HIV/AIDS Antiretroviral Newsletter

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Regional Office for the Western Pacific

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.

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Clinical and Laboratory Monitoring of Antiretroviral Therapy in Resource-Limited and Unlimited Settings

Introduction

Monitoring commences prior to the initiation of antiretroviral therapy (ARV), with the clinical status of the patient and laboratory markers guiding when to recommend commencement of therapy.

Traditionally, this decision is based on the predictive values for disease progression and death of CD4 lymphocyte count and HIV- RNA. The presence or absence of HIV-related signs and symptoms also significantly influences the decision to initiate therapy.

Increasingly, concerns related to drug toxicities, pill burden and the ability of patients to adhere to strict and complicated treatment regimens have complicated the decision-making process for physicians and patients alike. Despite promised price-reductions and increased availability of generic drugs in some counties, cost remains a major factor in deciding when to start therapy in many parts of the world. Guidelines vary from country to country. Early intervention in an asymptomatic patient is commencement of ARV if the CD4 lymphocyte count is less than 500 cells/ml^3. A less aggressive approach is to recommend therapy when the count is below 350 cells/ml^3. In Thailand, depending on the financial resources of the patient, treatment typically is delayed until the CD4 count is 200 cells/ml^3. In addition to these guidelines, a declining CD4 count and/or rising viral load over time may be considered reasons to initiate therapy. Most physicians would recommend therapy for patients with symptomatic HIV conditions, such as the presence of recurrent oral candida, oral hairy leukoplakia (OHL) or unexplained weight loss. The commitment of the patient to commencing therapy, an understanding of the lifelong nature of such treatment and of the importance of adherence to drug regimens on a daily basis all affect the timing of the recommendation.

Once treatment begins, the clinical progress of the patient needs to be reviewed regularly. Laboratory monitoring is focused on markers of efficacy of the regimen and drug toxicities. The frequency of review is dictated by the drugs selected, the development of adverse events and the available resources

Efficacy Monitoring

Virological markers

Quantification of HIV-1 RNA in plasma is the basis of ARV efficacy monitoring. The ultimate goal of combination ARV is undetectable plasma HIV-RNA (viral load). This should be achievable in most treatment-naive patients receiving highly active ARV therapy (HAART). The "gold standard" remains a triple drug combination of two nucleoside reverse transcriptase inhibitors (NRTI) plus a protease inhibitor. However, some studies have shown that a triple nucleoside combination or a combination of two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) can result in a similar ("or even higher") percentage of patients achieving undetectable viral load as regimens containing two NRTIs and a PI. Latest generation ultrasensitive HIV-1 RNA assays are recommended if available. There are three commercially available assays; Amplicor HIV-1 Monitor, Quantiplex HIV-RNA bDNA and the nucleic acid sequence base amplification (NASBA) assay. They are similar in terms of sensitivity, specificity, cost and laboratory personnel training requirements. The Amplicor HIV-1 Monitor is the only commercial assay licensed by the US Food and Drug Administration. The ability of the assay to detect all HIV subtypes with equivalent accuracy is important in South-east Asia where subtype E (and A/E mosaic) predominates.

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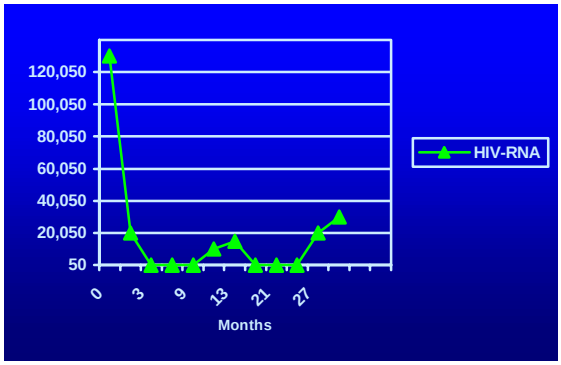
ASSAY	Method	Lower Limit of Detection Standard	Lower Limit of Detection Ultrasensitive	Ability to detect all HIV subtypes
Amplicor HIV-1 Monitor (v1.5)	Target amplification	400 copies/ml	50 copies/ml	YES*
Quantiplex HIV-RNA bDNA	Signal amplification	500 copies/ml	50 copies/ml	YES
NASBA	Target amplification	400 copies/ml	40 copies/ml	False low results reported with subtypes A and E

*The addition of primer sets (SK145 and SK151) improves accuracy of detection of subtypes E and A/E

Case Study: Interpretation of viral load results



This ARV-naive patient had a viral load of 130,000 copies on two occasions, one month apart and CD4 count of 320 cells/mm^3. He commenced zidovudine, lamivudine and indinavir at standard doses and had a typical decline in viral load to below 50 copies (undetectable) at 3-month review. At 12 months, there was an unexpected "bleep", which persisted when rechecked one month later. This may have been due to poor adherence, intercurrent infection or vaccination. In this case it was incorrect timing of drug doses and, with indinavir dosing corrected to every 8 hours and AZT/3TC to every 12 hours, his viral load returned to undetectable at the next visit. After two years, he had a sustained rebound in viral load. The principle of management here is to change as many drugs in the combination as possible with new drugs, based on a thorough understanding of ARV cross-resistant patterns. Genotypic and phenotypic viral resistance assays (if available) may be useful tools in guiding drug choices following failure of the initial regimen. The monitoring in this case is typical of a patient being managed in a resource unlimited setting. In situations where the high cost of these assays is prohibitive, it is reasonable to perform baseline viral load followed by repeat testing every 3-6 months. In some countries viral load measurement is unavailable and monitoring of therapy is by CD4 count changes only. However, it is possible to adequately manage a patient on ARV therapy with regular clinical assessment for signs of disease progression and body weight.

In resource unlimited countries, a typical monitoring schedule for a patient on triple therapy is monthly visits for the first 3 months then every 3 months, with clinical examination and re-enforcement of adherence. Recommended laboratory tests at each visit are full haematology and clinical chemistry, T-cell subsets and HIV-RNA.

In resource limited settings, a clinical review 1 month after commencing ARV, followed by assessments every 3-6 month, if the patient experiences no problems, is sufficient. Clinically, the efficacy of the ARV regimen may be evident with weight gain and regression of CDC B symptoms such as OHL and oral candida. The treating physician will need to prioritize laboratory monitoring depending on available resources. Useful and inexpensive tests are haemoglobin, total lymphocyte count and liver enzymes. T-cells subsets are affordable in many middle income countries in the Asia Pacific region and should be performed every 3-6 month. Viral load testing is often unavailable.

Immunological markers

Following successful initiation of HAART, a rise in CD4 lymphocyte count of 90-150 cells would be expected. To some extent, this rise is dependent on the CD4 count at the time of commencement of therapy, with a lesser response expected with a lower initial count. There is often a biphasic response with an initial rise in CD4 count after 1-2 months of therapy as cells are redistributed from bone marrow. This may be followed by a decline in CD4 cell numbers followed by a second, slower rise with continued suppression of viral replication. This second-phase rise in CD4 cell numbers may continue for more than 12 months. As HIV disease progression is unlikely in a patient with a CD4 count above 350 cells/mm^3, this should be the minimum immunological goal of therapy. However, risk of disease progression is significantly reduced if the CD4 cell count can be maintained above 200 cells/mm^3

Laboratory Toxicity Monitoring

Drug Class	Drug	Laboratory Abnormality	Laboratory Tests
nucleoside reverse transcriptase inhibitors	zidovudine	anaemia, leucopenia, neutropenia myopathy	full haematology CPK
	didanosine	pancreatitis	amylase
	lamivudine	few	nil specific
	stavudine	hepatotoxicity pancreatitis	liver enzymes amylase
	abacavir	hepatotoxicity hypersensitivity	liver enzymes CPK, creatinine, haematology
	zalcitabine	pancreatitis	amylase
non-nucleoside reverse transcriptase inhibitors	nevirapine	hepatotoxicity	liver enzymes
	efavirenz	hepatotoxicity hypercholesterolaemia	liver enzymes serum cholesterol
	delavirdine	hepatotoxicity	liver enzymes
protease inhibitors	indinavir	renal calculi, crystalluria, haematuria nephrotoxicity hepatotoxicity, hyperbilirubinaemia hyperglycaemia, diabetes hyperlipidaemia	urinalysis serum creatinine liver enzymes urinalysis, BSL serum lipids
	saquinavir	hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia	liver enzymes urinalysis, BSL serum lipids
	nelfinavir	hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia	liver enzymes urinalysis, BSL serum lipids
	ritonavir	hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia elevated CPK, uric acid	liver enzymes urinalysis, BSL serum lipids CPK, uric acid
	amprenavir	hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia	liver enzymes urinalysis, BSL serum lipids

This list covers the more important and clinically relevant laboratory adverse events associated with ARV, some class-specific and some peculiar to individual drugs. Prior to the commencement of ARV in a resource-unlimited clinic, it is recommended that the following set of laboratory tests at baseline and each follow-up visit be performed:

- full blood count (FBC) and differential
- liver enzymes
- serum creatinine and serum amylase
- fasting serum glucose
- fasting serum cholesterol / triglycerides
- electrolytes
- CPK
- T-cell subsets
- HIV RNA

Where resources are limited, regular FBC, serum AST (or ALT) and amylase are the minimum requirements for safety monitoring.

Toxicities associated with ARV may appear soon after the commencement of therapy. An NNTRI-induced rash or an abacavir hypersensitivity reaction may present within days. A clinically significant decline in haemoglobin, sufficient to require interruption of therapy, may occur within the first month of zidovudine therapy.

Some toxicities appear in the medium term. Lipodystrophy and significant hyperlipidaemia associated with PI therapy typically present following 6-18 months of therapy. Adverse reactions to ARV are not always typical and can be unpredictable. Renal colic associated with indinavir and pancreatitis caused by ddI can occur at any time. Further, laboratory monitoring is not always helpful in predicting such events.

Indications for changing therapy

Changing therapy may be necessary due to treatment failure, toxicity, patient intolerance to the combination or inability of the patient to adhere to the treatment regimen.

Clinical disease progression is a marker of treatment failure and necessitates a review of the patient's therapy. Virological treatment failure can be defined as a failure to achieve undetectable HIV-RNA or at least a 2 $\log_{10}$ decline in viral load from baseline, after a reasonable time on therapy, typically 1-2 months. A viral load rebound to detectable levels or a rebound of 0.5 $\log_{10}$ from the nadir (preferably repeated and in the absence of an identifiable cause such as recent infection) also indicates failing therapy.

Immunological failure is less easily defined, as individual CD4 count responses to ARV are less predictable. The response is dependent on such variables as disease stage, prior ARV and the drugs taken. As stated above, a patient with a CD4 count of less than 200 cells/mm^3 is at significant risk of HIV disease progression and a failure to achieve this level indicates the need to review the therapy. A declining CD4 count over time is also a marker of treatment failure.

The situation can present where a patient has well-preserved CD4 count (>350 cells/mm^3) but evidence of virological failure with a persistently elevated viral load (>10,000 copies/ml). This clinical picture may be seen in patients on therapy with two ARV drugs (as in many countries in the Asia Pacific region) or in a heavily pre-treated patient on a salvage combination of drugs. In this scenario, a partially suppressive regimen may be reducing viral fitness sufficiently to maintain the CD4 count at a level that makes disease progression unlikely. Decisions to change therapy can be straightforward or, as in this example, require a thorough review of the patient's clinical status, immunological and virological markers, treatment history and available, useful drugs. The role of resistance assays in guiding therapy changes is still being developed.

Clinical Monitoring

As stated above, laboratory monitoring cannot always predict the development of complications and a patient taking ARV requires regular clinical evaluation. Probably the most common long-term side effects of combination ARV are NRTI-associated lipo-atrophy and PI-associated lipodystrophy (and the related abnormalities in serum lipids and glucose). The exact aetiology of these metabolic complications remains uncertain. However, it is clear that NRTIs cause mitochondrial toxicity resulting in multiple end-organ damage. The clinical picture includes peripheral fat loss, hepatic and pancreatic toxicity and peripheral neuropathy. Treatment with protease inhibitors can result in a similar, but quite distinct syndrome, of fat redistribution and metabolic abnormalities. It is critical that patients be clinically assessed for the early development of these side effects, particularly the body composition changes. To date, there is no definite evidence that these are reversible. In fact, the changes may be permanent in many patients, even if the drugs are stopped. While serum lipids and liver enzymes may help predict those patients at risk, the best method of monitoring these newly emerged toxicities is regular clinical review.

References and further reading

(1) Dept. of Health and Human Services (DHHS) and Henry J. Kaiser Family Foundation guidelines for the Use of Antiretroviral Agents in HIV-infected adults and adolescents. January 2000. Available at: www.hivatis.org
(2) British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. Available at :www.aidsmap.com/bhiva
(3) WHO Guidance Modules on ARV Treatments. Module 4: Safe and Effective Use of ARV Module 5: Laboratory Requirements for Safe and effective use of ARV.
www.who.int/HIV_AIDS/antiretroviral_modules/indexar.htm

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New publication: Safe and effective use of antiretroviral treatments in adults with particular reference to resource-limited settings

Based on experiences with the use of antiretroviral therapies in resource-limited settings where the capacity of health systems and the profile of patients seeking ART differs from that in industrialized countries. It discusses the universal principles of antiretroviral therapy which are the standard of care, and outlines the health system requirements as well as the counseling needs, clinical evaluation and monitoring needs of patients that will enable safe and effective use of antiretroviral drugs in resource-limited settings.

www.who.int/HIV_AIDS/WHO_HSI_2000.04_1.04/index.htm

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