HIV/AIDS

Antiretroviral Newsletter

Issue No. 7

Revised versions of the first six issues

2002
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PREFACE

The HIV/AIDS antiretroviral newsletter was first published by the World Health Organization Regional Office for the Western Pacific in August 1999. Issues are published every six months. The aim of this newsletter is to provide health workers in the Region with a brief, up-to-date summary of the latest developments in antiretroviral therapies. As such, it is a compilation of many aspects of antiretroviral therapy, including usage, information provision, advocacy and guidance for practice. The information included is intended to be useful for practising physicians and an attempt has been made to present a complex and rapidly changing subject in a brief, easy to understand manner.

Topics covered include:
- access to care in developing countries;
- new recommendations on when and how to start antiretroviral therapy;
- drug toxicity;
- clinical and laboratory monitoring of antiretroviral therapy;
- new antiretrovirals in development;
- mother to child transmission of HIV;
- complications of antiretrovirals;
- drug resistance.

Selection of material was based on issues which were topical at the time the issues were published. For example, the most recent issue summarized current knowledge of antiretroviral drug resistance. While drug resistance testing may not be currently available in many countries of the Western Pacific Region, an understanding of the principles of drug resistance and cross resistance is essential if physicians are to plan logical and effective second-line and subsequent regimens following first-line drug failure.

The material presented in the newsletter is intended to be relevant to a region where there is a diversity of health infrastructures and resources. The newsletters are mostly distributed through the Regional Office website. The HIV/AIDS antiretroviral newsletters are among the most frequently downloaded documents from this website. Print versions are also available.

The objective of this publication is to update and publish the first six newsletters in one publication. All material contained in this monograph is current as of November 2002.

Further biannual publications of the HIV/AIDS antiretroviral newsletter are planned and will be available at http://www.wpro.who.int
INTRODUCTION

Recently, there have been significant advances in access to care for people living with HIV and AIDS (PLHA) in developing countries. The cost of antiretroviral drugs continues to fall. The Global Fund to Fight AIDS, Tuberculosis and Malaria announced the first “fast-track” round of funding allocations in April 2002. In the first half of 2002, WHO announced a series of initiatives to improve access to quality HIV care. These initiatives complement existing programmes, such as Accelerating access to HIV/AIDS care and treatment in developing countries.

In April, WHO released Scaling up antiretroviral therapy in resource-limited settings: Guidelines for a public health approach. This document was the result of a year-long consultative process involving clinicians, scientists and representatives of government, civil society and PLHA. The guidelines are intended to support and facilitate effective implementation of antiretroviral therapy for the estimated 3 million PLHA who will need ARV by 2005. Coinciding with the document's publication was the announcement that 12 antiretroviral drugs had been included in the WHO Model List of Essential Medicines.

In March, WHO, in collaboration with other United Nations organizations (UNAIDS, UNICEF, UNDP) released the first publication from the Access to Quality HIV/AIDS drugs and Diagnostics Project. This project aims to improve access to HIV/AIDS drugs and diagnostics of acceptable quality. It will publish regularly updated lists of suppliers of HIV-related products, including antiretrovirals, which have been found acceptable for procurement by UN agencies.

The Global Fund to Fight AIDS, Tuberculosis and Malaria

The Global Fund was set up in January 2002 as a financial instrument, complementary to existing programmes addressing HIV/AIDS, tuberculosis and malaria. The purpose of the Global Fund is to attract, manage and disburse additional resources through a new public-private partnership aiming to mitigate the impact caused by HIV/AIDS, tuberculosis and malaria in countries in need, and to contribute to poverty reduction.
The Global Fund will base its work on programmes that reflect national ownership and partnerships within countries. Proposals are assessed for soundness of approach, technical feasibility and potential for sustainability. The Global Fund will provide support for antiretroviral programmes, including the purchase of drugs, training in their use and the provision of adequate laboratory monitoring infrastructure. Many countries in the Asia Pacific region were successful in attracting support from the Global Fund for projects submitted as part of the “fast-track” approval process.

Inclusion of antiretrovirals in the essential medicines list

*Essential drugs are those drugs that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford.*

The inclusion of antiretroviral drugs and drug combinations in the *WHO Model List of Essential Medicines* is an important step in improving access to these medicines in developing countries. A number of drugs used in the clinical management of HIV-related diseases were already included on the essential medicines list. In addition, the 12th revision list (April 2002) includes antiretroviral drugs that are recommended for the combination treatment of HIV infection in adults and children.

Footnotes to the list of ARV recommend the use of three- or four-drug combinations according to WHO treatment guidelines. The use of fixed dose preparations is also recommended, as long as pharmaceutical quality and interchangeability with the single products can be demonstrated. Although fixed dose combinations, such as zidovudine (AZT) 300mg and lamivudine (3TC) 150mg are increasingly available in many countries, including Japan and Thailand, it is recommended that the dosage of AZT should depend on the patient’s body weight: 400mg BID if < 60 kg and 600 mg BID if >60 kg. In addition, ritonavir is recommended for use in combination with indinavir (IDV), lopinavir (LPV) and saquinavir (SQV) as a pharmacokinetic booster.

**Antiretrovirals included in the WHO Model List of Essential Medicines**

<table>
<thead>
<tr>
<th>NsRTI (Nucleoside analog reverse transcriptase inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abacavir (ABC)</td>
</tr>
<tr>
<td>• Didanosine (ddI)</td>
</tr>
<tr>
<td>• Stavudine (d4T)</td>
</tr>
<tr>
<td>• Zidovudine (AZT/ZDV)</td>
</tr>
<tr>
<td>• Lamivudine (3TC)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTI (Non-nucleoside reverse transcriptase inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Efavirenz (EFV)</td>
</tr>
<tr>
<td>• Nevirapine (NVP)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI (Protease inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indinavir (IDV)</td>
</tr>
<tr>
<td>• Ritonavir (RTV, r)</td>
</tr>
<tr>
<td>• Lopinavir + low dose ritonavir (LPV/r)</td>
</tr>
<tr>
<td>• Nelfinavir mesylate (NFV)</td>
</tr>
<tr>
<td>• Saquinavir (SQV)</td>
</tr>
</tbody>
</table>
Scaling up ARV therapy in resource limited settings

Currently, fewer than 5% of people who require ARV treatment can access these medicines in developing countries. The guidelines, Scaling up Antiretroviral Therapy in Resource-Limited Settings, Guidelines for a Public Health Approach, produced by WHO, are intended to support and facilitate the proper management and scale-up of ARV using a public health approach to achieve the following goals.

1. Scaling up of antiretroviral treatment programmes to meet the needs of people living with HIV/AIDS in resource-limited settings;
2. Standardization and simplification of ARV regimens to support the efficient implementation of treatment programmes; and
3. ARV treatment programmes based on the best scientific evidence.

The topics addressed in these guidelines include initial choice of ARV regimens, reasons for changing ARV, and second-line regimens. The guidelines also address how treatment should be monitored in resource-limited settings, with specific reference to the side-effects of ARV, and makes specific recommendations for certain patient subgroups, such as children and patients with HIV/tuberculosis co-infection. The key points in the guidelines are as follows.

When to start ARV therapy in HIV-infected adults and adolescents

While the total lymphocyte count correlates relatively poorly with CD4 count, when used in combination with clinical staging, it is a useful marker of prognosis and survival. In these guidelines, viral load is not considered essential to start therapy. This recommendation reflects the situation in many countries where viral load testing is not available but ARV therapy is critically needed.

If CD4 Testing Available:
- WHO Stage IV disease irrespective of CD4 cell count
- WHO Stage I, II or III with CD4 cell counts below 200/mm³

If CD4 Testing Unavailable:
- WHO Stage IV disease irrespective of total lymphocyte count
- WHO Stage II or III disease with a total lymphocyte count below 1200/mm³

WHO recommended first and second-line regimens

<table>
<thead>
<tr>
<th>First-line regimen</th>
<th>Second-line regimens for treatment failure</th>
<th>Alternative second-line regimens for treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV/3TC + EFV or NVP</td>
<td>d4T/ddI + RTV boosted PI</td>
<td>RTV boosted PI + ABC/ddI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NFV + ABC/ddI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NFV + d4T/ddI</td>
</tr>
<tr>
<td>ZDV/3TC + ABC</td>
<td>NNRTI + LPV/r +/- d4T or ddl</td>
<td>RTV boosted PI + d4T/ddI</td>
</tr>
<tr>
<td>ZDV/3TC + RTV-boosted PI</td>
<td>NNRTI + d4T/ddl</td>
<td>NNRTI + ABC/ddI</td>
</tr>
<tr>
<td>ZDV/3TC + NFV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note 1 Ritonavir is recommended to boost indinavir (IDV/r), saquinavir (SQV/r) and lopinavir (LPV/r)
Note 2 ZDV/3TC is listed as the initial recommendation for dual NRTI component based on efficacy, toxicity, clinical experience and availability of fixed dose formulation. Other dual NRTI components can be substituted including d4T/3TC, d4T/ddI and ZDV/ddI depending upon country-specific preferences. ZDV/d4T should never be used together because of proven antagonism.
WHO staging system for HIV infection in adults and adolescents

### Clinical stage I
1. Asymptomatic
2. Persistent generalized lymphadenopathy
   Performance scale I: asymptomatic, normal activity

### Clinical stage II
3. Weight loss <10% of body weight
4. Minor mucocutaneous manifestations (seborrhoeic dermatitis, fungal nail infections, recurrent oral ulcers, angular cheilitis)
5. Herpes zoster within the past 5 years
6. Recurrent upper respiratory tract infections (bacterial sinusitis)
   And/or performance scale 2: symptomatic, normal activity

### Clinical stage III
7. Weight loss >10% of body weight
8. Unexplained chronic diarrhoea > 1 month
9. Unexplained prolonged fever (intermittent or constant) > 1 month
10. Oral candidiasis (thrush)
11. Oral hairy leukoplakia
12. Pulmonary tuberculosis, with 1 year
13. Severe bacterial infections (pneumonia, pyomyositis)
   And/or performance scale 3: bed-ridden, <50% of the day during past month

### Clinical stage IV
AIDS-defining illness
   And/or performance scale 4: bed-ridden, >50% of the day during past month

**NB:** Both definitive and presumptive diagnoses are acceptable

### When to change ARV therapy

ARV may need to be changed because of treatment failure, toxicity or inability of the patient to adhere to the treatment. Treatment failure can be evaluated clinically, immunologically (CD4 count) and/or virologically (viral load). However, as viral load are not normally available in resource-limited settings, it is recommended that ARV programmes in such settings use clinical and CD4 count criteria (if available) to define treatment failure. Clinical failure is defined as disease progression with the development of new or recurrent opportunistic infection or malignancy, and immunological failure is defined as a fall in CD4 count greater than 30% from the peak value or a return to pre-therapy baseline.

Toxicity can be monitored clinically based on patient reports and physical examination. Monitoring may include a limited number of laboratory tests, depending on the specific combination regimen that is utilized. If a change in regimen is needed because of treatment failure, a new second-line regimen will need to be used. If a change is indicated because of toxicity, either an entirely new second-line regimen can be prescribed, or, when the toxicity is related to an identifiable drug in the regimen, the drug can be replaced with another drug that does not have the same side-effects.
Access to HIV/AIDS drugs of acceptable quality

Recent efforts to accelerate access to HIV-related drugs through negotiation and generic competition have highlighted the importance of quality assurance for procurement of drugs and diagnostics. WHO has begun a project to assess the quality of pharmaceuticals for HIV/AIDS related care and treatment. HIV/AIDS pharmaceuticals have been chosen because of the overwhelming need to increase access to these drugs in developing countries, particularly in Africa. If successful, the pilot project will be used as a model for sourcing pharmaceuticals for other priority diseases.

By September 2002, fifty-eight products from nine branded and generic manufacturers were evaluated and met WHO recommended standards. The list of pre-qualified products and suppliers is published on the WHO website and will be updated regularly, http://www.who.int/medicines/

The pre-qualification process has two main components: product dossier evaluation and assessment for compliance with good manufacturing practices. A team of independent inspectors evaluates each product dossier for data on product quality and bio-availability/bio-equivalence. Compliance with good manufacturing practices is assessed by site inspection.

In addition to many antiretrovirals produced by research and development companies, generically produced zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP) (NVP) from several different manufacturers have been included in the published list.

Accelerating Access Initiative

Five United Nations organizations (WHO, UNICEF, UNFPA, World Bank, UNAIDS) entered into a partnership offered by five pharmaceutical companies (Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Merck & Co., Inc., GlaxoSmithKline, and F. Hoffmann-La Roche Ltd – later joined by Abbott Laboratories) in May 2000 to address the lack of affordability of HIV medicines and to work together to increase access to HIV/AIDS care and treatment in developing countries. The Accelerating Access Initiative aims to assist countries in implementing comprehensive packages of HIV/AIDS 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 which have formally indicated that they wish to expand access to HIV care, support and treatment.

The objectives of the initiative are:
- To make HIV/AIDS drugs more affordable and accessible in developing countries
- To improve technical collaboration in the development of national programme capacities to deliver care, treatment and support

Ongoing political commitment by national governments is essential for the successful implementation of any strategy to improve ARV access. The process of accelerating
access 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. 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.

This project maintains a database containing information relevant to drug procurement for use by countries and donor agencies. Regular progress reports are posted at: [http://www.unaids.org/acc_access/index.html](http://www.unaids.org/acc_access/index.html)

By the end of March 2002, 80 countries had indicated their interest in the Initiative: 41 from Africa, 24 from Latin America and the Caribbean, 5 from Europe, 5 from Asia, and 5 from the Middle East. Thirty-nine of these countries have completed or are in the advanced stages of developing national care and treatment plans. With support from UNAIDS/WHO, 19 of these countries have reached agreement with manufacturers on significantly reduced drug prices in the context of national plans.

**The price of medicines**

Multiple approaches are needed to make HIV treatments affordable 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 pharmaceutical industry and generic manufacturers) to reduce prices.

**Regional and 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.

**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.

**Generic production:** Countries such as Brazil, India and Thailand have produced many generic antiretroviral drugs. In Thailand five antiretrovirals (AZT, 3TC, d4T and NVP) are produced. Saquinavir (SQV) will be produced during 2002. In addition, two fixed dose combinations are available; zidovudine (AZT) + lamivudine (3TC), stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP). These drugs are exported to other countries under certain conditions.
**Parallel importation:** If a manufacturer has patented a product in several countries, it may sell it at a different price in different countries. If the price in country A is substantially lower than that in country B, an importer in country B may buy the product at the cheaper price in country A, and sell it in country B at a price which is lower than the price set by the patent holder. This is called parallel importation.

**Compulsory licensing:** This means that the law allows the granting of a license without permission from the patent holder. In practical terms, a country may allow the national authority to grant a third party the permission to manufacture or commercialize a drug which is still under patent.

Some key documents on the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement and access to drugs can be found at the websites below;

  
  [www.who.or.id/en/publications_dep6.htm](http://www.who.or.id/en/publications_dep6.htm)

- Integrating public health concerns into patent legislation in developing countries
  
  [www.southcentre.org/publications/pubindex.htm](http://www.southcentre.org/publications/pubindex.htm)

- Globalization and access to medicines

- Globalization, TRIPS and access to pharmaceuticals

- Pharmaceuticals and the WTO TRIPS Agreement: Questions and Answers

- Implications of the Doha Declaration on the TRIPS Agreement and Public Health
  
  [www.who.int/medicines/library/docseng_from_a_to_z.shtml](http://www.who.int/medicines/library/docseng_from_a_to_z.shtml)
CLINICAL AND LABORATORY MONITORING OF ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED AND UNLIMITED SETTINGS

INTRODUCTION

Monitoring commences before the initiation of antiretroviral (ARV) treatment, with the clinical status of the patient and laboratory markers guiding when to recommend commencement of therapy. ARV is recommended in all patients with HIV-related symptoms (WHO stages for II, III and IV). WHO also recommends that ARV therapy should begin in asymptomatic and symptomatic adult and adolescent patients with a CD4 count below 200 cells/mm³ or total lymphocyte count (TLC) below 1200/mm³. In most developed countries, the recommendation is to delay initiation of ARV therapy until the CD4 count is below 350 cells/ml³ in asymptomatic patients.

The commitment of the patient to beginning 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 drugs selected, the development of adverse events and the available resources dictate the frequency of review.

The frequency and type of ARV monitoring also depends on the availability of resources. The current WHO guidelines for the scaling up of antiretroviral therapy in resource-limited settings recommend the following.

Once antiretroviral therapy has begun, a reasonable schedule for the clinical monitoring includes a first follow-up visit one month after initiation (which may also be useful to evaluate and possibly reinforce adherence to ARV treatment), and a minimum of every three/four months thereafter. Monthly visits, which can be combined with drug dispensing, are encouraged, as they are useful opportunities to reinforce adherence.

Adherence

High levels of adherence to ARV treatment are required to maintain optimal viral suppression. Studies indicated that 90% to 95% of doses need to be taken to maintain suppression of viral replication, while lower levels of adherence are often associated with virological failure. Based on experiences of the provision of ARV in
many parts of the world and on the situation of countries in the Region, the following strategies are suggested to ensure adherence.

**Suggested Strategies to Improve Adherence**

1. **Prepare a health team;** to serve as educator, source of information, continuous support and monitoring and involving physicians, nurses, pharmacists, peer educators, volunteers, and other relevant personnel

2. **Prepare PHA group, families and volunteers;** to support adherence, preferably developing a comprehensive peer support mechanism for spiritual, psychological and socioeconomic support, basic management of opportunistic infections and health education, linked to health services and home/community based care (e.g. day care center model in Northern Thailand)

3. **Ensure affordable and continued supply of antiretroviral drugs**

4. **Support individual patient**
   1) Establish trust with health worker or the health team
   2) Provide necessary information including process and goals of HIV treatment
   3) Establish readiness and ensure willingness to initiate ARV therapy
   4) Develop a concrete plan for the regimen, relation to meals, daily schedule, side effects, with daily or weekly pill boxes or other mechanical aids to support adherence
   5) Mobilize family, friends and peers to support the plan
   6) Reduce dose frequency and number of pills if possible
   7) Avoid adverse drug interaction
   8) Provide access between visits for question and problems
   9) Monitor ongoing adherence and intensify support in periods of low adherence and for special needs (e.g. more frequent visits, mobilizing family, friends and peer, referral for mental health services)
   10) Consider impact of new diagnosis on adherence (e.g. depression, liver disease)

**Clinical monitoring**

Whether CD4 cell count or viral load testing is available or not, history taking and physical examination are essential to evaluate responses to ARV therapy including development of a new HIV-related opportunistic illnesses (OI) and to identify drug side-effects. Laboratory monitoring cannot always predict the development of complications. Clinical parameters for history taking and physical examination should include; changes in body weight changes in HIV-associated illnesses (e.g. fever, diarrhoea, candidiasis), signs of immune reconstitution syndromes or HIV-related disease progression and signs of drug side-effects.

Probably the most common long-term side effects of combination ARV are NRTI-associated lipoatrophy and PI-associated lipodystrophy (and the related abnormalities in serum lipids and glucose). The exact etiology 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.

**Laboratory monitoring**

**Prioritized laboratory tests**
Routine laboratory testing is useful for monitoring appearance or progression of HIV-associated illness and drug side effects. In order to facilitate the scaling up of ARV use in resource-limited settings, WHO prioritized currently available testing into four categories as shown in the table below

<table>
<thead>
<tr>
<th>Category</th>
<th>Laboratory Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute minimum</td>
<td>HIV antibody test, hemoglobin or hematocrit</td>
</tr>
<tr>
<td>Basic</td>
<td>White blood cell count and differential (total lymphocyte count)</td>
</tr>
<tr>
<td></td>
<td>Serum alanine or aspartate aminotransferase</td>
</tr>
<tr>
<td></td>
<td>Creatinine and/or blood urea nitrogen</td>
</tr>
<tr>
<td></td>
<td>Serum glucose</td>
</tr>
<tr>
<td></td>
<td>Pregnancy tests for women</td>
</tr>
<tr>
<td>Desirable</td>
<td>Bilirubin, Amylase, Serum lipids, CD4 count</td>
</tr>
<tr>
<td>Optional</td>
<td>Viral load</td>
</tr>
</tbody>
</table>

**Absolute minimum** tests are pre-requisites for starting ARV. Documentation of positive HIV status is essential before committing the patient to ARV. Screening for anaemia is essential prior to commencing zidovudine (AZT).

**Basic** recommended tests, white blood cell count and differential, allow for monitoring of neutropenia, which can occur with NRTIs, especially zidovudine (AZT). Total lymphocyte count (TLC) can be used as a trigger for commencing ARV if no CD4 count or viral load is available. It can also be used as a marker of when to commenceOI prophylaxis. While the correlation between CD4 count and total lymphocyte count is variable, primary PCP prophylaxis can be recommended if the TLC is < 1200/mm³ and primary fungal prophylaxis (cryptococcal meningitis) if TLC is < 600-800/mm³. Primary antifungal prophylaxis is recommended only in some countries, such as Thailand.

Serum ALT or AST will screen for possible hepatitis co-infection and monitor hepatotoxicity of ARV. Creatinine and glucose are not essential, but useful baseline markers, especially if protease inhibitor (PI) therapy is planned. Indinavir (IDV) is associated with renal toxicity and all the PIs can cause insulin resistance and diabetes.
Desirable tests include bilirubin (indinavir (IDV)), amylase (NRTI-induced pancreatitis), serum lipids (PI-induced hyperlipidaemia) and CD4 count. CD4 count estimation is still the best indicator of immunological response to ARV. It is also the best marker to guide initiation of ARV and OI prophylaxis. WHO recommends that CD4 count testing should be more widely available in resource limited settings.

Viral load testing is currently optional because of the cost. In situations of limited laboratory monitoring, close clinical monitoring becomes even more crucial.

Drug side effects and laboratory tests
The following table lists the more important and clinically relevant laboratory adverse events associated with ARV. The events can be class-specific or specific to individual drugs. It is important that the clinician and the patient be aware of these possible events.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Toxicity</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>nucleoside RTI</td>
<td>Zidovudine (AZT)</td>
<td>anaemia, leucopenia, neutropenia myopathy lactic acidaemia</td>
<td>haematology CPK serum lactate</td>
</tr>
<tr>
<td></td>
<td>Didanosine (ddI)</td>
<td>lactic acidaemia</td>
<td>amylase serum lactate</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (3TC)</td>
<td>few</td>
<td>nil specific</td>
</tr>
<tr>
<td></td>
<td>Stavudine (d4T)</td>
<td>hepatotoxicity pancreatitis lactic acidaemia</td>
<td>liver enzymes amylase serum lactate</td>
</tr>
<tr>
<td></td>
<td>Abacavir (ABC)</td>
<td>hepatotoxicity hypersensitivity</td>
<td>liver enzymes CPK, creatinine, haematology</td>
</tr>
<tr>
<td></td>
<td>Zalcitabine (ddC)</td>
<td>pancreatitis lactic acidaemia</td>
<td>amylase serum lactate</td>
</tr>
<tr>
<td>nucleotide RTI</td>
<td>Tenofovir (TNF)</td>
<td>Not recommended in patients with renal insufficiency</td>
<td>creatinine, creatinine clearance</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Nevirapine (NVP)</td>
<td>hepatotoxicity</td>
<td>liver enzymes</td>
</tr>
<tr>
<td></td>
<td>Efavirenz (EFV)</td>
<td>hepatotoxicity hypercholesterolaemia</td>
<td>liver enzymes serum cholesterol</td>
</tr>
<tr>
<td></td>
<td>Delavirdine (DLV)</td>
<td>hepatotoxicity</td>
<td>liver enzymes</td>
</tr>
<tr>
<td>PI</td>
<td>Indinavir (IDV)</td>
<td>renal calculi, crystalluria, haematuria nephrotoxicity hepatotoxicity, hyperbilirubinaemia hyperglycaemia, diabetes hyperlipidaemia</td>
<td>urinalysis serum creatinine liver enzymes urinalysis, BSL serum lipids</td>
</tr>
<tr>
<td></td>
<td>Saquinavir (SQV)</td>
<td>hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia</td>
<td>liver enzymes urinalysis, BSL serum lipids</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir (NLF)</td>
<td>hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia</td>
<td>liver enzymes urinalysis, BSL serum lipids</td>
</tr>
<tr>
<td></td>
<td>Ritonavir (RTV)</td>
<td>hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia elevated CPK, uric acid</td>
<td>liver enzymes urinalysis, BSL serum lipids CPK, uric acid</td>
</tr>
<tr>
<td></td>
<td>Amprenavir (AMP)</td>
<td>hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia</td>
<td>liver enzymes urinalysis, BSL serum lipids</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/low dose ritonavir combination (LPVr)</td>
<td>hepatotoxicity hyperglycaemia, diabetes hyperlipidaemia</td>
<td>liver enzymes urinalysis, BSL serum lipids</td>
</tr>
</tbody>
</table>
Immunological markers

Immune reconstitution (as measured by rising CD4 count) following commencement of ARV therapy is extremely variable and depends on factors such as the initial viral load, CD4 count and the regimen. No precise figures can be given for the rise in CD4 count with initiation of ARV. However, following successful initiation of HAART, a rise in CD4 lymphocyte count of 90-150 cells would be expected. 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$^3$. Consequently, it is now recommended that primary prophylaxis against opportunistic infections can safely be stopped following immune reconstitution. Typically, cotrimoxazole PCP prophylaxis may be stopped if the patient has a CD4 count greater than 200 cells/mm$^3$ on two occasions three months apart.

Virological markers

Quantification of HIV-1 RNA in plasma (viral load) is the basis of ARV efficacy monitoring in resource unlimited settings. 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). HAART is currently defined as combination therapy which includes two NRTIs plus either a PI, efavirenz (EFV) or abacavir (ABC). Regimens with similar efficacy include two NRTIs plus nevirapine (NVP). Ultrasensitive viral load 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. Version 3.0 of the bDNA assay and version 1.5 of the Amplicor assay are commonly used in this Region.
**Indications for changing therapy**

Reasons for changing therapy include treatment failure, drug toxicity and inability of the patient to adhere to the treatment regimen and active tuberculosis or pregnancy. Decisions to change therapy require a thorough review of the patient's clinical status, treatment history, the availability of useful drugs and immunological and virological markers if available. The role of genotypic and phenotypic resistance assays in guiding therapy changes is now well established in countries where these tests are available.

Clinical disease progression is a marker of treatment failure and necessitates a review of the patient's therapy. WHO guidelines recommend changing the ARV regimen in the event of clinical failure, defined as clinical disease progression with the development of an opportunistic infection or malignancy when the ARV therapy has been given sufficient time to induce a protective degree of immune restoration.

WHO guidelines define immunological failure as a fall of over 30% in CD4 counts from the peak value or a return to or below the pre-therapy baseline. A patient with a CD4 count of less than 200 cells/mm³ is at significant risk of HIV disease progression and a failure to achieve this level indicates the need to review the therapy. However, it should be noted that individual CD4 count response is dependent on such variables as disease stage, prior ARV and the drugs taken.

Virological treatment failure has no uniformly accepted definition but repeated, continued detectable viremia is indicative of incomplete viral suppression. One of the possible definitions is a failure to achieve undetectable HIV-RNA or at least a 2 log₁₀ 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 log₁₀ from the lower point (preferably repeated and in the absence of an identifiable cause such as recent infection) also indicates failing therapy.

It is possible for a patient to have a well-preserved CD4 count (>350 cells/mm³), but for there to be evidence of virological failure with a persistently elevated viral load (>10,000 copies/ml). This clinical picture may be seen 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.
3

UPDATED VERSION OF ISSUE NO. 3

COMPLICATIONS OF ANTIRETROVIRAL THERAPY

INTRODUCTION

Recognized complications associated with ARV therapy include a diverse group of abnormalities, such as bone marrow suppression, hepatic, renal and pancreatic body-composition changes (lipodystrophy and lipo-atrophy), skin and nail abnormalities, gynaecomastia, diabetes, hypersensitivity reactions, hyperlipidaemia, osteopenia, avascular bone necrosis, hypertension, atherosclerosis, hypothyroidism, hypogonadism and gout.

Current guidelines generally recommend delayed initiation of ARV therapy compared with two-three years ago. The timing of the introduction of ARV is a balance between the clearly demonstrated benefit of therapy and the potential for numerous, sometimes life threatening, side effects. The safe use of antiretroviral therapy requires careful clinical and laboratory monitoring.

This discussion provides an overview of common ARV-related side effects with a focus on new developments in the fields of ARV-associated cardiovascular disease, lipodystrophy, gynaecomastia, neuromuscular disorders and lipid abnormalities.

Common side effects of ARV

Class Specific Toxicities

<table>
<thead>
<tr>
<th>Class Specific Toxicities</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside analog reverse transcriptase inhibitor (NsRTI)</td>
<td>Lactic acidosis and hepatic toxicity</td>
</tr>
<tr>
<td>Nucleotide analog reverse transcriptase inhibitor (NtRTI)</td>
<td>Renal toxicity</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitor (NNRTI)</td>
<td>Rash and hepatitis</td>
</tr>
<tr>
<td>Protease inhibitor (PI)</td>
<td>multiple metabolic disorders (insulin resistance, hyperlipidemia, lipodystrophy, hepatitis, bone disorders and increased bleeding in hemophiliacs.</td>
</tr>
<tr>
<td>Adverse Effect</td>
<td>Possible Drug(s)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>NVP; EFV less common ZDV, ddI, d4T RTV</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>ddI, d4T</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>All NRTIs</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>ABC; NVP</td>
</tr>
<tr>
<td>Severe peripheral neuropathy</td>
<td>ddI, d4T, 3TC</td>
</tr>
</tbody>
</table>
Other complications: ARV may be continued or stopped depending on clinical and laboratory markers

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Possible Offending Drug(s)</th>
<th>Clinical Signs / Symptoms or Laboratory Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>ZDV</td>
<td>Regular laboratory monitoring</td>
<td>In case of severe anaemia, replace ZDV or reduce dosage if it can not be replaced. Transfusion can be required.</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>DDI, ZDV, APV, LPV, NFV, RTV, SQV</td>
<td>It occurs almost invariably in the first weeks of treatment. It is frequently mild and self-limited.</td>
<td>If mild, wait for spontaneous resolution and/or treat symptomatically with loperamide</td>
</tr>
<tr>
<td>Other gastrointestinal symptoms</td>
<td>ABC, DDI, DDC, ZDV, TDF, DLV, NVP, APV, LPV, RTV, SQV</td>
<td>They occur most frequently in the first weeks of treatment. They are frequently self-limited.</td>
<td>They can be treated symptomatically. They rarely lead to discontinuation of the responsible drug.</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>NVP; EFV ZDV, DDI, D4T, RTV, IDV</td>
<td>Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia</td>
<td>Monitor serum transaminases, bilirubin. NVP should be permanently discontinued.</td>
</tr>
<tr>
<td>Nephrolithiasis (recurrent in 50%)</td>
<td>IDV</td>
<td>Crystalluria, hematuria, flank pain</td>
<td>Possibly temporarily discontinue IDV, increase hydration. 3 litres per day. Treat pain. Restart after the episodes resolves</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>ZDV</td>
<td>Regular laboratory monitoring</td>
<td>If absolute neutrophil count is &lt; 500/ml, replace ZDV or reduce dosage if it can not been replaced</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>DDI, D4T, 3TC</td>
<td>Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.</td>
<td>Stop suspect NRTI; Switch to different NRTI that does not have neurotoxicity (e.g., ZDV, ABC). Symptoms usually resolve within 2-3 weeks from discontinuation.</td>
</tr>
</tbody>
</table>

**Lipodystrophy**

Lipodystrophy is a syndrome of changes in body fat distribution and associated metabolic abnormalities. It includes increased waist size, increased breast size, ‘buffalo hump’ (fat accumulation around the neck and upper back), fat accumulation around the neck and jaw (‘moon face’), fat deposits in other locations, facial wasting,
especially of the cheeks, wasting of the buttocks, thinning of arms and legs, and prominent leg veins. Common metabolic abnormalities include elevated cholesterol and triglycerides, insulin resistance and diabetes.

**Pathogenesis**

Lipodystrophy is no longer regarded as a direct consequence of protease inhibitors alone. There are many causes of body fat changes and they are more complex than first thought. Despite a number of emerging theories, the exact mechanisms that result in body fat and metabolic changes in patients taking ARV have not been identified.

Rare forms of genetically inherited lipodystrophy have been identified and acquired forms of lipodystrophy, which resemble those reported in HIV, have also been reported in uninfected individuals. The syndrome has also been reported in HIV-negative people taking ARV as post-exposure prophylaxis. It is now quite clear that both nucleoside analog reverse transcriptase inhibitors (NsRTI) and protease inhibitors (PI) play a role in the development of body fat and metabolic changes, perhaps via different mechanisms. Non-nucleoside reverse transcriptase inhibitors, such as efavirenz (EFV), also cause changes in serum cholesterol.

NRTI-induced body fat changes are caused by mitochondrial toxicity induced by this class of ARV. The role of mitochondrial dysfunction in the pathogenesis of many of the complications seen in association with ARV is discussed later.

**Prevalence**

Estimates of the prevalence of lipodystrophy in patients taking protease inhibitors vary widely. The substantial variability in reports of the incidence and cumulative prevalence of this lipodystrophy (from < 20% to > 80%), is due largely to the lack of a standardized definition of the syndrome.

Australian researchers reported that 83% of the PI treated patients experienced some symptoms of lipodystrophy after 21 months of therapy, while 11% experienced severe body fat changes. Other studies have reported a lower incidence of between 5%-30%.

Spanish and French studies have also reported that a majority of patients experienced lipodystrophy after two years of treatment. A review of 624 French patients who had been taking at least one PI for an average of 18 months showed that 85% had experienced at least one physical change during that time. In the Spanish study, of 158 patients treated with protease inhibitors for more than six months, 22% showed signs of lipodystrophy. Further statistical analysis performed as part of this study suggested a 75% chance of developing lipodystrophy after two years of treatment.
Risk factors for the development of lipodystrophy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing patient age (especially &gt;40 years)</td>
<td></td>
</tr>
<tr>
<td>Duration and type of PI therapy (ritonavir reported as more likely)</td>
<td></td>
</tr>
<tr>
<td>Duration and type of NRTI therapy (d4T reported as more likely)</td>
<td></td>
</tr>
<tr>
<td>Advanced HIV disease</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis and monitoring

The diagnosis of lipodystrophy/lipo-atrophy can be made clinically with the typical body composition changes (see photographs) clearly visible to the physician and patient. Attempts have been made to quantify these changes using DEXA and CT scanning, BIA (bio-impedance assay), anthropometry and measurement of hip/waist ratios. To date, DEXA and CT scans remain the most reliable and popular methods. Abnormal liver enzymes and elevated serum lactate are associated with mitochondrial toxicity. Other serum tests used in monitoring are fasting lipids and glucose.

Management

Rational decision-making in the management of lipodystrophy, lipo-atrophy, hyperlipidaemia and insulin resistance is difficult in the absence of a known etiology. There is no known treatment for these body composition changes. Stopping and/or switching therapy has produced variable results in clinical studies. Therefore, it is essential the patients are fully informed about lipodystrophy and that they know the changes may be permanent even if ARV is ceased. It is uncertain whether there will be clinical benefits from drug therapy for hyperlipidaemia and insulin resistance. The clinical options include the following:

- doing nothing,
• switching the PI,
• switching the NRTI(s)
• prescribing diet or exercise
• treating specific abnormalities with medications

Switching from a PI to non-PI regimen has not demonstrated significant improvement in lipodystrophy in studies to date. The use of efavirenz (EFV) may itself be associated with hyperlipidemia.

Researchers report that diet and exercise may reduce triglyceride levels by 20%. There are drug-interaction issues with the use of lipid-lowering drugs because all of the statins except pravastatin are metabolised by cytochrome P450. The fibrates are indicated for the treatment of hypertriglyceridemia and are reasonably effective.

Treatment of hyperglycaemia is more difficult. Sulfonylureas may lead to hepatic or renal toxicity. Metformin is contraindicated in the presence of renal or liver dysfunction. Insulin may be the safest therapy for symptomatic hyperglycemia.

**Antiretroviral switch studies**

One strategy in the management of ARV-induced lipodystrophy and metabolic abnormalities is to replace drugs in the ARV regimen thought to be responsible for the side effects with drugs not associated with these side effects.

In summary, most early switch studies involved a change from PI-containing to NNRTI-containing regimens, and generally concluded that switching improves metabolic abnormalities, especially insulin resistance, but body fat redistribution does not change substantially. In some studies, body fat changes have been shown to partially reverse when assessed by DEXA and CT scan but, to date, no studies have demonstrated any significant visual improvement. The effect of the switch on serum lipids depends upon the added drug, with efavirenz (EFV) more likely to cause hyperlipidemia than nevirapine (NVP).

More recent switch studies have evaluated triple-NRTI combinations. In the MITOX study, researchers studied the replacement of stavudine (d4T) or zidovudine (AZT) as part of combination ARV therapy with abacavir (ABC). The major finding was that the switch from stavudine (d4T) to abacavir (ABC) resulted in an increase in total limb fat of 500 g or 10%, while continued stavudine (d4T) was associated with no change. Even though the differences between groups were highly significant, the absolute magnitude of the change was small and not visually apparent to the study subjects. Visceral fat content also declined slightly.

Serum lactate levels fell in those who switched to abacavir (ABC) but not in those who continued stavudine (d4T). The switch was associated with maintained viral suppression and few side effects, although there was a 10% rate of hypersensitivity reactions to abacavir (ABC).

These results provide evidence that lipo-atrophy is reversible, but the degree of reversibility is relatively modest over 6-12 months. It is unclear if the increase in subcutaneous fat will continue. If reversibility is related to alterations in proliferation or survival of adipocytes, the increase may continue. Further observation of these study groups will provide very important information on the issue.
Mitochondrial dysfunction

Mitochondria generate cellular energy by the process of oxidative phosphorylation. Most cells contain hundreds of mitochondria that perform multiple cellular functions. The process is complicated but the end result is the production of energy.

Mitochondrial dysfunction is the inability of mitochondria to produce the energy necessary to the survival of the cell.

Clinical presentations of NRTI mitochondrial toxicity

<table>
<thead>
<tr>
<th>Body as a whole</th>
<th>progressive weight loss, fatigue, elevated serum lactate, elevated anion gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>myopathy, myalgia, muscle wasting, weakness, fatigue, elevated CPK</td>
</tr>
<tr>
<td>Heart</td>
<td>cardiomyopathy</td>
</tr>
<tr>
<td>Nerve</td>
<td>pain, paraesthesiae, sensory loss, areflexia, muscle weakness</td>
</tr>
<tr>
<td>Liver</td>
<td>hepatomegaly, elevated liver enzymes, lactic acidosis</td>
</tr>
<tr>
<td>Pancreas</td>
<td>pancreatitis, elevated serum amylase</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>lipo-atrophy (typically peripheral)</td>
</tr>
</tbody>
</table>

Recently, NRTIs have been recognized as causing mitochondrial disruption, particularly following long-term therapy. Nucleoside analogues inhibit DNA polymerase resulting in decreased mitochondrial DNA synthesis and increased mitochondrial DNA mutation. They also inhibit oxidative metabolism as the final common pathway. The process appears to be reversible, at least in part, on stopping the NRTI.

Motor weakness: a new side-effect of NRTI therapy?

New evidence has linked neuromuscular disorders with hyperlactataemia and the use of NRTI therapy. The US Food and Drug Administration has identified 25 cases: 22 were taking stavudine (d4T) and 3 taking zidovudine (AZT) at the time of diagnosis. There have been seven fatalities. The symptoms, predominantly ascending motor weakness, appear to progress over days or weeks, and may progress even after therapy is discontinued. The presentation was similar to Guillain-Barré syndrome. Electrophysiologic studies in a few patients suggested the presence of an axonal neuropathy.

Cardiovascular disease

Evaluation of the impact of antiretroviral therapy on cardiovascular disease is complex because the background incidence of other risk factors, such as age and smoking, and the number of drugs now implicated in causing lipid abnormalities.
A database, which includes 11 of the largest prospective cohort studies in Europe, North America and Australia, has been established to study the association between cardiovascular disease and ARV.

A total of 20,421 HIV-infected patients were studied, with an average age of 39 and a mean CD4+ cell count of 420 cells/mm³. Approximately 25% were female, 25% had an AIDS diagnosis, and 12% were antiretroviral-naive. Overall, 88% had a history of prior NRTI use for a mean duration of 3.6 years, 73% were protease inhibitor (PI)-experienced for a mean of 2.8 years, and 40% were NNRTI-experienced for a mean of just over 1 year. 12% had a family history of cardiovascular disease, 50% smoked, 20% had increased total cholesterol.

The proportion of individuals with abnormal total cholesterol was lowest in treatment-naive patients, and was progressively higher in those on NRTIs alone, NRTIs plus an NNRTI, and NRTIs plus PIs, with the highest proportion in individuals on NRTIs plus both a PI and NNRTI, of whom approximately 44% had abnormal total cholesterol. Differences in elevated triglycerides were highest in the NRTI+NNRTI+PI group.

Data linking ARV-induced elevations of cholesterol and triglycerides to myocardial infarction and stoke are limited. So far, it appears that hypercholesterolemia may not be as serious a problem as previously considered.

Hypertriglyceridaemia, especially high levels (>1,000 mg/dl), are associated with pancreatitis. In a clinical setting, currently it appears more important to treat elevated triglycerides (with fibrates) than it is to treat elevated cholesterol.

**Hypersensitivity reactions**

Drug hypersensitivity reactions are 100 times more common in HIV infected patients compared with non-HIV infected people. Typically, such reactions are seen following therapy with:

- NNRTIs (nevirapine (NVP), efavirenz (EFV), delavirdine),
- cotrimoxazole
- abacavir (ABC)

Clinical features include rash, hepatitis, mucosal inflammation, and constitutional symptoms such as fever and malaise.

- NNRTI hypersensitivity reactions are often self-limiting and may be managed with a 'treat through' approach, involving frequent clinical review of the patient and antihistamines.
- The incidence of nevirapine (NVP)-induced rash is reduced by the recommended introduction of a reduced initial dose (200 mg/day) escalating to 400 mg/day after two weeks. Severe reactions may necessitate withdrawal of the drug. The special case of abacavir (ABC) is discussed below in more detail.
Abacavir (ABC) hypersensitivity

Approximately 3% of patients treated with abacavir (ABC) develop an idiosyncratic hypersensitivity reaction that resolves on discontinuation, but returns with greater severity of symptoms on reintroduction of abacavir (ABC). The median time to onset of the hypersensitivity is 11 days, with 94% of cases occurring within 6 weeks of initiation of abacavir (ABC) therapy.

The most frequent symptoms are fever (80%), rash (70%), gastrointestinal symptoms (50%), and malaise (40%). Respiratory symptoms have been reported in approximately 20% of patients and include dyspnoea, pharyngitis and cough. Wheezing is infrequently reported. Approximately half of patients have three or four symptoms, and an additional 20% have fever and rash. Fever and/or rash are present in 98% of cases.

An important clue to the diagnosis is the evolution of the symptoms (over several days) and evidence of multi-organ system involvement. The rash can be mild. Gastrointestinal symptoms without either fever or rash are more likely to indicate common adverse events to antiretroviral therapy and not hypersensitivity. Laboratory abnormalities reported in association with abacavir (ABC) hypersensitivity reaction included lymphopenia, thrombocytopenia, elevated ALT and CPK.

If abacavir (ABC) is re-introduced, the resultant reaction may develop within hours and is more severe. **Rechallenge with abacavir (ABC) following initial hypersensitivity reaction should never be undertaken.**

Gynaecomastia

There have been recent reports of gynaecomastia in patients receiving ARV from all three drug classes. Breast enlargement in men and women may also be part of the lipodystrophy syndrome.

Causes of true gynaecomastia include endocrine abnormalities (thyroid, adrenal, pituitary, testes) liver disease, tumors and drugs, including PIs, NRTIs and NNRTIs. A syndrome of transient gynaecomastia following the commencement of ARV therapy has been described and may represent another manifestation of immune reconstitution disease. Gynaecomastia in patients receiving ARV therapy is often unilateral. If bilateral, it is commonly asymmetrical. It may be of rapid onset or gradual over several months and may be tender. Treatment options for patients in whom the condition does not resolve spontaneously include stopping the offending drug(s), hormonal therapy and surgery.
INTRODUCTION

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.

Phenotypic 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 an 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.

The issue on Drug Resistance Part II will be published in 2003.
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 analog reverse transcriptase inhibitor (NsRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI).

Mechanisms 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 (Table 1).

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>20</th>
<th>30</th>
<th>36</th>
<th>46</th>
<th>48</th>
<th>50</th>
<th>54</th>
<th>63</th>
<th>71</th>
<th>82</th>
<th>84</th>
<th>88</th>
<th>90</th>
<th>101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td></td>
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<tr>
<td>Indinavir</td>
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<tr>
<td>Nelfinavir</td>
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<tr>
<td>Ritonavir</td>
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<tr>
<td>Saquinavir</td>
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<tr>
<td>Lopinavir/r*</td>
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<td></td>
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</tbody>
</table>

- **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.
- **Lopinavir/low dose ritonavir**.
- **Additional lopinavir/r mutations reported**: 10, 24, 53, 84, 32, 33, 150, 147, 73.
- Primary and secondary mutations for lopinavir/r have not been designated since there are currently no clear data defining which mutations are selected first.
### Table 2: Mutations in the reverse transcriptase gene selected by NsRTI, NtRTI and NNRTI.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Associated Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC</td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td></td>
</tr>
<tr>
<td>AZT + 3TC</td>
<td></td>
</tr>
<tr>
<td>d4T</td>
<td></td>
</tr>
<tr>
<td>ddI / ddC</td>
<td></td>
</tr>
<tr>
<td>NAMS*</td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
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<tr>
<td>Efavirenz</td>
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<tr>
<td>Nevirapine</td>
<td></td>
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<tr>
<td>Tenofovir</td>
<td></td>
</tr>
</tbody>
</table>

- **Primary mutations**: clearly associated with drug resistance.
- **Secondary mutations**: add to the resistance caused by primary mutations.
- **NAMS**: cross resistance to AZT, ddI, ddC, d4T, tenofovir & abacavir (ABC)

*Nucleoside analogue mutations*

### Nucleoside RTIs

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 IC₅₀ 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 with 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.

**Nucleoside analogue mutations (NAMS)**

NAMS (M41L, D67N, K70R, L210W, T215Y/F and K219Q/E) are associated with cross-resistance to all NRTIs except lamivudine (3TC). They are also associated with cross resistance to tenofovir, the first available nucleotide RT inhibitor. In patients taking NRTI containing combination therapy and with incomplete suppression of viral replication, NAMS accumulate over time. The presence of NAMS will result in reduced virological response to second-line NRTI-containing regimens. So, switching the nucleoside backbone (eg. from ZDV/3TC to D4T/ddI or vice versa) when introducing the second line regimen after failure may not be as good a strategy as previously thought. If NAMS is suspected or proven, then combinations of PIs with NNRTIs can be used.

**Nucleotide RTIs**

**Tenofovir** currently is the only available drug in this class. In vitro data suggest that four or more NAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) will lead to a significant degree of resistance. Reduced susceptibility has also been demonstrated with the 69-insertion complex and the K65R mutation.

**NNRTIs**

All drugs in this class, although structurally different, bind to the same site on the reverse transcriptase enzyme. They do so by creating a binding pocket and act 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 (EFV), nevirapine (NVP) and delavirdine) and Y181C (nevirapine (NVP) 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 the 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 is also strongly linked to achievable plasma drug concentrations. For example, recent data suggest that early resistance to indinavir (IDV) can be overcome by pharmaco-enhancement of indinavir (IDV) plasma drug levels with low doses of ritonavir.

In Table 1, primary and secondary mutations for lopinavir/r have not been designated since there are currently no clear data defining which mutations are selected first.

### 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 and 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 range from US$400-US$550 for genotype testing of protease and reverse transcriptase to US$700-US$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: The recommendations of the International AIDS Society Consensus Panel on the use of antiretroviral resistance testing

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary HIV infection</td>
<td>Consider testing</td>
<td>Detect transmission of drug resistant virus. Modify therapy to optimise response&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Established HIV infection&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Consider testing</td>
<td>Detect prior transmission of drug resistant virus, although may not always be possible with current tests</td>
</tr>
<tr>
<td>First regimen failure&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Recommend testing</td>
<td>Document drugs to which there is resistance to guide choice of second line regimen</td>
</tr>
<tr>
<td>Multiple regimen failures&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Recommend testing</td>
<td>Optimise the number of active drugs in the next regimen and exclude drugs to which response is unlikely</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Recommend testing</td>
<td>Optimise maternal treatment and prophylaxis for the neonate</td>
</tr>
</tbody>
</table>

1. For example, 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%-30% of the amplified product may not be detected with currently available assays.
Drug selection pressure at the time of testing may also affect 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 (3TC) 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 appropriate 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**

This new concept 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, a 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 $C_{\text{min}}$) divided by a measure of viral susceptibility to that drug ($IC_{50}$). The equation can be written $IQ = \frac{C_{\text{min}}}{IC_{50}}$.

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 drug. Therapeutic drug monitoring (TDM), whereby individual drug levels are measured in the patient's blood, 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 IC₅₀ increase) to indicate resistance to all antiretrovirals.

However, studies have recently demonstrated that a 1.8 fold increase in IC₅₀ 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, individualised 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 than 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 realised 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://hivdb.stanford.edu/

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION AND TREATMENT OF HIV-INFECTED CHILDREN

INTRODUCTION

There have been significant advances in the field of perinatal transmission since the publication of the first clinical trial (PACTG 076) to demonstrate the reduction in HIV transmission with the use of zidovudine (AZT) monotherapy. Effective regimens include treatment of the mother in the third trimester of pregnancy and during labour plus treatment of the infant and treatment begun at the time of labour followed by treatment of the infant. The latter is less effective. When pre-natal care is not available, treatment of the infant alone, especially if done within the first 48 hours of life, also provides a reduction in transmission risk. This discussion includes new data from perinatal and mother-to-child transmission (PMTCT) clinical trials, and summarizes new knowledge in the areas of elective caesarian section, the risks of breastfeeding, antiretroviral resistance, maternal and infant drug toxicities.

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Breast feeding?</th>
<th>Antepartum</th>
<th>Intrapartum</th>
<th>Postpartum mother</th>
<th>Postpartum infant</th>
<th>Risk of transmission in treated mothers/infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA/ France PACT 076</td>
<td>ZDV</td>
<td>No</td>
<td>100 mg orally five times daily from 14-34 weeks gestation</td>
<td>2 mg/kg IV infusion over 1 hour, followed by continuous infusion of 1 mg/kg/hr</td>
<td>No</td>
<td>2 mg/kg orally 6th hourly for 6 weeks</td>
<td>8.3% (at age 18 months)</td>
</tr>
<tr>
<td>Thailand CDC Modified 076</td>
<td>ZDV</td>
<td>No</td>
<td>300 mg orally twice daily from 36 weeks gestation</td>
<td>300 mg orally every 3 hours</td>
<td>No</td>
<td>No</td>
<td>9.4% (at age 6 months)</td>
</tr>
<tr>
<td>Ivory Coast Retroci</td>
<td>ZDV</td>
<td>100%</td>
<td>300 mg orally twice daily from 36 weeks gestation</td>
<td>300 mg orally every 3 hours</td>
<td>No</td>
<td>No</td>
<td>16.5% (at age 3 months)</td>
</tr>
<tr>
<td>Ivory Coast/ Ditrane ANRS 049</td>
<td>ZDV</td>
<td>92% at 6 months</td>
<td>300 mg orally twice daily from 36-38 weeks gestation</td>
<td>600 mg orally at onset of labor</td>
<td>No</td>
<td>No</td>
<td>18% at 6 months</td>
</tr>
<tr>
<td>Retroci and Ditrane/ ANRS 049 pooled analysis</td>
<td>ZDV</td>
<td>98% at 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21.5% at 15 months</td>
</tr>
<tr>
<td>Africa PETRA Arm A</td>
<td>ZDV/3TC</td>
<td>74%</td>
<td>ZDV 300 mg + 3TC 150 mg orally twice daily from 36 weeks gestation</td>
<td>ZDV 300 mg orally every 3 hours + 3TC 150 mg orally every 12th hrly</td>
<td>ZDV 300 mg + 3TC 150 mg orally twice daily for 1 week</td>
<td>ZDV 4mg/kg + 3TC 2mg/kg orally twice daily for 1 week</td>
<td>5.7% at 6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.9% at 18 months</td>
</tr>
<tr>
<td>Africa PETRA Arm B</td>
<td>ZDV/3TC</td>
<td>74%</td>
<td>No</td>
<td>ZDV 300 mg orally every 3 hours + 3TC 150 mg orally every 12th hrly</td>
<td>ZDV 300 mg + 3TC 150 mg orally twice daily for 1 week</td>
<td>ZDV 4mg/kg + 3TC 2mg/kg orally twice daily for 1 week</td>
<td>8.9% at 6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.1% at 18 months</td>
</tr>
<tr>
<td>Uganda HIVNET 012 Arm A</td>
<td>NVP</td>
<td>98.8% at birth</td>
<td>Single 200mg dose orally at the onset of labor</td>
<td>No</td>
<td>No</td>
<td>Single dose of 2mg/kg within 72 hours of birth</td>
<td>8.1 At birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.8 6-8 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.6 14-26 wks</td>
</tr>
<tr>
<td>Uganda HIVNET 012 Arm B</td>
<td>ZDV</td>
<td>98.8% at birth</td>
<td>No</td>
<td>600mg orally at onset of labor then 300 mg orally every 3 hours</td>
<td>No</td>
<td>ZDV 4mg/kg orally twice daily for 1 week</td>
<td>16 At birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.3 6-8 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20.0 14-26 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.1 16 months</td>
</tr>
</tbody>
</table>

If no antenatal drug is administered in the 12 hours before the commencement of labour, a loading dose of 600 mg ZDV is administered followed by 300 mg orally every 3 hours.
New data from PMTCT clinical trials

HIVNET 012

The HIVNET 012 trial compared nevirapine (NVP) given as a single oral dose of 200 mg to the mother at the onset of labor and a single oral dose of 2 mg/kg given to the infant at age 24-72 hours to zidovudine (AZT) given to the mother at the onset of labor as a single oral dose of 600 mg followed by 300 mg every 3 hours until delivery. The infant received AZT 4 mg/kg twice daily for 7 days. The two regimens were well tolerated and adverse events were similar both parts of the study. In the study, 645 pregnant women were randomly selected to receive nevirapine (NVP), AZT or a placebo. The placebo group was dropped (19 women received the placebo) following the results of the Centers for Disease Control and Prevention (CDC) Thai short-course AZT trial. 302 first-born evaluable infants received nevirapine (NVP) and 307 received AZT. 98.8% of the infants were breast-fed from birth and 95.6% were still being breast-fed at 14-16 weeks.

The study initially reported transmission rates that were 47% lower in the nevirapine (NVP) group (13.1% at 14-16 weeks) compared to the AZT group (25.1% at 14-16 weeks). These data have resulted in the wide-spread adoption of the single-dose nevirapine (NVP) regimen in many developing countries.

Long-term follow-up data were presented at the 9th Conference on Retroviruses and Opportunistic Infections (CROI) in February, 2002. At 18 months, HIV transmission rates were 16% in the nevirapine (NVP) arm compared to 26% in the AZT arm. The nevirapine (NVP) arm maintained 41% greater efficacy over the AZT arm. Still, the steady rise in the transmission rates in both arms of this largely breast-feeding population over the first 18 months of life underscores the contribution that breast-feeding makes to transmission of HIV in the newborn.

In a subgroup analysis, the 18-month transmission rates were described by maternal viral load and CD4 count at study entry. These are presented in Table 2. No transmissions occurred in women whose HIV-RNA was <500 copies/ml before study entry. Transmission rates were higher in women with higher viral loads. Even in women with high viral load and low CD4 counts, the efficacy of NVP over AZT was maintained.

<table>
<thead>
<tr>
<th>Viral load copies/ml</th>
<th>&lt;500</th>
<th>500-10,000</th>
<th>10,000-50,000</th>
<th>&gt;50,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>0%</td>
<td>12.3%</td>
<td>21.2%</td>
<td>44.6%</td>
</tr>
<tr>
<td>Nevirapine (AZT)</td>
<td>0%</td>
<td>6.2%</td>
<td>17.3%</td>
<td>24.9%</td>
</tr>
<tr>
<td>CD4 count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td></td>
<td>350-500</td>
<td>200-350</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>12.4%</td>
<td>24.7%</td>
<td>29.8%</td>
<td>54.9%</td>
</tr>
<tr>
<td>Nevirapine (AZT)</td>
<td>11.2%</td>
<td>10.5%</td>
<td>22.6%</td>
<td>31.6%</td>
</tr>
</tbody>
</table>
In a substudy, infant nevirapine (NVP) concentrations were examined before administration of the infant dose of nevirapine (NVP). Concentrations were lower in infants whose mother received nevirapine (NVP) later in the peripartum period. Possibly ineffective levels (<100 ng/mL) were present in the majority of infants whose mothers had received nevirapine (NVP) less than 2 hours prior to delivery. Based on these results, it has been recommended that nevirapine (NVP) should be administered to the mother as early as possible in labor. If it is administered less than 2 hours before delivery, an extra nevirapine (NVP) dose should be given to the infant immediately after birth in addition to the dose given at 48-72 hours.

**PACTG 316**

The PACTG 316 (Brazil, various European countries and the United States of America) compared the combination of AZT and NVP with AZT alone. In women receiving combination antiretroviral therapy, the addition of nevirapine (NVP) (one dose during labour and one dose to the infant) did not further reduce the rate of mother-to-child transmission.

**SAINT**

The SAINT (South Africa Intrapartum Nevirapine (NVP) Trial) compared the single dose NVP regimen given to mother and infant with AZT + 3TC given intrapartum and postpartum to the mother and to the infant for one week. Transmission rates at eight weeks were 14% in the nevirapine (NVP) arm and 10.8% in the ZDV+3TC arm. These rates were statistically equivalent.

**Alternative nucleoside analogue regimens compared to zidovudine (AZT) in a non-breast-fed population.**

- 373 HIV-infected women from South Africa at 34-36 weeks of pregnancy were randomized to one of the following treatment arms:
  - Stavudine (d4T) 40 mg twice a day to the mother from study entry until delivery, then 1 mg/kg to the infant twice a day for 6 weeks
  - Didanosine (ddl) 200 mg twice a day to the mother from study entry until delivery, then 120 mg/m² twice a day to the infant for 6 weeks
  - Didanosine (ddl) + stavudine (d4T) combined, each at the same doses as above
  - Zidovudine 300 mg twice a day to the mother from study entry until delivery, then 4 mg/kg twice a day to the infant for 6 weeks

At age 24 weeks, the rate of mother-to-child transmission was 8.0% in the overall study population. Rates of transmission were 11.0% for d4T, 10.6% for ddl, 4.6% for d4T + ddl, and 5.6% for ZDV. Treatments appeared to be safe and well tolerated in this study. However, given reports of several cases of maternal mortality secondary to lactic acidosis in pregnant women with prolonged use of stavudine (d4T) and didanosine (ddl) together, the current recommendation is to avoid this combination in pregnancy.
Elective caesarean section

Antiretroviral use and elective caesarean section have been reported as independent, additive variables in reducing mother to child transmission of HIV. The International Perinatal HIV Group published results of a meta-analysis of 15 prospective North American and European studies to examine the impact of mode of delivery on MTCT. (N Engl J Med 340: April 1 1999).

In this analysis, elective caesarean section reduced MTCT of HIV-1 by approximately 50% and, in conjunction with AZT, by approximately 87%. However, new data suggests that, in the presence of combination antiretroviral regimens, elective caesarian section may not confer additional benefit in reducing transmission rates. Also presented at CROI, The Pediatric Spectrum of Disease (PSD) Project reviewed data from 600 HIV-exposed infants at six North American sites between 1995 and 2000. There were marked increases in both the use of combination therapy, defined as two or more drugs (1.3% to 65.5%) and of caesarian section (18.9% to 46.8%). There were significantly lower transmission rates when combination regimens were used compared to monotherapy. In women receiving monotherapy, transmission rates were lower when elective caesarian section was employed. However, in women receiving combination therapy, the transmission rates for vaginal delivery and elective caesarian section were 5.5% and 4.5% respectively. The authors concluded that, in the presence of combination antiretroviral therapy, elective caesarian section conferred no additional benefit in terms of reduction in HIV transmission rates compared with vaginal delivery.
Breast-feeding & mother-to-child transmission

Current estimates are that a child breast-feeding from an HIV-positive mother has up to 15% risk of infection by this route, with transmission of HIV occurring at a rate of approximately 0.5% per month that the infant is breast-fed. Long term follow up data have been reported for the PETRA, HIVNET (see above), RETROCI and DITRAME studies (Table 1).

The PETRA study, conducted in South Africa, Tanzania, and Uganda, investigated the combination of AZT and 3TC in a 4-arm, randomized, placebo controlled study. The placebo arm was discontinued in February 1998. 1457 women were randomized and 1501 children born. Risk of transmission has been reported at 6 weeks and at 18 months of life. An analysis of infection (by PCR detection of HIV-1 DNA, or HIV-1 RNA, or both) in infants at age 6 weeks found a relative risk reduction 63% for mother to child transmission in arm A compared to placebo and a relative risk reduction 62% in arm B compared with the placebo arm. However, at age 18 months, there was no statistically significant difference between the treatment and placebo arms in the risk of HIV infection or death in the infants (arm A: 14.9% arm B: 18.1% placebo: 22.2%). The increase in HIV infection between 6 weeks and 18 months of age was attributable to breast-feeding. In follow-up from week 6, continued HIV transmission was rare among non-breast-fed infants.

An analysis of pooled data from the RETROCI and DITRAME trials found a cumulative transmission risk of 30.1% in the placebo arms and 22.1% in the ZDV arms at age 24 months compared to 16% at six weeks. The difference between ZDV and placebo was statistically significant. The median duration of breast-feeding was 13.8 months.

The long-term follow up data from all these trials suggest that the benefit of perinatal antiretroviral treatment is diminished in breast-fed infants compared with those who are not breast-fed. Further, it appears that in a breast-fed population, perinatal antiretroviral treatment may only transfer part of the risk of infection from the peripartum period to several months later. This situation is complicated by the lack of viable alternatives to breastfeeding in many developing countries. Researchers are now calling for studies to test strategies of shortened breast-feeding times (6 months) at the same time as administering preventive antiretrovirals to the mothers and to uninfected infants.

WHO currently recommends:

- Exclusive breast-feeding should be protected, promoted and supported for six months. This applies to women who are known not to be infected with HIV and for women whose infection status is unknown.

- When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breast-feeding by HIV-infected mothers is recommended; otherwise, exclusive breast-feeding is recommended during the first months of life.
To minimize HIV transmission risk, breast-feeding should be discontinued as soon as feasible, taking into account local circumstances, the individual woman’s situation and the risks of replacement feeding (including infections other than HIV and malnutrition).

HIV-infected women should have access to information, follow-up clinical care and support, including family planning services and nutritional support.

**Antiretroviral resistance**

The emergence of resistance mutations following perinatal antiretroviral exposure has been reported from several PMTCT trials. In Arm A of the PETRA study (ZDV/3TC from 36 weeks gestation, during labour and for one week after delivery; ZDV/3TC given to the infant for one week after birth), the M184V mutation associated with resistance to 3TC was detected in 2 of 24 women (8.3%) one week after delivery. The mutation was not detected in any of the samples from women in the other arms of the study. In both women, this mutation was not present prior to the administration of study treatment, was not associated with mother-to-child transmission, and became undetectable after 3 months.

Following single dose administration in the HIVNET trial, nevirapine-associated resistance mutations were detected in 19% of 111 women tested 6-8 weeks after delivery. Women with lower baseline CD4 counts and higher baseline viral loads were more likely to develop nevirapine (NVP) mutations. Resistant virus was not detectable in all women after 12-24 months. However, as is the case with other antiretrovirals, the re-introduction of nevirapine (NVP) may select for the re-emergence of these resistant strains in these women. Among infected infants, nevirapine (NVP) mutations were present in 46% at age 6-8 weeks, disappearing by 12 months.

The ANRS 075 trial compared AZT and 3TC to AZT alone. The researchers investigated lamivudine (3TC) resistance in the first 200 women enrolled in the study. At 6 weeks after delivery, approximately one-third of women had developed the M184V reverse transcriptase mutation associated with 3TC resistance. The risk of developing this mutation increased with duration of treatment (in 0/21 women receiving 3TC for <1 month; 14/70 receiving 3TC for 1-2 months, and 37/74 receiving 3TC for >2 months). Resistance testing was performed in 5 of 7 infected infants. Of these, 2 showed the M184V mutation, which was in both cases accompanied by a ZDV resistance mutation. No reverse transcriptase resistance mutations were detected in the other 3 cases.

**Maternal and infant drug toxicities**

Nucleoside reverse transcriptase inhibitors (NsRTI) as a class cause mitochondrial toxicity resulting in multiple metabolic abnormalities. There have been previous reports of the deaths in children taking AZT and 3TC. The United States Food and Drug Administration (FDA) has investigated lactic acidosis, hepatic steatosis, and/or pancreatitis among pregnant women receiving combination NRTI regimens. Maternal adverse events were checked among 420 women receiving AZT/3TC and 32 women receiving stavudine (d4T)/didanosine (ddI). Eight reports of lactic acidosis and/or pancreatitis were identified.
Three (all of whom received stavudine (d4T)/didanosine (ddI)) were associated with maternal or fetal deaths. Based on these findings, the FDA recommended that the use of combination d4T/ddI regimens should not be given to pregnant women.

**Lactic acidosis in infants exposed to perinatal antiretroviral therapy**

Hyperlactataemia is a marker of mitochondrial toxicity induced by exposure to antiretrovirals. Data were also presented at CROI on the incidence of hyperlactataemia in 25 HIV-negative infants exposed to ZDV, 3TC plus either nevirapine (NVP) or a protease inhibitor in utero and to AZT during the neonatal period. Median ARV exposure in utero was 17 weeks. 92% of the infants had elevated lactate levels, resolving by the age of 6 months in all infants. However, the authors suggest that infants exposed to ARV should have clinical follow-up for signs of lactic acidosis and monitoring of lactate levels, if available, during the first 6 months of life.

**Summary of guidelines for the use of ARV in paediatric HIV infection**

While the general principles underlying the use of antiretroviral therapy (ARV) are similar for all HIV-infected persons, there are unique considerations in the management of HIV-infected infants, children and adolescents.

- Differences in diagnostic evaluation in perinatally infected children
- Differences in immunological markers in young children
- Changing pharmacokinetic parameters as organ systems involved in drug metabolism and clearance develop and mature with age
- The effect on viral dynamics of primary infection occurring in immunologically immature persons
- In utero exposure to AZT, NVP and other antiretroviral agents in perinatally infected children
- Special considerations related to adherence in children

Identification of infants at risk of perinatal exposure is best accomplished by the identification of HIV-infected women before or during pregnancy. If this is not possible, counselling and testing should be provided during the immediate post-natal period.

**Diagnosis of HIV infection in infants**

Because all babies born to HIV-infected women have maternal antibodies up to 15-18 months (median 10 months) of age, HIV antibody tests cannot be used for diagnosis of HIV infection in infants until after this age. Early definitive diagnosis requires use of virological diagnostic assays such as HIV DNA PCR, plasma HIV RNA or immune complex dissociated (ICD) p24 antigen. Using these methods, most infected infants can be definitively diagnosed by age one month and virtually all by age 6 months.
Detection of HIV DNA by PCR is the gold standard diagnostic test. Where HIV DNA PCR or RNA assays are available, the preferred time of first test to identify babies infected in utero or at delivery is around 2 to 3 months of age, when test sensitivity nears 100%. However, in breast-fed infants, a negative test at age 2 to 3 months does not exclude infection because the risk of HIV transmission continues for the duration of breast-feeding. In such infants, once breast-feeding has ceased and if the child is older than age 18 months, an HIV antibody test alone can be used to diagnose infection.

**Monitoring of paediatric HIV infection**

CD4+ lymphocyte (absolute count and percentage) is considerably higher in healthy HIV-uninfected infants compared with adults and declines to adult levels by age 6 years. While the CD4+ absolute count used to stage the level immune suppression is age dependent, the CD4% is therefore, a better marker of disease progression in children.

High HIV RNA copy numbers persist in perinatally infected children for prolonged periods. In one prospective study (Shearer et al., N Engl. J Med 1997; 336:1337-42), mean HIV RNA level in the first year of life was 185,000 copies/ml. In contrast to the adult pattern, HIV RNA levels decline over the next few years of life. This pattern reflects the reduced efficiency of the immature but developing immune system in containing viral replication. Studies have shown that HIV RNA levels in children with rapidly progressive disease and those who are clinically stable overlap considerably. Given this and the difficulty of interpreting viral load results in the first year of life, the predictive value of specific HIV RNA levels for disease progression and death is moderate.

**When to initiate therapy**

WHO recommends that, in resource-limited settings, all infants born to HIV-infected mothers should be followed up, fully immunized and given nutritional support. Cotrimoxazole prophylaxis should be given for at least 6 months (12 months is recommended) to prevent pneumocystis carinii pneumonia (PCP). If the infant becomes symptomatic, virological testing, if available, should be performed to determine the infant’s HIV infection status. Current WHO guidelines for initiation of ARV in children are summarized in Table 4.
Table 4: Recommendations for initiating antiretroviral therapy in children

<table>
<thead>
<tr>
<th>CD4 testing</th>
<th>Age</th>
<th>HIV Diagnostic Testing</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>testing</td>
<td>&lt;18 months</td>
<td>Positive HIV virological test</td>
<td>• WHO pediatric stage III (AIDS)</td>
</tr>
<tr>
<td>available</td>
<td></td>
<td></td>
<td>• WHO pediatric stage I (asymptomatic) or II with CD4%&lt;20%</td>
</tr>
<tr>
<td></td>
<td>≥ 18 months</td>
<td>HIV virological testing not available but HIV seropositive or born to known HIV-infected mother</td>
<td>• WHO pediatric stage III (AIDS) and with CD4%&lt;20%</td>
</tr>
<tr>
<td>testing not</td>
<td>&lt;18 months</td>
<td>Positive HIV virological test</td>
<td>• WHO pediatric stage III</td>
</tr>
<tr>
<td>available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 18 months</td>
<td>HIV antibody seropositive</td>
<td>• WHO pediatric stage III (AIDS) irrespective of CD4 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• WHO pediatric stage I (asymptomatic) or II with CD4%&lt;15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV virological testing not available but HIV seropositive or born to known HIV-infected mother</td>
<td>Treatment not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV antibody seropositive</td>
<td>• WHO pediatric stage III</td>
</tr>
</tbody>
</table>

Table 5: WHO staging for HIV Infection in Children

<table>
<thead>
<tr>
<th>Clinical stage I</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, generalized lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Clinical stage II</td>
<td>Description</td>
</tr>
<tr>
<td>Unexplained chronic diarrhea, severe persistent or recurrent candidiasis outside the neonatal period, weight loss or failure to thrive, persistent fever, recurrent severe bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Clinical stage III</td>
<td>Description</td>
</tr>
<tr>
<td>AIDS defining opportunistic infections, severe failure to thrive, progressive encephalopathy, malignancy, recurrent septicemia or meningitis</td>
<td></td>
</tr>
</tbody>
</table>

Choice of antiretroviral therapy

Combination ARV is recommended for all infants, children and adolescents based on similar principles to those guiding adult therapy. In resource unlimited settings, highly active combination of two NRTIs and one protease inhibitor (PI) capable of inducing maximum suppression of viral replication offers the best chance of long term durability and immune preservation. The preferred PIs for children who cannot swallow pills or capsules are the combination of lopinavir/ritonavir (Kaletra liquid), ritonavir liquid or nelfinavir (NFV) powder. Indinavir (IDV) or saquinavir (SQV), both preferably boosted with ritonavir, are alternatives for children who can swallow capsules.
In recently published guidelines for the use of ARV in resource-limited settings, WHO recommends first line regimens for children are ZDV/3TC plus abacavir (ABC) or ZDV/3TC plus NNRTI. The combination of ZDV/3TC is chosen because it has the largest amount of clinical experience. Other combinations of two NRTIs can be used. ZDV/d4T should never be used together due to proven antagonism.

WHO currently recommends that country specific considerations and preferences should determine which regimen or regimens to make available.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>&lt;4 weeks: 4 mg/kg/dose twice daily; 4 weeks to 13 years: 180 mg/m²/dose twice daily; Maximum dose: ≥13 yr: 300 mg/dose twice daily</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>&lt;30 days: 2 mg/kg/dose twice daily; ≥30 days or &lt;60 kg: 4 mg/kg/dose twice daily; Maximum dose: &gt;60 kg: 150 mg/dose twice daily</td>
</tr>
<tr>
<td>Stavudine (D4T)</td>
<td>&lt;30 kg: 1 mg/kg/dose twice daily; 30 to 60 kg: 30 mg/dose twice daily; Maximum dose: &gt;60 kg: 40 mg/dose twice daily</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>&lt;3 months: 50 mg/m²/dose twice daily; 3 months to 13 years: 90 mg/m²/dose twice daily or 240 mg/m²/dose once daily; Maximum dose: ≥13 years or &gt;60 kg: 200 mg/dose twice daily or 400 mg once daily</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>&lt;16 years or &lt;37.5 kg: 8 mg/kg/dose twice daily; Maximum dose: &gt;16 years or ≥37.5 kg: 300 mg/dose twice daily</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>15 to 30 days: 5 mg/kg/dose once daily X 2 weeks, then 120 mg/m²/dose twice daily X 2 weeks, then 200 mg/m²/dose twice daily; &gt;30 days to 13 years: 120 mg/m²/dose twice daily X 2 weeks, then 200 mg/m²/dose twice daily; Maximum dose: ≥13 years or &gt;30 kg/m²: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>Capsule (liquid) dose for ≥3 yrs: 10 to 15 kg: 200 mg (270 mg = 9 ml) once daily; 15 to &lt;20 kg: 250 mg (300 mg = 10 ml) once daily; 20 to &lt;25 kg: 300 mg (360 mg = 12 ml) once daily; 25 to &lt;33 kg: 350 mg (450 mg = 15 ml) once daily; 33 to &lt;40 kg: 400 mg (510 mg = 17 ml) once daily; Maximum dose: ≥40 kg: 600 mg once daily</td>
</tr>
<tr>
<td>Nelfinavir (NLF)</td>
<td>&lt;1 year: 40 to 50 mg/kg/dose three times daily or 65 to 75 mg/kg/dose twice daily; ≥1 year to &lt;13 years: 55 to 65 mg/kg/dose twice daily; Maximum dose: ≥13 years: 1250 mg/dose twice daily</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir (LPVr)</td>
<td>&gt;6 months to 13 years: 225 mg/m² LPV / 57.5 mg/m² ritonavir twice daily; or weight-based dosing: 7 to 15 kg: 12 mg/kg LPV / 3 mg/kg ritonavir twice daily; 15 to 40 kg: 10 mg/kg LPV / 5 mg/kg ritonavir twice daily; Maximum dose: &gt;40 kg: 400 mg LPV / 100 mg ritonavir (3 caps or 5 ml) twice daily</td>
</tr>
</tbody>
</table>
NEW ANTIRETROVIRAL AGENTS, TREATMENT STRATEGIES, JOURNAL REVIEW AND DRUGS IN DEVELOPMENT

INTRODUCTION

New agents: Tenofovir

Tenofovir is the first nucleotide reverse transcriptase inhibitor approved by the United States Food and Drug Administration (FDA) for the treatment of HIV-1 infection when taken in combination with other antiretrovirals. Like nucleoside reverse transcriptase inhibitors (NRTIs) such as AZT, ddI and d4T, tenofovir diphosphate inhibits the activity of HIV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. It is given as a single 300 mg tablet once daily with food and as part of combination therapy (usually a NRTI and at least one non-nucleoside reverse transcriptase inhibitor or protease inhibitor). The most common adverse events in patients receiving tenofovir are gastrointestinal and include nausea, diarrhoea, vomiting, and flatulence. When administered with tenofovir, the C_{max} and AUC of didanosine (ddI) (buffered formulation) increased by 28% and 44% respectively. While no dose modification is recommended, patients receiving ddI and tenofovir should be closely monitored for ddI-related side effects, such as pancreatitis. In addition, the administration of tenofovir should be two hours before or one hour after ddI.

Reduced susceptibility to tenofovir has been demonstrated in patients with pre-existing nucleoside analogue mutations (NAMs). Following prior exposure to NRTIs, the mutation codon (41, 210 and 215) and number (three or more) of NAMs significantly affects tenofovir response. The safe and effective use of tenofovir in pregnant women and in children has not been determined.

Lopinavir/ritonavir (Kaletra)

Kaletra is a co-formulation of lopinavir (LPV) and ritonavir. Lopinavir is an inhibitor of HIV protease and ritonavir (at the co-formulated dose) inhibits the cytochrome P450-mediated metabolism of LPV providing increased LPV plasma levels. Each capsule contains 133.3 mg of LPV and 33.3 mg of ritonavir. The adult dose is three capsules twice daily. If taken with efavirenz (EFV) or nevirapine (NVP), the dose of Kaletra needs to be increased to four capsules twice daily. It is also available as a paediatric solution.
The following drugs are contra-indicated with Kaletra: flecainide, propafenone, astemizole, terfenadine, ergotamine derivatives, cisparide, pimozide, midazolam and triazolam. A complete list of drugs not recommended to be administered with Kaletra is included in the manufacturer’s product information. Adverse events associated with the use of Kaletra are similar to other PIs and include lipid abnormalities, lipodystrophy pancreatitis, diabetes and hepatotoxicity. The safety of the drug in pregnancy has not been established.

A recent study (M99-056) compared lopinavir/ritonavir 800 mg/200 mg once daily to 400 mg/100 mg BID. The median inhibitory quotient and 24-hour trough concentration were lower in the once-a-day dose, suggesting that twice daily is the optimal way regimen for lopinavir/ritonavir.

**Fixed Dose Combinations**

**Trisivir** is a fixed dose combination of zidovudine (AZT) 300mg, lamivudine (3TC) 150 mg and abacavir (ABC) 300 mg. It is given as one tablet twice daily. Trisivir offers one of the most convenient combination antiretroviral regimens available, thereby enhancing adherence. However, its use in developing countries currently is limited by cost and availability. The incidence of hypersensitivity reaction in people taking ABC (by itself or as part of trisivir) is 3%. It is characterized by rash, fever, malaise, fatigue and gastrointestinal symptoms such as nausea, vomiting, and diarrhoea. It generally occurs within four weeks of starting ABC, and usually resolves within one to two days after ceasing ABC treatment. Trisivir (abacavir) should be stopped immediately and NOT resumed since reintroduction can produce a life-threatening anaphylactic reaction.

**GPO-VIR** is a combination of stavudine (d4T) (30 mg or 40 mg) plus lamivudine (3TC) 150 mg plus nevirapine (NVP) 200 mg. It is also given as one tablet twice daily. GPO-VIR is produced by the Thai Government Pharmaceutical Organization and has been available in Thailand since February 2002. At THB 1,200 per month ($US 30), it is one of the cheapest triple combinations available. The same fixed dose triple combination is produced in India.

**Nevirapine (NVP)** is commenced at a lead-in dose of 200 mg once daily for two weeks, and then increased to 200 mg twice daily. The Thai Ministry of Public Health recommends that d4T, 3TC and NVP be taken separately for the first two weeks, before commencing the fixed dose tablet. Alternatively, patients can take one GPO-VIR in the morning and separate d4T and 3TC at night for the first two weeks, and then switch to one GPO-VIR twice daily.

Careful clinical monitoring is required during the first month of therapy due to the relatively high incidence of hypersensitivity (usually rash and fever) to NVP. Unlike EFV, where a ‘treat through’ approach is often successful in the event of initial hypersensitivity, NVP will usually need to be permanently stopped if the patient develops hypersensitivity with the initial 200 mg or at the time of dose-escalation to 200 mg BID. Stevens-Johnson Syndrome (severe rash, fever, mucosal ulceration) can be associated with NVP use, necessitating its immediate cessation. Hepatotoxicity is associated with NVP use and monitoring of liver enzymes is recommended if available.
New treatment guidelines


The full text of this and other guidelines for the treatment of children and for post-exposure prophylaxis can be found at: www.hivatis.org

Key new points:
- Initiate ARV in all adult patients who are symptomatic or who have CD4 count < 200 cells/mm³
- Generally offer ARV to adults with CD4 <350 cells/mm³ or HIV-RNA >55,000 copies/ml. However, the optimum time to initiate ARV in asymptomatic patients with CD4 >200 cells/mm³ is unknown
- Despite the strong association between a reduced risk of HIV transmission and a sustained low viral load, a person once infected with HIV can transmit HIV at any time
- ARV therapy can be associated with serious adverse events, including life-threatening lactic acidosis and hepatic steatosis
- The combination of stavudine (d4T) and didanosine (ddI) is not recommended in pregnancy following reports of fatal cases of lactic acidosis in pregnancy
- Tenofovir is included but not recommended as part of initial ARV therapy

Treatment strategies

Structured therapy interruption

It is hoped that structured therapy interruption will reduce the ARV cost and side-effects of ARV, and boost HIV-specific immunity. In the absence of data from large prospective clinical trials of STI, its use remains controversial. The largest of the current studies is STACCATO, which began in Australia, The Netherlands, Switzerland and Thailand in February 2002. 600 subjects (400 in Thailand) will be randomized to ARV therapy given continuously, week on/week off or guided by CD4 count. In the latter arm, subjects will stop ARV if the CD4 count is above 350 cells/mm³ and recommence when the CD4 drops below 350/mm³ cells. This study will run for 96 weeks.

In the meantime, small-scale studies of structured therapy interruption in the clinical settings of primary HIV infection, chronic (established) infection and prior to salvage therapy continue. The Swiss and Spanish Intermittent Treatment Trial (SSITT) is one of the largest cohorts of patients who have undergone structured treatment interruption (STI). Data from this study of 133 patients suggest that most patients with chronic HIV infection on long-term suppressive HAART could be safely managed without drugs for several months, potentially diminishing side-effects and the cost of therapy. However, repeated treatment interruption, in the schedule used
in this study, will rarely be sufficient to attain the goal of persistent low viremia without antiretroviral therapy. The researchers also concluded that frequent treatment interruption, which may act as a form of auto-vaccination to boost HIV-specific immune responses, is unlikely to be effective in chronic HIV infection. Currently, the structured therapy interruption strategy cannot be recommended until more data are available.

**Antiretroviral Switch Studies**

Metabolic complications of ARV therapy, such as insulin resistance, lipid abnormalities and, in particular, body composition changes, have led to clinical trials in which patients switch from PI-containing to non-PI-containing regimens. Switching from a PI to NVP or ABC improves lipid levels. A switch to EFV gives a more mixed result. A switch from a PI to abacavir (ABC) improves insulin resistance. A switch to EFV or nevirapine (NVP) varies from no change to improvement depending on the study. A switch from a PI to NVP, EFV or ABC has little effect on body composition changes. In general, switching therapy in response to lipodystrophy incurs risks (viral rebound, adverse events, especially from the NNRTI) and leads to improvements in fat mass that are perceptible only on DEXA scan, not to the human eye.

**Journal review**

Articles summarized below just examples of recent numerous important articles, which should enhance readers’ understanding of the previous chapters. According to readers’ interest and need, please refer to major journals focusing on HIV/AIDS.

*Indinavir (IDV) Acutely Inhibits Insulin-Stimulated Glucose Disposal in Humans: A Randomized, Placebo-Controlled Study*

Noor MA, Seneviratne T, Aweeka FT, et al. *AIDS*. 2002; 16 (5): F1-F8 March 29, 2002. There have been many reports of the development of diabetes mellitus among individuals receiving PI-containing regimens. In this randomized, double-blind, cross-over study the effects of a single dose of indinavir (IDV) (1200 mg) or placebo in six HIV-negative men were evaluated.

The experiment established that a single dose of IDV induced insulin resistance. The rate of insulin-stimulated glucose disposal fell in all six subjects by an average of 34%, from 14.1 to 9.2 mg/kg min per mcUI/mL (p <0.001). Following just one dose of IDV, storage of glucose in muscle cells and adipocytes is decreased. In addition, the impact of IDV appears to be dose-dependent. Insulin resistance is not restricted to IDV and has been reported *in vitro* with nelfinavir (NFV), ritonavir, amprenavir, and lopinavir (LPV).

*Raised Viral Load in Patients With Viral Suppression on Highly Active Antiretroviral Therapy: Transient Increase or Treatment Failure?*

Transient viral load "blips" (HIV-RNA >50 copies/mL) in patients whose viral load had been suppressed appear to be relatively common. In this study, 553 HIV-infected patients were followed for a median of 56 weeks after their first documented HIV-1 RNA <50 copies/mL. Approximately three quarters of the subjects were taking a PI-containing antiretroviral regimen.

A median of four viral load measurements was reported during the 65-week follow-up period. Thirty five percent of patients experienced at least 1 blip >50 copies/mL. Eight percent of subjects experienced virological failure, defined as two consecutive measurements >400 copies/mL. Of the 154 patients with a single viral load over 50 copies/mL who did not alter antiretroviral therapy, the subsequent viral load returned to <50 copies/mL in 54%. Of the subjects who had a blip >400 copies/mL, 51% became virologic failures compared with 8% of those whose blip was <400 copies/mL.

Blips and/or virological failure were more likely to occur in subjects taking more than four drugs and in those with greater treatment experience. These data demonstrate that blips are common and may not indicate impending virological failure if the blip is <400 copies/mL. However, a blip to >400 copies/mL was associated with a high level of subsequent failure.

In combination with two nucleoside analogues, efavirenz (EFV) offers HIV control superior to that provided by nevirapine (NVP).

\textit{J Infect Dis} 2002;185:1062-1069. May 06

Non-nucleoside reverse transcriptase inhibitors in combination with two NRTIs have been demonstrated to have equivalent efficacy to protease inhibitor-containing regimens. However, there are limited data that directly compare drug regimens containing efavirenz (EFV) and nevirapine (NVP). Researchers from Royal Free and University College Medical School in London evaluated the virological and immunological responses of 694 patients' regimens that included two NRTIs plus EFV or NVP. In the multivariate analysis, the risk of virological failure was twice as high in the NVP-treated patients compared to the EFV-treated patients.

The frequency of drug discontinuation was higher in the NVP group during the first 12 to 16 weeks of treatment, the investigators say, but after the first 24 weeks of treatment, discontinuation rates were similar for the two groups. The authors conclude that a randomized clinical trial comparing the two drugs is needed to confirm their findings. Such a trial is the 2NN study that is comparing EFV to NVP to both NNRTI drugs in combination with D4T and 3TC. Results are expected in late 2002.

\textbf{Drugs in development}

\textbf{Entry inhibitors}

Inhibition of HIV entry is currently the most dynamic area of antiretroviral drug development. HIV entry into cells can be divided into 3 steps:

- HIV binding via the gp120 envelope protein to the CD4 molecule on the cell surface
• gp120 binding to a second receptor (either CCR5 or CXCR4)
• gp 41-mediated fusion of the viral envelope with the cell membrane, thus completing HIV entry.

At least one inhibitor targeting each step in this pathway has reached the stage of clinical development. The peptide fusion inhibitors T-20 and T-1249 block the final step of HIV entry (gp41 mediated fusion). The first agent, T-20, has already produced some exciting short-term surrogate marker outcomes. The follow-up compound, T-1249, is in the early stages of clinical development. Data from the open-label TORO 1 study were presented in April 2002. The study included 491 HIV-1 infected patients who were treatment-experienced and/or had documented resistance to the three existing classes of antiretrovirals. At the beginning of the study, patients had a mean HIV RNA level of >5 log10 copies/mL. Patients were randomized at a ratio of 2:1 to receive either a combination of three to five ARVs plus T-20 or the ARV regimen alone. T-20 was delivered as a 90 mg subcutaneous self-injection twice daily.

Patients randomized to the T-20 regimen experienced a 1.697 log10 copies/mL drop in viral load at 24-weeks compared with 0.763 log10 copies/mL in control-arm patients.

The drug has fast-track designation from the US Food and Drug Administration; regulatory approval is expected by early 2003. Data from a Phase I trial of the follow on drug T1249 show that it also is likely to benefit those in whom resistance has developed to the current three classes of antiretroviral drugs. A group of 63 subjects, 58% of whom showed triple-class resistance, were given T-1249 by single daily injection (an improvement on the twice-daily T-20 regimen) in doses from 6.25 to 50 mg/day. Viral suppression response at 14 days was related to dose (-0.1 to -1.4 log10 copies/mL) and was unaffected by pre-existing resistance to other HIV drugs.

The chemokine receptors CCR5 and CXCR4 are used in addition to CD4 by many strains of HIV-1 to enter cells. AMD-3100 is a blocker of the CXCR4 co-receptor but, like other drugs in this class, has demonstrated cardiac toxicity, including premature ventricular contractions and atrial tachycardia. SCH-C and SCH-D are CCR5 blockers that can be administered orally. They have demonstrated potent in vivo antiviral activity and appear well tolerated. Their use also has been associated with ECG abnormalities. Other novel entry inhibitors, such as BMS-806, which competitively inhibits the binding of gp120 to CD4, are the subjects of early research.

Others

The once-daily protease inhibitor atazanavir (BMS 232632) is currently in Phase III study and is likely to be the next agent after T-20 to be evaluated for approval by the FDA. Atazanavir appears to have a favorable lipid profile with data from Phase II studies showing an increase in total cholesterol of approximately 5% and in triglycerides level of approximately 10%. A 400-mg once-daily dose of atazanavir is being used in the Phase III studies. Efavirenz (EFV) lowers atazanavir levels substantially. There appears to be a favorable and useful interaction between atazanavir and saquinavir (SQV), allowing once-daily dosing of saquinavir (SQV).
At an earlier stage of development is tipranavir, which must be administered with ritonavir to improve its pharmacokinetics. The exact dose combination to be taken into Phase III trials is currently being determined.

**Integrase inhibitors** block HIV-1 integrase, the enzyme necessary for the integration of HIV-1 proviral DNA into host-cell chromosomes. They have potent antiviral activity, can be taken orally and are currently the subject of Phase I/II volunteer studies.

There are few new data on investigational nucleoside or nucleotide reverse transcriptase inhibitors.

Following the successful completion of Phase II pharmacokinetic (PK) studies, the new extended release formulation of stavudine (d4T-ER) is the subject of current Phase III trials. The PK studies support the use of the once-daily stavudine (d4T) preparation and marketing approval is expected soon.

**DPC 817** is a nucleoside analogue of cytidine, which demonstrates activity against AZT and 3TC-resistant isolates and has a long half life, which may allow for once daily dosing. The compound is rapidly triphosphorylated and has a prolonged intracellular half-life. Phase I studies have just begun.

Moderate levels of intolerance, including rash, central nervous system effects and liver toxicity, limit currently available NNRTIs. They are generally potent and convenient to take but have low genetic barrier to resistance. Several second generation NNRTIs, including TMC 125 and DPC 083, have demonstrated activity against efavirenz (EFV) and nevirapine (NVP)-resistant isolates. DPC-083 will go into a Phase III clinical trial at a dose of 100 mg once daily. It appears to have less CNS toxicity but the same rash rate as efavirenz (EFV). DPC 083 has a molecular structure very similar to that of efavirenz (EFV) but has substantially greater potency than efavirenz (EFV). It is less protein bound, raising the possibility that it will be active in patients with NNRTI-resistant virus.

TMC 125 has been shown in small-scale proof of principle studies to be potent and well tolerated. At 25 mg per day, the main side-effects of TMC 125 are headache and bad taste. It has activity against nevirapine (NVP) and efavirenz (EFV) resistant isolates.

**Internet web sites**

- [www.natap.org](http://www.natap.org) Site of National AIDS Treatment Advocacy Project (NY), with free e-mail and paper-based monthly reports. This site was used in part as a reference source for the preparation of this newsletter
- [www.aidsmap.com](http://www.aidsmap.com) Monthly online treatment updates and fact sheets
- [www.infoweb.com](http://www.infoweb.com) Links to many HIV sites
TRIPS, INTELLECTUAL PROPERTY RIGHTS AND ACCESS TO MEDICINES

THE TRIPS AGREEMENT

The Agreement on Trade-related Aspects of Intellectual Property Rights (or the TRIPS Agreement) is an integral part of the World Trade Organization (WTO) Agreements, which create binding international obligations among WTO Member States. The TRIPS Agreement is subject to the WTO’s dispute settlement mechanism, which may -as a last resort- allow Member Countries to apply trade sanctions against a non-compliant Country, thereby ensuring enforcement of the WTO’s rules and agreements.

TRIPS AND PATENTS

Patents are a public policy tool; they were designed to promote and reward innovation, while at the same time ensuring disclosure of the invention, in order to make it widely known and available. Before TRIPS, countries could -and did- devise a patent regime that was in line with their level of development and their overall, national priorities.

The TRIPS Agreement has to a large extent harmonised the standards for patents; notably, it makes it mandatory for countries to ensure that patent protection is available in all fields of technology, for both process and product inventions. Thus, it is no longer possible for countries to exempt pharmaceuticals from patent protection (as a number of countries did, before TRIPS came into force). Nor can countries like India continue to limit pharmaceutical patents to process patents only.

The distinction between product and process patents is important, since if a product is patented, only the patent holder may make or sell that product; nobody else may do so, unless the patent holder has given permission (a license). In the case of a process patent, nobody may make that product by using the process that is protected.

However, if someone can produce the same product in a different way, he/she may do so. Since for most pharmaceuticals multiple routes of synthesis can be devised, process patents offer considerably less protection than product patents. Until 2004, India recognized only process patents for drugs. Thus, India implicitly provided incentives for local manufacturers to “invent around” the patent (i.e. to develop a different production method); generics thus produced were legal in India, and, as a result, generic versions of newly developed drugs used to be available relatively quickly in India. This will change, because from 2005 onwards India will implement TRIPS (see also below).

TRIPS furthermore requires that the minimum duration of patent protection is 20 years (prior to TRIPS, the patent term was 20 years in certain industrialized countries, but shorter in many developing countries), and mandates effective enforcement.

The introduction of these TRIPS standards will delay the marketing of generic versions of new drugs, and, thus, the competition they entail; hence it is anticipated that prices of new drugs will remain high for a longer time which will result in reduced access for many people, notably in developing countries.

ACCESS TO DRUGS

Access to medicines depends on many factors, notably rational selection and use of drugs, adequate and sustainable financing, affordable prices, and reliable supply systems. Prices are only one factor. Yet prices are an important factor, especially in developing countries, since, while in developed countries pharmaceuticals are largely publicly funded, through reimbursement and insurance schemes, in developing countries, typically, 50-95% of drugs are paid by the patients themselves (see Figure 1). Thus, in developing countries, prices have direct implications for access to medicines.

TRIPS has however reinforced process patents.

TRIPS does not apply retroactively, therefore there are no implications for drugs that were already off-patent when TRIPS came into force.

It should also be noted that patents are not the only reason for high drug prices; distribution costs, high mark-ups and taxes can also play an important role.

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1 This ARV newsletter has been updated in January 2006.
TRIPS SAFEGUARDS

It is however important to realize that TRIPS is a framework agreement; it is to be operationalized via countries’ national laws. Moreover, TRIPS does contain limited flexibility, as well as some safeguards, which can be used to mitigate the anticipated negative impact on drug prices and on access to drugs.

The most important safeguards are (i) compulsory licensing, (ii) parallel importation and (iii) provisions for early working (often referred to as “Bolar provision”).

The “Bolar provision” allows testing and regulatory approval of generic versions of a drug, before its patent expires; thus, it allows generic producers to get ready, so that they can start the production and sale of a generic drug as soon as its patent expires. In this way, a Bolar provision facilitates generic competition.

Parallel importation refers to importation, without the consent of the patent holder, of a patented product that is marketed in another country. Parallel importation allows one to ‘shop around’ for a good price; for example, if a company sells drug X in country A at a price of $10, while the same company sells the same drug X in country B for $1, then someone may import drug X from country B and sell it in country A, charging for example $3. As a result, in this example, country A would save $7 on product X. In other words, parallel importation also enables competition, but in a different way.

The TRIPS Agreement states that parallel importation cannot be challenged under the WTO dispute settlement mechanism, thus de facto leaving countries the freedom to choose whether or not to allow parallel importation. Moreover, during the WTO’s Ministerial Meeting in November 2001, the Ministers clarified, in the Doha Declaration on the TRIPS Agreement and Public Health, that countries are free to use parallel importation.

A compulsory license is a license to use an invention, which has been granted without the permission of the patent holder. A compulsory license can be used to allow the production and sale of generics before expiry of the patent - thus, again, increasing opportunities for competition (and competition drives prices down, as can be seen in Figure 2).

The basic rationale for a compulsory license is that, since a patent is a privilege granted by the government, the government retains the right to limit that privilege if necessary. Many countries, including many developed countries, have provisions for compulsory licenses in their national laws, and compulsory licenses are allowed under TRIPS.

TRIPS mentions that a compulsory license can be issued for reasons of national emergency or extreme urgency, public non-commercial use and other reasons. However, it is important to note that TRIPS does not limit the grounds, or reasons, for issuing a compulsory license.
But the TRIPS Agreement does specify *conditions*, which are to be imposed by governments when issuing a compulsory license. These conditions include⁶:

- case-by-case decision
- first try to obtain a voluntary license
- adequate remuneration to the patent holder
- predominantly for the supply of the domestic market
- a compulsory license should be non-exclusive and non-assignable.

So while these conditions have made the process somewhat cumbersome, it is possible to issue a compulsory license in a TRIPS-compliant way.

A special case of compulsory licensing is ‘Government use’ (or a compulsory license for public non-commercial use). TRIPS imposes less stringent conditions in case of ‘Government use’; hence countries may find that using this mechanism is easier/faster than compulsory licensing.

However, the safeguards provided for in TRIPS can only be used when incorporated in the national law. Thus, it is important that countries design and enact legislation which allows them to protect the public interest, including the public health interest.

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⁶ The list is not exhaustive; moreover, certain conditions may be waived in specific circumstances. For instance, the condition to first try to obtain a voluntary license does not apply if a compulsory license is issued to remedy anti-competitive behavior of the patent holder, in case of an emergency or in case of public non-commercial use.

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**Figure 2: Influence of competition on drug prices**

1996 prices taken as reference (100%)

<table>
<thead>
<tr>
<th>Year</th>
<th>ARV 1</th>
<th>ARV 2</th>
<th>ARV 3</th>
<th>ARV 4</th>
<th>ARV 5</th>
<th>ARV 6</th>
</tr>
</thead>
<tbody>
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<td>1996</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<td>1998</td>
<td>40</td>
<td>40</td>
<td>40</td>
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<td>40</td>
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</tr>
<tr>
<td>1999</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<td>2000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: UNAIDS, 2000

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**Flexibility in TRIPS**

In addition, as mentioned above, there is some flexibility in TRIPS. For example, one of the conditions for issuing a compulsory license is that the patent holder should receive adequate remuneration. But TRIPS does not define “adequate”; thus, countries have some leeway in this respect.

Similarly, TRIPS leaves countries free to use either very strict or more flexible criteria for patentability. Applying flexible criteria of novelty and inventiveness enables for instance the issuing of patents for formulations or for isomers of known drugs, thus allowing pharmaceutical companies to apply for additional patents, and providing them with opportunities to expand the duration of protection beyond that of the original patent. In this way, originator companies can seek to postpone generic competition.

Yet whether this flexibility is actually used in order to facilitate access to medicines ultimately depends on national standards and (administrative) procedures.

**Other TRIPS Provisions**

Patents are not the only type of intellectual property rights addressed in TRIPS, and some of the other forms of intellectual property can also have implications for access to drugs. For example, TRIPS mandates protection of undisclosed data submitted to national Drug Regulatory Authorities in order to obtain marketing authorization for new drugs. These registration data have to be protected against disclosure, and against unfair commercial use. Thus, the national
Some parties however try to argue for data exclusivity, which means that the regulatory authorities would not be allowed to rely on these data for the purpose of registration of generic versions of the drug. By implication, as long as the exclusivity lasts, generic producers would either have to submit their own data - which would oblige them to repeat the clinical trials and other tests- or they would have to delay the launch of their product until the end of the exclusivity period. Thus, data exclusivity diminishes the likelihood of speedy marketing of generics, and delays competition and price reductions.

TRIPS, however, mandates data protection, but not data exclusivity and national laws need not have requirements that are more stringent than TRIPS7.

Similarly, it is important that national trademark laws do not hinder pro-public health measures such as generic prescription, generic substitution and/or requirements that a drug’s label includes the generic name.

COUNTRY EXPERIENCES

Two countries that are at the forefront of the fight against HIV/AIDS, especially with regard to making HIV/AIDS drugs, including antiretrovirals (ARVs), available and affordable, are Thailand and Brazil. Thailand focuses on producing and selling generic ARVs at the lowest possible price8, while Brazil is providing free ARV treatment in its public health facilities. Their strategies, with regard to intellectual property rights, are summarized below:

THAILAND

The Government Pharmaceutical Organization (GPO) in Thailand is producing a number of generic ARVs. The GPO is only producing products that are not patented in Thailand, or for which the Thai patent has expired. One important drug, didanosine or ddI, used to be under patent in Thailand; however, the patent only applied to ddI tablets. Hence the GPO has been producing ddI powder; the powder form, while not as convenient or as accurate a dosage form as tablets, did not infringe the patent.

Some years later, following a challenge by NGOs representing people living with HIV/AIDS, Thailand’s Central Intellectual Property and International Trade Court has ruled that the ddI patent was only valid for tablets containing 5-100 mg ddI. Since then, it has been possible for generic producers, such as the GPO, to produce ddI tablets outside that dosage range (e.g. tablets containing 125 mg ddI).

BRAZIL

Brazil, like Thailand, has a government-owned company that produces generic versions of certain ARVs, which are not under patent in Brazil. In addition, Brazil has used the fact that it is capable of producing generic versions of crucial HIV drugs, and that it would be willing to issue a compulsory license if necessary, to negotiate substantial price discounts for those drugs that are patented. So far, this strategy has been quite successful, and Brazil has not yet had to actually issue a compulsory license.

MALAYSIA AND INDONESIA

Increasingly, other countries are also taking action in order to make ARVs more available and affordable. In Oct. 2003, Malaysia decided to apply ‘Government use’ provisions in its national law in order to import generic ARVs. A year later, Indonesia used the ‘Government use’ mechanism for domestic production of several generic ARVs.

OPTIONS FOR OTHERS

So what can other countries do? What options are available to increase access to HIV/AIDS drugs? Clearly, the answer will vary considerably from country to country, depending on relevant national laws, production capacity and other factors. But in principle, the following options exist:

Countries with pharmaceutical production capability could initiate local production of generic versions of those drugs that are not patented or whose patents have expired9. They could also consider, if their national law and regulations allow, to apply compulsory licensing or ‘Government use’ to enable local production of generic versions of those drugs that are patent protected.

Countries where local production is not feasible or not viable can import generics, for example from India, provided the drug concerned is not under patent in their territory. In case the drug of interest is patent protected in the importing country, parallel importation could be considered, as long as national legislation allows it - and if a cheaper source of the drug can be found.

The option to (parallel) import obviously is also open to countries that do have manufacturing facilities. Yet a problem looms: major international producers of generics are primarily located in countries such as India, which now have to comply with TRIPS (see Figure 3; India falls in category c). Fortunately, transitional provisions in India’s new patent law allow the continued production of generic medicines marketed before 2005. However, Indian pharmaceutical enterprises will have to wait until patent expiry before they can commence the production of new generics. Thus, even when patents in their own territory do not stand in the way, importing countries may face problems in finding a source of supply of generic versions of second line ARVs and other new drugs.

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7 Unfortunately, data exclusivity and other requirements that go beyond TRIPS are increasingly being incorporated in bilateral/regional free trade agreements.

8 The Thai Ministry of Public Health also provides highly subsidized ARV treatment via its universal coverage scheme (the ‘30 Baht scheme’).

9 The first generation of ARVs that were patented in the 1980s will continue to come off patent.
Meanwhile, countries that lack national production capacity would face difficulties in making effective use of compulsory licensing provisions. The basic problem is that while the importing country could use compulsory licensing or ‘Government use’ for importation of the drug from abroad, foreign companies would -because of TRIPS’ condition that a compulsory license should be issued “predominantly for the supply of the domestic market”- face potentially severe restrictions on their capacity to export.

During the WTO meeting in Doha, Ministers recognized this problem, and instructed the WTO’s TRIPS Council to find an expeditious solution. But because of diverging views there has been considerable debate on how to best tackle this inconsistency.

A solution was finally agreed to on 30 August 2003. This solution, which may require two compulsory licenses to be issued (one in the importing and one in the exporting country) and has been criticized as being cumbersome, has not yet been used in practice. This may, among other reasons, be due to the fact that most exporting countries would have to amend their national laws before they can actually export generic medicines produced under a compulsory license – something that Canada, Norway, India, South Korea and China have recently done.

<table>
<thead>
<tr>
<th>Figure 3: Deadlines for implementation of the TRIPS Agreement</th>
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<tr>
<td>a) Developed countries</td>
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<td>b) Developing countries (except those under c)</td>
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<tr>
<td>c) Developing countries that did not grant pharmaceutical</td>
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<tr>
<td>product patents prior to TRIPS</td>
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<tr>
<td>d) Least developed countries</td>
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</table>

* The original TRIPS implementation deadline for least-developed countries was 2006; however during the WTO Ministerial Meeting in Doha, it has been agreed to extend this deadline.

**FURTHER READING**


Documents 1, 2, 5 and 7 (as well as other relevant materials) can be downloaded from: [http://www.who.int/medicines/](http://www.who.int/medicines/)

Documents 3 and 6 can be found at: [http://www.southcentre.org/](http://www.southcentre.org/)

**ACKNOWLEDGEMENTS**

The Western Pacific Regional Office of the World Health Organization would like to express sincere thanks to Ms Karin Timmermans for preparing this overview and to acknowledge valuable comments from a number of experts including Dr Peter Drahos, Dr Chris Duncombe and Dr Carlos Correa.

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10 Using a compulsory license for importation appears to be permissible under TRIPS.

11 In addition, there are requirements to report to the WTO and on labelling/packaging of the concerned medicines.