

# Clinical issues in **HIV/AIDS**

This series focuses on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

The tenth bulletin addresses important questions regarding the role and clinical utility of HIV drug

resistance testing in the treatment of both drug-experienced and drug-naive patients.

The review section takes a look at the Global Treatment Access Campaign website, plus two of the best HIV/AIDS news services on the web.

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## Commentary

'It is the virus, stupid' is an observation, attributed to AIDS research pioneer David Ho, that signalled a landmark in the development of management strategies for the treatment of HIV infection. In this issue, Deenan Pillay of the Public Health Laboratory Service Antiviral Susceptibility Reference Unit explores the clinical utility of having qualitative knowledge about specific HIV infections as well as quantitative measures of plasma concentrations of the virus. In most aspects of medicine, every advance poses new questions for the clinician, and the treatment of HIV is no exception.

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# Commentary continued

At present, there is an ever increasing array of unanswered questions in our clinic rooms. Among these are:

- What is the best starting antiretroviral therapy combination in treatment-naive patients?
- What is the best course of action when patients who are doing well on antiretroviral therapy develop small blips of low-grade viraemia?
- What is the best way to manage lactic acidosis?
- What is the best way to manage patients with disorders of fat metabolism and lipodystrophy?

These questions, seen in relation to the complexities of therapeutic drug monitoring (dealt with in the ninth issue of *Clinical issues in HIV/AIDS*) and to the role of viral resistance testing discussed by Dr Pillay, indicate the need for increased effort in, and funding of, research.

In the UK we have limited numbers of HIV-infected patients (about 20,000 patients in active treatment), distributed in over 300 treatment centres across the country. Although the overwhelming majority of patients are attending treatment centres in or around large cities, particularly London, there is a lack of any integrated approach towards their management. The trials that are offered to patients depend on which treatment centre they attend. Some centres have a tradition of making therapies licensed elsewhere in the world available on a named-patient or compassionate basis, while others do not. Some centres have forged links among themselves to develop collaborative audit and common guidelines, whereas others have not.

The clinician and the patient must select antiviral therapies based on the combination of efficacy, durability, tolerability, convenience and impact on quality of life. The evaluation of studies examining each of these elements – and impact on quality of life in particular – is essential in order to reach an appropriate conclusion for individual patients.

*The national strategy for sexual health and HIV*<sup>1</sup> clearly identifies the development of clinical networks as an essential target. If this is to be meaningful, then we must break down barriers

between units treating people with HIV by using joint appointments, integrated information systems, and collaborative audit, guidelines and research. If we are to develop a national protocol for the effective treatment of people with HIV which encompasses a critical and robust research framework, then it is essential to establish the principle that all HIV treatment providers have access to information and have the capacity to refer individuals who wish to participate in clinical research trials. An individual diagnosed with HIV being managed within a particular clinic should, therefore, have information about all the research studies available in that sector, within regional networks, and about national, or indeed international, studies. It is essential that this is co-ordinated by the national provider.

The recent emphasis on infectious diseases set out by the Chief Medical Officer,<sup>2</sup> coupled with *The national strategy for sexual health and HIV*, must result in investment in political and organisational change. This would enable us to develop a national treatment service which would set about answering the unanswered questions, defining best clinical practice and rigorously ensuring that the introduction of viral resistance testing is, as Dr Pillay rightly observes, given appropriate expert support, training and evaluation.

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# Is a resistance test essential for optimal HIV care?

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A multitude of reviews on HIV resistance testing have been published over the last five years. Many of these have listed lots of key resistance-associated mutations, and have described the different test methodologies available. In addition, every local, national or international educational HIV meeting appears to include the seemingly mandatory 'state-of-the-art' talk on drug resistance. How is it, therefore, that even when bombarded with so much information, such confusion reigns within the clinical community over the relevance of resistance testing to patient care?

In part, this is because of the sheer complexity of the HIV resistance reports landing on physicians' desks. On top of this, the rapid rate at which resistance research generates clinically applicable data means that physicians struggle to keep up.

## **Peculiarities of HIV resistance assays as routine diagnostic tests**

Diagnostic tests for viral infections have become increasingly sophisticated, such as quantitative polymerase chain reaction for HIV/hepatitis C virus/cytomegalovirus viral load. However, even taking such tests into account, it is difficult to appreciate the sheer complexity of the gene-sequencing techniques entering the diagnostic arena. Until very recently, such high throughput sequencing techniques were limited to basic biological research establishments, such as those involved in the Human Genome Project. The key problem in HIV resistance testing is the huge amount of information generated from each patient. If these raw data were passed directly to the clinic they would be unmanageable, which is why software interpretation systems are an essential adjunct to sequence-based assays.

Indeed, it is the interpretation of resistance assay results, rather than the results themselves, which really determines the clinical utility of such tests. Phenotypic assays are even more demanding technically, as results are provided as a quantitative 'fold resistance' compared with wild-type (non-resistant) virus. At first sight, this may appear more user-friendly than a list of mutations generated by genotypic assays. However, on closer inspection, it is apparent that clinically significant reductions in fold-susceptibility are likely to be different for each drug, and therefore need to be established first to allow best use of these quantitative results. Studies have provided this data for abacavir, lopinavir and ritonavir.<sup>1,2</sup>

A second issue is the high cost of resistance tests. The charge for genotypic assays reaches £200–£300 per test, and charges for phenotypic assays are even higher. This immediately limits their availability, so criteria are required for their use, which in turn require an evidence base. It would be surprising if very routine laboratory tests, such as full blood counts, were ever subject to randomised controlled trials to justify their use, and it is doubtful that their clinical utility would be very high. Nevertheless, as they cost very little, this does not matter. In contrast, HIV resistance tests have been intensively studied, and, not surprisingly, the results on clinical utility are mixed.

## **When to use these tests**

Three lines of argument can be used to justify testing patients for resistance. First, and perhaps the most used in practice, is biological plausibility, that is it makes sense to select drug regimens to which the virus appears most susceptible. Second, multiple retrospective studies demonstrate that genotype (presence and number of specific mutations in viral genes) or phenotype (fold

resistance of the virus to one or more drugs) testing at the time of virological failure predicts response to a subsequent drug regimen.<sup>3</sup> Third, results from prospective randomised studies, in which patients at time of failure may or may not be randomised to a resistance test before their subsequent regimen, demonstrate some virological benefit of testing.<sup>4-10</sup>

### Testing drug-experienced patients

The purpose of testing patients who have a rebound in viral load on therapy is to assist in the choice of the next regimen. Patients failing antiretroviral therapy are, of course, a highly heterogeneous group. Not only may they be failing first-, second- or third-line therapy, but their history may include many years of mono- and/or dual therapy, and the precise drugs received may differ significantly. In addition, levels of adherence may be vastly different. Consequently, it is not surprising that the utility of resistance testing observed in clinical trials is variable. For patients on regimens for which virological failure is characterised by the emergence of predictable resistance patterns, such as a regimen containing lamivudine<sup>11</sup> or non-nucleoside reverse transcriptase inhibitors,<sup>12</sup> the utility of resistance assays is reduced, since the presence of specific mutations in the viral genome can be more easily predicted, (that is from drug history alone). By contrast, failure of other regimens, including some protease inhibitors,<sup>13</sup> may be associated with a range of different resistance patterns which are more difficult to predict. This is also the case for heavily pretreated patients, since emergence of

resistance to one particular regimen is determined to some extent by the pre-existing presence of resistance.

The somewhat paradoxical situation therefore exists whereby resistance assay results from first-line failures are generally straightforward to interpret, although the clinical utility (the added value of resistance data over and above knowledge of viral load and drug history) is less likely to be high. In comparison, resistance tests with multidrug-experienced patients are more difficult to interpret, yet probably offer more clinical utility. The utility of testing such drug-experienced patients has been formally assessed by a number of prospective studies (Table 1<sup>4-10</sup>). In view of the different follow-up periods and preliminary nature of many of the results, the results are not described here in full. In general, however, undertaking resistance assays in these patients contributes a further 0.5 log<sub>10</sub> viral load reduction at 12-24 weeks, due to improved selection of appropriate drugs. This is a significant benefit for such drug-experienced patients.

In addition, one study (HAVANA)<sup>8</sup> included 'expert opinion' within its randomisation criteria, and demonstrated that when these 'experts' guided therapy, the benefit of resistance tests was further enhanced. This observation is explained not only by the familiarity of specialists with resistance patterns, but also by their consideration of previous drug history in the context of the resistance test. It is increasingly recognised that viral variants arising through the course of infection may increase and diminish within plasma, but that they will all be archived within the body, and can therefore easily re-emerge at a subsequent date. As a result, a resistant virus emerging under the selective pressure of first-line therapy may not be detected on failure of the next regimen.

For instance, following failure of a first-line, non-nucleoside analogue-containing regimen, the presence of either of the RT mutations K103N or Y181C is likely to be present in plasma virus. However, if the patient subsequently changes to a non-nNRTI containing regimen, and then fails again, plasma virus may not appear to contain these mutations. If a resistance test at the latter date is taken purely on face value, drugs may then be used which rapidly select for the earlier resistant strain. Thus, it is essential that the full drug history is considered when interpreting assay results. As patients start to be resistance tested for a second or third time, it is vital that all the results are available

**Table 1. Some randomised trials of HIV drug resistance assays**

Trial	Method	Duration
VIRADAPT	G vs SC	24 weeks <sup>4</sup>
GART	G+EA vs SC	12 weeks <sup>5</sup>
VIRA3001	P vs SC	16 weeks <sup>6</sup>
NARVAL	P/G vs SC	12 weeks <sup>7</sup>
HAVANA	G±EA vs SC±EA	24 weeks <sup>8</sup>
ARGENTA	G+EA vs SC+EA	24 weeks <sup>9</sup>
CCTG 575	P vs SC	52 weeks <sup>10</sup>

G, genotypic; SC, standard care; EA, expert advice; P, phenotypic

to the physician deciding on the next treatment. Preliminary data do indeed suggest that response to therapy in multidrug-experienced patients is better predicted by combining results of two previous resistance tests than by considering the latest results only.<sup>14</sup>

### Testing drug-naive patients

The purpose of undertaking resistance testing before initiating antiretroviral therapy is to detect the presence of pre-existing resistance (transmitted drug resistance), which may limit the efficacy of initial therapy. However, the high cost of testing has generally inhibited widespread application of the assay to these patients until such time as surveillance data show a significant degree of transmitted resistance. A cost-benefit analysis has demonstrated the advantage of testing in prevalence rates above 10%,<sup>15</sup> levels which have now been reached in UK<sup>16</sup> cohorts.

However, some drug-resistant strains of HIV-1 have reduced 'fitness' compared to 'wild-type' virus.<sup>17</sup> Therefore, following transmission of such viruses, ongoing evolution of the virus can lead to reversion of resistance mutations, and resistance will not be detected by standard methods. Testing chronically infected patients before therapy may, therefore, underestimate transmitted resistance, even though these transmitted strains are present as archived virus. This reversion occurs because of the reduced fitness generated by resistance mutations, which is not beneficial to the virus in the absence of therapy. The virus, therefore, evolves into its fittest form.

Until recently, this has been a valid argument, leading to the recommendation that samples from the time of primary infection should be tested for resistance, but not necessarily samples from those presenting with chronic infection at a later stage (the majority of new diagnoses). Recent data have led to a re-evaluation of this position and it is now recognised that some sets of resistance-associated mutations persist for considerably longer than had previously been thought. More importantly, for the most common resistance mutation – T215Y in reverse transcriptase, associated with reduced zidovudine (ZDV) susceptibility – transmission of viruses leads to the evolution of novel amino acids at this position not observed in other situations.<sup>18</sup> These mutations restore full ZDV susceptibility and increased fitness to such viruses, and can therefore persist in the absence of therapy. However, reversion back to ZDV resistance

from these novel forms is easier than from the wild-type form, and may compromise subsequent therapy. These novel forms, therefore, represent a 'marker' for transmitted resistant virus, which, as discussed above, will remain archived within the body.<sup>19</sup> The recognition of such long-surviving markers of transmitted resistance also suggests that more widespread testing of drug-naive patients (newly and chronically infected) may be justified in communities in which transmitted resistance is well documented.

Unlike the case in drug-experienced individuals, it is very difficult to formulate randomised trials of resistance tests in the drug-naive, and therefore the basis for recommending such testing is biological plausibility. Resistance is not 'all or none', and also may or may not confer cross-resistance to more than one drug. Therefore, transmitted resistance may or may not impact on the success of first-line therapy. Indeed, the presence of a single mutation before therapy may only compromise treatment at a later time (second- or third-line therapy). The long-term impact of transmitted resistance can only be determined by follow-up of patients tested for resistance before therapy. Ideally, this should be done in seroconverter cohorts, in whom the impact of transmitted resistance on progression of disease can better be assessed.

## Conclusions

Sufficient data from clinical trials as well as cohort studies now exist to justify the implementation of more widespread HIV drug resistance testing. This should not only occur in drug-experienced patients at each time of treatment failure, but also in those yet to receive therapy for communities in which transmission of resistance has been well documented. However, the interpretation of these results is a key determinant of their clinical utility, and HIV physicians should ensure that the relevant expert support is in place to maximise the benefit these data have on the care of their patients.

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## Website review

● Around 95% of the world's 36 million people with HIV/AIDS have no access to affordable life-extending medication according to the Global Treatment Access Campaign (GTAC), which seeks to redress this deficiency, utilising the internet as one of its 'action tools'. GTAC is an international network which supports partnerships between activist groups in the developed and the developing world. It originated in July 2000 at the 13th International AIDS Conference in Durban, South Africa, as a coalition of organisations and individuals advocating debt cancellation and increased access for essential medications and technologies in countries facing an escalating AIDS epidemic.

The GTAC website can be found at [www.globaltreatmentaccess.org](http://www.globaltreatmentaccess.org) and is very accessible, self-contained and straightforward in design. Its Resources page allows posters, flyers and palm cards to be downloaded as PDFs. The list of links covers a wide range of countries but is not very large and the Media Tools section is a bit limited in its range of ideas. When I last visited the site at the start of April, the Press Center page only seemed to extend to the end of 2001 but again was universal in outlook.

Around 60% of the world's population live in low-income countries but only 5% of the world's internet users come from such areas. Nevertheless, the ability to access information from sites like GTAC's and to interact with people via the relatively cheap medium of email is an invaluable option where technological accessibility may be limited. Even in areas like Africa, where the number of internet users is small (about four million), the use of web-based mail accounts in internet cafés makes this a realistic method of communication.

● If you really want an up-to-date AIDS news service, try the American Association for the Advancement of Science website ([www.aidsscience.com](http://www.aidsscience.com)). The site is produced by the publishers of *Science* magazine as a centralised, global, online source of information on all aspects of AIDS prevention and vaccine development. The site

map is of an unusual design, being laid out in a tree structure like a PC's hard drive – I found it remarkably easy to navigate.

When I visited the Literature and News section, there was a fascinating article on the implications of the 11 September terrorist attacks for HIV prevention programmes. This section allows you to download content, submit responses, search for articles by the same author or look for similar articles and titles – not only in this journal but in others as well.

You can subscribe for free to receive notification when weekly issues of *AIDScience* are published online, and I would recommend doing so.

● The US-based [www.kaisernetwork.org](http://www.kaisernetwork.org) is a good information resource for all major healthcare issues, although Flash 6.0 (free when you visit) is helpful. The site is funded by the Henry J Kaiser Family Foundation and this fantastic service is a credit to Henry. In particular, the *Kaiser Daily HIV/AIDS Report* provides an awesome amount of information, although it is strongly biased towards the American perspective.

I found some of the site difficult to navigate, particularly the Calendar section, which offers a searchable list of events in reproductive healthcare as well as HIV and AIDS (again focused on North America). There is a complete listing of live and archive web-casts of seminars, press conferences, interviews and congressional hearings and you can sign up to receive an email reminder in advance of individual broadcasts.

Finally, the Adwatch page is a library of health policy issue advertisements from interest groups. The analysis of trends in pharmaceutical advertising and the review of controversial AIDS drug advertisements brought to mind the imbalance between the developed and the developing worlds which GTAC is seeking to eradicate.

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