

aids treatment update

tuberculosis

In the UK, August is traditionally the month when the media regale us with fascinating tales of philandering politicians and low-grade celebrities. Largely spurious public health scares have also been popular. In particular, reports on the spread of tuberculosis in this country have appeared regularly. If you've been concerned as to how this information may relate to you, or to others living with HIV, Julian Meldrum's review article overleaf should prove timely.

A piece of news on tuberculosis which you may have missed in the popular press recently relates to the new research possibilities opening up as part of the revolution in genetics that led to the human genome project. The gene sequence of TB's causative agent, *Mycobacterium tuberculosis*, was recently worked out by researchers at the Wellcome Trust's Sanger Centre in Cambridge and the Institut Pasteur in Paris. This revealed previously unsuspected similarities to fungi, another type of pathogen. In theory, this discovery means that anti-fungal drugs such as fluconazole – used in the treatment of several AIDS-related conditions – might also act against tuberculosis. If this works in practice, at dosages that people can tolerate, these will be the first 'new' treatments for tuberculosis in many years, and could come into use quite rapidly. The gene sequence has also identified entirely new targets, opening the way to high-speed laboratory screening tests for new anti-tuberculosis drugs.

tuberculosis and HIV 2

data analysis 6

news in brief 11

tuberculosis and HIV

2 as the UK press scaremongers readers over the spread of tuberculosis, we review the issues of relevance to HIV-positive people by julian meldrum

Tuberculosis (TB) has been in the news recently, with reports of cases among London clubbers. Is this any reason to be concerned? What is the current position on TB, its prevention and treatment, for people with HIV in Britain? How does this compare with what may have been experienced by readers who have lived in Africa or Asia?

While media reports linking TB and night clubs might suggest that transmission takes place in public places, this is very unlikely. The highest risk of infection with the mycobacteria that cause TB continues to be from lengthy exposure to someone with active TB in their lungs or larynx (the entrance to the lungs). Specifically, this means breathing in airborne droplets generated from coughs and sneezes, while sharing living space with the person who is coughing. Infection can also take place through the mouth or gut, but this is much less common. Even more rarely, infection can take place through the skin.

TB transmission is most easily detected in a family household, such as from parents or grandparents to young children. Contacts can be traced, tested to see if they have caught the infection and, if their risk of developing disease is considered high, they can be given preventive drug treatment. This is important. It saves people's lives and stops transmission to others.

Similarly, risks to health workers and hospital patients from people with infectious TB can be identified and responded to. (Basic hospital precautions include the use of single negative pressure rooms for separation of patients who are coughing from patients and staff who are

vulnerable to infection. Negative pressure rooms contain a ventilation system which removes stale air from the room.)

Most adult TB cases are not due to new infection, but to reactivation of long-established "latent" infection, usually from exposure in childhood. This progression occurs as people get older, or can be set off by illnesses that damage immunity, such as HIV. Tuberculosis in Britain is a disease that has never gone away, with 6,000 new cases reported last year, although this is very low by comparison with most of the world. Many of these cases are now in people who grew up in countries where TB is more common than in the UK, or in people with continuing family connections overseas.

Rising levels of nutrition and housing standards have brought about most of the reductions in TB seen in the UK in the last two hundred years, with medical treatment having made most impact in the last fifty years. TB is a treatable disease and remains so even where there is resistance to some of the drugs that are used, and also in people with HIV and AIDS. However, TB treatment is not easy for the people who take it and depends on maintaining well-organised health services. If people are not given adequate support, or are treated with one drug at a time instead of in combinations, then their TB can become resistant to the drugs they are treated with.

Diagnosing latent TB

According to US TB guidelines, people with HIV should be tested for TB when HIV is first diagnosed, though this practice appears less

well supported by doctors in the UK. The test most often used is a “tuberculin” or “PPD” (for “purified protein derivative”) skin test. This works on the principle of injecting a small amount of purified TB protein into the skin. After three days, the injection site may show a reaction – a reddening and hardening – which means that there is an immune response to the protein. The larger the size of this reaction, the more likely it is that someone has been infected by TB in the past and has active TB disease or latent infection.

A negative reaction does not prove the absence of TB. HIV disease is one of a number of things that can reduce the immune response so a skin test is negative, despite TB being present in the body. (This is called “anergy”.) Successful treatment of HIV may bring this immune response back, leading to a positive skin test without any new infection or exposure. In addition, the use of BCG vaccination (see below) in countries such as the UK makes interpretation of skin tests difficult – one reason why some UK doctors do not favour routine use of these tests in HIV-positive people.

In people who are HIV-negative, the lifetime risk of latent TB becoming active TB is about one in ten. In people who are HIV-positive (and have no access to modern antiretroviral therapy), this risk rises to between five and ten per cent *every year*; a lifetime risk of 50%. For this reason, once it is clearly established that there is no active disease, many doctors recommend a course of anti-TB drugs to try and get rid of the latent infection. There is some evidence that six months of isoniazid, or two months of a combination of pyrazinamide and rifampicin or rifabutin can greatly reduce the risk of active TB later on.

This approach remains controversial, because:

- If the TB is in fact active, but has not been properly diagnosed, then giving such treatment is likely to select for drug-resistant TB and make it harder to treat the disease properly. The same may happen if the treatment is taken inconsistently.
- There can be interactions with anti-HIV treatment drugs. Rifampicin, and to a lesser

extent rifabutin, interact with protease inhibitors, NNRTIs, and a range of other drugs including opiates. Rifampicin should not be combined with the antiretrovirals named; rifabutin requires dose adjustments.

- The side-effects of the drugs can be serious and require careful monitoring. Isoniazid can cause peripheral neuropathy, which may also be caused by HIV and by antiretroviral drugs such as d4T, ddI, and ddC. Pyridoxine can and should be used to protect against peripheral neuropathy due to isoniazid.
- The evidence for the usefulness of the drugs is weaker in people who are anergic to TB, i.e. who don’t know if they are infected.
- Where resources are very limited, they may be better spent on diagnosing and treating people with active disease.

Treating active TB

There’s an important difference to be understood, between “active TB” and “infectious TB”. Active TB is when the mycobacteria which cause the disease are multiplying, not properly controlled by the immune system, and causing disease. This may happen in the lungs or larynx, in which case it is also likely to be infectious. The disease is considered most infectious when mycobacteria can be seen under the microscope in the “sputum” (phlegm) that people cough up. Sometimes, especially in the later stages of the disease, the sputum may have blood in it. However, mycobacteria rarely reach high levels in blood. TB can spread through the body in the blood, but is really not a blood-borne disease.

When active TB disease develops in other parts of the body, it often affects lymph nodes, which may be around the lungs or in the gut. TB may appear almost anywhere, including in the bones – most seriously, in the spine; around the heart; or even as a form of meningitis. In each of these cases the disease can be life-threatening and needs urgent treatment, but is not at all likely to infect anyone else.

People with HIV are *less* likely to develop typical active TB in the lungs and larynx and

glossary

see also page 7.
bacteria Single-celled micro-organisms.
immune system The body’s mechanisms for fighting infections and eradicating dysfunctional cells.
lymph nodes Special areas in the body where white blood cells and other important immune cells are found. Also known as glands.
NNRTI Non nucleoside reverse transcriptase inhibitors, a class of anti-HIV drugs including efavirenz and nevirapine.
peripheral neuropathy Damage to the nerves of the hands and/or feet, causing symptoms ranging from numbness to severe pain.
protease inhibitor Family of anti-HIV drugs, includes indinavir, ritonavir, nelfinavir, saquinavir.
resistance A drug resistant TB strain is one which is less susceptible to the effects of one or more anti-TB drugs because of its genotype.

tuberculosis and HIV continued

more likely to develop other forms of active TB, especially in more advanced stages of HIV/AIDS.

Treating active TB depends first on a doctor identifying it. Usually, symptoms come on slowly and may be difficult to tell apart from other HIV-related problems. X-rays can give clues, but are not diagnostic alone. Usually, a diagnosis is made both because symptoms which would usually respond to other treatment persist even when that treatment has been given, and because laboratory tests on sputum or other samples suggest that TB mycobacteria seem to be present.

Standard “first-line” treatment for TB varies a little from country to country. Typically, four drugs are used, such as daily isoniazid, rifampicin, pyrazinamide and ethambutol (the preferred option in the British Thoracic Society guidelines), for the first two months. The US Centers for Disease Control recommend that when this is given to people with HIV, every dose should be supervised. Since streptomycin, another anti-TB drug, has to be injected, any combination including this drug would normally be given by a health worker. This is known as DOTS for “Directly Observed Therapy, Short-course”. After that two month period, there is a longer continuation phase, which varies between countries. In resource-poor countries the continuation phase is six months of treatment with two drugs, such as daily isoniazid and ethambutol. In countries such as the UK and US, the second phase involves four months’ treatment with two drugs.

Remembering that TB is only infectious when it is active in the lungs or larynx, this infectiousness usually goes away in the first two weeks of effective treatment, though this may take longer in people who have HIV. The patient also feels a great deal better as the disease comes under control. However, it is

vital to go on and complete the full course of treatment. Failure to do this is likely to cause relapse and, worse, drug resistance.

Whether treatment needs to be in hospital or as an out-patient will depend on the circumstances in which a person is living as well as the state of their health.

One of the biggest dilemmas in treating TB when someone has HIV is whether to treat the TB first and then consider antiretroviral treatment, or to go ahead with both. Given the interactions already mentioned between protease inhibitors, NNRTIs and the TB drug rifampicin, the general view, reflected in treatment guidelines, has been to delay treatment with antiretrovirals if possible, or even to stop antiretrovirals if a person is already taking them, at least for the first stage of TB treatment.

However, the most recent revision of the US Centers for Disease Control guidelines on treating TB and HIV moves away from this. It recommends that with the use of rifabutin instead of rifampicin, and with adjustment of dosages in some cases, both antiretroviral and anti-TB treatment can and should be given together, if both are needed according to current guidelines for HIV treatment.

In Africa, parts of Asia and Latin America, a drug called thiacetazone, or thioacetazone, has been an important first-line drug against TB, mainly because it was very cheap. This drug has not been used in Europe and North America, mainly because white Europeans (and also Chinese people) appear to be more vulnerable to its side-effects – including severe skin-reactions, which can be life-threatening – than Africans. With HIV, these side-effects become more common and severe for everyone, so this drug should not be used.

The drug streptomycin is given by injection, so this has gone out of favour in some countries where HIV is now common but where disposable syringes are too expensive for routine use.

Multi-drug resistant TB

If TB is resistant to the most powerful first-line drugs, especially isoniazid and rifampicin, then treatment becomes more complicated and lengthy. Such TB is called "multi-drug resistant" or MDR-TB.

If MDR-TB is suspected or diagnosed, initial treatment will normally be in hospital. People diagnosed with TB will normally be nursed in single rooms for as long as they are likely to be infectious. These may have special ventilation and visiting will be restricted.

MDR-TB is no more transmissible than "wild-type" TB but if someone does acquire it, especially someone with HIV, the consequences are more serious because the drugs available to treat it are less effective and may take longer to act than the standard treatments. The main reason for this is that "second-line" drugs are mostly "bacteriostatic" rather than "bactericidal", i.e. they stop the mycobacteria multiplying rather than killing them. This means that treatment has to be continued until the mycobacteria die off. Infection control precautions need to be even more rigorous than for other TB cases, for as long as a person remains infectious.

Following outbreaks of MDR-TB affecting people with HIV treated at a number of hospitals internationally, including two in London, the Department of Health reviewed UK policy on treating MDR-TB and treating TB in the context of HIV infection. The report issued by the Department in 1998 stands as a valuable reference along with other guidance from the US Centers for Disease Control and the World Health Organisation.

Vaccines

The BCG vaccine given to babies and as a booster to adolescents in this country does not prevent infection with TB. What it does, most effectively, is reduce the risk of active disease developing, particularly the severe forms such

as meningitis (where the brain is affected) in children. Some countries, such as the USA, do not use BCG because it can interfere with the ability to get clear results from skin tests. In other countries, the level of protection given by BCG is much lower than it is in Britain; this may be due to natural protection from exposure to other harmless mycobacteria, hiding the protective effect of BCG.

Children known to have AIDS should not receive BCG, as it can itself cause illness when the immune system is damaged (as it is a weakened form of cattle tuberculosis). HIV-positive mothers should ask their doctors for advice about vaccinating children whose HIV status is uncertain.

The global challenge

Outside Britain, and in regions of the world most severely affected by HIV, tuberculosis remains a serious public health problem in its own right and is also the single most important public health problem linked to HIV and AIDS. In Africa, Asia and Latin America, and in the countries of the former Soviet Union, the success or failure of efforts to control TB is going to be crucial for the lives of millions of people with HIV.

Viewed another way, good TB treatment services could hold the key to delivering effective treatment for HIV in countries where that is not currently available. Most TB drugs are relatively cheap, and the World Health Organisation has recently announced price reductions for the use of the more expensive "second-line" drugs in developing countries, agreed with the main manufacturers. As the costs of antiretroviral treatment and monitoring come down, they too could be added into systems that are working to deliver treatment for TB.

The inclusion of TB alongside HIV and malaria as a priority for the new Global AIDS and Health Fund is a recognition of its importance by world leaders, as more than "just another health issue". The big question is whether and for how long our governments can sustain this commitment. Perhaps we all have a part to play in that.

further reading

The Interdepartmental Working Group on Tuberculosis report, *The Prevention and Control of Tuberculosis in the United Kingdom: UK Guidance on the Prevention and Control of Transmission of: 1. HIV-related Tuberculosis; 2. Drug-resistant, including Multiple Drug-resistant, Tuberculosis September 1998* is available online at <http://www.doh.gov.uk/tbguide.htm>

US Centers for Disease Control TB guidelines are listed under 'HIV/AIDS' at http://www.cdc.gov/nchstp/tb/pubs/mmwrhtml/maj_guide.htm

World Health Organisation guidelines and a clinical manual are available at <http://www.who.int/gtb/>

Global AIDS and Health Fund

For more information on this fund see the news archive (19 June 2001) at NAM's website aidsmap.com



data analysis

6 how randomised controlled trials of HIV treatments are analysed, and how this influences views about new drugs by caroline sabin

The gold-standard approach to assessing whether a new antiretroviral combination is effective is through the use of a randomised controlled trial (RCT). As the name suggests, RCTs have two main features: Firstly, they are controlled – this means that the trial has a comparative element (e.g. a new treatment combination may be compared to one in current use). Secondly, participants are allocated to treatments randomly, ensuring that the individuals in each treatment arm are similar in terms of baseline characteristics at the outset of the trial (provided the numbers involved are sufficiently large). This means that any difference in outcome at the end of the trial can be attributed to the treatment combination received.

Most RCTs in HIV infection are carried out to a high standard. However, it is still possible to draw very different conclusions about the results of a trial depending on the statistical

methods used to analyse the results. In particular, the choice of trial endpoint can have a large influence on the results of a trial. This is of importance when results from a number of different RCTs are compared.

What is a trial endpoint?

A trial endpoint is an outcome measure that captures the beneficial (or harmful) effects of the new treatment. These endpoints are primarily concerned with efficacy, but may also reflect the negative aspects, such as the development of toxicities. In most trials a number of different outcomes reflecting risks and benefits are considered. However, it may be difficult to interpret the results of the trial if the results from these endpoints are different. Therefore it is usual to define one of these endpoints (usually one relating to efficacy) as the primary endpoint of the trial; all other endpoints (relating to both efficacy and toxicity) are secondary endpoints. Conclusions

about the relative benefits of the treatments are based primarily on the results of the primary endpoint, with the secondary endpoints being used to provide supportive data.

Clinical and surrogate endpoints

Prior to the introduction of HAART, many RCTs of antiretroviral drugs had a clinical endpoint (e.g. the development of a new AIDS-defining event or death). However, the small number of clinical events which now occur in treated individuals as a result of HAART's effectiveness, means that it is difficult to carry out RCTs using clinical endpoints. As a result, most RCTs now use "surrogate (substitute) marker" endpoints based on virological or immunological results are the primary endpoint. For example, the primary endpoint of an RCT may be the proportion of individuals with a viral load below the level of detection (e.g. 50 copies) at a certain timepoint (e.g. 48 weeks), or could be the change in viral load between the start of the trial and that timepoint. Although surrogate marker endpoints have a number of disadvantages (the link between short-term virological response and long-term clinical outcome remains uncertain, and short-term responses do not capture the long-term toxicities of some regimens), they allow more rapid judgements to be made about the effectiveness of new drugs.

Protocol deviations in RCTs

In most RCTs the treatment actually received by participants often differs from that specified in the protocol, with participants choosing to change drugs or stop therapy altogether. These events are referred to as protocol deviations, although they usually reflect the type of treatment changes seen in clinical practice outside a trial setting. In the context of a trial, however, two main issues relating to these protocol deviations must be resolved. Firstly, information that is missing as a result of an individual stopping treatment or leaving a trial should be allowed for in the analysis in some way. Secondly, a decision must be made about how to include information from individuals who change treatments. The following sections consider the different methods of resolving these issues.

Missing data in RCTs

As long as an individual is receiving care somewhere, it may be relatively easy to obtain information on the development of clinical endpoints. However, collection of surrogate marker data is more difficult: viral loads can only be measured if the individual has attended the clinic and had a blood sample taken. Consequently, surrogate endpoint data is more likely to be missing than clinical endpoint data. At best, where the missing data do not depend on the treatment received (i.e. there is no tendency for those in one treatment group to have more missing data than those in the other), then the reduction in the number of individuals included in the analysis may mean that the trial lacks statistical power (so we are less likely to draw a firm conclusion about the relative efficacy of the treatment combinations). The results of the trial can be seriously biased, however, if there is a tendency for one treatment group to have more missing data than the other.

Methods to deal with missing data

Various statistical methods can be used to address the problem of missing data when analysing a RCT¹. However, many of these methods are complex and so simpler approaches are commonly used. In order to illustrate these approaches, a hypothetical dataset has been generated from a RCT of two treatment combinations, with 20 individuals allocated to each treatment arm. The figure on the following page illustrates the viral load data for one group of these individuals. Each dot represents a viral load measurement; a filled dot indicates a viral load less than 50 copies whereas an empty dot indicates a viral load greater than 50 copies. The primary endpoint is the proportion of individuals with a viral load below 50 copies at 48 weeks. By week 48, nine of the 20 individuals randomised to this treatment group have missing values.

A **complete-case analysis** only includes individuals in the analysis if they have a viral load measurement at 48 weeks. So, in this example, only 11 of the participants would be included in the analysis, of whom 9 (82%) have an undetectable viral load at this time

glossary

antiretroviral A substance that acts against retroviruses such as HIV.

baseline Starting point or value.

clinical event The occurrence of a physical sign or symptom, rather than an abnormality that can only be detected by laboratory tests.

clinical trial A research study with people, usually to show how well a new treatment works and how safe it is.

efficacy How well something works.

endpoint An event used by a clinical trial to evaluate whether a trial therapy is working.

HAART Highly Active Antiretroviral Therapy, a term used to describe HIV combination therapy with 3 or more drugs.

randomisation Process of selecting by chance the treatment that a clinical trial participant will receive.

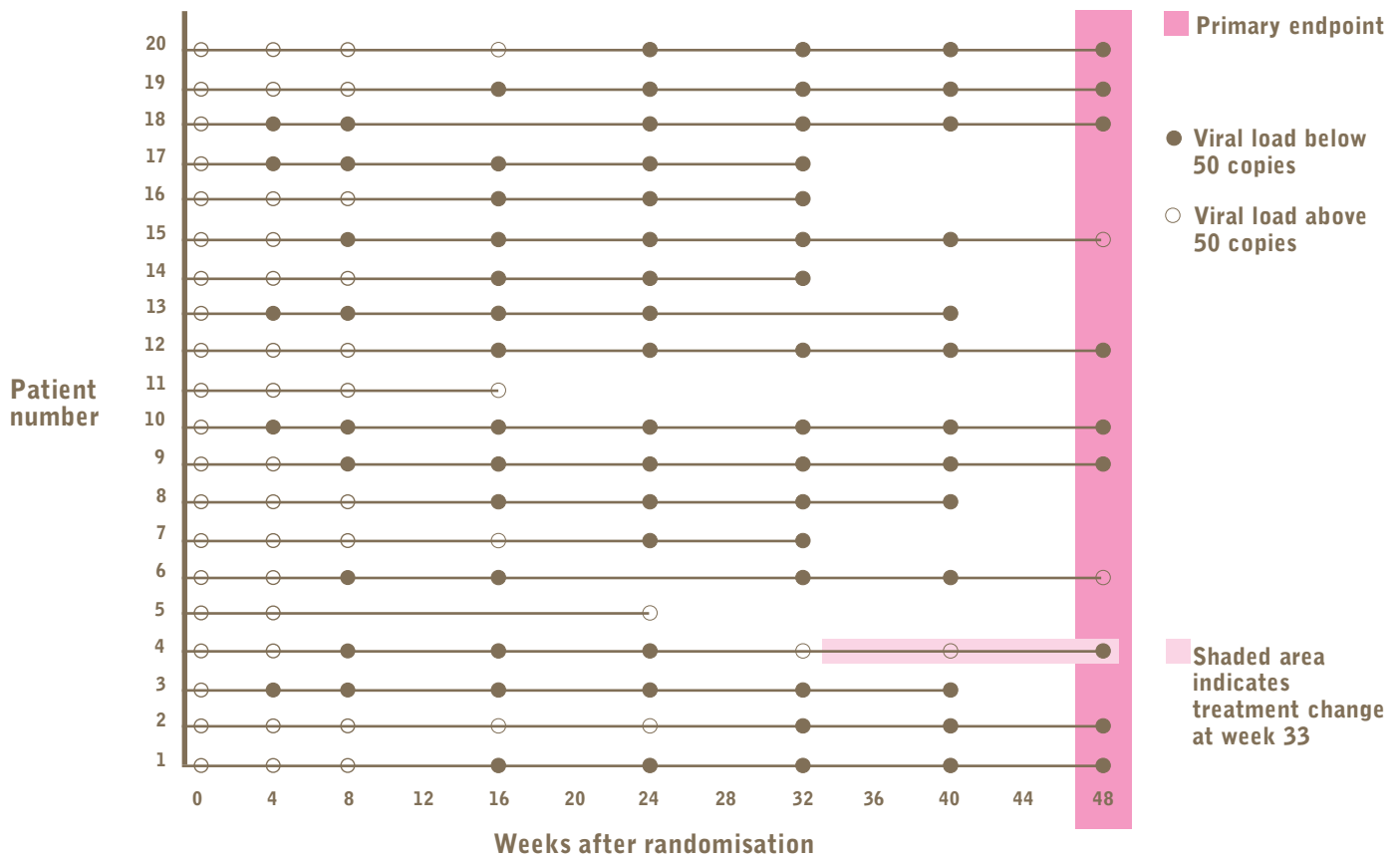
regimen A drug combination and the way it is taken.

side-effect Unwanted effect of a drug.

toxicity The extent or ways in which a drug is poisonous to the body.

viral load Measurement of the amount of virus in a sample. HIV viral load indicates the extent to which HIV is reproducing in the body.

data analysis continued



point. Because participants with detectable viral loads were those who were most likely to drop out of this trial (as may often be the case in real life), the proportion with an undetectable viral load derived in this type of analysis is an overestimate of the true proportion. Therefore this approach tends to give a very optimistic view of the treatment's efficacy. Furthermore, as only a subset of the randomised participants are included, the value of randomisation may be lost, and, also, the study will have reduced statistical power.

A missing equals failure (often referred to as **M=F**) approach assumes that all individuals with a missing viral load at 48 weeks have viral loads above 50 copies, i.e. they are considered to have experienced treatment failure. Every individual in the trial, including those with missing data, can be included in the analysis,

which means that the power of the trial is not reduced and the value of randomisation is not lost. Under this assumption, 9 of the 20 participants (45%) in our example have a viral load less than 50 copies. As the denominator is increased but the number with a viral load below 50 copies has not changed, this response rate will always be lower than that generated from a complete-case analysis, unless there are no missing data at all. Therefore this approach tends to give a more pessimistic view of the effect of the treatment.

Under a last observation carried forward (or **LOCF**) approach, if an individual has a missing viral load at week 48, the last available viral load prior to week 48 for that individual is used in the analysis. Thus, in the figure, participants 3 and 5 who had missing values at week 48 would be assumed to have

undetectable and detectable viral loads, respectively. The response rate under this assumption would be 80% (16 out of 20). Whilst all participants can be included in this analysis, which maintains the power of the trial, it is unreasonable to assume that a person's viral load has remained constant for a long period of time. For example, under this approach, the week 48 viral load for participant 11 would be assumed to be detectable, even though the last viral load for this person had been measured at week 16, 32 weeks before the end of the trial.

Switches in treatment

Participants recruited to a RCT may change or stop antiretroviral drugs at any stage of the trial, either because the drug combination does not appear to be effective (i.e. the viral load is not suppressed), because the drug combination is inconvenient to take, or because it has toxicities which make it hard to tolerate. The recommended analytic approach is to include all individuals in the analysis within the groups to which they were originally randomised, irrespective of changes in therapy – indeed, medical journals that adhere to the CONSORT guidelines² now require this approach as standard. This is known as an **intent-to-treat (ITT) analysis** and gives the only unbiased estimate of the treatment effect. This approach can be thought of as a comparison of the different treatment strategies, rather than of the specific drug combinations received.

However, the ITT approach has problems if a lot of participants change treatment. It may appear inappropriate to judge a treatment on the basis of a response which may have been achieved after switching to a completely different regimen. For example, participant 4 in our dataset experienced virological failure at week 32. Treatment was changed in this individual such that the viral load was re-suppressed by week 48. Clearly, in this case the undetectable viral load at week 48 is largely the consequence of the new treatment, rather than the original one.

One approach to deal with this problem is to undertake an **on treatment analysis**, whereby patients are only included in the analysis up to

the time when they change or stop their drugs. Patient 4 would therefore be included in the analysis only up to week 32, and any subsequent viral load results would be ignored (indeed, in some trials, viral load results after a change in treatment may not even be collected). Unfortunately, individuals who experience the best virological responses with the least adverse effects tend to be those who stay on their original treatment for the longest period. Thus, this analysis tends to favour these individuals and does not reflect the true range of responses among all individuals randomised to this treatment. A second, statistical argument against on treatment analyses is that by selectively excluding patients in this way, the similarity in baseline characteristics between the treatment groups achieved by randomisation is lost, and thus any difference in outcomes is subject to biases and cannot solely be attributed to the treatment combinations being compared. Proponents of this approach argue that an on treatment analysis allows you to consider the best possible effect of treatment if individuals continue to take the drug as prescribed.

An alternative approach is to incorporate treatment switches as part of the endpoint of the trial³ (i.e. participants are considered to have experienced treatment failure if they change drugs). Whilst all trial participants are included in this analysis, and therefore it is an ITT analysis, the hypothesis being tested relates to the initial regimen rather than the whole treatment strategy. In addition, defining treatment failure can be difficult, and so the endpoints may be less robust.

Interpretation in clinical practice

Comparisons of the proportions of treated individuals with viral loads below the limit of detection on different treatment regimens in different RCTs are commonly presented. Indeed, these figures are often used by pharmaceutical company personnel to justify why one treatment combination should be used over another. However, even if the participants appear to be similar, and all the studies have used an ITT approach, the way in which missing data and treatment switches have been dealt with can have an impact on the

author credit

NAM is delighted to welcome Dr Caroline Sabin as a contributor to *ATU*. Caroline is a Reader in Medical Statistics and Epidemiology at the Royal Free and University College Medical School, London.

references

- 1 Wu MC et al. *Stat Med* 2001; 20: 93-108.
- 2 Moher D et al. *Ann Int Med* 2001; 134: 657-662.
- 3 Gilbert PB et al. *JAMA* 2001; 285: 777-784.
- 4 Bartlett J et al. *AIDS* 2001;15:1369-1377.

further reading

See *ATU* issue 73 for an introduction to how trials work, available at <http://www.aidsmap.com/publications/atu/index.asp>

The Avanti Steering Committee. Analysis of HIV-1 clinical trials: statistical magic? *Lancet* 1999; 353: 2061-2064.

Hollis S et al. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999; 319: 670-674.

Le Corfec E et al. Visit-driven endpoints in randomized HIV/AIDS clinical trials: impact of missing data on treatment difference measured on summary statistics. *Stat Med* 1999; 18: 1803-1817.



proportion with undetectable viral loads. If all analyses are carried out on an ITT M=F basis, as in a commonly quoted analysis by Bartlett⁴, there may still be differences in the follow-up of patients in different trials, (e.g. the frequency of follow-up visits, the additional support provided for adherence and toxicity management), which means that these comparisons should be treated cautiously.

The choice of the analysis approach remains under debate and, to a certain extent, depends upon the hypothesis being tested. Whilst a

missing=failure approach tends to give a pessimistic estimate of the proportion of individuals with undetectable viral loads at any time point, especially if a large number of participants have left the trial, this is thought to be preferable to a complete-case approach which tends to overestimate this proportion. It is important, however, to include all trial participants in the analysis, even if they switch treatments, either by including treatment switches explicitly as failures in the definition of the endpoint, or by including their viral load results ignoring any treatment switches.

key conclusions

- The way in which a trial endpoint is defined, and the way in which missing data and treatment switches are dealt with in the analysis, can have a large impact on the results of the trial.
- Analyses which only include those patients with complete data (a complete-case analysis) usually overestimate the proportion of individuals with an undetectable viral load at any timepoint. Those which consider those individuals with missing viral loads to have experienced treatment failure (missing=failure analyses) may give a more realistic view of the true effect of therapy, but this may cause problems if people stop treatment because of side-effects rather than because of virological failure.
- An intent-to-treat analysis, whereby patients are included in the analysis in the treatment groups to which they were originally randomised, gives the least biased estimate of the treatment effect. On treatment analyses tend to favour those individuals with the best treatment response and least toxicities, and therefore do not reflect the true range of treatment responses in all patients.

PI drug levels

A large clinical trial has reported that the use of tests to monitor drug levels of protease inhibitors may result in improved response to anti-HIV treatment. Results from the ATHENA study were presented at an HIV conference in Buenos Aires in July.

ATHENA was a randomised comparison of drug level testing versus no drug level testing in people starting a protease inhibitor. Tests were performed on random samples taken at regular clinic visits, and results were reported back to the trial doctors within four weeks of the sample being taken. Doctors would then act on these results based on criteria laid down by the trial investigators.

Forty-eight week results were reported for 55 indinavir recipients and 92 nelfinavir recipients. At this timepoint, access to drug level monitoring improved viral load responses, and reduced the numbers stopping treatment in recipients of each of these drugs. Indinavir users benefited mainly from decreased side-effects, (due to excess drug levels), whilst the benefit amongst nelfinavir recipients was mainly due to a reduction in the risk of virological failure, (as a consequence of inadequate drug levels). Adherence appears to have been a key factor in this group. Of those who had low levels of nelfinavir when first sampled, 50% were above the target level on their second sample. The only intervention offered between these two samples was a reiteration of nelfinavir's dietary requirements – the drug should be taken with food.

Reference: Burger D. First IAS Conference on HIV Pathogenesis and Treatment, abstract 30, 2001.

Adherence crucial

One of the largest ever studies to observe treatment adherence amongst people taking anti-HIV therapy has reported initial results over a one year period. US researchers are following 1,141 people enrolled in two trials run by the Community Programs for Clinical Research on AIDS (CPCRA). One trial involves people new to treatment, whilst the other is for those with some treatment experience.

Participants self-reported their adherence over the preceding seven days using a questionnaire.

Five hundred and forty people have completed twelve months of follow-up. During this period, adherence levels diminished over time, and were generally lower throughout in people who were treatment experienced. The study confirmed that reported adherence levels were accurate predictors of participants' subsequent viral load and CD4 response – low adherence increased the risk of treatment failure.

Follow-up of an observational cohort of 1,200 Canadians starting HAART indicates that adherence is a crucial factor in the successful treatment of those who begin anti-HIV drugs with very low CD4 counts – the group at greatest risk of serious illness or death.

Adherence levels were measured using pharmacy records of the frequency with which participants returned to fill their antiretroviral prescriptions. Where at least 95% of drugs prescribed during the first six months of treatment had been accurately dispensed, participants were regarded as adherent.

During 30 months of follow-up, there were 82 deaths from AIDS-related causes. These deaths were clustered amongst those people who began treatment with a CD4 count below 50 cells, and who were less than 95% adherent. 50% of adherent individuals who began treatment with less than 50 CD4 cells, had a count above 200 cells after this 30 month period.
References: Friedland G, abstract 33, and Montaner J, abstract LB-010, both presented at First IAS Conference on HIV Pathogenesis and Treatment, 2001.

NAM forum

This month's NAM Patient Information Forum takes place on Monday, 17th September, when our guest speaker, Dr Martin Fisher of the Royal Sussex County Hospital, Brighton, will be discussing treatment interruptions, and answering questions from the audience. Forums are free, and take place at the University of London Union, Malet Street, London WC1. A sign language interpreter is available.



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any questions

For an introduction to HIV treatment issues

The booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series covers six key topics: Viral Load, Clinical Trials, Nutrition, Anti-HIV Drugs, Resistance, and a Glossary.

The HIV & AIDS Treatments Directory

This 600 page book, published twice a year, is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV, £64.95 to professionals.

<http://www.aidsmap.com>

NAM's resources are also available online at [aidsmap.com](http://www.aidsmap.com). These include our extensive and searchable treatments database, the latest news on treatment developments, our online directory of AIDS service organisations, hundreds of links to recommended HIV-related sites, and free downloadable resources.

Monthly NAM information forums in London

Each month an expert speaker discusses a treatment-related topic. Entry is free. Future forums are advertised inside this newsletter.

AIDS Treatment Phonenumber 0845 9470 047

From Terrence Higgins Trust: Mon & Wed 3-9pm, Tue 3-6pm.

NAM recommends that you discuss all your treatment decisions with your doctor.



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