

aids treatment update

one hundred issues of ATU

This month we mark the 100th issue of *ATU* with a specially extended, sixteen page edition. Launched in 1992 as a complement to NAM's *UK Directory of HIV/AIDS Treatments and Trials*, *ATU* was designed to fill a gap by offering treatments information with a UK-focus. The formula is little changed today – *ATU* exists to help people with HIV understand their treatment options, and to encourage productive communication between doctors and patients.

Though *ATU*'s strong reputation has been built on the quality of its contributors – particularly Edward King, editor from 1992-98 – the distinctive support provided by NAM's Medical Advisory Panel should not go unmentioned. Many of our current panel have been involved since the first issue, and continue to provide indispensable commentary on content prior to publication; and to do so on a voluntary basis. NAM is similarly indebted to our Peer Panel of people living with HIV, whose contribution is consistently thoughtful and relevant.

Finally, thank you to our funders, who have supported the provision of free subscriptions to people personally affected by HIV. As editor, it's my privilege to dedicate this issue to NAM's present and past Directors – Colin Nee, Will Anderson and Peter Scott.

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changing treatment

2 options for people who have taken lots of anti-HIV treatments by keith alcorn

Many readers of *ATU* have now taken more than four drug regimens since they began anti-HIV treatment, according to the results of our readers survey conducted last December. In some cases, the number of different regimens taken extends to eight, nine or even ten.

A typical history goes something like this:

- AZT/ddI (in the Delta study from 1994)
- added saquinavir (through expanded access programme in December 1995)
- changed to d4T/3TC/indinavir (after the Vancouver conference in 1996)
- d4T/ddI/nevirapine (after failure of indinavir in 1998)
- d4T/3TC/ritonavir/saquinavir (after failure of nevirapine in 1999, and chosen prior to the availability of resistance testing).

This individual is likely to be cross-resistant to all current NNRTIs and most of the NRTIs, and may have some cross-resistance to protease inhibitors (PIs). Add in problems such as peripheral neuropathy (caused by d4T), and you have a very limited selection of drugs available. What options are left for someone with rising viral load in this situation?

Resistance testing to select treatment

The first possibility is using resistance testing to define which drugs might still work. (Developments in the area of resistance testing are the subject of this month's second article). Two types of resistance test are available.

Genotypic tests look for specific changes, or mutations, in the virus which may predict resistance to a drug. Phenotypic tests measure the amount of drug which is needed to control viral replication. As the virus grows more resistant, the amount of drug needed to control replication will increase. This is called loss of sensitivity or susceptibility.

In people with lots of drug experience, resistance tests have shown rather limited benefits. Though this may be due to the relative lack of effective treatment options, the chief advantage of resistance testing in these circumstances probably lies in ruling out drugs which will definitely not work (especially in the absence of a detailed medical history).

Boosted protease inhibitors

The development of resistance is not an all or nothing process. As the number of resistance mutations increases, drug sensitivity decreases, so people develop anything from borderline to total resistance to a drug.

In this situation, it may be possible to overcome lower levels of resistance by boosting the amount of a PI that gets into the blood and into HIV-infected cells. The amount of boosting needed will vary from one individual to another depending on the amount of resistance which has developed, and also that individual's pattern of drug metabolism (see *Therapeutic drug monitoring* below).

The first PI to be boosted was the old formulation of saquinavir (*Invirase*), which was paired with ritonavir due to the latter's ability to slow elimination of other PIs (thus greatly

boosting drug levels). This approach was followed up in the development of the new PI lopinavir, which has been co-formulated with ritonavir and is marketed as *Kaletra*. Lopinavir/ritonavir achieves high blood levels of lopinavir which may overcome resistance to other PIs, and two studies in NNRTI naïve individuals who have failed at least one PI-containing regimen show that in people with moderate levels of PI resistance, this regimen sustains undetectable viral load in around two thirds of people for at least one year.

In study M98-957, where people took lopinavir/ritonavir, efavirenz and two NRTIs, the number of resistance mutations linked to lopinavir resistance, and the degree of drug sensitivity, were associated with the likelihood of reaching and maintaining a viral load below 50 copies after 24 weeks on the new regimen. People with fewer mutations and greater sensitivity to lopinavir had the best response¹.

However, the marketing of *Kaletra* as a solution for PI-experienced patients has triggered fierce controversy amongst PI manufacturers, because Merck, Roche and GlaxoSmithKline all believe that, when boosted with ritonavir, their own PIs achieve very high drug levels and would be equally suitable for use by PI-experienced individuals. For example, Roche has argued that even though its PI saquinavir appears to reach lower levels in the blood, it has very good penetration into HIV-infected cells compared to other PIs. GlaxoSmithKline, meanwhile, is developing a new form of amprenavir which can be dosed once daily with ritonavir, and which might achieve much higher blood levels.

The difficulty in assessing these arguments lies in the absence of any comparative trials, or any data gathered in people who have failed on all three currently available classes of drugs.

US studies have tended to look at the effects of new PIs with efavirenz or nevirapine in people who have failed with several PIs, because US treatment practice has been to use PIs as first-line therapy. This means that lots of people are NNRTI-naïve in the US. In contrast, NNRTIs have been heavily prescribed in the UK (perhaps more so than anywhere else).

Another alternative is the use of two PIs (excluding ritonavir), known sometimes as "dual PI" therapy. The ACTG 398 study randomised individuals to receive amprenavir, efavirenz and adefovir plus either nelfinavir, indinavir, saquinavir or placebo. Once again, NNRTI naïve patients responded better in this study, but those who received two PIs also did better in this study, regardless of which PIs they had taken previously².

A number of clinicians are now talking about double boosting PIs, using ritonavir to increase blood levels of two other PIs, for example by combining *Kaletra* and amprenavir.

The drawback of PI boosting is the increased risk of drug side-effects. For example, raising blood levels of indinavir also increases the risk of kidney problems. While the incidence of this side-effect is around 4-5% when an 800mg dose of indinavir is used alone, it rises to between 10 and 20% (depending on the definition of kidney toxicity used) when dosed with 100mg of ritonavir.

treatment history

Treatment may fail for several reasons. Some of these, e.g. intolerance, may be improved by new formulations, which may allow drugs you have taken before to be 'recycled' within a new regimen.

new drugs

For more information on experimental drugs which will become available in the near future, see last month's ATU, and the Emerging Therapies section on NAM's website aidsmap.com

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changing treatment continued

Similarly, the incidence of seriously elevated cholesterol and triglyceride levels on lopinavir/ritonavir increases from 9% in treatment naive individuals taking this boosted PI as first line therapy³ to around 40% in individuals taking lopinavir/ritonavir as their third or fourth PI⁴.

In the ACTG 398 study noted above, a third of participants stopped treatment within six months due to toxicity (which was largely PI-related).

New PIs which might overcome drug resistance are now being developed, of which BMS-232632 is the most advanced. A study of this drug in people who have experienced more than one PI may begin in the UK later this year, and it is possible that if the drug continues to prove safe and effective in ongoing clinical studies, an expanded access programme could begin by the end of this year in Europe.

Other PIs are far less advanced, although drugs under development by Du Pont, Tibotec and Boehringer Ingelheim may become available to limited numbers of people at a few UK centres through trials this year.

Therapeutic drug monitoring

There are big variations between individuals in the drug levels achieved when a group of people take the same dose of a drug, so it may not be helpful to report that an individual has developed a tenfold loss of sensitivity according to a standard scale, unless we also know whether that person was getting average drug levels to begin with. Any attempt at boosting may be unsuccessful unless we know how much drug is really needed to overcome resistance, rather than just making a guess based on average drug levels in previous clinical trials.

Companies which make resistance tests are trying to bring together the results of

resistance testing and therapeutic drug monitoring to provide doctors with a single package of information that can predict the optimal therapy for an individual.

Stopping treatment: loss of CD4 cells

For many people with advanced treatment failure, stopping therapy until new drugs become available may appear to be an attractive option. However, people who are in this position are likely to be the group of patients at greatest risk from trying this strategy. This is because people who have exhausted most available options probably started treatment five or six years ago, and with very low CD4 counts.

One of the few consistent findings from studies of treatment interruptions is that if you stop treatment, your CD4 count eventually falls back to its pre-treatment level. A study of 68 patients who interrupted therapy after an average CD4 cell increase of 164 cells above their pre-treatment average of 157 cells found that after a median of fifteen weeks their CD4 counts were only 39 cells above the pre-treatment level. The researchers calculated that the CD4 count would return to baseline after an average of 24 weeks off therapy⁵. The Royal Free group has previously reported that the average rate of CD4 cell loss is approximately 25% per month in people who stop a failing PI-based therapy in late stage disease⁶.

A second analysis of 252 patients from six cohorts found that those with the highest CD4 cell increases on treatment – or the lowest pre-treatment CD4 counts – experienced the biggest declines when they stopped treatment⁷.

Taken together, these findings suggest that stopping treatment will not be a long-term option for people with advanced treatment

failure who may previously have experienced AIDS-defining illnesses. In this group of people, the major consequence of a long period off treatment could be the re-emergence of old infections as the immune system declines.

Stopping treatment: impact on resistance

Stopping treatment for a shorter period has been proposed as a means of purging drug resistance, on the grounds that in the absence of drug pressure, drug resistant mutants will be less fit than wild type viruses and will gradually disappear. However, several studies have shown that this approach may not work.

People with higher viral load at the time they stop therapy, and people with higher levels of drug resistance at the time they stop therapy have typically fared less well when they start treatment again^{8,9}, but people with higher CD4 counts have been shown to do better (an average of 192 cells in the responders versus 59 cells in the non-responders).

Robert Siliciano reported to the 8th Annual Retroviruses Conference in February that archived resistant viruses are can be found in resting CD4 cells (the "HIV reservoir"). This means that these cells could later be re-activated to pump out drug resistant viruses. This is not a problem off treatment, because these viruses will tend to be too weak to take over as the majority species. But on treatment, they could form the basis for an upsurge in virus activity if the drug resistance mutations they carry allow them to replicate in the presence of one or more of the drugs that you are taking.

Researchers from Frankfurt have also reported on the effectiveness of treatment interruptions as a means of purging resistance, and on subsequent response to mega-HAART⁹. Twenty-eight out of 45 people who stopped therapy for more than two months experienced a "disappearance" of drug-resistant virus, i.e. resistance mutations were not detected through resistance testing. Individuals were resistant to a median of eight drugs, and those who failed to lose resistance had been on treatment significantly longer – a median of 5.5 years versus 3.5 years in those who lost resistance.

Resistance was also found to decline within six weeks of stopping PI-based therapy in a group of 16 San Francisco patients with rising viral load, nine of whom stopped treatment¹⁰. The decline in resistance was associated with a big increase in viral load, which appeared to be caused by an improvement in the ability of virus to replicate as resistance declined. However, in five patients who stopped treatment, PI-resistant virus could still be found twelve weeks after stopping treatment, suggesting that the restoration of drug treatment would immediately permit a rebound in drug resistant virus to occur, unless viral replication could be reduced to very low levels very rapidly.

Patients resumed therapy after a twelve week break, and after 24 weeks back on treatment, six out of fifteen had viral load below 200 copies. Those with undetectable viral load were more likely to be NNRTI-naïve, suggesting that treatment interruption alone may not greatly improve the chances of responding to a new PI-containing regimen.

Continuing with "failing" treatment

If you have detectable viral load and few immediate options for new treatment, continuing with existing treatment may have its advantages, up to a point.

Johns Hopkins University, Baltimore, reported that people who experienced rebound after their first HAART regimen continued to derive benefit more than two years later. After two years of viral load above 1,000 copies despite taking HAART, 84 patients in the clinic's cohort had a median CD4 count that was still 116 cells above the pre-treatment level¹¹.

Veronica Miller of Goethe University in Frankfurt has reported that when patients on HAART and patients not on HAART were matched according to their CD4 count and viral load, it was evident that people taking HAART had a significantly lower risk of disease progression¹². A person with a CD4 count of 100 and a viral load of 50,000 taking PI-containing HAART is almost 50% less likely to develop an AIDS-defining illness than someone with similar counts not on HAART.

glossary

adherence

Taking a treatment exactly as prescribed.

antiretroviral

A substance that acts against retroviruses ,e.g. HIV.

baseline

Starting point or value.

CD4

Molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

cholesterol

A waxy substance, mostly made by the body and used to produce steroid hormones, associated with hardening and narrowing of arteries.

HAART

Highly Active Antiretroviral Therapy, a term used to describe anti-HIV therapy with three or more drugs.

median

The central value of a range of values.

metabolism

The mechanisms which sustain life, turning sugar to energy.

mutation

A single change in gene sequence.

naïve

Never having taken anti-HIV drugs before.

neuropathy

Damage to the nerves.

NNRTI

Non nucleoside analogue reverse transcriptase inhibitor. Antiretroviral family which includes efavirenz, nevirapine.

NRTI

Nucleoside analogue reverse transcriptase inhibitor. Antiretroviral family which includes AZT, ddI, ddC, 3TC, d4T, abacavir.

changing treatment continued

Steven Deeks of San Francisco General Hospital reported on what had happened to 302 patients in his clinic who had had detectable viral load since 1996 whilst taking PI therapy. After four years of detectable viraemia, patients had a 41% probability of developing an AIDS-defining illness; the risk after two years was 18%¹³.

Mega-HAART

The most recent report on therapy with six or seven drugs (termed mega-HAART), for people with lots of prior treatment experience suggested that less than 30% of individuals could expect to maintain viral load below the limit of detection after one year, and treatment was poorly tolerated by many in the study¹⁴. Dr Steven Deeks suggested in a recent editorial in the journal *AIDS* that undetectable viral load

may be an unrealistic goal for people with extensive drug resistance, and pointed out that no evidence currently exists to show that the mega-HAART approach is superior to continuing with failing therapy in terms of increasing the CD4 cell count, preventing illness or making treatment easier to tolerate.

Looking to the future, an international clinical trial called OPTIMA plans to randomise treatment experienced people to receive either mega-HAART (defined as more than five drugs), or a minimal regimen of three drugs or less. In addition, everyone will also be randomised to change treatment immediately or to interrupt treatment for three months before changing treatment. This study will be recruiting 1,300 participants from the US, Canada and the UK.

key conclusions

- Resistance tests are recommended to guide selection of therapy when changing treatments, though they are more able to rule out drugs than rule them in.
- Boosting protease inhibitor blood levels using ritonavir appears to overcome protease inhibitor resistance, at least to some extent. However, this is a relatively new strategy and we don't yet know which boosted PI is best. The drawback of raising drug blood levels in this way may be a higher risk of side-effects.
- Stopping treatment may be an attractive option. However, people with lots of drug experience, and who began treatment with advanced disease, appear to bear the greatest risks from interrupting treatment.
- There is evidence that remaining on treatment despite viral load rebound results in less illness than coming off treatment, though quality of life needs to be considered on an individual basis.
- Mega-HAART has not so far been proven more effective than taking fewer drugs but continues to be investigated.
- Randomised trials, such as OPTIMA, will provide the strongest evidence on optimal treatment approaches in highly treatment experienced individuals.

resistance testing

new guidelines, new data & new testing systems by **anna poppa**

In a recent issue of the medical journal, *AIDS*, a pan-European expert panel convened some two years ago, published guidelines on the use of drug resistance tests in HIV care¹. *AIDS Treatment Update* last covered the subject of resistance testing in issue 90. What has been learnt in the last twelve months which has advanced the use of resistance tests in HIV management, and how influential will these new guidelines be?

The EuroGuidelines HIV Resistance Group aims to provide recommendations on the state-of-the-art use of resistance testing in HIV management that are based on evidence, where available, and on expert opinion. The group includes clinicians and virologists, along with representatives of the biotech and pharmaceutical industries, and of the European AIDS Treatment Group, an activist organisation. A number of UK-based professionals are involved.

The process of updating the UK's antiretroviral treatment guidelines is currently underway. However, for over a year it has been the British HIV Association's (BHIVA) recommendation that resistance testing should be used to inform the selection of a new regimen whenever treatment is changed because of virological failure, and in people who begin treatment very soon after infection (primary infection). Inequity of access to resistance tests remains an important issue nonetheless, as both the EuroGuidelines Group and BHIVA recognise. At a recent educational event organised by NAM for HIV doctors, it was apparent that the existing BHIVA recommendations regarding the use of resistance tests are not being

observed uniformly in UK treatment centres, and that access to them continues to depend on where you live.

These disparities arise for complex reasons, though a major influence is clearly the provision of funds. Nevertheless, resistance tests are difficult to perform and interpret, and remain several steps behind the eagerness of many in the HIV community to adopt them into routine care.

Testing before starting treatment

The EuroGuidelines Group recommend that resistance testing prior to starting anti-HIV treatment should always be considered, and that where the risk of infection with drug resistant virus is high, testing is advised. However, the ability of resistance tests to detect transmitted resistant virus will be greatest during primary infection, and will lessen as the time from infection progresses. Over the course of HIV infection, the viral population evolves. In the absence of HIV treatment, the factor which drives this evolution is the 'fitness' of different HIV strains. The dominant virus, tends to be that referred to as 'wild-type', whereas drug resistant strains tend to be less fit. This means that even if an individual is infected with drug resistant HIV, after several years of infection it is likely that this resistant virus will exist only as an archive, which may go unrecognised by resistance tests, but will rapidly re-grow if treatment is introduced to which the archived virus is resistant. The EuroGuidelines Group advise that blood samples taken early in infection should therefore be stored for later resistance testing.

glossary

PI

Protease inhibitor.

placebo

A pill which looks and tastes exactly like a real drug but contains no active substance.

protease inhibitor

Antiretroviral family which includes saquinavir, indinavir, ritonavir.

randomisation

The process of selecting by chance the treatment that a trial participant will receive.

regimen

A drug combination and the way it is taken.

resistance

A drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs.

toxicity

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

triglycerides

The basic 'building blocks' from which fats are formed.

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.

viraemia

The presence of virus in the blood.

wild-type virus

Virus that has not been exposed to anti-HIV drugs yet.

resistance testing continued

There is some evidence that people with low-level resistance to NNRTIs may still benefit from drugs in that class. However, the detection of certain mutants which are associated with resistance to PIs has been linked to poorer response to treatment in some individuals.

Transmission of drug resistant HIV

The reported incidence of transmission of drug resistant virus in countries where HIV treatments are in widespread use varies. The trend in the US is for transmitted resistance to be on the increase. One study, involving 400 people infected in nine US cities since 1995, found 3.5% of those infected during 1995-98 were infected with resistant virus, but that this proportion rose to 14% during 1999-2000. This was reflected in an increase in resistance to all three main drug classes, and in an increase from 0.4% to 5.8% in multi-drug resistant virus².

In the UK, the incidence of transmitted resistance is being monitored by the Public Health Laboratory Service Antiviral Susceptibility Reference Unit in Birmingham. These data show an increase in prevalence since 1994, with around 25% of new infections in the year 2000 being with HIV containing at least one drug resistance mutation³.

The EuroGuidelines Group suggest that a local incidence rate of 10% and above is high enough to merit resistance testing to guide therapy choices in people who are recently infected, and should also be available where it is suspected that the source of infection is a person who has used anti-HIV treatment.

Treatment in primary infection, (and when taken as post-exposure prophylaxis), is expected to be of greatest benefit the sooner after infection it is begun. Rather than delay

starting treatment whilst the results of a resistance test are gathered, it may be preferable to begin treatment which can then be modified based on the test results.

As was noted above, the case for using resistance tests prior to starting treatment in people who have been infected for longer periods (chronic infection) is less strong owing to the likelihood that minority resistant viruses will not be detected using current testing methods. This situation may change in future as technology develops. Moreover, 'super-infection' with a drug resistant strain appears possible, if poorly understood, and may provide a reason for resistance tests to be used before starting treatment in some individuals.

Testing following virological failure

Though antiretroviral treatment may fail for a number of reasons, drug resistance is both an important cause of initial failure, and can be a consequence of failure which stems from other causes. Resistance testing may therefore guide the selection of a new regimen both by eliminating drug options which are unlikely to have any antiviral activity, and by helping doctor and patient understand the possible causes of failure of the old regimen.

Four randomised, prospective trials, three involving genotypic tests and the other phenotypic tests, have found that access to resistance testing where a failing treatment is changed can improve the response to the new regimen, at least over the short-term (see *AIDS Treatment Update* issues 87 and 80). Their usefulness was found to depend on several additional factors however, such as the incorporation of 'expert interpretation' of the test results, and ensuring the new drugs are being adequately absorbed, (requiring a further experimental blood test known as therapeutic

genotypic testing looks for changes in HIV's genes which are associated with development of resistance

phenotypic testing measures the amount of a drug needed to stop HIV reproducing: the amount increases as drug resistance develops

drug monitoring), in the case of regimens involving PIs.

A key factor however, is the availability of drugs which will be effective against highly resistant virus. Whilst resistance testing may provide a full and accurate picture of drug susceptibilities within an individual, it cannot produce new treatment options where these do not exist. The NARVAL study, which failed to show a benefit in treatment response where resistance testing was used to guide selection of therapy, is considered to have fallen foul of exactly this problem, because many participants in the study had few viable treatment options left.

The circumstances in which resistance testing is likely to be of greatest benefit are yet to be defined, but this is under investigation in a number of international controlled trials. One of these, ERA (Evaluation of Resistance Assays), is ongoing in the UK. ERA aims to evaluate the relative benefits of genotypic and phenotypic tests (see sidebar: ERA study sites).

New data from controlled trials

The Spanish HAVANA study was a randomised, controlled study which compared the use of genotypic testing, with or without expert advice, to no test, in people changing their anti-HIV therapy⁴. After 24 weeks of treatment, the likelihood of viral load falling below 400 copies was greater in the genotyping arm than in the no test arm, and in the expert advice arm compared to no expert advice. The best responses were seen in those who received both genotyping and expert advice (69% below 400 copies), and the worst in those who received neither genotyping nor expert advice (36% below 400 copies). Drug experience in this study varied. Genotyping was found to be of greatest benefit in those switching regimens

after three or more regimen failures, compared to after one or two failures.

The Italian ARGENTA study randomised 174 people who were changing therapy to receive or not receive a genotypic resistance test⁵. Again, treatment experience varied, with a quarter having failed more than three HAART regimens, and 41% having experience of all three main drug classes. Responses at 12 weeks showed a benefit in the genotyping arm, but this was lost by 24 weeks. This study also assessed adherence using a self-complete questionnaire. Overall, the best responses were seen in those with better adherence and who switched regimens with lower viral load.

Testing in pregnancy

Drug resistance is also an important consideration in pregnancy, where it may threaten the effectiveness of anti-HIV therapy in preventing mother-to-child transmission, and because resistant virus can itself be transmitted to the child.

The EuroGuidelines Group recommend that:

- pregnant women with detectable viral load on treatment take a resistance test and change regimen accordingly before delivery
- choice of therapy in pregnant women who are new to treatment should be guided by resistance testing, but that this should not delay initiation of treatment in women with very advanced HIV disease, as this can be adjusted later.

Testing in newborn children

The EuroGuidelines Group advise that children born to mothers who have detectable viral load at the time of delivery should receive resistance testing to guide therapy choices. The evolution

ERA study sites

Many UK treatment centres are participating in the ERA study. For a complete list see the NAM/BHIVA website aidsmap.com or NAM's *HIV & AIDS Treatments Directory*.

PENTA 8 (PERA)

PENTA 8 is a pan-European trial investigating the use of resistance testing in children who are changing their HIV therapy, and whose most recent viral load is above 2,000 copies. The study allocates children at random to receive or not receive a genotypic resistance test before changing combinations. Eligible children up to 18 years of age must have taken at least two classes of drugs, (or at least three NRTIs, or two NRTIs for more than two years).

further reading

A booklet in NAM's information series for positive people, *Resistance*, offers a basic introduction to HIV drug resistance and resistance testing. The booklet is free to people personally affected by HIV, and costs 50p to others. Contact NAM for details. All six titles in this series can be downloaded in pdf format from the NAM/BHIVA website aidsmap.com

resistance testing continued

of drug resistance in HIV-positive children is less well understood than in adults. However, the use of resistance tests in children failing treatment is currently under investigation in the PENTA 8 study, (also known as PERA), which is recruiting at UK treatment centres (see sidebar: PENTA 8).

Which test should be used?

A range of resistance testing methods are available, though as yet no one test has been demonstrated to be superior to others, and the EuroGuidelines Group do not advocate the use of any specific test. A straw poll amongst UK doctors at a recent NAM educational event would suggest that where resistance tests are used, these are usually genotypic tests.

The relative pros and cons of the two testing methods, genotyping and phenotyping, are illustrated in the table below:

Defining cut-offs for phenotypic testing

Phenotypic resistance tests measure changes in susceptibility to a drug compared to 'control' viruses that are known to be drug-sensitive. Phenotypic resistance is usually expressed as a fold-change in susceptibility, where greater than a four fold loss of susceptibility is considered to indicate a degree of drug resistance. However, this catch-all cut-off is unlikely to reflect variability between different drugs, or the fact that even within the context of some loss of susceptibility, a drug may still contribute a degree of antiviral activity.

Advantages and disadvantages of drug resistance tests

All tests	Insensitive to minority resistant species, e.g. that make up less than 10-20% of the sample Difficult to obtain reliable results at viral loads less than 1,000 copies Dependent on PCR technology which <i>may</i> be less sensitive to some HIV subtypes
Genotypic	Faster turnaround Easier to perform Cheaper Mutational changes may predate shifts in phenotype, allowing earlier detection of resistance Knowledge of mutational patterns and interactions associated with the development of resistance to specific drugs and regimens is incomplete
Phenotypic	Take several weeks to perform More complex to perform More expensive Provide direct measure of a person's virus against specific drugs, which is not dependent on knowledge of resistance mutations Cut-off points which indicate clinically relevant resistance to specific drugs not yet established

Researchers have established clinically relevant cut-offs for two anti-HIV drugs – lopinavir/ritonavir and abacavir. At the recent Retroviruses Conference, GlaxoSmithKline demonstrated that people with up to a 4.5 fold loss of susceptibility to abacavir nevertheless gained a maximum viral load response to abacavir intensification over 24 weeks of treatment. People with a greater than 7 fold loss of susceptibility obtained no benefit⁶.

Meaningful cut-offs for other drugs need to be established. Researchers at the Chelsea and Westminster Hospital are investigating this issue.

The *Virtual Phenotype*

The choices offered have been broadened by the availability of a new testing system from Virco called the *Virtual Phenotype*. Virco, a Belgian-British biotech company, have one of the world's largest reference databases of viruses isolated from people with HIV. This contains many thousands of different genotypes and their matching phenotypes. By entering a genotype from a specific patient, Virco use this stored information to estimate the likely (hence 'virtual') phenotype. Thus the *Virtual Phenotype* is designed to deliver phenotypic information through the relatively simple genotyping method, without needing to go to the trouble of conducting an actual phenotypic test. It is considered to provide a more sophisticated interpretation of genotypic information, given that it incorporates elements of genotypic and phenotypic analyses.

The assumption behind the development of the *Virtual Phenotype* is that phenotypic information is ultimately of greater significance than genotypic information. However, this has not been proven, and as yet there is no evidence gathered prospectively from randomised clinical trials that phenotypic testing is more beneficial in patient management than genotypic testing. NARVAL, the only study comparing the two which has so far reported results, was unable to find clear evidence of benefit from either method, but did find a trend towards greater benefit in the genotyping arm.

Virco have demonstrated that the *Virtual Phenotype* correctly calls the real phenotype

from a given genotype in 85-90% of cases⁷. At the Retroviruses Conference in February they presented data on the retrospective use of the *Virtual Phenotype* in the VIRA3001 study⁸. This study evaluated the use of phenotypic testing in people changing from a failing regimen, finding that those who switched on the basis of phenotypic test results fared better than those who switched without a test. Re-testing samples using the *Virtual Phenotype*, Virco found their new test accurately predicted response to the new regimen, and appeared more able to predict the likelihood of viral load falling below 50 copies than the real phenotype.

Whilst the *Virtual Phenotype* lags behind other resistance testing systems in terms of evaluation of its use in patient management, it is already in use in limited settings, such as the Chelsea and Westminster Hospital, London. Moreover, Virco have already phased out their phenotypic test, the *Antivirogram*, in preference to the *Virtual Phenotype*. Real phenotypic testing is not dead yet however, and remains commercially available from biotech companies such as ViroLogic, as well as from academic research labs.

Good practice

Regardless of which testing method is used, there are certain 'rules' to resistance testing which must be observed. Firstly, blood must be taken while the individual is still taking the failing drug combination. When drugs are stopped, the selective pressure which they exert on the viral population goes with them, allowing resistant viruses to fade into the background, and so evade the capacity of resistance tests to detect them.

Technology involved in resistance testing is unusually complex. Therefore, in the view of the EuroGuidelines Group, testing should only be undertaken by laboratories which have been externally accredited and which work under strict quality assurance standards. In addition, results should be provided to the clinician with expert interpretation.

Inhibitory quotients: Whose IQ is best?

Treatment failure is often multi-factorial, and as the VIRADAPT study illustrated, drug

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resistance testing continued

absorption has an important bearing on drug resistance. The concept of inhibitory quotients, or IQ, is a relatively new one for many in the HIV community, but may find an application in HIV care in the future.

IQ is a measure derived from the lowest blood levels which a specific drug fall to in an individual (called the trough level or Cmin), divided by the quantity of drug needed to suppress 50% of viral replication (the phenotype or IC50). So, written as a mathematical equation, $IQ = C_{min} \div IC_{50}$. If the IQ is low, i.e. one or below, the risk of resistance is high because the drug trough level does not exceed the amount of drug needed to control HIV replication.

But what of it? Well, researchers at Abbott Labs have already made much of the fact that IQ predicts response in people switching to a

regimen containing their boosted PI, lopinavir/ritonavir⁹. Now, using the *Virtual Phenotype*, they've derived a 'virtual IQ'; a surrogate of a surrogate as it was disparagingly referred to when presented to the Retroviruses Conference. Thirty-seven people with viral load above 50 copies on an indinavir-containing regimen received intensification with ritonavir. In this small patient group, the virtual IQ was a better predictor of response over 48 weeks of treatment than either genotypic resistance testing or *Virtual Phenotype*¹⁰.

As regular users of aidsmap.com will know, pharmaceutical companies continue to wrangle over the relevance of these measures to their particular products. At present, IQ occupies a place far from routine patient management, and although a logical concept, may turn out to be one more fad within an often fashion-driven therapy area.

key conclusions

- Current UK treatment guidelines recommend that resistance tests are used to guide therapy choices in people changing treatment, and in people who are recently infected. It appears, however, that this recommendation is not being observed in all UK centres.
- Transmission of drug resistant virus is increasing in the UK, and in the US.
- The case for resistance testing to guide therapy in people who have been infected for several years is less strong than in people who are recently infected. Tests taken in later disease are unlikely to detect minority resistant viruses, therefore storing samples from early in infection is desirable where possible.
- Several trials have shown resistance testing with expert interpretation is beneficial when therapy is changed, though the patient groups who may benefit most are not well-defined.
- Resistance testing may also be useful to guide therapy choices in pregnancy and in newborn children.
- The best type of resistance test to use is not known at present.

readers survey

reporting back from the annual *ATU* readers survey by anna poppa

Last Autumn, NAM surveyed the 6,000 people who have a free subscription to *AIDS Treatment Update*. This yearly exercise is one of the most important methods by which we learn about who is using our resources, and how effectively they are meeting needs.

As well as using this information internally to generate ideas for the development of new and existing resources, these data are crucial in supporting funding applications. Though the response to this survey is always good, in 2000 the return rate hit a new high – 25% of those surveyed sent back a completed questionnaire.

Who responded?

Eighty five per cent of respondents were male; 70% were gay men; and 90% were White. Just under half lived in London; most were in their 30s or 40s; 11% had dependent children; and 26% were born outside the UK.

Eighty nine per cent were HIV-positive, and of these, 20% had had an AIDS diagnosis, and 42% had experienced symptoms of HIV disease. Use of anti-HIV treatments reflected this – 69% of respondents were currently on treatment, and for the majority, their current combination was not their first. Drug experience varied. A third of those on

treatment were taking their first combination, a quarter were on their second, and one in six had taken three combinations.

Access to the internet has grown dramatically in recent years and *ATU* readers fit this trend. In 1999's survey we were surprised to find that 60% of respondents had access to the internet. Last year the figure grew to 72%, and for most this meant being online at home rather than at the office, or via an HIV support agency.

How is *ATU* rated?

Seventy one per cent of respondents read all or almost all of each issue of *ATU*, and 91% found the language we use about right. Amongst HIV-positive readers, 95% described *ATU* as being helpful in making decisions about treatments.

An open question invites respondents to suggest changes which would improve *ATU*, and your answers here are important in directing editorial decision-making. It's striking how many readers want more information on treatment side-effects, and complementary therapies are always mentioned frequently. New publications on these subjects are currently in development, and we look forward to bringing them to you later in the year.

“I find *ATU* very informative and helpful. The information it contains I trust and find to be honest and helpful. It also brings information that I would otherwise not hear about.” – *ATU* reader

New BHIVA guidelines

The process of updating the UK's antiretroviral treatment guidelines is underway. The British HIV Association's (BHIVA) guidelines are arguably the most influential document concerning the treatment of people with HIV in the UK, and will no doubt be met with great interest overseas.

Revised sections of the 2000 guidelines are now available in draft form at the NAM/ BHIVA website, aidsmap.com. Comments are welcomed from all sections of the HIV community and should be forwarded to Dr Anton Pozniak (email anton.pozniak@chelwest.org).

We'll also be covering the revised guidelines in detail in future issues of *ATU*.

Women & depression

According to new research from the United States, depression has a significant impact on disease progression in HIV-positive women. Women with chronic (long-term) depression were twice as likely to die than women with either limited or no depressive symptoms, and experienced a more rapid fall in CD4 count.

These data come from 765 HIV-positive women enrolled in the HIV Epidemiological

Research Study (HERS), who were followed from April 1993 to March 2000. Rates of depression were high – over the seven year period of follow-up, 42% of women reported depression. Determining cause and effect between HIV disease progression and depression was difficult. Depressive symptoms were more common at low CD4 counts and high viral loads. However, the relationship between chronic depressive symptoms and mortality remained significant even when disease stage was accounted for, leaving the researchers to suggest that depression was a *contributor* to mortality rather than being a response to poor health.

A *Factsheet* on Mental health (No. 34, April 1999) is available from NAM free of charge, and through our website aidsmap.com.
Reference: Ickovics. Journal of the American Medical Association 285:1466-74, 2001.

Steroids in women

Anabolic steroids are synthetic versions of the male hormone testosterone, that promote the formation of lean body mass, skeletal muscle, and masculine sexual characteristics in the body. Anabolic steroids have been shown to increase muscle mass, and so may be used to treat AIDS wasting and weight loss. However, most studies have investigated their use in men, and in comparison, the use of anabolic steroids

in the treatment of HIV-positive women is much less well understood.

Although testosterone is considered a male hormone, it also occurs naturally in women, but at lower levels. A study investigating the use of testosterone patches in women with AIDS wasting found weight and quality of life improved in some women, and the development of 'masculine', or 'virilising', features, such as hair growth, or a coarsening of the voice, was not reported.

At February's 8th Annual Retroviruses Conference in Chicago, Dr Kath Mulligan reported results from ACTG 329, a clinical trial of an anabolic steroid, nandrolone decanoate, in HIV-positive women diagnosed with wasting.

Nandrolone is approved in the US for treatment of men and women with anaemia associated with chronic kidney disease, where it has been shown to increase lean body mass. It has also been found to increase lean body mass in open-label studies involving HIV-positive men.

38 women were randomized to receive either twelve weeks treatment with placebo or with nandrolone, dosed 100mg once every two weeks by injection into muscle. For the next twelve weeks, everyone in the study received nandrolone, with a follow-up assessment at 36 weeks. Participants:

- had involuntary weight loss of at least 5% in the past year, or a body mass index below 20kg per metre squared
- had been on stable anti-HIV therapy for at least 30 days
- and were consuming more than 80% of their resting energy requirement.

During the blinded phase, there was a significant increase in weight and lean body

mass in the women receiving nandrolone compared to placebo. In the open-label phase, women who had previously received placebo, gained weight and lean body mass, and women who had previously received nandrolone sustained their gains. Women had not been offered advice on exercise, and this was not investigated in this study.

Side-effects were rare, but occurred primarily in the nandrolone group (and included hoarseness, hirsutism, and clitoral enlargement). These were not considered severe, and were found to resolve off treatment.

A separate study investigating the use of low-dose testosterone in HIV-positive women is ongoing in the US.

Reference: Mulligan. 8th CROI abs 641, 2001.

Drug interactions

Researchers from the Netherlands have reported the cases of five men taking nevirapine-containing HAART alongside the herbal anti-depressant St John's Wort (hypericin). All five experienced reductions in blood levels of nevirapine, a potential risk for treatment failure. St John's Wort has previously been reported to reduce levels of indinavir. It is recommended that this herbal treatment is not combined with anti-HIV drugs.

At the 8th Annual Retroviruses Conference held earlier this year, US researchers reported that garlic supplements, commonly used to reduce cholesterol, lowered blood levels of the protease inhibitor saquinavir. This study involved HIV-negative volunteers who were exposed to saquinavir as a sole antiretroviral. Though this report suggests a need for caution in the use of garlic supplements where saquinavir is taken as a sole protease inhibitor, there are no similar data on the use of saquinavir with another PI, e.g. ritonavir.

Reference: de Maat. AIDS 15:420-21, 2001. Piscitelli. 8th CROI, abs 743, 2001.



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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>

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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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