HIV/AIDS Antiretroviral Newsletter

The aim of this biannual newsletter is to provide health workers in the Region with a brief, up-to-date summary of the latest developments in antiretroviral therapies.

World Health Organization

Regional Office for the Western Pacific

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Part 1. Accelerating Access to HIV/AIDS Care and Treatment in Developing Countries

BACKGROUND

With 95% of the world's 36 million HIV-infected people living in the developing world, improved access to HIV care in these countries is essential. Medical care in industrialised countries is significantly extending the lives of people living with HIV/AIDS (PLWHA). The challenge now is to improve access to care, including treatments for opportunistic infections and antiretroviral (ARV) therapy, in the most affected regions of the world.

ACCELERATING ACCESS TO CARE

The aim of the *"Accelerating Access to HIV/AIDS Care and Treatment in Developing Countries"* is to assist countries in implementing comprehensive packages of HIV care by providing expertise in the areas of advocacy and policy guidance at the global level. It also involves "fast track" support for those developing countries who have formally indicated that they wish to expand access to HIV care, support and treatment.

The objectives of this initiative are:

- to enhance progressively the capacity of countries to improve access to care and support for PLWHA;
- to increase the availability and access to HIV related drugs and technologies;
- to strengthen national capacity to prevent HIV infection.

Five pharmaceutical companies (Boehringer Ingelheim, Bristol-Myers Squibb, Merck, GlaxoSmithKline, and Roche) as well as suppliers of generic drugs, UN agencies, (WHO, UNICEF, UNFPA, World Bank, UNAIDS) and governments are participants. The initiative programme will facilitate negotiation with Research and Development (R&D) companies, to facilitate pre-qualification of generic ARV suppliers, to set standards for the quality of ARVs and identify independent quality control laboratories.

The initiative currently is not offering country group negotiations or bulk purchasing of ARVs. Such negotiations are subject to the countries' health ministry and R&D companies. The initiative may provide technical support to countries on how to negotiate with R&D companies

Part 1 of this edition of the *HIV/AIDS Antiretroviral Newsletter* focuses on initiatives contained within the comprehensive package to improve access to ARV therapy.

A COUNTRY DRIVEN PROCESS

Ongoing political commitment by national governments is essential for the successful implementation of any strategy to improve ARV access. The process is initiated by the national government, which is responsible for the implementation of its decisions. At the request of a member country, UN agencies and their partners in this initiative will provide technical support.

DRUG PROCUREMENT

Following a request for assistance by a country and an analysis of the current situation, an action plan will be developed to cover all aspects of HIV care delivery relevant to the country's needs. With reference to ARV supply, the country action plan will include the following:

- the mechanism by which the government will purchase drugs;
- how the purchase of drugs will be financed;
- how the rational use of drugs will be supported (e.g., training of health care workers, improved laboratory services).

Expressions of interest have been requested from research-based and generic pharmaceutical

manufacturers interested in becoming potential suppliers of ARVs as part of this initiative.

A drug procurement system can operate at three levels, involving individual countries, groups of countries in a particular region or sub-region or globally, using existing schemes operated by UNICEF, UNFPA or WHO.

UN agencies, in co-operation with Medecins Sans Frontieres (MSF), initiated a joint project to identify potential suppliers. Applications had been received from 34 manufacturers of antiretroviral drugs from 16 countries (including 29 manufacturers of generic products) and 11 manufacturers of other diagnostics and commodities. Information supplied included:

- the registrational status of the product in the country of origin;
- cost of the product in the county of origin;
- production capacity of the manufacturer;
- possession of Good Manufacturing Practice (GMP) certification and manufacturing license.

This project will produce and maintain a database containing information relevant to drug procurement for use by countries and donor agencies. More facts on the availability and prices of ARVs, published in the background paper entitled *Selected drugs used in the care of people with HIV: sources and prices*, can be found at www.unaids.org. Further information is available by contacting The Technical Services Centre, UNICEF Supply Division (supply@unicef.dk or fax + 45 35 269421).

THE PRICE OF MEDICINES

Multiple approaches are needed to make HIV treatments available to people living with HIV/AIDS in countries with limited resources. These approaches include:

***Tiered pricing*:** Pharmaceutical companies make antiretrovirals available in developing countries at highly reduced prices, while established markets are protected.

Competition: between suppliers (both research-based and generic manufacturers) to reduce prices.

***Regional & sub-regional procurement*:** Groups of countries or regions collaborate to purchase larger volumes of drugs, and thereby benefit from further discounts.

***Licensing agreements*:** Companies with patent medicines offer licenses to other manufacturers based in developing countries if they are able to produce the same quality medicines at lower cost.

***Compulsory licences*:** Using the emergency health safeguards built into trade arrangements, international agreements and national intellectual property legislation allow for countries to issue compulsory licences to manufacture patented medications, in situations of national emergency.

***New funding mechanisms*:** Public and private sector funding may need to be increased dramatically to help pay for treatment, which, even at the lowest prices, may still be out of reach of many of the poorest people living with HIV/AIDS.

Three countries, Rwanda, Senegal and Uganda, have reached agreements with four research-based pharmaceutical companies to provide antiretrovirals at significantly reduced prices

Negotiated ARV costs in Uganda	Cost per day ($US)
AZT + 3TC	2.00
3TC	0.58
Nevirapine	1.22
ddI	0.85
d4T	0.75
Indinavir	2.75
Efavirenz	2.93

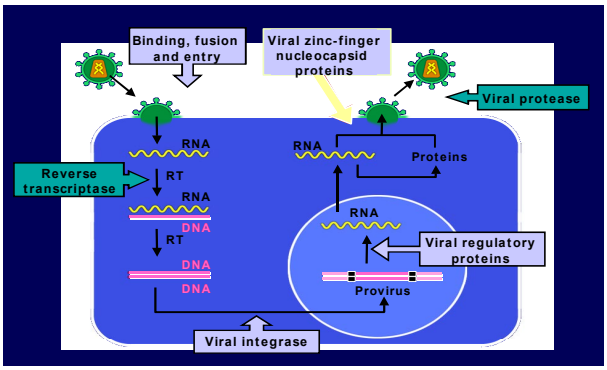
Table 1: Negotiated prices (per daily dose) in Uganda. These prices are similar in Rwanda and Senegal.

Antiretroviral	Unit	Minimum price ($US)	Maximum price ($US)	Price in the United Kingdom ($US)
Zidovudine	100 mg capsule	0.18	0.30	1.68
Lamivudine	150 mg tablet	0.89	0.89	3.83
Stavudine	40 mg capsule	0.30	0.85	4.32
Didanosine	100 mg tablet	0.61	0.61	2.06
Nevirapine	200 mg tablet	1.50	1.50	3.94

Table 2: Prices (US$) of antiretrovirals as supplied by manufacturers for the joint UNAIDS/UNICEF/WHO/MSF database and compared to prices (converted to US$) in the United Kingdom (British National Formulary March 2000)

Part 2. Recent developments in antiretroviral therapy

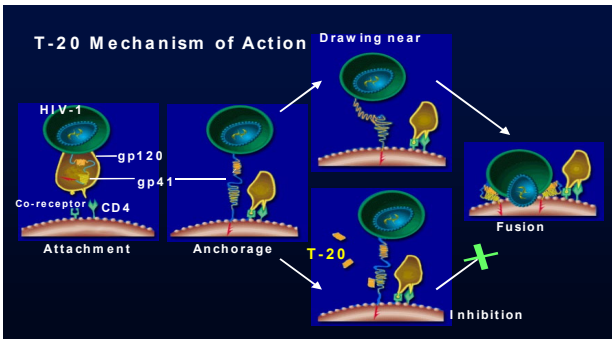
VIRAL ENTRY AND FUSION INHIBITORS



Currently, there are 16 licensed antiretroviral drugs that inhibit HIV replication by blocking transcription (nucleoside and non-nucleoside reverse transcriptase inhibitors) or assembly (protease inhibitors). However, these drugs are limited by problems of resistance, latent viral reservoirs and toxicity. New classes of ARVs with different mechanisms of action are needed. One approach is to block HIV entry into human cells.

Fusion inhibitors, such as T-20, prevent HIV from fusing with and inserting its genetic material into host cells. Although there appear to be few side effects related to T-20, it must be administered by subcutaneous injection twice daily.

In phase II studies, T-20 has been studied in combination with highly active antiretroviral therapy (HAART). The drug appears well tolerated but localised injection site reactions were seen in two thirds of patients. Resistance to T-20 has been demonstrated. T-1249 is a new fusion inhibitor that appears to be a substantial improvement over the initial T-20 preparation. T-1249 binds to a slightly different part of gp41, so the gp41 mutations that prevent T-20 binding do not appear to result in resistance to T-1249. It also has a much longer half-life than T-20 and can be administered once daily.



STRUCTURED TREATMENT INTERRUPTION

The strategy of structured treatment interruption involves deliberately ceasing ARV therapy for a fixed period of time and restarting therapy according to pre-set criteria, such as CD4 count decline or increase in viral load. Another approach to STI starts and stops therapy in week on/week off cycles.

Structured treatment interruption has been evaluated in acute and chronic HIV infection and as part of salvage therapy. In the first two situations, the rationale for this strategy is to reduce long-term drug toxicity and cost in addition to stimulating or preserving HIV-specific CD4 T-cell responses. Intermittent therapy may also enhance adherence by allowing patients to take "drug holidays". In the situation of salvage therapy, treatment interruptions prior to the commencement of the salvage regimen have led to the re-emergence of drug-susceptible virus. There are potential dangers associated with this strategy, including emergence of drug-resistant virus, declines in CD4 cell counts, viral load rebound and the development of new or recurrent opportunistic infections. While several small-scale studies in HIV-infected adults have demonstrated the feasibility of this novel approach, a large randomised clinical trial is needed to establish whether these regimens are safe and whether they reduce drug side effects and cost.

The largest ongoing study of structured treatment interruption in patients with chronic HIV infection is the Swiss-Spanish Intermittent Treatment Trial (SSITT). This study enrolled 128 patients who initiated antiretroviral therapy with HAART and who had viral load less than 50 copies/ml for at least 6 months. Patients interrupted therapy for 2 weeks, and were then treated for 8 weeks. After 4 of these cycles, patients stopped therapy until viral load increased to > 5000 copies/ml. 21% of the 99 patients who have reached week 52 have successfully remained off therapy with viral load < 5000 copies/ml. Predictors of response included the absence of viral rebound after 2 weeks of structured treatment interruption and lower pre-therapy viral load levels. These data suggest that a minority of patients with chronic HIV can successfully stop therapy after 4 cycles of this structured treatment interruption schedule. Again, the findings suggest that more study is needed before adopting this structured treatment interruption strategy in the clinic

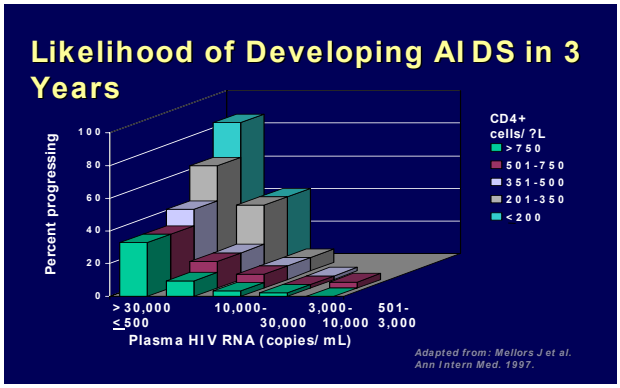
INITIATING THERAPY: WHEN TO START AND WHAT TO START WITH?

The US Dept of Health and Human Services (DHHS) guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents were recently updated. The current guidelines are published at http://hivatis.org/trtgdlns.html.

The main changes in the current guidelines refer to initiation of therapy in asymptomatic patients. Previously, the guidelines had recommended initiating treatment in individuals with symptomatic HIV infection and in asymptomatic patients with CD4+ cell counts < 500 cells/mm^3 or plasma HIV-1 RNA levels greater than 20,000 copies/ml.

However, the new DHHS guidelines recommend that treatment be delayed until the CD4+ cell count is less than 350 cells/mm^3 or viral load is greater than 55 000 copies/ml. The guidelines are clear that these recommendations are not absolute and that many experts would recommend earlier treatment in a motivated, well-informed individual. Other experts might wait until the CD4+ cell count falls even further, especially if the viral load is low. In developing countries with limited resources, treatment of asymptomatic patients may be delayed until CD4 count is < 200 cells/mm^3.

Data from the MACS (Massachusetts AIDS Cohort Study) cohort of patients published by John Mellors in 1997 also assists physicians and patients in making the important decision on when to start therapy.



On the issue of what therapy to start with, the DHHS guidelines recommend that efavirenz, indinavir, nelfinavir, lopinavir plus ritonavir, indinavir plus ritonavir, or saquinavir plus ritonavir be used in conjunction with 2 nucleoside reverse transcriptase inhibitors (NRTI). Recommended dual-NRTI regimens are zidovudine plus lamivudine, stavudine plus lamivudine, stavudine plus didanosine and zidovudine plus didanosine. Nevirapine, amprenavir, abacavir, and saquinavir (soft gel formulation) are not included in the strongly recommended list of drugs but are included as recommended alternatives.

NEW RECOMMENDATIONS IN PREGNANCY

On May 4th 2001, The United States Public Health Service Task Force for the use of antiretroviral drugs in pregnant HIV-1 infected women published updated guidelines.

The use of ARV during pregnancy, whether primarily to treat HIV infection, reduce perinatal transmission, or both, should be accompanied by counselling regarding the potential short and long term benefits and risks of such therapy for infected women and their infants. Although considerations associated with pregnancy may affect decisions regarding timing and choice of therapy, pregnancy is not a reason to defer standard therapy.

In general, combination ARV to maximally suppress viral replication (and incorporating zidovudine) should be recommended for all HIV-infected pregnant women. The provision of highly active combination antiretroviral therapy can be expected to correlate with both reductions in viral load and low rates of vertical transmission. As a minimum for the reduction of perinatal HIV transmission in developed countries, ZDV prophylaxis according to the PACTG 076 regimen is recommended unless the woman is intolerant of ZDV. In developing countries, such as Thailand, modified, abbreviated courses of ZDV are commonly used.

In these US guidelines, it is recommended that plasma HIV-1 RNA levels should be monitored during pregnancy according to the guidelines for management of HIV-infected adults. The most recently determined viral load value should be used when counselling a woman regarding mode of delivery.

Perinatal HIV-1 transmission is reduced by scheduled caesarean section among women not on antiretroviral therapy or those receiving ZDV for prophylaxis of perinatal transmission with unknown HIV RNA levels. Plasma HIV RNA levels were not available in these studies to assess the potential benefit among women with low plasma HIV RNA levels. Women with HIV-1 RNA levels greater than 1 000 copies/ml should be counselled regarding the benefit of scheduled caesarean delivery in reducing the risk of vertical transmission. Women should be informed of the risks associated with caesarean delivery, and these risks should be balanced with potential benefits expected for the neonate. Women should also be counselled regarding the limitations of the current data regarding caesarian section. The woman's autonomy to make an informed decision regarding route of delivery should be respected.

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Drug Resistance: Part 1

What is it; how to measure and interpret the results?

Next issue: Drug Resistance: Part 2 Application to clinical practice

THE BASICS

Drug resistance is a major contributing factor to the failure of antiretroviral therapy. The development of drug resistance further complicates clinical management because of the high level of cross-resistance within all three drug classes, nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). The nucleoside sequence that determines a gene is known as the genotype. The characteristics or properties of a virus are known as the phenotype, which is in turn determined by the genotype. Mutations in the genes that encode for the replicative enzymes, reverse transcriptase and protease, confer resistance to antiretroviral drugs.

Primary mutations cause decreased binding of the drug to its enzyme target and are the first mutations selected during therapy. This results in an increased amount of drug required to inhibit the enzyme. Secondary mutations contribute to drug resistance by improving the fitness of viruses carrying primary mutations. They have little direct effect on inhibitor binding or on the level of resistance in the absence of primary mutations. Genotypic resistance assays detect mutations in these key genes. Resistance mutations (such as the lamivudine M184V mutation) are described using a number to denote the mutant codon with letters before and after the codon number denoting the amino acid associated with "wild-type" and mutant virus respectively. The tables presented below indicate the mutant codon position.

Phenonotypic resistance assays measure susceptibility of the virus to antiretroviral drugs in terms of the concentration of drug required to inhibit viral replication *in vitro* by a defined amount such as 50% (IC_{50}) or 90% (IC_{90}).

The rapid turnover of HIV (estimated at 10^9 new viral particles each day), and the high error rate of the reverse transcriptase enzyme during viral replication, results in an extensive genetic diversity of the virus population. HIV is a RNA virus and, as such, lacks the proof-reading mechanisms that DNA-based organisms possess to identify and correct genetic mutations that occur during replication. The result is that drug resistant mutants (quasi-species) pre-exist in any viral population. There is also definitive evidence that resistant strains of HIV, including multidrug resistant strains, can be transmitted. If viral replication is not completely suppressed, there is rapid selection of drug resistant mutants from the viral pool.

Table 1: Mutations in the protease gene selected by protease inhibitors

Drug	Associated Mutations													
	20	30	36	46	48	50	54	63	71	82	84	88	90	101
Amprenavir														
Indinavir														
Nelfinavir														
Ritonavir														
Saquinavir														
Lopinavir														

Primary mutations: clearly associated with drug resistance.
Secondary mutations: add to the resistance caused by primary mutations.
Natural variants: natural variants of the virus that can add to drug resistance.

Table 2: Mutations in the reverse transcriptase gene selected by NRTIs and NNRTIs

Drug	Associated Mutations																
	41	65	67	70	74	75	103	115	116	151	181	184	188	210	215	219	333
3TC												■					
Abacavir		▩		▩	■			■				■		▩	▩		
AZT	■		■	■										■	■	■	
AZT + ddI/ddC									▩	■							
AZT + 3TC																	■
d4T		■			■							■					
ddI / ddC		■			■							■					
MNR					▦				▦	▦				▦	▦		
Delavirdine							■				■						
Efavirenz							■						■				
Nevirapine							■				■		■				

■ Primary mutations: clearly associated with drug resistance.

▩ Secondary mutations: add to the resistance caused by primary mutations.

▦ Multinucleoside resistance (MNR): also includes mutations at 62, 77 and 69

These mutations confer resistance to AZT, ddI, ddC, d4T, 3TC and ABC

THE MECHANISM OF DRUG RESISTANCE

Antiretroviral resistance secondary to replicative mutations in HIV develops differently depending on the drug class and can evolve via different pathways for specific drugs. Single point mutations associated with the NNRTI drug class and with lamivudine (3TC) result in rapid, high-level resistance. Step-wise accumulation of mutations is required for high-level resistance to other drugs such as zidovudine (AZT) and PIs.

NRTIs

The resistance pathway for AZT starts with the selection of the K70R mutation, which is associated with an eight-fold decrease in sensitivity. Progressive mutations at codons 215 and 41 lead to rapid replacement of the K70R mutant with these two variants and a further 60-fold decrease in the IC_{50} for AZT. Further viral evolution results in mutations at codons 67 and 219. The presence of all five mutations results in a 500-1000 fold reduction in sensitivity compared to wild type virus. At a molecular level, recent research suggests that a major mechanism of AZT resistance is enhancement of pyrophosphorolysis. NRTIs act as DNA chain terminators by inserting into the growing viral DNA chain as it is being copied by reverse transcriptase. Once inserted, further DNA synthesis is blocked. This process is called phosphorolysis. Pyrophosphorolysis (primer unblocking) is the reverse of this process whereby the nucleoside (AZT-triphosphate) is removed from the chain, allowing reverse transcription to resume. Pyrophosphorolysis enhancing mutations are shared between AZT and stavudine (d4T) and this may, in part, explain the cross-resistance between these two NRTIs seen in clinical practice. That AZT and d4T, both thymidine nucleoside analogues, share common resistance mutations led to the coining of the term "TAMS" (thymidine analogue mutations).

However, this set of mutations, when combined with the M184V mutation, blunts the response to abacavir, a guanosine analogue. Some researchers now believe that resistance to NRTIs cannot be grouped into analogue-specific clusters. Sets of mutations have now been described that confer resistance to all of the available NRTIs. (See Table 2)

NNRTIs

All drugs in the NNRTI, although structurally different, bind to the same site on the reverse transcriptase enzyme. They do so by creating a binding pocket and acting as non-competitive inhibitors of the enzyme. Mutations are found in clusters between codons 100-108 and 179-190 and confer broad-based cross-resistance to all three available drugs in this class. The most commonly selected mutations are K103N (efavirenz, nevirapine and delavirdine) and Y181C (nevirapine and delavirdine). In a partially suppressive regimen, resistance emerges rapidly due to these point mutations.

PROTEASE INHIBITORS

Protease inhibitors compete with substrate for binding at the active site on the HIV-1 protease enzyme. Forty-two mutations occurring at 27 codons have been associated with PI resistance. Many of these map to the binding site of proteases and interfere with PI binding. Secondary mutations map to other regions and improve the activity of proteases without directly effecting inhibitor binding. Resistance to PIs results from step-wise accumulation of mutations, which occur rapidly if these drugs are administered at inadequate doses or as part of non-fully suppressive drug regimens. The presence of two or more of the key PI mutations (D30N, G48V, I50V, V82A, F, T or S, I184V, L90M) is likely to confer broad cross resistance to most currently available PIs.

However, studies have demonstrated that PI-resistant virus has reduced replicative capacity. This may explain why viral load levels can remain partially suppressed in the presence of high-level PI resistance. An understanding of PI resistance is complicated by extensive polymorphism (naturally occurring variations in sequences) found in viral isolates from PI-naïve patients. Additionally, PI resistance is not only dependent on drug susceptibility but also is strongly linked to achievable plasma drug concentrations. For example, recent data suggests that early resistance to indinavir can be overcome by pharmaco-enhancement of indinavir plasma drug levels with low doses of ritonavir.

MEASURING DRUG RESISTANCE IN PRACTICE

Resistance testing in the management of HIV-infected patients is now considered standard in developed countries. In developing countries, resistance testing remains limited largely to the research setting.

Retrospective studies have shown that pre-treatment genotyping or phenotyping is significantly predictive of virological response. Prospective studies have shown that treatment decisions based on resistance assay data are associated with improved virological outcome. In the VIRADAPT study, patients on a PI-containing regimen with viral load >10,000 copies/ml were randomly assigned to have their therapy changed based on clinical judgement or with access to genotypic testing. In six months of follow-up, significantly more patients in the genotype guided group had viral load <200 copies/ml (32% versus 14%). The VIRA3001 study demonstrated a significantly greater reduction in viral load at week 16 in patients failing first line PI-containing therapy whose salvage regimen was based on phenotypic assay results. In the NARVAL study, patients were randomized to genotyping *versus* phenotyping *versus* a control arm. There was no significant benefit seen in terms of short-term virologic outcome between the randomized groups, but a trend favouring genotyping was noted.

Data from these and other studies have been used to perform cost-effectiveness analyses of resistance testing. Current costs in US$ range from $400-$550 for sequencing of protease and reverse transcriptase to $700-$900 for phenotypic testing. Given the high cost of ARV and the savings that result from not using ineffective drugs, these assays are highly cost-effective in a developed country setting. The economics are not dissimilar in developing countries, especially when second-line drugs are employed. Despite recent ARV price reductions, the drugs used in salvage therapy remain generally expensive and should be used in the most cost-effective manner. More widespread use of resistance assays in the future seems likely in certain situations in developing countries.

Table 3: International AIDS Society Consensus Panel recommendations for antiretroviral resistance testing

Clinical situation	Rationale
Primary HIV infection	Detect transmission of drug resistant virus. Modify therapy to optimize response[1].
Established HIV infection[2]	Detect prior transmission of drug resistant virus, although may not always be possible with current tests.
First regimen failure[3]	Document drugs to which there is resistance to guide choice of second-line regimen.
Multiple regimen failures[3]	Optimize the number of active drugs in the next regimen and exclude drugs to which response is unlikely.
Pregnancy	Optimize maternal treatment and prophylaxis for the neonate.

1. E.g., ritonavir boosting if viral suppression to below the level of detection is not rapidly achieved.
2. In untreated established infection, wild-type virus may replace drug resistant quasi-species over time. These quasi-species will rapidly be selected by drug pressure once the patient commences antiretroviral therapy. Drug resistance results should be interpreted with caution in this situation.
3. The results are most reliable for drugs that are being taken by the patient at the time of testing.

LIMITATIONS OF RESISTANCE ASSAYS

The use of genotypic and phenotypic resistance assays is complicated by a number of factors. In general, plasma samples with more than 500 to 1,000 HIVRNA copies/ml are needed to generate a result. Resistance data from the predominant species may not reflect important minority populations, since viral species constituting less than 20% to 30% of the amplified product may not be detected with currently available assays.

Drug selection pressure at the time of testing may also effect the result. False negative results may occur if blood is drawn after therapy is changed or stopped because susceptible wild-type variants outgrow the resistant virus. For example, the M184V mutation is rapidly lost after lamivudine withdrawal. Blood should be drawn for resistance testing before the failing drugs are stopped.

Interactions between resistance mutations may complicate interpretation of results. To use M184V again as an example, this mutation partially reverses resistance to AZT conferred by mutations in codons 41, 67, 70, 210, 215 and 219. A thorough knowledge of drug cross resistance and mutation interactions in all the classes of ARV is necessary to interpret results and to plan an appropriated change of therapy.

In addition to resistance testing, other important factors need to be considered when making a decision to switch regimens. These include adherence, drug treatment history, viral load, medication tolerance, concomitant medical conditions and medications.

NEW RESEARCH

VIRTUAL PHENOTYPE

Virtual phenotype is a new concept which employs a database with thousands of clinical isolates in which both the genotype and phenotype are known. The virtual (or derived) phenotype is determined by taking a patient's genotype and matching it with genotypes in the database. Given the complexity of interpreting genotypic assay results, this new technology may allow for an objective and quantifiable method to interpret the genotype in a consistent manner. In addition, since it is based on a genotypic test, virtual phenotype is likely (although not certain) to be cheaper and faster than phenotypic tests.

INHIBITORY QUOTIENTS AND BIOLOGICAL CUT-OFFS

There has been much interest recently in the use of inhibitory quotients (IQs) as a better measure of resistance. The IQ is based on the actual or expected minimum drug concentration (plasma C_{min}) divided by a measure of viral susceptibility to that drug (IC_{50}). The equation can be written $IQ = C_{min}/IC_{50}$.

Theoretically, the IQ is a better measure of resistance because, for most drugs, viral resistance is relative to drug concentrations. A measure that includes an assessment of drug concentration relative to the level of viral resistance may more accurately predict response to that particular is a necessary component for the calculation of the inhibitory quotient. TDM is employed in many areas of medicine and will probably be used increasingly in the context of refining antiretroviral therapy.

Another difficulty in the interpretation of phenotypic test results is the lack of 'biological cut-offs' that truly define virologic response to a particular drug. These are an attempt to establish clinically relevant levels for individual drugs, which tell the clinician whether or not the virus is resistant to that drug. Commercial phenotypic assays have used arbitrary cut-offs (e.g. 2.5 or 4 fold IC_{50} increase) to indicate resistance to all antiretrovirals. However, studies have recently demonstrated that a 1.8 fold increase in IC_{50} to d4T is associated with a significantly blunted viral load response compared to wild-type virus. Two important cut-offs can be defined for any antiretroviral agent: the first point at which the response to the drug becomes attenuated but some antiviral activity still remains; a second point at which the drug has no meaningful activity. Researchers are working to define these cut-offs, individualized for each antiretroviral drug.

SUMMARY

At present, genotypic and phenotypic resistance assays are commercially available. The virtual phenotype shows promise as a clinically useful tool. Measures of IQ may eventually prove more useful then either the genotype or phenotype alone, but require that therapeutic drug monitoring be made part of clinical practice. This would require timed blood specimens, which add to the cost and complexity of patient management. However, knowing the IQ is only useful if one can manipulate the pharmacokinetic parameters of the drug in question. This can be done for many of the currently available PIs by means of ritonavir boosting, but may be less applicable for the other available antiretrovirals. Finally, the full potential of phenotyping will only be realized when clinically defined biological cut-offs have been determined for all the drugs used in practice.

FURTHER READING AND RESISTANCE WEBSITES

www.viral-resistance.com/
www.hivresistance.com/
http://hivinsite.ucsf.edu/medical/resistance/2098.474c.html
http://hivdb.stanford.edu/

Little SJ, Daar ES, D'Aquila RT, et al. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. JAMA. 1999;282:1142-1149. Available at: http://jama.ama-assn.org/issues/v282n12/abs/joc91355.html

Hirsch MS, Brun-Vézinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection. Recommendations of an International AIDS Society-USA panel. JAMA. 2000;283:2417-2426. Available at: http://jama.ama-assn.org/issues/v283n18/ffull/jst90018.html