

HIV/AIDS

Antiretroviral

Newsletter



World Health Organization

Regional Office for the
Western Pacific

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

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

BACKGROUND

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

ACCELERATING ACCESS TO CARE

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

The objectives of this initiative are:

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

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

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

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

A COUNTRY DRIVEN PROCESS

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

DRUG PROCUREMENT

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

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

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

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

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

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

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

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

THE PRICE OF MEDICINES

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

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

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

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

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

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

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

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

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

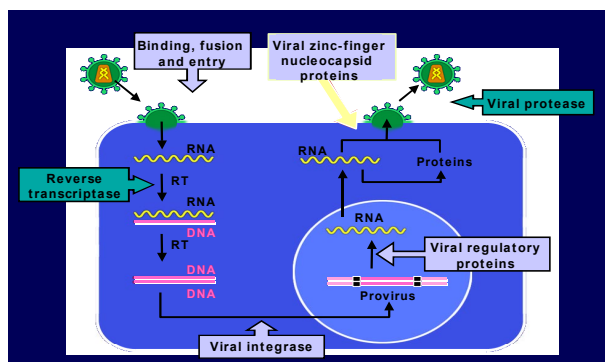
Table 1: Negotiated prices (per daily dose) in Uganda. These prices are similar in Rwanda and Senegal.

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

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

Part 2. Recent developments in antiretroviral therapy

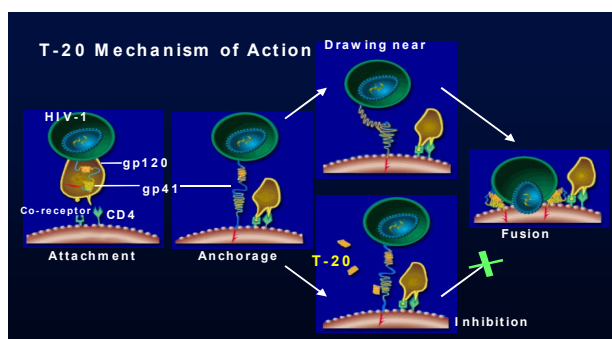
VIRAL ENTRY AND FUSION INHIBITORS



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

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

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



STRUCTURED TREATMENT INTERRUPTION

The strategy of structured treatment interruption involves deliberately ceasing ARV therapy for a fixed

period of time and restarting therapy according to pre-set criteria, such as CD4 count decline or increase in viral load. Another approach to STI starts and stops therapy in week on/week off cycles.

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

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

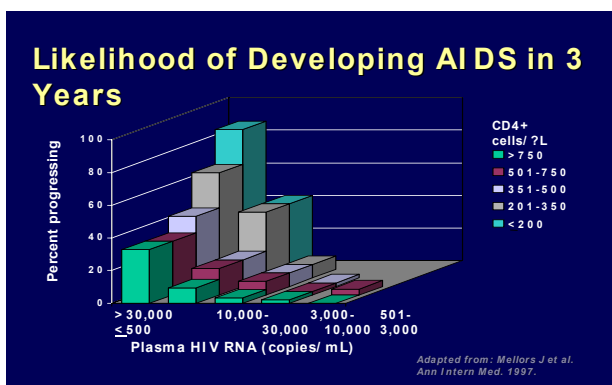
INITIATING THERAPY: WHEN TO START AND WHAT TO START WITH?

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

The main changes in the current guidelines refer to initiation of therapy in asymptomatic patients. Previously, the guidelines had recommended initiating treatment in individuals with symptomatic HIV infection and in asymptomatic patients with CD4+ cell counts < 500 cells/mm³ or plasma HIV-1 RNA levels greater than 20,000 copies/ml.

However, the new DHHS guidelines recommend that treatment be delayed until the CD4+ cell count is less than 350 cells/mm³ or viral load is greater than 55 000 copies/ml. The guidelines are clear that these recommendations are not absolute and that many experts would recommend earlier treatment in a motivated, well-informed individual. Other experts might wait until the CD4+ cell count falls even further, especially if the viral load is low. In developing countries with limited resources, treatment of asymptomatic patients may be delayed until CD4 count is < 200 cells/mm³.

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



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

NEW RECOMMENDATIONS IN PREGNANCY

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

The use of ARV during pregnancy, whether primarily to treat HIV infection, reduce perinatal transmission, or

both, should be accompanied by counselling regarding the potential short and long term benefits and risks of such therapy for infected women and their infants. Although considerations associated with pregnancy may affect decisions regarding timing and choice of therapy, pregnancy is not a reason to defer standard therapy.

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

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

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



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