SCALING UP
ANTIRETROVIRAL THERAPY IN
RESOURCE-LIMITED SETTINGS

GUIDELINES FOR A
PUBLIC HEALTH APPROACH

EXECUTIVE SUMMARY

Full guidelines available at http://www.who.int

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World Health Organization
April 2002
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ABBREVIATIONS

ABC Abacavir
AIDS Acquired immune deficiency syndrome
APV Amprenavir
ARV Antiretroviral
ART Antiretroviral Therapy
d4T Stavudine
ddC Zalcitabine
ddi Didanosine
DLV Delavirdine
EFZ Efavirenz, also abbreviated as EFV
ELISA Enzyme linked immunosorbent assay
HIV Human immunodeficiency virus
IDV Indinavir
LPV Lopinavir
MTCT Mother-to-child transmission of HIV
NFV Nelfinavir
NIH U.S. National Institutes of Health
NNRTI Non-nucleoside reverse transcriptase inhibitor
NsRTI Nucleoside analog reverse transcriptase inhibitor
NtRTI Nucleotide analog reverse transcriptase inhibitor
NVP Nevirapine
OI HIV related opportunistic infection
PCP Pneumocystis carinii pneumonia
PCR Polymerase chain reaction
PI Protease Inhibitor
RTV, r Ritonavir
RTV-PI Ritonavir boosted Protease Inhibitor
SQV Saquinavir
QA Quality assurance
RT Reverse transcriptase
STI Sexually transmitted infection
TB Tuberculosis
TDF Tenofovir disoproxil fumarate
UN United Nations
UNAIDS United Nations Joint Cosponsored Programme on HIV/AIDS
VCT HIV voluntary counselling and testing
WHO World Health Organization
ZDV Zidovudine, also known as AZT
PREFACE

Less than a decade ago, someone living with HIV/AIDS had little hope. HIV infection brought a steady inexorable decline towards the complete destruction of the immune system and death. The introduction of highly active antiretroviral therapy in 1996 was a turning point for hundreds of thousands of people with access to sophisticated health care systems. Although they cannot cure HIV/AIDS, antiretrovirals (ARVs) have dramatically reduced mortality and morbidity, prolonged lives, and improved the quality of life of many people living with HIV/AIDS.

Today we are once again at a turning point - this time in favour of the developing world. Thanks to the work of hundreds of individuals and activists in NGOs, governments, UN agencies and the private sector, prices of ARVs have fallen and we are now in a position to consider scaling up access in resource limited settings.

Scaling up will not be possible in the absence of a clear public health approach that promotes the rational and safe use of these powerful and precious medicines. These technical guidelines, developed with the support of the US National Institutes of Health, present such an approach, promoting the use of standardized regimens and simplified monitoring. They recommend standards for the large-scale introduction of ARVs that prevent misuse. This is essential for good patient adherence and correct use by prescribers.

WHO estimates that in 2002, some 6 million people in developing countries are in need of life-sustaining ARV therapy now. Instead, only 230,000 have such access today, and half of these live in one country, Brazil. We believe that the countries of the developing world should be able to have 3 million people on ARVs by the end of 2005 – provided that the world follows through on the international concerted effort to expand access to HIV treatment and care. This ten-fold increase matters for many reasons. Three million people will be granted a new lease on life, wider access to treatment will stimulate prevention and there will be positive impacts on social and economic development as people living with HIV live longer and more productive lives.
These guidelines offer a chance of hope to those who despaired. They affirm the human rights and dignity of people living with HIV. They represent an opportunity to build upon the solidarity and energy of the global movement against HIV/AIDS by redressing the inequities between rich and poor in access to care. They will be updated on a regular basis as new information and evidence becomes available. As we look to the future, WHO will continue to work with its partners around the world to further increase access to care and support to all who need it.

Tomris Türmen
Executive Director
Family and Community Health
World Health Organization
Geneva
April 2002
I. INTRODUCTION

Less than a decade ago, when the one available class of antiretroviral (ARV) drugs was unable to adequately inhibit replication of the Human Immunodeficiency Virus (HIV), the lives of people living with HIV/AIDS the world over followed an often immutable course: gradual destruction of the immune system, initiation of prophylaxis to prevent opportunistic infections, early retirement, wasting, periods of wellness and illness punctuating an inexorable decline towards complete immune depletion and finally, death.

Since 1996, the advent of new classes of ARV drugs and their use in combination have changed the way people in the world’s richest countries think about HIV/AIDS. Although these treatments are not a cure and present new challenges of their own to people living with HIV/AIDS, they have dramatically improved rates of mortality and morbidity, prolonged lives, improved quality of life, revitalised communities and transformed perceptions of HIV/AIDS from a plague to a manageable, chronic illness.

Unfortunately, most of the 36 million people in the developing world currently living with HIV/AIDS do not share this vastly improved prognosis. WHO conservatively estimates that in 2002, some 6 million people in resource limited settings are in need of life-sustaining ARV therapy now. Instead, only 230,000 have access to them, and half of these live in one country, Brazil.

In the wake of the International AIDS Conference in Durban in 2000 and the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) in 2001, the resolve of the international community to address this appalling disparity between treated and untreated, between rich and poor, is stronger than ever before. The world recognizes the pressing moral, social, political and economic imperatives to expand access to antiretroviral therapy to many more millions of people living with HIV/AIDS as soon as practicable, and has begun to mobilize the “great global alliance” which UN Secretary General Kofi Annan has called for to achieve the UNGASS goals.

These guidelines are part of the World Health Organization’s ongoing commitment to this great global alliance. Their development involved a year long process of international consultative meetings in 2001, in which
more than 200 clinicians, scientists, government representatives, representatives of civil society and people living with HIV/AIDS from more than 60 countries participated. The recommendations included in this publication reflect the best current practices based on a review of existing evidence. Where the body of evidence was not conclusive, expert consensus was used as a basis for recommendations. In this rapidly evolving field, WHO recognizes that these recommendations will need to be updated on a regular basis.

Although it is an important step, this publication is not intended to be a “magic bullet” for expanding access to ARV treatment. Drug access for the millions who need it will be improved not only by guidance on the rational selection and use of ARV drugs, but also by improved affordability and sustainability of drug financing and by accessible, appropriate and competent health services. These other critical elements continue to be promoted by actors within and beyond the UN system in the following ways:

- The Accelerating Access initiative, which has led to dramatic reductions in the cost of ARV drugs in 20 developing countries by January 2002;

- The mapping of sources and prices of HIV related drugs by UNICEF, UNAIDS, Medecins-Sans-Frontieres (MSF) and WHO;

- The assessment of the patent situation for HIV related drugs by WHO and UNAIDS;

- Increased financial and human resources for efforts by WHO to strengthen health systems capacity in HIV/AIDS, including the launch of an international network of training institutions for HIV care;

- The Global Fund to Fight AIDS, Tuberculosis and Malaria, launched by UN Secretary General Kofi Annan in 2001, involving a significant new investment of financial resources against these three major infectious diseases.
II. PUBLICATION’S OBJECTIVES

Currently, fewer than five per cent of those who require ARV treatment can access these medicines in resource-limited settings. WHO believes that at least three million people needing care should be able to get medicines by 2005—a more than ten-fold increase.

These guidelines are intended to support and facilitate the proper management and scale-up of ART in the years to come by proposing a public health approach to achieve these goals. The key tenets of this approach are:

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;

3) Ensuring that ARV treatment programmes are based on the best scientific evidence, in order to avoid the use of substandard treatment protocols which compromise the treatment outcome of individual clients and create the potential for emergence of drug resistant virus.

While it is hoped that this publication will be useful to clinicians in resource-limited settings, it is intended primarily for use by Treatment Advisory Boards, national AIDS programme managers, and other senior level policymakers involved in the planning of national and international HIV care strategies in resource-limited settings. The guidelines serve as a framework for selecting the most potent and feasible antiretroviral regimens in as part of an expanded national response. The framework aims to “standardize” and simplify antiretroviral therapy, much like TB treatment in National TB control programmes, while acknowledging the relative complexity of HIV treatment. Accordingly, options for first-and second line regimens are presented, bearing in mind the needs of health systems that often lack sophisticated manpower and monitoring facilities, without compromising the quality and outcomes of the treatments offered.

The topics addressed in these guidelines include ART, which ARV regimens to start, reasons for changing ART, and what regimens to continue if treatment needs to be changed. It also addresses how treatment should be monitored, with specific reference to the side effects of ART, and makes specific recommendations for certain patient subgroups.
III. WHEN TO START ARV THERAPY

WHO recommends that in ARV treatment programmes in resource-limited settings HIV infected adolescents and adults should start ARV therapy when they have:

- WHO stage IV of HIV disease (clinical AIDS), regardless of CD4 count
- WHO Stages I, II or III of HIV disease, with a CD4 count below 200/m$^3$
- WHO Stages II or III of HIV disease with TLC below 1200/mm$^3$

Wherever possible, countries are encouraged to use CD4 cell counts in their ARV treatment programmes and consider the use of simple, low cost CD4 methodologies that are currently available to enable the wider use of CD4 cell counts in their programmes. However, in cases where CD4 counts cannot be assessed, the presence of a total lymphocyte count below 1200/mm$^3$ may be used as a substitute indication for treatment in the presence of symptomatic HIV disease (i.e. WHO stages II or III). While the total lymphocyte count correlates relatively poorly with CD4 count, in combination with clinical staging it is a useful marker of prognosis and survival. An assessment of viral load (e.g. using plasma HIV-1 RNA levels) is not considered essential to start therapy.

In children, WHO recommends offering ARV combination therapy to HIV-positive infants under the age of 18 months if they have virologically proven infection (using either HIV PCR or immune complex dissociated HIV p24 antigen detection or HIV culture) and WHO Pediatric Stage III HIV disease (i.e. clinical AIDS) or WHO Pediatric Stages I and II disease and a CD4 percentage < 20%. In settings where virologic confirmation is not available, ARV combination therapy can be offered to HIV-positive infants who have WHO Stage III HIV disease and have a CD4 percentage < 20%. For children over the age of 18 months who are HIV antibody positive, WHO recommends ART if they have WHO Stage III HIV disease (i.e. clinical AIDS) regardless of CD4 percentage. For those older children with WHO stage I or II HIV disease, ART is recommended if the CD4 percentage is < 15%.
Table A. Recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection

<table>
<thead>
<tr>
<th>If CD4 Testing Available:</th>
<th>If CD4 Testing Unavailable:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• WHO Stage IV disease irrespective of CD4 cell count</td>
<td>• WHO Stage IV disease irrespective of total lymphocyte count</td>
</tr>
<tr>
<td>• WHO Stage I, II or III$^a$ with CD4 cell counts below 200/mm$^3$.b</td>
<td>• WHO Stage II or III$^a$ disease with a total lymphocyte count below 1200/mm$^3$.c</td>
</tr>
</tbody>
</table>

$^a$ Treatment 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.

$^b$ The precise CD4 level above 200/mm$^3$ at which to start ARV treatment has not been established but the presence of symptoms and the rate of CD4 cell decline (if measurement available) should be factored into the decision making. A CD4 level of 200/mm$^3$ corresponds to a CD4 percentage of approximately 15%.

$^c$ A total lymphocyte count of below 1200/mm$^3$ can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less useful in the asymptomatic patient. 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 B: Recommendations for initiating antiretroviral therapy in infants and children

<table>
<thead>
<tr>
<th>D4 Testing</th>
<th>Age</th>
<th>HIV Diagnostic testing</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If CD4 testing is available</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 18 months</td>
<td>Positive HIV virologic test&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• WHO Pediatric Stage III (AIDS), irrespective of CD4 cell percentage&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV virologic testing not available but infant HIV seropositive or born to known HIV-infected mother (Note: HIV antibody test must be repeated at age 18 months to obtain definitive diagnosis of HIV infection)</td>
<td>• WHO Pediatric Stage III disease (AIDS) with CD4 cell percentage &lt; 20%</td>
</tr>
<tr>
<td></td>
<td>≥ 18 months</td>
<td>HIV antibody seropositive</td>
<td>• WHO Pediatric Stage III disease (AIDS) irrespective of CD4 cell percentage&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV virologic testing not available but infant HIV seropositive or born to known HIV-infected mother</td>
<td>• WHO Pediatric Stage I disease (asymptomatic) or Stage II disease with CD4 percentage &lt; 15%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>If CD4 testing is not available</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 18 months</td>
<td>Positive HIV virologic test</td>
<td>• WHO Pediatric Stage III&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV virologic testing not available but infant HIV seropositive or born to known HIV-infected mother</td>
<td>• Treatment not recommended&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>≥ 18 months</td>
<td>HIV antibody seropositive</td>
<td>• WHO Pediatric Stage III&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> HIV DNA PCR or HIV PCR RNA or immune complex dissociated p24 antigen assays, or HIV culture.

<sup>b</sup> Initiation of ARV can also be considered for children who have advanced WHO Pediatric Stage II disease including such as severe recurrent or persistent oral candidiasis outside the neonatal period, weight loss, fevers, or recurrent severe bacterial infections, irrespective of CD4 count.

<sup>c</sup> The rate of decline in CD4 percentage (if measurement available) should be factored into the decision-making.

<sup>d</sup> Many of the clinical symptoms in the WHO Pediatric Stage II and III disease classification are not specific for HIV infection and significantly overlap with those seen in children without HIV infection in resource-limited settings; thus, in the absence virologic testing and CD4 cell assay availability, HIV-exposed infants <18 months of age should generally not be considered for ART regardless of symptoms.
IV. RECOMMENDED FIRST-LINE REGIMENS IN ADULTS

Countries are encouraged to use a public health approach to facilitate the scale-up of ARV use in resource-limited settings. This means that antiretroviral treatment programmes should be developed and requires that ARV treatment be standardized. In particular, it is suggested that countries select a single first and a limited number of second line regimens for large scale use, recognising that individuals who cannot tolerate or fail the first and second line regimens would be referred for individualized care by specialist physicians.

Considerations in the selection of ARV treatment regimens at both the programme level and at the level of an individual patient should include the potency, side effect profile, the potential for maintenance of future treatment options, the anticipated adherence of the patient population with a regimen, coexistent conditions (e.g., co-infections, metabolic abnormalities), pregnancy or the risk thereof, the use of concomitant medications (i.e. potential drug interactions), the potential for primary acquisition of resistant viral strains, and cost and access. Additional considerations relevant to resource limited settings may include access to only a limited number of ARV drugs, limited health service infrastructure, the need to deliver drugs to rural areas, a high incidence of tuberculosis and hepatitis B and/or C, and the presence of varied HIV groups and subtypes.

Taking all of these considerations except the cost of drugs into account, the preferred first-line antiretroviral regimens in adults and adolescents are listed in the Table C. All regimens consist of a dual nucleoside component, and a potent third drug to complement it. Zidovudine (ZDV)/lamivudine (3TC) is listed as the initial recommendation for the dual nucleoside component based on efficacy, toxicity, clinical experience and the availability of ZDV/3TC as a fixed dose combination. Other dual nucleoside combinations can be substituted for ZDV/3TC, including stavudine (d4T)/3TC, d4T/didanosine (ddI) and ZDV/ddI depending upon country-specific preferences. However, ZDV/d4T should never be used together because of proven antagonism between the two drugs.

Of note is that dual nucleoside drug regimens alone are no longer recommended as they do not adequately suppress HIV replication and are likely to lead to the rapid emergence of resistance.
Table C. Recommended first-line ARV combination regimens in adults and adolescents with documented HIV infection

<table>
<thead>
<tr>
<th>Regimen(^a)</th>
<th>Pregnancy Considerations</th>
<th>Major Toxicities</th>
</tr>
</thead>
</table>
| ZDV/3TC/EFZ or ZDV/3TC/NVP | Substitute NVP for EFZ in pregnant women or women for whom effective contraception cannot be assured | ZDV-related anemia  
EFZ-associated CNS symptoms  
Possible teratogenicity of EFZ  
NVP-associated hepatotoxicity and severe rash |
| ZDV/3TC/ABC | ABC safety data limited | ZDV-related anemia  
ABC hypersensitivity |
| ZDV/3TC/RTV-PI\(^b\) or ZDV/3TC/NFV | LPV/r safety data limited  
NFV: most supportive safety data | ZDV-related anemia  
NFV-associated diarrhea  
IDV-related nephrolithiasis  
PI-related metabolic side effects |

\(^a\) ZDV/3TC is listed as the initial recommendation for dual NsRTI component based on efficacy, toxicity, clinical experience and availability of fixed dose formulation. Other dual NsRTI 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.

\(^b\) RTV-PI includes IDV/r, LPV/r, and SQV/r.

In the dual nucleoside plus non-nucleoside regimens, the advantage is that the drugs are widely available at affordable cost and reasonable pill counts, and the regimens are potent. The main disadvantages are development of drug resistance, the potential hepatotoxicity of nevirapine (NVP), and the need to have separate regimens for men and women due to the potential teratogenic effects of efavirenz (EFZ), which precludes its use in pregnant women or women of childbearing age who are at risk of an unintended pregnancy. Countries with a significant prevalence of HIV-2 as well as Group O HIV-1 viruses might consider reserving the use of the non-nucleoside-containing regimens to patients with proven HIV-1 infection, as HIV-2 as well as Group O HIV-1 viruses are naturally resistant to this class of drugs.

The ZDV/3TC/abacavir (ABC) regimen is the most user-friendly from both a patient and programme perspective (2 pills a day and absence of
significant drug interactions). Its main disadvantages are some uncertainty whether it works when viral load is very high in patients with very advanced disease, uncertainty that the drugs—in particular ABC—will become available at an affordable cost, and the potential of causing fatal hypersensitivity reactions that could escape detection in resource-poor settings. There is relatively limited data on the efficacy of other potential triple nucleoside reverse transcriptase inhibitor (NsRTI) combinations. This precludes WHO from recommending them at this time.

Advantages of the dual nucleoside plus protease inhibitor (PI) regimen are proven high potency in reducing viral loads. Disadvantages are higher pill counts, significant interactions with other drugs that preclude or complicate their use during TB treatment using rifampicin, metabolic abnormalities and the need for a functioning cold chain for ritonavir-boosted regimens.

V. REASONS FOR CHANGING ARV THERAPY

ART may need to be changed for either treatment failure or toxicity. Treatment failure can be evaluated clinically, immunologically using measurement of the CD4 count, and/or virologically by measuring viral loads. However, as the latter are not normally available in resource-limited settings, it is recommended that programmes in such setting should primarily use clinical and where possible CD4 count criteria to define treatment failure.

Toxicity is related to the inability to tolerate the side effects of the medication and to significant organ dysfunction that may result. This can be monitored clinically based on patient reports and physical examination, and 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 it 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 offending drug can be replaced with another drug that does not have the same side effects.
VI. CHOICE OF SECOND-LINE ARV REGIMENS

WHO recommends that the full regimen be changed from a first to a second line combination regimen in the case of treatment failure. The new second line regimen will need to use drugs which retain activity against the patient’s virus strain and ideally include at least three new drugs, with at least one from a new class, in order to increase the likelihood of treatment success and minimize the risk of cross resistance.

Table D lists the second line regimens one could consider in adolescents and adults for each of the first line regimens identified in Table A. A reasonable dual nucleoside component alternative to ZDV/3TC is d4T/ddI. In addition, ZDV/ddI can replace d4T/3TC and vice versa with the caveat that nucleoside analog cross resistance is an increasing concern.

When ZDV/3TC was used in the first line regimen, nucleoside cross-resistance may compromise the potency of d4T/ddI in the second line regimen, in particular in the presence of long-standing virologic treatment failure. As the chances of cross-resistance are somewhat reduced when switching to ABC/ddI compared to switching to d4T/ddI, the former might also be considered as the nucleoside backbone for a second line regimen if the first line regimen did not include ABC. However, high level ZDV/3TC resistance also confers diminished susceptibility to ABC.

Given the diminished potential of almost any second line nucleoside component, an RTV-PI component [indinavir (IDV)/r, lopinavir (LPV)/r, saquinavir (SQV)/r] is preferred to nelfinavir (NFV) in second line regimens given their potency. NFV can be considered as an alternative for the PI component if a RTV enhanced PI is not available or if there is a clinical contraindication to its use.
Table D. Recommended second-line regimens in adults and adolescents

<table>
<thead>
<tr>
<th>First-line regimens</th>
<th>Second-line regimens for treatment failure</th>
<th>Alternative second-line regimen for treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV/3TC/EFZ or ZDV/3TC/NVP</td>
<td>d4T/ddI + RTV-PI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ABC/ddI + RTV-PI ABC/ddI + NFV or d4T/ddI + NFV</td>
</tr>
<tr>
<td>ZDV/3TC/ABC</td>
<td>NNRTI&lt;sup&gt;b&lt;/sup&gt; + LPV/r with or without d4T or dd</td>
<td>d4T/ddI + RTV-PI</td>
</tr>
<tr>
<td>ZDV/3TC/RTV-PI or ZDV/3TC/NFV</td>
<td>d4T/ddI + NNRTI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ABC/ddI + NNRTI&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> RTV-PI can be either IDV/r, LPV/r or SQV/r

<sup>b</sup> NNRTI can be either EFZ or NVP
VII. CONSIDERATIONS FOR SPECIFIC SUBGROUPS OF PATIENTS

A. Women of childbearing potential or who are pregnant

WHO recommends the use of ZDV, 3TC, NVP, NFV and SQV combined with low dose ritonavir, as these have been the most widely used ARVs in pregnant women. EFZ is not recommended for use in women who could become pregnant due to its potential teratogenic effect on the fetus in the first trimester.

The choice of ART in women with the potential to become pregnant must include consideration of the possibility that the ARV drugs may be received during the early first trimester, prior to recognition of pregnancy and during the primary period of fetal organ development. Women who are receiving ART should have available to them effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. It is important to note that some antiretroviral drugs (the NNRTIs NVP and EFZ and all the RTV boosted PIs) can lower blood concentrations of oral contraceptives and additional or alternative contraception needs to be used to avoid pregnancy in women receiving these drugs.

For pregnant women, it may be desirable to initiate ART after the first trimester, although for pregnant women who are severely ill, the benefit of early therapy outweighs any potential fetal risks. Additionally, the dual NRTI combination of d4T/ddI should only be used during pregnancy when no other alternatives exist, due to the potential increased risk of lactic acidosis with this combination in pregnant women.

B. Children

The limited studies of HAART in children suggest that broadly similar improvements are seen in surrogate markers with many different ART regimens.

Most ARVs available for adults are also available for children with specific child formulations including dosages that are based on either body surface area or weight. First line treatment options for children include ZDV/3TC plus either a non-nucleoside (NVP or EFZ) or ABC. A caveat is that EFZ cannot be used in children under the age of 3 years due to
lack of appropriate dosing information. However, EFZ would be the non-nucleoside of choice in children on rifampicin, in case ARV needs to start before anti-tuberculous therapy is completed. Second line therapy for children in the event of first-line regimen failure would include a change in nucleoside backbone (e.g., from ZDV+3TC to d4T+ddI) plus a protease inhibitor. Use of protease inhibitors other than LPV/r and NFV is problematic in children due to lack of suitable pediatric drug formulations for IDV and SQV.

Table E. Recommended first-line antiretroviral regimens for children

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV/3TC(^b) plus ABC</td>
<td>Preferred if concomitant anti-tuberculosis therapy being received</td>
</tr>
</tbody>
</table>
| ZDV/3TC\(^b\) plus NNRTI | NNRTI choice:  
  • if < 3 years or < 10 kg, NVP  
  • if ≥ 3 years or ≥10 kg, NVP or EFV |

\(^a\) Country-specific considerations and preferences should determine which regimen or regimens to make available.  
\(^b\) ZDV/3TC is the first choice dual NRTI regimen for children as it has the largest amount of clinical experience. Other dual NRTI components can be substituted for children, including ZDV/ddI, d4T/3TC, d4T/ddI, and ddI/3TC. ZDV/d4T should never be used together due to proven antagonism.

Table F. Recommended second-line antiretroviral regimens for children

<table>
<thead>
<tr>
<th>First-line regimen</th>
<th>Second-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV/3TC/ABC</td>
<td>d4T/ddI/LPV/r(^a) or d4T/ddI/NFV or d4T/ddI/NNRTI(^b)</td>
</tr>
<tr>
<td>ZDV/3TC/NNRTI(^b)</td>
<td>d4T/ddI/LPV/r(^a) or d4T/ddI/NFV</td>
</tr>
</tbody>
</table>

\(^a\) For children who can swallow capsules and for whom the current capsule formulations allow appropriate weight or body surface area calculated dosing, additional options to replace LPV/r include SQV/r and IDV/r.  
\(^b\) NNRTI choice: if < 3 years or < 10 kg, NVP; if ≥ 3 years or ≥10 kg, NVP or EFV.
C. People with tuberculosis and HIV co-infection

WHO recommends that people with TB/HIV complete their TB therapy prior to beginning ARV treatment unless there is a high risk of HIV disease progression and death during the period of TB treatment (i.e., a CD4 count < 200/mm³ or disseminated TB is present). In cases where a person needs TB and HIV treatment concurrently, first line treatment options include ZDV/3TC or d4T/3TC plus either a non-nucleoside or ABC. If a non-nucleoside regimen is used, EFZ would be the preferred drug as its potential to aggravate the hepatotoxicity of TB treatment appears less than that of NVP. However, its dosage may need to be increased to 800 mg/day. Except for SQV/r, protease inhibitors are not recommended during TB treatment with rifampicin due to their interactions with the latter drug.

Table G. Antiretroviral therapy for individuals with tuberculosis co-infection

<table>
<thead>
<tr>
<th>Situation</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB and CD4 count &lt; 50/mm³ or extrapulmonary TB</td>
<td>Start TB therapy. Start one of these ART's as soon as TB therapy is tolerated:</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/ABC</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/EFZ</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/SQV/r</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/NVP</td>
</tr>
<tr>
<td>Pulmonary TB and CD4 50-200/mm³ or total lymphocyte count below 1200/mm³</td>
<td>Start TB therapy. Start one of these regimens after completing 2 months of TB therapy:</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/ABC</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/EFZ</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/SQV/r</td>
</tr>
<tr>
<td></td>
<td>ZDV/3TC/NVP</td>
</tr>
<tr>
<td>Pulmonary TB and CD4 &gt; 200/mm³ or total lymphocyte count &gt; 1200/mm³</td>
<td>Treat TB. Monitor CD4 counts if available. Start ART according to Tables A or B after completion of TB treatment.</td>
</tr>
</tbody>
</table>
D. Injecting drug users

Injecting drug users who are eligible for ART should be ensured access to this life saving therapy. Special considerations for this population include dealing prospectively with life style instability which challenges drug adherence and accounting for the potential drug interactions of ARV’s with agents such as methadone. Development of programmes which integrate care of drug dependence and HIV is encouraged. In such settings, approaches such as directly observed therapy can be implemented. Once daily ARV regimens are already being explored in this arena and lend themselves to such approaches.

F. Adherence to antiretroviral therapy

WHO recommends that innovative approaches to enhance adherence to ART be developed, due to the lifelong nature of this treatment.

Strategies to enhance adherence include minimizing pill counts and dosage frequencies by preferentially using combination pills on a once or twice daily basis. A number of fixed dose combination products containing two or three ARV drugs are currently marketed that can be used twice a day. However, while a number of ARV drugs have now been approved for once daily administration, relatively few three or four drug once daily regimens have been rigorously tested in clinical trials. Other approaches which might facilitate adherence include: enlisting the assistance of family or community members to support patients in taking their medications on a regular and timely basis; extensive counselling and patient education; and directly observed therapy. Psychosocial issues that can also contribute to low adherence to therapy need to be taken into consideration especially for injection drug users and other vulnerable populations.

G. Drug resistance surveillance

WHO recommends that countries planning to implement ART programmes also concurrently implement an HIV drug resistance sentinel surveillance system. This will allow countries to detect potential drug resistance at the population level and modify recommended treatment regimens accordingly. A Global HIV Drug Resistance Surveillance Network is being established by WHO in collaboration with partner organizations to assist member states in this area.
H. Clinical and laboratory monitoring of antiretroviral use

WHO recommends that in resource-limited settings the basic clinical assessment prior to the initiation of ART include documentation of past medical history, identification of current and past HIV related illnesses, identification of co-existing medical conditions that may influence choice of therapy (such as TB or pregnancy) as well as current symptoms and physical signs.

In order to facilitate the scale up ARV use in resource-limited settings, WHO prioritized currently available testing into 4 categories:

- absolute minimum tests;
- basic recommended tests;
- desirable tests; and
- optional tests.

Absolute minimum tests are prerequisites for introduction of ARV therapy in a national programme. Basic recommended tests are commonly used in the clinical setting and are needed to provide effective monitoring of most ARV regimens. In light of the urgency to provide potentially life prolonging care to so many millions of people, WHO wants to minimize the impediments to care. As such, the basic recommended lab tests were not considered to be absolutely essential to start treatment, although they need to be available where resources are available. Desirable tests would make monitoring and evaluation of programme effectiveness much more effective, while optional tests can be used in resource-rich settings.

The absolute minimum laboratory tests to have before initiating ART are an HIV antibody test and a haemoglobin or hematocrit level. The rationale is that proof of HIV infection is needed prior to starting ARV therapy in the first instance, and screening for anemia is essential prior to starting zidovudine containing regimens.

Basic recommended testing should include a white blood cell count and differential (to permit assessment of neutropenic side effects and the total lymphocyte count), serum alanine or aspartate aminotransferase level to assess the possibility of hepatitis co-infection and to monitor for hepatotoxicity, serum creatinine and/or blood urea nitrogen to assess baseline renal function, a serum glucose, and pregnancy tests for women. While these tests are not absolutely essential, they are highly recommended in
order to be able to provide monitoring for safe use of these agents and inform decisions about switching between regimens. CD4 cell counts are at present not listed as basic recommended tests. However, it is hoped that with introduction of simple and less costly methods to assess CD4 cell counts, these tests will become more widely available. WHO recommends that this be considered a priority issue because CD4 cell counts are the best indicator of immunologic response to treatment.

Desirable tests include bilirubin, amylase and serum lipids and CD4 cell testing. These tests, while not absolutely essential, are felt to provide significant information that would be beneficial in the monitoring of ARV use in resource limited settings.

Viral load testing is currently considered optional because of resource constraints. Clinical monitoring is essential for the provision of safe and effective ARV therapy. Where laboratory monitoring is limited, close clinical monitoring becomes even more crucial.

WHO also has categorized laboratory tests according to the levels in the health service where they could be used. Simple rapid HIV diagnostic tests and sample referral for CD4 testing should be feasible at the primary health care and district levels. District levels facilities should also be able to offer pregnancy testing, hemoglobin, liver function tests, creatinine, and glucose testing. In addition to the above mentioned tests, provincial level facilities should be able to offer CD4 cell tests.

Viral load testing and viral resistance assays would, resources permitting, be made available at the central level.
## Appendix A. Dosages of antiretroviral drugs for adults and adolescents

<table>
<thead>
<tr>
<th>Drug class/Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside RTI’s</strong></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (ZDV)</td>
<td>300 mg twice daily</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>40 mg twice daily (30 mg twice daily if &lt; 60 kg)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>400 mg once daily (250 mg once daily if &lt; 60 kg)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>300 mg twice daily</td>
</tr>
<tr>
<td><strong>Nucleotide RTI</strong></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td><strong>Non-Nucleoside RTI’s</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFZ)</td>
<td>600 mg once daily</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>200 mg once daily for 14 days, then 200 mg twice daily</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>1250 mg twice daily</td>
</tr>
<tr>
<td>Indinavir/ritonavir (IDV/r)</td>
<td>800 mg/100 mg twice daily(^{b, d})</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>400 mg/100 mg twice daily (^{b, d}) when combined with EFZ or NVP</td>
</tr>
<tr>
<td>Saquinavir/ritonavir (SQV/r)</td>
<td>1000 mg/100 mg twice daily(^{c, d})</td>
</tr>
</tbody>
</table>

\(^a\) These dosages are in common clinical use. The dosages featured in this table were selected based on the best available clinical evidence. Dosages that can be given on a once or twice daily basis were preferred in order to enhance adherence to therapy. The dosages listed are those for individuals with normal renal and hepatic function. Product specific information should be consulted for dose adjustments that may be indicated with renal or hepatic dysfunction or for potential drug interactions with other HIV and non-HIV medications.

\(^b\) This dosage regimen is in common clinical use. Other IDV/r dosage regimens that range from 800 mg/200 mg bid to 400 mg/100 mg bid are also in clinical usage.

\(^c\) Both the hard-gel and soft-gel capsule formulations can be used when SQV is combined with RTV.

\(^d\) Dosage adjustment when combined with an NNRTI is indicated but a formal recommendation cannot be made at this time. One consideration is to increase the RTV component to 200 mg bid when EFZ or NVP is used concomitantly. More drug interaction data are needed.
Appendix B. Summary of pediatric drug formulations and doses

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Formulations</th>
<th>Pharmacokinetic data available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside ANALOGUE reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (ZDV)</td>
<td>Syrup: 10 mg/ml</td>
<td>All ages</td>
</tr>
<tr>
<td></td>
<td>Capsules: 100 mg; 250 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tablet: 300 mg</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Oral solution: 10 mg/ml</td>
<td>All ages</td>
</tr>
<tr>
<td></td>
<td>Tablet: 150 mg</td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination of ZDV plus 3TC</td>
<td>No liquid available</td>
<td>Adolescents and adults</td>
</tr>
<tr>
<td></td>
<td>Tablet: 300 mg ZDV plus 150 mg 3TC</td>
<td></td>
</tr>
<tr>
<td>Didanosine (ddl, dideoxyinosine)</td>
<td>Oral suspension pediatric powder/ water: 10 mg/ml. In many countries needs to be made up with additional antacid</td>
<td>All ages</td>
</tr>
<tr>
<td></td>
<td>Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg</td>
<td></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Oral solution: 1 mg/ml</td>
<td>All ages</td>
</tr>
<tr>
<td></td>
<td>Capsules: 15 mg, 20 mg, 30 mg, 40 mg</td>
<td></td>
</tr>
<tr>
<td>Age (WEIGHT), DOSE* and DOSE frequency</td>
<td>Other comments</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>&lt; 4 weeks: 4 mg/kg/dose twice daily</td>
<td>Large volume of syrup not well tolerated in older children</td>
<td></td>
</tr>
<tr>
<td>4 weeks to 13 yrs: 180 mg/m²/dose twice daily</td>
<td>Needs storage in glass jars and is light sensitive</td>
<td></td>
</tr>
<tr>
<td>Maximum dose: ≥ 13 yrs: 300 mg/dose twice daily</td>
<td>Can give with food</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doses of 600 mg/m²/dose twice daily required for HIV encephalopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not use with d4T (antagonistic antiretroviral effect)</td>
<td></td>
</tr>
<tr>
<td>&lt; 30 days: 2 mg/kg/dose twice daily</td>
<td>Well tolerated</td>
<td></td>
</tr>
<tr>
<td>≥ 30 days or &lt; 60 kg: 4 mg/kg/dose twice daily</td>
<td>Can give with food</td>
<td></td>
</tr>
<tr>
<td>Maximum dose: &gt; 60 kg: 150 mg/dose twice daily</td>
<td>Store solution at room temperature (use within one month of opening)</td>
<td></td>
</tr>
<tr>
<td>Maximum dose: &gt; 13 yrs or &gt; 60 kg: 1 tablet/dose twice daily</td>
<td>Tablet should not be split</td>
<td></td>
</tr>
<tr>
<td>&lt; 3 mos: 50mg/m²/dose twice daily</td>
<td>Keeps suspension refrigerated; stable for 30 days; must shake well</td>
<td></td>
</tr>
<tr>
<td>3 mos to &lt; 13 yrs: 90 mg/m²/dose twice daily or 240 mg/m²/dose once daily</td>
<td>Ideally taken 1 hour or 2 hours after food; may be less important in children</td>
<td></td>
</tr>
<tr>
<td>Maximum dose: ≥ 13 years or &gt; 60 kg: 200 mg/dose twice daily or 400 mg once daily</td>
<td>Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food</td>
<td></td>
</tr>
<tr>
<td>&lt; 30kg: 1 mg/kg/dose twice daily</td>
<td>Large volume of solution</td>
<td></td>
</tr>
<tr>
<td>30 to 60 kg: 30 mg/dose twice daily</td>
<td>Keep solution refrigerated; stable for 30 days; must shake well. Needs to be stored in glass bottles</td>
<td></td>
</tr>
<tr>
<td>Maximum dose: &gt; 60 kg: 40 mg/dose twice daily</td>
<td>Capsules opened up and mixed with small amount of food are well tolerated (stable in solution for 24 hours if kept refrigerated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not use with AZT (antagonistic antiretroviral effect)</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Formulation</td>
<td>Delivery Options</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Abacavir (ABC)</strong></td>
<td>Oral solution: 20 mg/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tablet: 300 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Fixed-dose combina-</strong></td>
<td>No liquid available</td>
<td></td>
</tr>
<tr>
<td><strong>tion of ZDV plus 3TC</strong></td>
<td>Oral suspension: ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tablet: ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Nucleoside reverse transcriptase inhibitors</strong></td>
<td><strong>Nevirapine (NVP)</strong></td>
<td>Oral suspension: 10 mg/ml</td>
</tr>
<tr>
<td></td>
<td>Tablet: 200 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Efavirenz (EFZ)</strong></td>
<td>Syrup: 30 mg/ml (note: syrup requires higher doses than capsules, see dosing chart)</td>
<td>Capsules: 50 mg, 100 mg, 200 mg, 600 mg</td>
</tr>
</tbody>
</table>
< 16 years or ≤ 37.5 kg: 8 mg/kg/dose twice daily
Maximum dose: > 16 years or > 37.5 kg: 300 mg/dose twice daily

Syrup well tolerated or can crush tablet
Can give with food
MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION.
ABC should be stopped permanently if hypersensitivity reaction

Maximum dose: > 40 kg: 1 tablet/dose twice daily

Tablet cannot be split.
MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION.
Abacavir should be stopped permanently if hypersensitivity reaction

15 to 30 days: 5 mg/kg/dose once daily x 2 weeks, then 120 mg/m^2/dose twice daily x 2 weeks, then 200 mg/m^2/dose twice daily
> 30 days to 13 yrs: 120 mg/m^2/dose twice daily for 2 weeks, then 200 mg/m^2/dose twice daily
Maximum dose: > 13 yrs: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily

If rifampicin coadministration, increase NVP dose by ~ 30%, or avoid use (see Tuberculosis section)
Store suspension at room temperature; must shake well
Can give with food
MUST WARN PARENTS ABOUT RASH. Do not dose escalate if rash occurs (if mild/moderate rash, hold drug; when rash cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug)
Drug interactions

Capsule (liquid) dose for > 3 yrs: 10 to 15 kg: 200 mg (270 mg = 9 ml) once daily
15 to < 20 kg: 250 mg (300 mg = 10 ml) once daily
20 to < 25 kg: 300 mg (360 mg = 12 ml) once daily
25 to < 33 kg: 350 mg (450 mg = 15 ml) once daily
33 to < 40 kg: 400 mg (510 mg = 17 ml) once daily
Maximum dose: ≥ 40 kg: 600 mg once daily

Capsules may be opened and added to food but have very peppery taste; however, can mix with sweet foods or jam to disguise taste
Can give with food (but avoid after high fat meals which increase absorption by 50%).
Best given at bedtime, especially first 2 weeks, to reduce central nervous system side effects.
Drug interactions
### Protease inhibitors

| Nelfinavir (NFV) | Powder for oral suspension (mix with liquid): 200 mg per level teaspoon (50 mg per 1.25 ml scoop): 5 ml  
|                 | Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water) | All ages  
|                 |  | However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants < 1 year |

| Lopinavir/ritonavir, (LPV/r) | Oral solution: 80 mg/ml lopinavir plus 20 mg/ml ritonavir  
|                            | Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir | 6 months of age or older |

* Meter² body surface area calculation: square root of (height in centimeters times weight in kilograms divided by 3600)
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year:</td>
<td>40-50 mg/kg/dose three times daily or 65-75 mg/kg/dose twice daily</td>
<td>Powder is sweet, faintly bitter, but gritty and hard to dissolve; must be reconstituted immediately prior to administration in water, milk, formula, pudding, etc. – do not use acidic food or juice (increases bitter taste)</td>
</tr>
<tr>
<td>&gt; 1 yr to &lt; 13 years:</td>
<td>55 to 65 mg/kg/dose twice daily</td>
<td>Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given</td>
</tr>
<tr>
<td>Maximum dose: &gt; 13 years:</td>
<td>1250 mg/dose twice daily</td>
<td>Powder and tablets can be stored at room temperature</td>
</tr>
<tr>
<td>&gt; 6 months to 13 yrs:</td>
<td>225 mg/m² LPV/57.5 mg/m² ritonavir twice daily</td>
<td>Take with food</td>
</tr>
<tr>
<td>or weight-based dosing: 7-15 kg:</td>
<td>12 mg/kg LPV/3 mg/kg ritonavir/dose twice daily</td>
<td>Drug interactions (less than ritonavir-containing protease inhibitors)</td>
</tr>
<tr>
<td>15-40 kg:</td>
<td>10 mg/kg lopinavir/5 mg/kg ritonavir twice daily</td>
<td>Preferably oral solution and capsules should be refrigerated; however, can store at room temperature up to 25 °C (77 °F) for 2 months</td>
</tr>
<tr>
<td>Liquid formulation has low volume but bitter taste</td>
<td>Preferably needs to be refrigerated</td>
<td></td>
</tr>
<tr>
<td>Capsules large</td>
<td>Should be taken with food</td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SCALING UP ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS
SCALING UP
ANTIRETROVIRAL THERAPY IN
RESOURCE-LIMITED SETTINGS

GUIDELINES FOR A
PUBLIC HEALTH APPROACH

EXECUTIVE SUMMARY

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WORLD HEALTH ORGANIZATION – Family and Community Health Cluster – Department of HIV/AIDS
20, avenue Appia – CH-1211 Geneva 27 – SWITZERLAND – E-mail: hiv-aids@who.int

World Health Organization
April 2002