</sup> amongst gay men in San Francisco recently infected with HIV has found that their viral load is closely correlated with viral load in the person who transmitted HIV to them.

The study found evidence that 40% of infections in the transmitting partners were also recent.

Gay men with an average estimated time since infection of 2.4 months, six at most were asked about sexual contacts, with contact tracing undertaken. Consensual genetic matching of viruses identified 24 cases where a source partner could be paired with an infected partner.

The infected partners had an average viral load of 86,000 copies/ml and the source partners 24,000 copies/ml.

The researchers discovered a strong link between the viral loads of the two partners. For every tenfold increase in the receiving partner's viral load, the viral load in the source partner was 2.7 times higher. In the nine infected partners who did not start antiretroviral drugs

(ARVs) during the study, this correlation persisted over a two-year period.

Nine (40%) of the source partners showed signs of recent infection themselves.

Three of the infecting partners had viral loads under 1000 copies/ml and one only 100 copies/ml, though their viral load at the time of transmission could have been higher.

Not all pairs were correlated but the correlation was especially strong where the source partner's viral load was high: in five of seven cases where the source partner's had a viral load of 100,000 copies/ml or more, so did the infected partner.

Two source partners were currently on ARVs and two had been; the minimum viral load in these patients was 6880. Two cases of transmission of multidrug-resistant HIV were found.

The researchers write: “Closely related viruses result in similar levels of viremia in two different hosts.” They urge more research to find whether this is caused by genetic factors which influence viral fitness. It could, however, simply be related to the quantity of virus transmitted, in which case it may strengthen the idea that treating people with ARVs to reduce their viral loads may be a key component in HIV prevention.

## Tuberculosis

### Many UK prisoners have resistant TB

Tuberculosis (TB) in British prisons is four times as common as in the general population, and drug-resistant TB four times as likely to be diagnosed, a study published in the *Journal of Epidemiology and Community Health* has found.<sup>1</sup>

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The study also found that while fewer prisoners died of TB, they died younger (48 vs 70 years), were less likely to complete their treatment, and were more likely to be infectious.

The UK is a low-prevalence country for TB with 14 new cases of TB per 100,000 people a year. During this study, 205 new cases were diagnosed in the UK prison population: 60 per 100,000 a year.

Prisoners were twice as likely to have been born in the UK as other TB patients, with prisoners of black Caribbean ethnicity nine times more likely to develop TB than Caribbeans in the general population.

Prisoners were 20% more likely to be infectious than other TB patients and four times more likely to have TB resistant to the key drug isoniazid. Drug-resistant-TB cases were ten times more common in UK-born prisoners than in the UK-born general public.

The authors recommended TB screening at prison entry, directly observed therapy (DOT) for all diagnosed, and continuity of care for released prisoners.

### Weight

## Weight gain good, too much bad

Another study by the same researchers as the hospitalisation study above<sup>1</sup> has found that obese patients have lower CD4 count rises after starting HIV therapy than patients of normal weight, or who are overweight but not obese. (The clinical definition of obesity is a body mass index [BMI] of over 30 kilograms per square metre.)

Weight gain in people after starting HIV therapy is generally seen as a good thing, and a recent study from Africa, where HIV patients are more likely to be malnourished, confirmed that failure to

gain weight six months after the start of antiretroviral therapy (ART) increased the chance of death tenfold, when compared with those who had gained over ten kilograms.<sup>2</sup>

Little research, however, has been done into the effect of being overweight.

The US study looked at a thousand patients, 40% of them diagnosed in the pre-ART era. At this time being obese was actually protective: patients obese at diagnosis lost only 50 CD4 cells/mm<sup>3</sup> a year compared with 125 cells (normal BMI) and 158 (underweight), probably because weight loss is a sign of illness.

In the post-ART era, however, obese patients only gained an average of 50 cells/mm<sup>3</sup> a year compared with 116 in merely overweight patients. Underweight patients continued to make no CD4 cell gains at all, however.

Mechanisms for this lower CD4 gain are unknown; researchers speculate obesity could adversely affect immune function or that drug levels may be lower in the obese.

### Infectiousness

## Infectiousness beliefs and STI risks linked

A study<sup>1</sup> from the US has found that people with recent sexually transmitted infections (STIs) are more likely to believe that having an undetectable HIV viral load means you are uninfected – but less likely to actually know their viral load.

Researchers at the University of Connecticut recruited 490 people living with HIV in Atlanta, Georgia, between 2005 and 2009. Participants were asked whether they had been diagnosed with an STI in the previous three months. They

also indicated their strength of agreement with the following statements:

- People with HIV who take HIV medications are less likely to infect their sex partners during unsafe sex.
- HIV treatments make it easier to relax about unsafe sex.
- It is safe to have sex without a condom if my viral load is undetectable.
- People with an undetectable viral load do not need to worry so much about infecting others with HIV.

Ten per cent of participants reported having been diagnosed with an STI at the initial assessment; a further 4% were diagnosed soon afterwards.

Under a quarter of people with STIs had an undetectable viral load, compared to half of those without. People with STIs were 25% less likely to know their most recent viral load measurement – but one-third more likely to believe that people with an undetectable viral load are not infectious.

However, people with STIs who *did* know they had a detectable HIV viral load were the most likely to use condoms. So the study shows that people with HIV are taking viral load into account when making safer-sex decisions, but not always accurately.

The 'Swiss Statement' (that some people with undetectable viral loads are uninfected) excluded people with STIs because these conditions may increase viral loads in genital and rectal fluids.

People with STIs were younger and had fewer years of education than others in the study. Researchers comment that expanded use of HIV treatment for prevention purposes will need to educate people about infectiousness and aggressively control STIs.

# How long have I got, doc?

Can people with HIV really live as long as anyone else? *Gus Cairns* investigates.

Last month we featured a news report about a couple of studies,<sup>1,2</sup> presented at a recent conference, which found that certain groups of HIV-positive people could expect to live as long as comparable HIV-negative people.

A study from the Netherlands looked at people who were diagnosed between 1998 and 2007 and then excluded those who had had to go on treatment within six months of diagnosis. Once this group, who'd mostly have been diagnosed with a low CD4 count, was excluded, then the average remaining life expectancy of someone who was diagnosed at the age of 25 was calculated to be 52.7 years – in other words they would die, on average, at the age of nearly 78: just five months short of a 25-year-old member of the general Dutch population.

This group had a high average CD4 count of 480 cells/mm<sup>3</sup>, and the study extrapolated life expectancy from an average of just 3.3 years of mortality data, and a maximum of ten; we need to be careful about interpretation because, as we see below, things may take a turn for the worse later.

The other study was an analysis of the COHERE cohort, a group of over 80,000 HIV-positive people from more than 30 European countries. It included all people in COHERE who had started treatment later than 1998, thereby excluding people who had taken pre-HAART drug regimens, who are the ones most likely to have significant drug resistance. It didn't estimate a life expectancy: instead it calculated something called the standardised mortality ratio (SMR). This is the amount the death rate in a group differs from the death rate in the general population.

The headline finding was a correction to any assumption that most people with HIV are now living normal lifespans. Over the whole group, which included people of every CD4 count, the death rate was 4.4 times what you'd expect to see in 80,000 people of the same age and sex picked at random from the general population.

However, the SMR in men whose current CD4 count was over 500, and who had maintained it for over three years (or just one year if you excluded injecting drug users) was 1.1: statistically, the same as people without HIV.

There were fewer actual deaths in women than men, but mortality in HIV-positive women was twice as high as in women in the general population because the death rate among HIV-negative women of similar age is considerably lower than in men.

There's no doubt that life expectancy for people with HIV, at least in the developed world, has improved vastly since treatment became available. But is it continuing to improve? Will more of us achieve a normal lifespan as time goes on? And what do we need to do to ensure this happens?

Several other studies have addressed these questions in the last decade.

One of the problems besetting life-expectancy studies is that very different groups of patients are selected for study. For instance, a study from the USA<sup>3</sup> found that, from the point of diagnosis, people with HIV on average lived 21 years fewer than HIV-negative people of the same sex and age. But one-third of this group had a CD4 count under 200 cells/mm<sup>3</sup>, and many were not accessing health care.

Another problem is that very different measures of mortality are used so it's not easy to make comparisons. These include **absolute mortality**, the **excess mortality** compared with the general population (as in COHERE): the expected average number of **years of life lost**, given this excess mortality (for instance, smokers will lose an estimated ten years of life to their habit, compared to non-smokers), and **life expectancy**.

Jonathan Sterne of the Antiretroviral Therapy Cohort Collaboration, author of one of the studies we quote in this piece, says: "Life expectancy is a strange concept in that it extrapolates into the future a present state of affairs. It says: 'Given the current mortality rates, if nothing changes, how long can people expect to live'?"

"It's rarely going to reflect what people's average lifespan actually ends up being, because it can't take account of future developments.

"For instance, the life expectancy of people with HIV may improve, because treatments get better. But on the other hand, it may also unexpectedly decrease if we see in future a sudden increase in the death rate at a certain age, or after a certain time spent taking HIV drugs."

One study<sup>4</sup> of another cohort, called CASCADE, took account of this by observing the excess mortality, compared with the general population, over specific two-year slots post-diagnosis.

This study found that there were 1239 deaths in 7034 patients diagnosed between 1996 and 2006, where in the general population you'd only expect 178.7 deaths. That means over the whole study period deaths in people with



HIV were sevenfold higher than they were in HIV-negative people.

However, this excess mortality went down in every period of the study. In 1996-97 people with HIV had 17 times the death rate of the general population. By 2004-2006 it was 3.4 times the rate.

Furthermore, because in this study the date people were infected was approximately known, changes in the number of excess deaths over time could be looked at.

By the year 2001, people who had been under 35 at diagnosis were no more likely to die than the general population in the first five years after being diagnosed, and by the year 2006 this had extended to people diagnosed under 45. By this time the *ten*-year death rate was also starting to approach normal among the under-45s.

However, the death rate amongst people diagnosed for 15 years was still very much higher than in the general public amongst all groups: seven times higher in people diagnosed up to the age of 25 (meaning they'd be up to 40 years old now): 5.5 times higher in people diagnosed before 35 (so now in their 50s): and 2.4 times higher in people diagnosed up to the age of 45 and now in their 60s.

Here's the possible reason why the death rates seen in this study, and the life expectancy one might derive from them, are higher in this study than in the Dutch one that predicted normal life expectancies. If you only look at death

rates in people with HIV for the first decade after they test positive, you may miss most of the excess deaths, whereas CASCADE followed some people up to 24 years after infection.

In the CASCADE study the death rate in people with HIV, as measured in 2006, was very little higher than in the general population until about eight to nine years after infection. After this it began to outpace the expected death rate.

Was this because eight to nine years after seroconversion is when HIV starts to make people ill? Or were people with HIV diagnosed before 1998 more likely to have taken suboptimal drug regimens which led to the development of drug resistance?

Kholoud Porter of the UK Medical Research Council says that using 'time since infection' rather than age to distinguish different mortality rates was vital because "a 45-year-old may have only just been infected, or they may have had 25 years of living with HIV and HIV medications. If you don't take time since infection into account you may over- or underestimate mortality."

Just two weeks after the CASCADE study came out, an even larger study called the Antiretroviral Therapy Cohort Collaboration study<sup>5</sup> was published, which did extrapolate life expectancy in 43,355 patients from North America and Europe.

It found that deaths had declined, from one death per 60 patients a year in 1996-99 to one per 100 in 2003-05. And it

found that life expectancy had increased, from 36.1 years for a 20-year-old in 1996-98 (so they could, on average, expect to live till they were 56) to 43.1 in 2003-5 (living till 63). Thirty-five-year-olds could expect to live till 60 in 1996-99 and 72.3 in 2003-5. But SMRs were still in the region of six to eight times that of the general population, depending on year of diagnosis.

## Conclusions

The lessons to take from all this? Australian HIV Expert Professor David Cooper commented on this study in an editorial.<sup>6</sup>

"These figures will help clinicians raise the hopes and expectations of patients during discussions of life choices and goals," he said. "But life expectancy is still not normal: about ten years is shaved off a normal lifespan."

Life expectancy is continuing to improve in people with HIV, and in certain groups of people who test and access care and treatment promptly it may be approaching that of the general population.

But there is still a long way to go. Those diagnosed late still face a 20-year life deficit.

Life expectancy also doesn't tell us about quality of life as we age. The next generation of research needs to concentrate on health as well as death statistics: not just whether we will have an old age, but whether we will have a healthy one. ■

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#### Weight gain good, too much bad

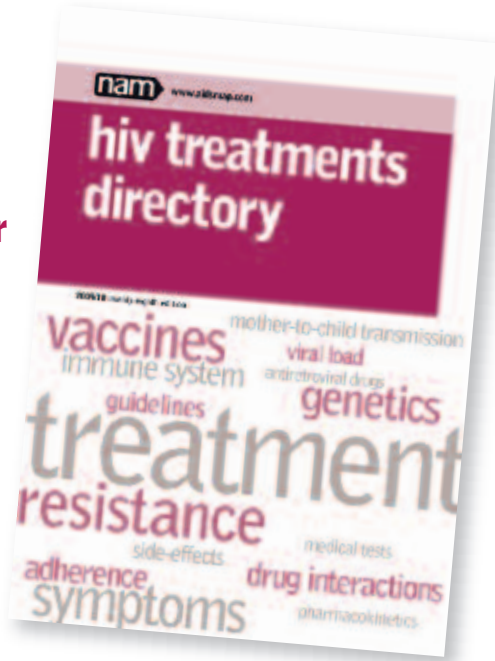
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