

Pressure by AIDS activist groups, compassion by the pharmaceutical industry and action by the United Nations Secretary General have resulted in a global fund to enable developing countries to purchase cheaper AIDS drugs. Here, the authors describe the World Health Organization's first attempts to devise guidelines for their widespread use in these resource-poor nations.

Antiretroviral guidelines for resource-limited settings: The WHO's public health approach

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Attempts to confront the human immunodeficiency virus (HIV) pandemic are at a crucial point. There are now 40 million persons worldwide living with HIV; the mortality since the epidemic's onset has been approximately 25 million. Resource-limited countries bear more than 90% of the global disease burden. Efforts at prevention, including the development of an HIV vaccine, are crucial priorities requiring increased and sustained funding, but there is now also an unprecedented multisectorial mobilization to treat millions of infected persons around the world, in particular by providing antiretroviral (ARV) drug therapy.

As part of its broad response to the HIV pandemic, the World Health Organization (WHO) recently issued guidelines for ARV therapy in resource-limited settings (http://www.who.int/HIV_AIDS/first.html). This was the culmination of a process more than a year long bringing together experts in a variety of disciplines from around the world; a 21-member writing committee authored the final document. It is hoped that this publication will be a watershed in attempts to advise on the delivery of life-sustaining therapy to regions of the world where broad access to ARV drugs has not previously been feasible.

WHO has issued two previous documents on the use of ARVs in resource-poor settings: the Guidance Modules on Antiretroviral Treatments, Module 4: Safe and Effective Use of Antiretrovirals (1998); and Safe and Effective Use of Antiretroviral Treatments in Adults with Particular Reference to Resource Limited Settings (2000). Whereas these publications described the use of ARVs largely on the basis of state-of-the-art practices in the United States and Europe and were directed primarily at the clinician-patient interface, the new guidelines propose an innovative approach to scaling up ARV use in developing country settings. Although the new guidelines are designed to be useful to clinicians, their primary targets are the national treatment advisory boards and senior-level policymakers who assist with systematic program development. The guidelines are thus meant to outline a public health approach to enable the treatment of 3 million individuals in the next 3 years.

This is really the first time that the world's leading health policy organization has called for the implementation of ARV treatment programs. Several factors have combined to make the creation of HIV treatment programs in developing

countries more feasible than ever before: the price of ARVs in developing countries has decreased, and the advent of the Global Fund to Fight AIDS, Tuberculosis & Malaria should make it

possible to pay for them. Also, the WHO placed ARVs on the Essential Drug List for the first time in April. The WHO defines essential drugs as "those 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 (WHO Expert Committee on the Use of Essential Drugs, 1999). Careful selection of a limited range of essential medicines results in a higher quality of care, better management of medicines (including improved quality of prescribed medicines), and more cost-effective use of health resources." (<http://www.who.int/medicines/organization/par/edl/infedlmain.shtml>).

These changes have increased the need for guidance to developing countries on the rational use of antiretroviral drugs on a large scale. Given the limitations on trained manpower and infrastructure in developing countries, a defined treatment program is the most feasible and responsible way to introduce ARVs to maximize the benefits for patients and reduce the likelihood of harm arising from resistance.

We further believe that the dissemination of these guidelines comes at a time when the world is focusing as never before on the devastation being wrought by the AIDS epidemic in developing countries. In addition to the launch of the Global Fund, a number of agencies and foundations are mobilizing forces to address the difficulties involved in putting treatment programs into place. One such example is the Mother-To-Child-

Table 1 When to start: recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection

If CD4 testing is available:

WHO Stage IV disease, irrespective of CD4⁺ cell count
WHO Stage I, II or III^a with CD4⁺ cell counts 200/mm³ or lower^b

If CD4 testing is unavailable:

WHO Stage IV disease, irrespective of total lymphocyte count
WHO Stage II or III^a disease with a total lymphocyte count 1,200/mm³ or lower^c

^aTreatment is also recommended for patients with advanced WHO Stage III disease, including recurrent or persistent oral thrush and recurrent invasive bacterial infections, irrespective of CD4 cell or total lymphocyte count. ^bThe precise CD4 level above 200/mm³ at which to start ARV treatment has not been established, but the presence of symptoms and the rate of decline of CD4 cells (if measurement is available) should be considered. A percentage CD4 count of <15% corresponds approximately to a total CD4 count <200/mm³. ^cA total lymphocyte count of 1,200/mm³ or lower can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less useful in asymptomatic patients. Thus, in the absence of CD4 cell testing, asymptomatic HIV-infected patients (WHO Stage I) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.

Table 2 What to start with: Recommended first-line antiretroviral regimens in adults and adolescents^{a,b}

Regimen	Pregnancy considerations	Major toxicities
ZDV/3TC ^c plus EFZ or NVP	Substitute NVP for EFZ in pregnant women or women for whom effective contraception cannot be assured	ZDV-related anemia EFZ-associated central nervous system symptoms Possible teratogenicity of EFZ NVP-associated hepatotoxicity and severe rash NsRTI-related metabolic side effects
ZDV/3TC/ABC ^c	ABC safety data limited	ZDV-related anemia ABC hypersensitivity NsRTI-related metabolic side effects
ZDV/3TC ^c plus RTV-enhanced PI (IDV/rTV, LPV/rTV, SQV/rTV) or NFV	LPV/rTV safety data limited NFV has most supportive safety data	ZDV-related anemia NFV-associated diarrhea IDV-related nephrolithiasis PI- and NsRTI-related metabolic side effects

^aCountry-specific constraints and preferences should determine which regimen(s) to make available. ^bFixed-dose formulations are preferred whenever possible because they promote enhanced drug adherence. ^cZDV/3TC is listed as the initial recommendation for a dual-NsRTI component on the basis of efficacy, toxicity, clinical experience and the availability of fixed-dose formulation. Other dual-NsRTI components, including d4T/3TC, d4T/ddI and ZDV/ddI, can be substituted depending upon country-specific preferences. ZDV and d4T should never be used together because of proven antagonism. 3TC, lamivudine; ABC, abacavir; d4T, stavudine; ddI, didanosine; EFZ, efavirenz; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NsRTI, nucleoside-analog reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; rTV, ritonavir; SQV, saquinavir; ZDV, zidovudine.

Transmission (MTCT) Plus initiative, a \$50–100-million program sponsored by eight foundations and lead by Allan Rosenfield, dean of the Mailman School of Public Health at Columbia University. The plan is to use MTCT prevention programs as entry points for the treatment of women and their families with ARV agents, and MTCT Plus-funded sites will be announced at the XIVth International AIDS Conference in Barcelona (7–12 July 2002). With such efforts and with the reduction in cost of many antiretroviral agents, treatment in its broadest sense should become an integral part of every country's prevention program.

What we believe we have shown is that, in the context of the 16 ARV agents approved in the United States and the recognized complexity of HIV disease management, it is possible to develop simple, standardized treatment programs that can be scaled up to a large degree. This 'public health approach' is aimed at expanding ARV treatment programs through the standardization and simplification of treatment regimens and the efficient implementation of treatment programs. The recommendations are based on the best available scientific evidence to ensure the provision of regimens of high antiviral efficacy that meet standards of care everywhere in the world. The document details first- and second-line ARV regimens for adults and adolescents infected with HIV and for special populations, including pregnant women, children, persons concurrently infected with tuberculosis and injecting drug users. The recommendations address the practicalities of monitoring ARV therapy in resource-limited settings and outline an approach to be used when monitoring of CD4 cell count and viral load are not available. Also emphasized are the importance of drug adherence and the threat of drug resistance.

ARV therapy management has traditionally been ruled by four questions: (i) when to start therapy, (ii) what initial regimen to choose, (iii) when to change therapy and (iv) what reg-

imens to switch to. The WHO guidelines follow this approach, but with the choices tailored to take into account limited laboratory monitoring. It is crucial that low-cost approaches to the monitoring of CD4 cell count and viral load be developed and made widely available. In the absence of such methods, however, treatment programs based on clinical criteria and rudimentary laboratory tests can and should be implemented. The core of the recommendations for initiating ARV treatment in HIV-infected adults and adolescents is summarized in Tables 1 and 2.

These guidelines do have limitations. The inability to monitor patients as closely as in the developed world may delay recognition of treatment failure and medication toxicities. The risk/benefit ratios in such situations have not been defined, and operational research to determine the optimal monitoring system for resource-limited settings is still needed. In addition, the issuance of guidelines will not by itself accomplish the desired goal of delivering treatment to patients on a large scale. Hence, this document should be seen as part of a broader plan that must include improving the affordability and sustainability of drug financing and developing infrastructure to ensure that competent health-care services are available.

Finally, the field of ARV therapy is evolving rapidly, particularly in regard to developing countries. Thus, recommendations about the rational use of ARV drugs in resource-limited settings need to be adaptable and to reflect scientific and political progress. The WHO guidelines will be reviewed and updated regularly, but their potential will only be realized if the global community seizes the opportunity for action now.

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