

**EXPERT REPORT IB(B)**

**TREATMENT AND FDCs**

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28 August 2003

**INTRODUCTION OF HAART THERAPY**

Since its emergence in 1979, the spread of the HIV virus around the globe remains pervasive, although unequally distributed. Unique viral characteristics of the HIV virus leave a solution or cure elusive. Medicines to target the HIV virus, known as antiretrovirals (“ARVs”) have a profound impact on the spread of the virus, and the health and life of those infected. As with the spread of the virus, access to these medicines is unequally distributed. Recent political momentum around the globe has focused considerable attention on this issue, prompting responses from a variety of sectors of society at the local, national, and international levels.

In a book entitled, *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach*, discussed below, the World Health Organisation (“WHO”) began a technical collaboration of researchers, clinicians and patients from around the world to amass information on clinical management from a variety of settings. The intention is to provide the technical know-how to redress the unequal access to ARVs in the world highlighted below.

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 ARVs 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 have dramatically reduced mortality and morbidity, prolonged lives, and improved the quality of life of many people living with HIV/AIDS... today we are again at a turning point – this time in favour of the developing world... a chance of hope to those despaired.<sup>2</sup>

Unfortunately, the mechanisms through which the HIV virus acts and the degree in which it assaults the human body makes treatment of those infected complicated. The factors for consideration related to individual treatment are numerous. The possibility of treatment failure requires contingencies. Nonetheless, some major conclusions regarding the treatment of HIV with ARVs are clear. According to Dr. Robin Wood, Principal Medical Specialist for the Provincial Administration of the Western Cape,<sup>3</sup> these are as follows.

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<sup>2</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 8-9 (2002).

<sup>3</sup> Additionally, Dr. Wood holds the following positions: Associate Professor of Medicine, University of Cape Town, Head of the Department of Medicine, Somerset Hospital and Director of the HIV Research Unit, at Somerset Hospital.

Based on scientific evidence, clinical trials and international consensus, three conclusions can be drawn. First, when left untreated, HIV profoundly depletes the immune system and may prove fatal because of the inability of the body to fight opportunistic infections (OIs) such as tuberculosis (TB), pneumonia and meningitis. Second, the use of highly active antiretroviral therapy (HAART) substantially reduces the incidence of OIs, resulting in substantial reductions in morbidity and mortality rates. Third, local and internationally recognised approaches to HAART recognise that in general, antiretroviral medicines (ARVs) cannot be considered as substitutable for each other, even within therapeutic classes.<sup>4</sup>

As the Joint Health and Treasury Task Team emphasises in their *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* (“Joint Task Team Report”),

[I]t should be emphasised that, ART [antiretroviral therapy] is one among a very large number of interventions to manage the AIDS pandemic. It can only be introduced at a particular stage of the progression of the condition, and must always be combined with the comprehensive package of other interventions, including nutrition and treatment of opportunistic infections.<sup>5</sup>

Acknowledging this, this paper will only focus on the salient issues in HIV treatment as they pertain to the current HIV epidemic in South Africa, including treatment effectiveness, therapy initiation, regimen selection, regimen modification, and the need for access to a wide variety of ARVs.

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<sup>4</sup> See Expert Affidavit of Dr. Robin Wood, pg. 2-3.

<sup>5</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 4 (August 1, 2003).

## EFFECTIVENESS OF HAART THERAPY

Infection with the HIV virus causes a deterioration of the immune system. As the virus propagates within the host body, the immune system weakens leaving the body vulnerable to other infection. These opportunistic infections (OIs), otherwise endured by a healthy immune system, in concert with nutritional deficiencies, eventually overwhelm the host body resulting in death. Prior to the introduction of antiretroviral medicines, care for those infected with HIV was limited to clinical management of OIs, with the inevitable result of premature death.

Without intervention, median survival time from infection with the HIV virus to AIDS-related death was found to be 9,8 years<sup>6</sup>, with median time from infection to AIDS as 9,4 years and from AIDS to death as 9,2 months in a study from Uganda.<sup>7</sup> However, intervention with highly active antiretroviral therapy (HAART) for HIV treatment suppresses HIV virus reproduction, significantly delaying the progression of immune system disease, particularly in previously untreated patients.<sup>8</sup> Delaying disease progression has several clinical benefits.

As highlighted by the Joint Task Team Report, “the best scientific knowledge available has demonstrated that, properly used and carefully managed, [ARVs] do help restore patients with AIDS to appreciable level of human functionality and they do defer death.”<sup>9</sup> According to the Clinical Guidelines of the South African HIV Clinicians Society, HAART therapy “significantly improves the quality and length of life of men, women and children with AIDS. In South Africa this has been convincingly demonstrated in managed health care programmes, mainly in the private sector.”<sup>10</sup>

Delay of disease progression enables the immune system to effectively react against HIV-induced OIs reducing morbidity and preventing premature mortality in persons infected with the

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<sup>6</sup> Studies from Uganda, Thailand, and Haiti indicate median survival time from infection to death for individuals unable to access antiretroviral treatment to differ by gender. Women tend to live somewhat longer than males, mostly due to the fact that they are infected at a much younger age than men, 9,4 and 8,6 years respectively. John Stover & Karen Stanekki, *Estimating and Projecting the Size and Impact of the HIV/AIDS Epidemic in Generalized Epidemics: The UNAIDS Reference Group Approach*, 2002 The UNAIDS Reference Group on Models, Estimates and Projections 9.

<sup>7</sup> There is widespread misconception that HIV-1 infection progresses much more rapidly in Africa than in industrialized nations. The authors conclude that survival with HIV-1 infection in Africa is similar to industrialized countries before the use of antiretroviral therapy. See Dilys Morgan & Jimmy Whitworth, *The Natural History HIV-1 Infection in Africa* 7:2 *Nature Medicine* 143, 144 (2001). “The progression of disease in patients infected with HIV-1 in Africa seems to be rapid; this is most likely to be due to the high prevalence of what could be taken as symptoms and signs of infection with HIV-1 in the general population. Studies that showed rapid progression of disease in patients in Africa could have led to the belief that HIV disease progresses more rapidly than elsewhere.” Dilys Morgan et al., *Progression to Symptomatic Disease in People Infected with HIV-1 in Rural Uganda: Prospective Cohort Study* 324 *British Medical Journal* 193, 196 (2002).

<sup>8</sup> World Health Organization, *THE USE OF ANTIRETROVIRAL TREATMENTS IN ADULTS*, 3 (2000).

<sup>9</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 12 (August 1, 2003).

<sup>10</sup> South African HIV Clinicians Society, *ANTIRETROVIRAL THERAPY IN ADULTS, SOUTH AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES* 14 (2002).

HIV virus.<sup>11</sup> Specifically, by strengthening the immune system, HAART therapy reduces the occurrence of OIs, like tuberculosis, a leading cause of death in South Africa. According to Dr. Robin Wood,

In my clinical practice, use of HAART has decreased the incidence of HIV-associated TB by 81% (Badri, Wilson and Wood, *Lancet* (2002) 359: 2059-2064), hospitalisation by 80% and deaths by 94%.<sup>12</sup>

Reductions in the occurrence of OIs consequently reduce the number of hospitalisations related to these infections. According to Dr. Leon Regensberg, Director of Aid for AIDS,

Antiretroviral therapy (ART), although costly, is clinically effective and reduces the need for hospitalisation. Making ART available at an appropriate time, coupled with careful monitoring plus education of patients and clinical support of doctors is regarded as a cost-effective and positive health intervention. This is because it prevents disease progression.<sup>13</sup>

The experience of AfA shows that HAART has reduced hospitalisation costs as well as resulted in a significant reduction in viral load of those who use it. There have also been significant increases in CD4 counts amongst patients currently receiving HAART.<sup>14</sup>

The clinical benefits of HAART “have been confirmed in all setting in which it has been used, including developing countries, e.g. Brazil, Senegal, Thailand, and Uganda.”<sup>15</sup> Use of HAART in South Africa shows the same result, according to the South African HIV Clinicians Society.

Research and ongoing treatment access in a variety of settings in South Africa have shown that people with HIV in poor and disadvantaged areas can adhere successfully to treatment regimens and thus can achieve treatment outcomes that are the same as in developed countries.<sup>16</sup>

Currently available ARV drugs belong to three major classes: nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). (Table 1 lists all ARV medicines available in South Africa by class.) In general, all of these drugs act by impeding the action of enzymes necessary for viral replication or functioning.

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<sup>11</sup> Frank Paella et al., *Declining Morbidity And Mortality Among Patients With Advanced Human Immunodeficiency Virus Infection* 338 *New England J Med* 853, 860 (1998).

<sup>12</sup> See Expert Affidavit of Dr. Robin Wood, pg. 4.

<sup>13</sup> See Expert Affidavit of Mr. Leon Regensberg, pg. 2.

<sup>14</sup> See Expert Affidavit of Mr. Leon Regensberg, pg. 4.

<sup>15</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 24 (2002). See J.R. Marins et al., *Dramatic Improvements in Survival Among Adult Brazilian AIDS Patients* 17(11) *AIDS* 1675 (2003).

<sup>16</sup> South African HIV Clinicians Society, ANTIRETROVIRAL THERAPY IN ADULTS, SOUTH AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES 14 (2002).

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ARVs target either a particular step in the life cycle of HIV or its interaction with host cells. The ARVs in general use in South Africa inhibit one or two key viral enzymes required by HIV for viral replication, targeting either reverse transcriptase (essential for the completion of the early stages of HIV replication) or protease (required for the assembly and maturation of new HIV).

NRTIs and NNRTIs work in different ways to inhibit the functioning of the reverse transcriptase enzyme.

The combination of HIV genetic material together with host cell mechanisms ultimately results in the production of the components necessary for assembly of HIV.

PIs work by binding to and inhibiting the function of the protease enzyme. Following further modification of the viral proteins, all the components of the virus are assembled and bud from the host cell. These processes result in the development of new infectious viruses.<sup>17</sup>

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<sup>17</sup> See Expert Affidavit of Dr. Robin Wood, pg. 5-6.

## NEED FOR COMBINATION HAART THERAPY

Therapeutic design of HAART regimes aims at the timely and sustained suppression of HIV viral replication. According to the WHO, for optimal efficacy, HAART regimes typically use three ARV drugs from different classes utilising varying modes of action.<sup>18</sup>

Dual [NRTI] therapy alone is not recommended as initial therapy because the regimen potencies are suboptimal and the emergence of drug resistance is predictable. However, it is recognized that many HIV-infected individuals in the developing world are being treated with dual [NRTI] combinations because potent three-drug and four-drug combinations are not affordable. As dual [NRTI] therapy is considered suboptimal in these and other published guidelines, persons currently doing well on dual [NRTI] should be considered for switching to one of the potent regimens outlined in this document.<sup>19</sup>

The only regimens potent enough to drastically reduce viral replication, prevent the emergence of resistance and, ultimately, prevent treatment failure for a significant amount of time, have involved combinations of at least three ARVs. Such regimens have been associated with immunological restoration, a slowing of disease progression, durable therapeutic responses, improvements in the quality of life, and prevention of the emergence of drug resistance.<sup>20</sup>

Presently, dual and mono-therapy are prescribed in South Africa.

A recent report published by the Centre for Actuarial Research (CARE) at the University of Cape Town, based on a survey of 77 schemes representing 80% of all private beneficiaries, provides the most up to date indicator of private health sector trends in relation to HIV benefits.<sup>21</sup>

The CARE report indicates that while many schemes are now offering HAART, some are still offering sub-standard mono- and dual therapy as well. This is because the high costs of drugs limit access to HAART within the available benefit structure.<sup>22</sup>

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<sup>18</sup> Rachael Jordan et al., *Systematic Review And Meta-Analysis Of Evidence For Increasing Numbers Of Drugs In Antiretroviral Combination Therapy*, 324(7340) *British Med J* 757, 762 (2002).

<sup>19</sup> World Health Organization, *SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS*, 29 (2002).

<sup>20</sup> World Health Organization, *SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS*, 24 (2002).

<sup>21</sup> See Expert Affidavit of Mr. Leon Regensberg, pg. 3.

<sup>22</sup> See Expert Affidavit of Mr. Leon Regensberg, pg. 4.

## UNEQUAL ACCESS TO HAART THERAPY

Unequal access to HAART therapy exists between and within countries. Although 95 percent of the HIV infections are in low and middle-income countries, only 5 percent of those in need of HAART treatment receive it, as of December 2002.<sup>23</sup> In sub-Saharan Africa, only 1 percent of the 4,1 million in need of HAART therapy receive it (See Table 2 for regional distribution of estimated need and coverage).

Joining the effort to redress “the inequalities between rich and poor in access to care,” the World Health Organization published *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach* (“the WHO Guidelines”).<sup>24</sup> The document provides guidance for the design of HIV treatment programmes by national AIDS control programmes in resource-limited settings. Issues addressed include therapy initiation, selection of HAART regimens, when it is necessary to change regimens, and finally, appropriate second-line regimens, tailored to resource-challenged environments with limited laboratory testing.

On 22 April 2002, the World Health Organisation (WHO) issued its first treatment guidelines for HIV/AIDS (WHO treatment guidelines) in resource-limited settings such as South Africa. At the same time, the WHO endorsed the inclusion of ARVs in the Core List of its Model Essential Medicines List. The Core List “presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions.”<sup>25</sup>

The WHO treatment guidelines deal with the rational use of HAART so that treatment will result in fewer side effects, less resistance to and better tolerance of ARVs. The guidelines are designed to ensure that people with HIV/AIDS are prescribed appropriate combinations of medicines, to ensure that HAART is simpler to use, as well as to guide and train health care workers in HAART. The guidelines form an integral part of WHO’s strategy to fight HIV/AIDS, which sees prevention, treatment and care as mutually reinforcing elements of a public health response to the HIV/AIDS pandemic.<sup>26</sup>

The WHO guidelines encourage countries to use a public health approach when expanding access to HAART in resource-limited settings, which includes the development of standardised HAART protocols. The guidelines recommend the selection of a single first and a limited number of second line regimens for large-scale use.<sup>27</sup>

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<sup>23</sup> This represents an increase from 4 percent in 2001. UNAIDS, 2002 AIDS EPIDEMIC UPDATE, 3,4 (2002).

<sup>24</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 9 (2002).

<sup>25</sup> See Expert Affidavit of Dr. Robin Wood, pg. 6.

<sup>26</sup> See Expert Affidavit of Dr. Robin Wood, pg. 6.

<sup>27</sup> See Expert Affidavit of Dr. Robin Wood, pg. 6.

In South Africa, the exact number of those receiving HAART therapy is unknown. Based on a variety of estimates, no more than 50,000 South Africans are currently receiving HAART therapy.<sup>28</sup> Most, if not all, of those currently treated with HAART therapy in South Africa are enrolled in a private medical insurance scheme. To date, the public sector, caring for approximately 80 percent of the population, does not administer HAART therapy, although health services for HIV-related OIs are available.

Well-established and widely disseminated guidelines are in place in the public health system for the treatment of a wide range of opportunistic infections, complications and malignancies associated with HIV and AID.<sup>29</sup>

The Joint Task Team Report of August of 2003, acknowledges that unequal access to HAART therapy in South Africa.

Noting that antiretroviral treatment can help to improve the conditions and health of people living with AIDS if administered at certain stages in the progression of HIV/AIDS and in accordance with international standards, Government committed to continue its efforts to remove systemic constraints on access to these drugs.<sup>30</sup>

Moreover, the Joint Task Team Report supports the use of the WHO Guidelines in expanding access to HAART therapy in South Africa.

Positive developments which further support the WHO guidelines include rapid reductions in prices, new medications and global experience in their utilization, opportunities emerging in the global trade regime, experience in the South African private sector, and the growing body of knowledge among local scientists and health practitioners who contributed to the work of the task team and who play a critical role in the operationalisation of government's decision in this regard.<sup>31</sup>

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<sup>28</sup> According to the South African HIV Clinicians Society, "it is estimated that 20,000 people are now using ART in South Africa." South African HIV Clinicians Society, ANTIRETROVIRAL THERAPY IN ADULTS, SOUTH AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES 14 (2002).

<sup>29</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 6 (August 1, 2003).

<sup>30</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 2 (August 1, 2003).

<sup>31</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 11 (August 1, 2003).

## INITIATION OF HAART REGIMENS

An HIV infected person passes through four stages. Those in Stages 1 and 2 are relatively asymptomatic. Those in Stage 3 suffer from weight loss and episodes of OIs. Stage 4 HIV infection is considered ‘full-blown’ AIDS disease. Without access to HAART therapy, survival time after classification as Stage 4 is approximately 12 to 18 months.<sup>32</sup>

According to the Joint Task Team Report, use of HAART therapy in Stage 3 and 4 provide substantial clinical benefits.

Antiretroviral therapy has been demonstrated to significantly extend life, reduce mortality, and improve health status in people with Stage 3 and 4 of HIV disease. Current evidence shows that most people infected with HIV will reach a stage by which time the immune system will have deteriorated to such an extent that nutrition, complementary treatments and treatments with antibiotics will not be sufficient to deal with major opportunistic infections. This is defined as the point at which the individual develops an “AIDS – defining illness” and is more likely to occur when the CD4 count drops below 200 cells/ $\mu$ l. At this stage in the progression of the disease the role of antiretroviral drugs become important.<sup>33</sup>

Ideally, classification of Stage of infection relies on CD4 counts and viral loads.

ART is complex, requiring careful monitoring of a patient’s CD4 count, viral load and side-effect profile. A CD4 count shows the extent to which HIV has weakened a person’s immune system. Viral loads are measures showing the amount of HIV virus or viral particles present in the patient with HIV. For ART to be effective, high levels of compliance are required. In addition, the education and support of patients is critical, as is clinical support for many doctors in managing patients with HIV/AIDS.<sup>34</sup>

Affordable and accurate testing of CD4 cell counts and viral loads is not always feasible in resource-limited environments. When these methods are unavailable, treatment programs can be based on low-cost methods, such as total lymphocyte count,<sup>35</sup> for determination of treatment initiation.<sup>36</sup> (Table 3 lists the WHO guidelines recommendations for therapy initiation.)

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<sup>32</sup> Rob Dorrington et al., *HIV/AIDS Profile in the Provinces of South Africa*, (2002) THE CENTRE FOR ACTUARIAL RESEARCH, MEDICAL RESEARCH COUNCIL, & THE ACTUARIAL SOCIETY OF SOUTH AFRICA 6.

<sup>33</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 8 (August 1, 2003).

<sup>34</sup> See Expert Affidavit of Mr. Leon Regensberg, pg. 3.

<sup>35</sup> Lymphocytes are produced in a variety of lymphoid organs throughout the body that is responsible for cellular and humoral immune responses. Total lymphocyte count (TLC) may be used as a surrogate for or in combination with CD4 count to determine when to start therapy and to enable routine monitoring.

<sup>36</sup> World Health Organization, *SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS*, 25 (2002).

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In South Africa, there are estimations of the number infected per Stage of infection. The Centre for Actuarial Research at the University of Cape Town (CARE), the Medical Research Council (MRC), and the Actuarial Society of South Africa (ASSA) estimated the percentage of HIV infections per Stage for all nine provinces in South Africa, as of July 2002. In those provinces with more advanced epidemics, like KwaZulu-Natal and Mpumalanga, approximately 50 percent of HIV infections are Stage 1. While, Stage 1 infections in provinces with lower overall prevalence rates, like Eastern Cape, Limpopo, Northern Cape, and Western Cape are estimated to be 60 percent. Currently in South Africa, 75 percent of HIV positive infections are Stage 1 or 2, while 25 percent of those infected are Stages 3 and 4. (Table X lists the number and percentage per Stage per province.)

Without use of CD4 cell count, the WHO Guidelines recommend initiation of HAART therapy for HIV infected persons in Stage 2 and 3 with total lymphocyte counts less than 1200/mm. Based on the CARE, MRC and ASSA estimates, Stage 2 and 3 infections total approximately 1,163,000 and 1,047,000 respectively.<sup>37</sup> Without knowledge of total lymphocyte counts, it is impossible to know how many people are clinically indicated for initiation of HAART therapy. These numbers suggest a range of those currently infected people that possibly indicated for initiation of therapy. It is reasonable to assume that some proportion of Stage 2 and 3 infections would require HAART therapy.

The WHO Guidelines definitively recommend initiation of HAART therapy for all Stage 4 infected persons regardless of CD4 cell counts. Based on the CARE, MRC and ASSA estimates, approximately 407,000 South Africans are in Stage 4 of HIV infection, requiring immediate initiation of HAART therapy. The Joint Task Team Report estimates between 400,000 and 500,000 at this stage.<sup>38</sup> Without intervention, all of these South Africans will die within the next 12 to 18 months. Currently, no more than 50,000 South Africans have access to HAART therapy, 407,000 are in immediate need of HAART, with some portion of the 1,163,000 and 1,047,000 Stage 2 and 3 infections, respectively potentially in need of HAART therapy.

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<sup>37</sup> CARE, MRC and ASSA report the percent in Stage 1 through 4. Based on their reported population estimates, the number of infections per Stage was calculated. This number was deflated by 10 percent as “preliminary estimates suggest from the next cycle of modelling that the next section will probably be about 10% lower than the estimates in this booklet.” Rob Dorrington et al., *HIV/AIDS Profile in the Provinces of South Africa*, (2002) THE CENTRE FOR ACTUARIAL RESEARCH, MEDICAL RESEARCH COUNCIL, & THE ACTUARIAL SOCIETY OF SOUTH AFRICA 1.

<sup>38</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 4 (August 1, 2003).

## SELECTION OF HAART REGIMENS

The WHO Guidelines recommend that HIV treatment programmes in resource-limited settings choose one potent first-line HAART regimen. Choice among the regimens generally relies on several considerations, including side-effect profiles, potential drug interactions, co-morbidities<sup>39</sup>, the maintenance of alternative options in the setting of treatment failure, drug availability, and cost.<sup>40</sup> The South African HIV Clinicians Society emphasises additional considerations. “Particular consideration should be given to those factors which may affect patient adherence, such as the regimen’s pill burden, dosing frequency, food requirements, convenience, toxicity and drug interaction profile.”<sup>41</sup>

Considering all factors, with the exception of cost, the WHO guidelines recommend three preferred options as first-line regimens for treatment in adults and adolescents. The three preferred first-line regimens recommended by the WHO Guidelines consist of AZT<sup>42</sup> and 3TC as the dual NRTI component, referred to as the ‘backbone’ of the regimen. This is based on efficacy, toxicity and clinical experience, as well as the availability of the medicines in a fixed dose combination. A third drug, 1) an NNRTI, 2) a PI or 3) ABC, a potent NRTI, should complement the dual NRTI backbone.<sup>43</sup> Dr. Robin Wood reviews the WHO Guideline recommendations below. (Table 5 lists the preferred first-line regimens.)

Other NRTIs may be substituted for the AZT/lamivudine dual NRTI component in first-line regimens. However, AZT/lamivudine would then be required as potential components for second line regimens. AZT can never be used together with d4T because of proven antagonism between these two specific drugs.

The advantage of a dual NRTI plus NNRTI regimen (such as AZT, lamivudine and nevirapine) is that the regimen is potent and the drugs are available at reasonable pill counts. Reasonable pill counts contribute to increased patient adherence to HAART. The main disadvantages of this regimen are the potential for the development of drug resistance and the potential hepatotoxicity of nevirapine. The alternative drug in the NNRTI class is efavirenz, however the potential teratogenic effects of efavirenz preclude its use in pregnant women or women of childbearing age who are at risk of falling pregnant.

The AZT/lamivudine/ABC regimen is the most user-friendly both from an individual patient and a programme perspective, as it entails only two pills a day and the absence of significant drug interactions. The fixed dose combination of the three ARVs is possible because the brand-name versions of these drugs are manufactured by a single company. Patent protection of ARVs manufactured by

<sup>39</sup> Co-morbidities refers to coexisting infections.

<sup>40</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 27 (2002). See also *See Expert Affidavit of Dr. Robin Wood*, pg. 7.

<sup>41</sup> South African HIV Clinicians Society, ANTIRETROVIRAL THERAPY IN ADULTS, SOUTH AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES 9 (2002).

<sup>42</sup> ARV drug abbreviations are listed in Table 1.

<sup>43</sup> *See Expert Affidavit of Dr. Robin Wood* for a discussion on the advantages and disadvantages of the recommended regimens, pg 9-13.

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different companies prevents the production of similar fixed dose combinations. There is, however, some uncertainty whether the AZT/lamivudine/ABC regimen works for people who have high viral loads and advanced HIV disease. In addition, ABC carries with it the potential of causing fatal hypersensitivity reactions that could escape detection in resource-poor settings.

The advantage of the dual NRTI plus PI regimen is proven potency in reducing viral loads. The disadvantages, however, include higher pill counts, significant interactions with other drugs that preclude or complicate their use during certain TB treatments, metabolic abnormalities and the need for a functioning cold chain for ritonavir-boosted regimens.

There is no single ARV regimen which will be ideal for either all patients or for all clinical situations. Therefore, it is necessary to have access to a combination of drug choices both within and between drug classes.<sup>44</sup>

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<sup>44</sup> See Expert Affidavit of Dr. Robin Wood, pg. 8-9.

## MODIFICATION OF HAART REGIMENS

Intolerance to drug side effects, drug toxicity, and occurrence of active tuberculosis, pregnancy, or treatment failure necessitate changes in HAART therapy. Complete regime change is not always necessary. A patient experiencing good clinical response that develops a clearly definable toxicity can make single drug substitutions without compromising the overall regimen.

HAART may need to be changed because of toxicity or treatment failure. In the case of HAART, toxicity relates either to the inability to tolerate the side effects of the medicines or to significant organ dysfunction.

If the reason for change is related to toxicity, an entirely new second line regimen may be used, or, where toxicity relates to an identifiable drug in the regimen, another drug in the same therapeutic class can replace the offending drug if that drug does not have the same side effects.<sup>45</sup>

However, in cases where the causal agent of the drug toxicity is unidentifiable or low-grade but intolerable side effects may frequently compromise adherence, a complete regimen switch is advised. Instances of treatment failure require a regimen ‘up-grade’ to a uniquely different second-line regimen according to the WHO Guidelines. Recommended second-line regimens consider possible resistance resulting from delay in detectable resistance, particularly when resistance monitoring is unavailable. (Options for second-line regimens are listed in Table 5.)

If a change in regimen is needed because of treatment failure, an entirely new second line regimen will have to be used, with the second-line regimen including at least one drug from a new therapeutic class. This type of regimen is recommended so that the likelihood of treatment success may be increased and the risk of cross-resistance minimized.<sup>46</sup>

If the first-line regimen was AZT/lamivudine and either nevirapine or efavirenz, the recommended second-line regimen is d4T/ddI and a ritonavir-boosted PI. Given the diminished potential of almost any second-line NRTI component, WHO recommends that a ritonavir-boosted PI be preferred to nelfinavir in any second-line regimen in order to ensure potency of therapy.

If the first-line regimen was AZT/lamivudine/ABC, the recommended second-line regimen is ritonavir-boosted lopinavir, and an NNRTI (efavirenz or nevirapine) with or without either d4T or ddI. The alternative second-line regimen being the dual NRTI component of d4T/ddI and a ritonavir-boosted PI.

Finally, if the first-line regimen was the dual NRTI component of AZT/lamivudine and a ritonavir-boosted PI or nelfinavir, WHO recommends a second-line regimen of the dual NRTI component of d4T/ddI and an NNRTI

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<sup>45</sup> See Expert Affidavit of Dr. Robin Wood, pg. 9-10.

<sup>46</sup> See Expert Affidavit of Dr. Robin Wood, pg. 9-10.

(efavirenz or nevirapine), with the alternative second-line regimen being the dual NRTI component of ABC/ddI and an NNRTI (efavirenz or nevirapine).<sup>47</sup>

## HAART REGIMENS FOR WOMEN AND CHILDREN

Treatment of HIV with HAART therapy requires additional consideration is several sub-populations. The treatment of two of these groups is especially relevant to treatment with HAART therapy in South Africa, children and pregnant women.

According to Dr. Mark Cotton, a Senior Specialist with a sub-specialty in Infectious Diseases at the Tygerberg Children's Hospital in Cape Town<sup>48</sup>,

All HIV-infected infants under a year of age should receive HAART. The reason for this approach is that up to 20% of perinatally infected infants show rapid disease progression in the first year of life. Thereafter, most experts support HAART for all children, even those with only minimal evidence of immune suppression.<sup>49</sup>

While most ARV triple combinations are beneficial, the relative merits of specific combinations have not yet been evaluated in children. The WHO recommends the various options as first- and second-line treatment regimens.<sup>50</sup>

In the result, I only emphasise that there are fewer combinations available for the treatment of children. This is because not all ARVs are available in paediatric formulations and because the experience of physicians treating children with HIV is largely limited to a smaller number of ARVs than is the case with adults.<sup>51</sup>

The WHO Guidelines make recommendations for use of HAART therapy with children. According to Dr. Robin Wood,

Not all available ARVs are suitable for children. While many are available in child-specific formulations including dosages based on weight or body surface area, some PIs (such as indinavir and saquinavir) are not recommended due to a lack of suitable paediatric drug formulations.<sup>52</sup>

AZT/lamivudine is the first choice dual NRTI regimen for children as it has the largest amount of clinical experience. While other dual NRTI components may be substituted, such as AZT/ddI, d4T/lamivudine, d4T/ddI and ddI/lamivudine, AZT/d4T should never be used together because of proven antagonism between the two drugs.<sup>53</sup>

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<sup>47</sup> See Expert Affidavit of Dr. Robin Wood, pg. 10.

<sup>48</sup> Dr. Cotton is also a member of the Faculty of Medicine at the University of Stellenbosch.

<sup>49</sup> See Expert Affidavit of Dr. Mark Cotton, pg. 3.

<sup>50</sup> See Expert Affidavit of Dr. Mark Cotton, pg. 6.

<sup>51</sup> See Expert Affidavit of Dr. Mark Cotton, pg. 6.

<sup>52</sup> See Expert Affidavit of Dr. Robin Wood, pg. 11.

<sup>53</sup> See Expert Affidavit of Dr. Robin Wood, pg. 11.

The WHO recommended first-line regimen for children is either AZT/lamivudine/ABC or AZT/lamivudine and an NNRTI, either nevirapine or efavirenz. The latter, however, cannot be used in children under the age of three because of a lack of appropriate dosing information. However, for children above three years of age, efavirenz is the NNRTI of choice for children receiving rifampicin for TB treatment if HAART has to be started before the TB treatment is completed.<sup>54</sup>

The recommended regimen changes for children in the case of treatment failure are as follows:

Following a first-line regimen of AZT/lamivudine/ABC, the recommended second-line regimen is the dual NRTI component of d4T/ddI, with lopinavir, nelfinavir or an NNRTI. Once again, if the child is under 3 years of age, only nevirapine can be used as the NNRTI. If the child is receiving rifampicin for TB treatment **and** is over three years of age, efavirenz is the NNRTI of choice.

Following a first-line regimen of AZT/lamivudine and an NNRTI, the recommended second-line regimen is the dual NRTI component of d4T/ddI, with either lopinavir or nelfinavir. For children who are able to swallow capsules and for whom the current capsule formulations are appropriate, taking into consideration weight or body surface area calculated dosing, lopinavir may be replaced by saquinavir or indinavir.<sup>55</sup>

Of the fourteen ARV medicines registered for use in South Africa,

Of these ARVs, nine are available in paediatric formulations:

NRTIs: AZT, lamivudine, ddI, d4T and ABC;

NRTIs: nevirapine; and

PIs: nelfinavir, ritonavir and amprenavir.<sup>56</sup>

The WHO Guidelines make recommendations for use of HAART therapy with pregnant women. According to Dr. Robin Wood,

WHO recommends that pregnant women only use a limited number of ARVs (AZT, lamivudine, nevirapine, nelfinavir and saquinavir) as these have been the most widely used ARVs in pregnant women. The dual NRTI combination of d4T/ddI is not recommended, unless no other treatment alternatives exist, as this combination has the potential to create an increased risk of lactic acidosis in pregnant women.<sup>57</sup>

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<sup>54</sup> See Expert Affidavit of Dr. Robin Wood, pg. 11.

<sup>55</sup> See Expert Affidavit of Dr. Robin Wood, pg. 11-12.

<sup>56</sup> See Expert Affidavit of Dr. Robin Wood, pg. 4.

<sup>57</sup> See Expert Affidavit of Dr. Robin Wood, pg. 10.

Regarding women of childbearing potential, the choice of ARVs must be based on a consideration of the possibility that HAART may be received during the first trimester, prior to the detection of pregnancy and during the primary period of foetal organ development. Thus efavirenz is not recommended because of its potential teratogenic effect on the foetus in the first trimester.<sup>58</sup>

### ACCESS TO A VARIETY OF ARV MEDICINES IS INTEGRAL

The HAART regimens recommended by the WHO Guidelines as preferred first-line regimens are based on a comprehensive review of data and research from over 60 countries with special consideration to factors relevant to resource-limited environments. These regimens reflect the current state of the art in antiretroviral therapy. Clinicians need sustainable and affordable supplies of, at least, the ARV medicines included in these regimens to have successful treatment efforts. Additionally, as Dr. Robin Wood concludes, there appears to be a variety of considerations that necessitate clinicians have flexibility in use of ARV medicines.

The nature of HAART, coupled with a further narrowing of choices in respect of pregnant women and women of childbearing potential, children and people with TB and HIV co-infection, leads to only one reasonable conclusion—that ARVs, even within the same therapeutic class, cannot be considered as fully substitutable for each other. Because of the matrix of interconnected factors relating to toxicity and effectiveness of treatment, access to a wide choice of ARVs is required in order to effectively administer HAART. At present no single registered ARV is fully substitutable by another.<sup>59</sup>

In other words, there is no single model HAART regimen for either all patients or for all clinical situations. The WHO Guidelines provide both clinicians and patients recommendations based on the aggregation and review of experience of clinical management of HIV from a variety of settings. Access to the antiretroviral medicines in the preferred regimens is integral to the success of HIV management in South Africa. However, this should not limit access to only the antiretroviral medicines in the preferred regimens. Specifically, there are **four** salient issues that necessitate wide availability of all antiretroviral medicines.

First, the HIV virus, like all other viruses, is evolving. Viruses respond to changes in the environment, including the presence of a medicine that interferes with replication. Moreover, not all HIV viruses are genetically equal. HIV viruses differ on a molecular level. Molecular differences can result in varying levels of drug resistance during antiretroviral drug treatment. “This information is important for determination of appropriate drug therapies.”<sup>60</sup> In South Africa, the work has begun to assess the molecular typing of HIV viral strains. Access to a variety of ARVs medicines would assist clinicians in their ability to counter viral strains unaffected by currently recommended treatment regimens.

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<sup>58</sup> See Expert Affidavit of Dr. Robin Wood, pg. 11.

<sup>59</sup> See Expert Affidavit of Dr. Robin Wood, pg.13.

<sup>60</sup> Peter Fonjongo et al., *Human Immunodeficiency Virus Type 1 Group M Protease in Cameroon: Genetic Diversity and Protease Inhibitor Mutational Frequencies*, 40(3) *Journal of Clinical Microbiology* 837 (2002).

The KwaZulu-Natal region of South Africa is experiencing an explosive outbreak of human immunodeficiency virus type 1 subtype C infections. Understanding the genetic diversity of C viruses and the biological consequences of this diversity is important for the design of effective control strategies... This work forms a baseline for future studies aimed at understanding the impact of genetic diversity on vaccine efficacy and on natural susceptibility on antiretroviral drugs.<sup>61</sup>

Second, the field of ARV therapy is evolving rapidly, particularly in regard to treatment in developing countries. “The availability of an increasing number of ARV’s and the rapid evolution of new information has introduced substantial challenges into treatment regimens,” while the potential clinical benefits to patients has increased.<sup>62</sup> Flexibility in use of ARVs is necessary as new information is uncovered. This is especially important in light of the fact that, in some instances, new information has completely contradicted previous practices. Illustrative of this point was made at the 6<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, when a British physician remarked,

The patients who have done best are those who lived long enough to realize that my previous advice was incorrect. (He was referring to a time prior to the availability of protease inhibitors, when he had recommended use of sequential NRTI monotherapy, followed by the addition of 3TC.)<sup>63</sup>

Regimens need to adapt to reflect scientific progress.<sup>64</sup> For instance, for the 2 NRTI + NNRTI regimen, data on the use of the first of the two NNRTIs, EFZ, is slightly more ‘clinically convincing’ than NVP, meaning that evidence suggests that it is more effective, although there is no study that directly compared the efficacy of the two drugs. However, EFZ is contraindicated, not recommended, for use in pregnant women because of EFZ-related symptoms affecting the central nervous system. EFZ should be used with caution with women at risk of pregnancy.<sup>65</sup> The availability of ARV medicines should reflect this.

For these reasons, the WHO included a wide range of ARVs on its Model List of Essential Drugs (12th edition, April 2002) including AZT, 3TC, ABC, d4T, ddI, nevirapine, efavirenz, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir and saquinavir. In deciding that a full range of ARVs should be included in the Model List, the WHO Expert Committee on the Selection and Use of Essential Medicines explained:

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<sup>61</sup> M. Gordon et al., *Molecular Characteristics of Human Immunodeficiency Virus Type 1 Subtype C Viruses from KwaZulu-Natal, South Africa: Implications for Vaccine and Antiretroviral Control Strategies* 77(4) *Journal of Virology* 2587 (2003).

<sup>62</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 8 (August 1, 2003).

<sup>63</sup> Jeffery Schouten et al., *Light at the End of the Tunnel?* 99(1) *STEP Perspective* 2 (1999). Available at [www.aegis.com/pubs/step/1999/](http://www.aegis.com/pubs/step/1999/)

<sup>64</sup> Scott Hammer et al., *Antiretroviral Guidelines for Resource-Limited Settings: the WHO’s Public Health Approach*, 8 *Nature Medicine* 649, 650.

<sup>65</sup> World Health Organization, *SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS*, 31-2 (2002). See Expert Affidavit of Dr. Robin Wood for a discussion on treatment recommendations in pregnant women

While accepting that there were many circumstances in medicine where one essential drug may substitute easily for other members of a class, thus allowing the placement of a single agent on the Model List (with appropriate advice about substitution), this was not possible with HIV treatment. Effective therapy requires commencement of three drugs simultaneously, and alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. The committee considered various approaches to the listing of these agents but agreed finally that if they were to be listed, all drugs recommended should be included in the Model List.

The WHO guidelines... recommend that HAART programmes make provision for those who cannot tolerate the first or second-line regimens and would therefore require individualised specialist care.<sup>66</sup>

Third, treatment with HAART in settings with high burden of disease is complex. This should not discourage treatment, but it does necessitate increased flexibility in regimen design. For instance, the 3 NRTI regimen including the drug ABC, is contraindicated for patients with some co-morbidities. “The risk of ABC hypersensitivity<sup>67</sup> in regions with a high incidence of febrile illnesses such as malaria and tuberculosis<sup>68</sup> could hinder accurate diagnosis of this potentially fatal side-effect.”<sup>69</sup>

Ordinarily, people with HIV/AIDS who also have TB should complete their TB treatment before beginning HAART. However, if there is a high risk of HIV disease progression or death during the period of the TB treatment, HAART should be started concurrently with TB therapy.<sup>70</sup>

In such cases, first-line treatment options include a dual NRTI component of AZT/lamivudine or d4T/lamivudine, plus either an NNRTI or ABC. If an NNRTI is chosen, efavirenz is preferred, as its potential to aggravate the hepatotoxicity of TB treatment appears to be less than that of nevirapine. Generally, PIs—with the exception of saquinavir combined with ritonavir—are not recommended because of their interactions with rifampicin, which is used to treat TB.<sup>71</sup>

Some AIDS related conditions are relative contra-indications to specific ARVs. Peripheral neuropathy is a degenerative condition of the sensory nerves to the limb extremities, which manifests as pain and numbness in the hands and feet.

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<sup>66</sup> See Expert Affidavit of Dr. Robin Wood, pg. 6

<sup>67</sup> ABC hypersensitivity may affect up to 5 percent of patients starting on the medication; World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 32 (2002).

<sup>68</sup> Both malaria and tuberculosis are infections commonly seen in South Africa, although the incidence for both infectious diseases is not exactly known.

<sup>69</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 32 (2002).

<sup>70</sup> See Expert Affidavit of Dr. Robin Wood, pg. 13.

<sup>71</sup> See Expert Affidavit of Dr. Robin Wood, pg. 13.

D4T may exacerbate the symptoms of peripheral neuropathy. Previous inflammation of the pancreas, a cause of severe abdominal pain, may be reactivated by use of ddI. Pre-existing inflammation of the liver (Hepatitis) may increase the incidence of nevirapine liver damage. These examples illustrate the need for a wide choice of ARVs, so as to be able to match a specific regimen for the many clinical situations which occur in HIV infection.<sup>72</sup>

Fourth, the risk of compliance related treatment failure would suggest a necessity of availability to a wide range of ARVs. Patient adherence is integral to successful treatment and access to those medicines that promote adherence is an absolute necessity. According to the Joint Task Team Report, among the several “guiding principles” critical for the successful implementation of HAART include, “A well-resourced adherence plan targeting patients, their families, and communities as well as health-care providers.”<sup>73</sup> Implementation of HAART therapy “would place considerable emphasis on a range of measures to maximise adherence to treatment by patients.”<sup>74</sup>

Adherence is necessary for patient well-being, as well as safeguarding against transmission of drug resistant strains of the HIV virus. As MSF highlighted in their 31 July 2003 letter to the Commission, “Treatment of AIDS with HAART requires good levels of adherence to achieve sustained viral suppression. Some experts argue that a rate of 80% adherence is needed to ensure, to the extent possible, treatment success and to avoid the onset of resistant strains of HIV.”<sup>75</sup> According to the South African HIV Clinicians Society clinical guidelines, “inadequate patient adherence to the prescribed regimen remains one of the most common reasons for treatment failure.”<sup>76</sup>

The WHO Guidelines recommend “the development of innovative strategies for enhancing adherence to ART because of its lifelong nature....Such strategies include minimizing pill counts and dosage frequencies by preferentially using combination pills on a once-daily or twice-daily basis.”<sup>77</sup>

In low- and middle-income countries, implementation of HAART is more recent and therefore there is less understanding about what factors influence adherence, although it is expected that they will not vary substantially from those associated with treatment adherence in wealthy settings. Indeed, early results of well-established national AIDS treatment programmes, such as the Brazilian

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<sup>72</sup> See Expert Affidavit of Dr. Robin Wood, pg. 13.

<sup>73</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 10 (August 1, 2003).

<sup>74</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 11 (August 1, 2003).

<sup>75</sup> Letter from Dr. Eric Goemaere, Head of Mission, MSF South Africa to Mr. Thulani Kunene, Senior Investigator: Enforcement and Exemptions, South African Competition Commission 8 (July 31, 2003).

<sup>76</sup> South African HIV Clinicians Society, *ANTIRETROVIRAL THERAPY IN ADULTS, SOUTH AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES* 9 (2002).

<sup>77</sup> World Health Organization, *SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS*, 16 (2002).

programme, found similar results to Western countries. In Senegal, a recent study reported very good levels of adherence on patients taking a once-a-day regimen. In Thailand, a progress review of the HAART programme acknowledges that the introduction of simpler regimens that have dramatically reduced the burden of pills have had a positive effect on adherence. Sensitive to the overwhelming evidence, the Southern African HIV Clinicians Society in its June 2002 clinical guidelines for antiretroviral therapy advises to prescribe regimens that imply the lowest possible burden of pills and lowest frequency of dosages.<sup>78</sup>

The advantage of combination pills to programmes in promoting patient adherence has been demonstrated in South Africa. In the MSF-run treatment programme in Khayelitsha, “a two pill regimen of zidovudine, lamivudine and nevirapine taken twice a day, has achieved viral suppression in 90% of the patients after three months of HAART. This level is maintained at longer periods, indicating extremely good levels of adherence.<sup>79</sup> Overall, it is reasonable to conclude that the use of combinations pills drastically simplify regimens.

Increased use and development of combinations pills referred to as fixed-dose combinations (FDCs), in the future present the potential of considerably increasing the likelihood of successful treatment of HIV. “There is countless evidence documenting the benefits of simplified regimens in terms of maximising adherence to therapies indicated for chronic conditions in general. In the case of AIDS treatment, numerous studies in countries where HAART has been available since its advent have demonstrated that a low burden of pills and a low frequency of daily dosages dramatically improve adherence.”<sup>80</sup> As more FDCs become available on the market, their availability for use in HIV treatment programmes will promote patient adherence. Given the significance, the issue of FDCs development and production requires further review.

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<sup>78</sup> Letter from Dr. Eric Goemaere, Head of Mission, MSF South Africa to Mr. Thulani Kunene, Senior Investigator: Enforcement and Exemptions, South African Competition Commission 8 (July 31, 2003). Citing Pinheiro et al. *Factors Associated With Adherence To Antiretroviral Therapy In HIV/AIDS Patients: A Cross-Sectional Study In Southern-Brazil* 35(10) Braz J Med Biol Res. 1173 (2002). Landman et al., *Once-A-Day Highly Active Antiretroviral Therapy In Treatment-Naïve HIV-1-Infected Adults In Senegal* 17(7) AIDS 1017 (2003).

<sup>79</sup> Letter from Dr. Eric Goemaere, Head of Mission, MSF South Africa to Mr. Thulani Kunene, Senior Investigator: Enforcement and Exemptions, South African Competition Commission 8 (July 31, 2003).

<sup>80</sup> Letter from Dr. Eric Goemaere, Head of Mission, MSF South Africa to Mr. Thulani Kunene, Senior Investigator: Enforcement and Exemptions, South African Competition Commission 8 (July 31, 2003)

## USE OF FIXED-DOSE COMBINATIONS

Currently, only two innovative pharmaceutical firms produce FDCs available on the South African, which make use of only their intellectual property.<sup>81</sup>

When available, fixed-dose combinations are advantageous with respect to the simplification of regimens and consequent improved adherence. The major pharmaceutical manufacturers currently produce three fixed-dose combinations included in these guidelines: [AZT]/3TC, [AZT]/3TC/ABC, and LPV/r. Fixed-dose combinations have also been produced by generic manufacturers (e.g. d4T/3TC/NVP and [AZT]/3TC/NVP, which may facilitate simplified regimens, decrease cost and promote adherence if they can be legally used and their quality and bioequivalence have been demonstrated.<sup>82</sup>

It is worth highlighting that patent protection likely prevents the development of medically relevant FDCs, as the patents for drugs that work well together may be held by competing firms. In fact, there is only one triple-combination FDC marketed by an originator firm (where a single company holds patents not only to the triple combination but also to each of the components); this is GSK's combination Trizivir® (zidovudine, lamivudine and abacavir), which is not highly recommended clinically. When patent barriers—either on individual ARVs or on combinations—are overcome, the most medically effective combinations can be developed and produced. The greater flexibility that generic producers have with regard to combinations is reflected in the numerous types of FDCs listed in Annex 3.<sup>83</sup>

Some of these ARVs are also available in various fixed-dose combination forms. The only combinations currently available in South Africa are AZT/lamivudine and lopinavir/Ritonavir. GlaxoSmithKline's Trizivir® (AZT/lamivudine/ABC) is not yet commercially available in South Africa.<sup>84</sup>

The WHO Guidelines substantiate MSF's claims. It regards the AZT + 3TC + ABC regimen as the most user-friendly both from an individual patient and a programme perspective, as it entails only two pills a day and the absence of significant drug interactions. However, there is some uncertainty whether this regimen works for people who have high viral loads and advanced HIV disease.<sup>85</sup>

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<sup>81</sup> Annex 3 of MSF's letter to the Commission lists all the FDCs that are currently available in the market from different manufacturers. Letter from Dr. Eric Goemaere, Head of Mission, MSF South Africa to Mr. Thulani Kunene, Senior Investigator: Enforcement and Exemptions, South African Competition Commission Annex 3 (July 31, 2003)

<sup>82</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 31 (2002).

<sup>83</sup> Letter from Dr. Eric Goemaere, Head of Mission, MSF South Africa to Mr. Thulani Kunene, Senior Investigator: Enforcement and Exemptions, South African Competition Commission 7,8 (July 31, 2003)

<sup>84</sup> See Expert Affidavit of Dr. Robin Wood, pg. 4-5.

<sup>85</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 29 (2002).

The bulk of the data for ABC-based triple [NRTI] regimens have been developed in relation to the use of this agent combined with [AZT] and 3TC but, given the comparable potency among the dual [NRTI] components listed, some flexibility is assumed. However, the availability of a fixed-dose combination containing [AZT], 3TC and ABC permits the delivery of a potent triple-drug combination with one pill administered twice daily...However, this regimen is of uncertain efficacy in patients with advanced disease...and only limited data on the use of ABC in pregnancy.<sup>86</sup>

When considering which of the five clinically viable options as dual NRTI backbones to recommend as first-line regime, the WHO Guidelines regard all “to possess comparable inherent antiviral activity in treatment-naïve persons.”<sup>87</sup> The recommendation of AZT + 3TC as the backbone for an initial first-line regimen is in part based on its current availability of the medicines in a FDC. “The panel considered in detail issues of resistance and toxicity and side-effects, and choose a combination of drugs specifically selected for ease of administration, compliance and their limited side-effects profile.”<sup>88</sup>

In addition to promoting adherence, FDCs have other advantages in terms of ensuring that patients take triple as opposed to mono or dual therapy minimize the risk of ‘pill-splitting’. Lessons from other treatment programmes requiring patients to take multiple pills for a sustained period of time indicate that within a household, health priorities may result in patients splitting a regimen. For instance, in tuberculosis treatment programmes, mothers frequently give children part of their 6-month course of medicine if they believe or know that their child is also sick with tuberculosis. Events such as these, invariably contribute to the emergence of drug resistant strains of the bacteria or virus. Increased use and development of FDCs would hinder this.

Development of FDC products does require demonstration of equivalence in safety and efficacy. Once appropriate combinations are identified, products must be tested for therapeutic synergy, pharmacological properties, meaning ‘how long the pill lasts’, and potential side-effects.

[REDACTED]

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<sup>86</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 32 (2002).

<sup>87</sup> World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 28 (2002).

<sup>88</sup> Joint Health and Treasury Task Team *Summary Report of the Joint Health and Treasury Task Team Charged with Examining Treatment Options to Supplement Comprehensive Care for HIV/AIDS in the Public Sector* 10 (August 1, 2003).

<sup>89</sup> [REDACTED]

REDACTED VERSION

Production should meet Good Manufacturing Production (GMP) standards. All of the manufactured FDCs listed in Annex 3 of MSF letters have demonstrated sufficient quality and safety, including those manufactured by generic firms. Little public information is available regarding production costs. **[REDACTED]**

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<sup>90</sup> **[REDACTED]**

**TABLE 1: Available ARV Medicines in South Africa**

<b>Active Ingredient</b>		
<b>Nucleoside analogue reverse transcriptase inhibitors (NRTIs)</b>		
zidovudine	AZT	Retrovir®
lamivudine	3TC	3TC®
abacavir	ABC	Ziagen®
stavudine	d4T	Zerit®
didanosine	ddI	Videx®
zalcitabine	ddC	Hivid®
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</b>		
nevirapine	NVP	Viramune®
efavirenz	EFZ	Stocrin®
<b>Protease inhibitors (PIs)</b>		
nelfinavir	NFV	Viracept®
indinavir	IDV	Crixivan®
ritonavir	RTV	Norvir®
saquinavir	SQV	Invirase®
amprenavir	APV	Preclir®
lopinavir	LPV/r	Kaletra®

**TABLE 2: Coverage Of Antiretroviral Therapy (ART) In Developing Countries, December 2002**

Region	Number of people on ART	Estimated Need	Coverage
Sub-Saharan Africa	50,000	4,100,000	1 %
Asia	43,000	1,000,000	4 %
North Africa & Middle East	3,000	7,000	29 %
Eastern Europe & Central Asia	7,000	80,000	9 %
Latin America, Caribbean	196,000	370,000	53 %
<b>TOTAL</b>	<b>300,000</b>	<b>5,000,000</b>	<b>5 %</b>

Source: International HIV Treatment Access Coalition. "A Commitment to Action for Expanded Access to HIV/AIDS Treatment." December 2002.

**TABLE 3: Recommendations for Initiation of HAART  
In Adults and Adolescents with Documented HIV Infection**

**If CD4 testing is available**

- WHO stage IV irrespective of CD4 cell count
- WHO stage I, II or III with CD4 cell counts less than 200/mm

**If CD4 testing is not available**

- WHO stage IV irrespective of TLC
- WHO stage II or III with TLC less than 1200/mm

**TABLE 4: Percent and Number of Infections per Stage of Infection per Province, July 2001**

	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga <sup>a</sup>	Northern Cape	North West	Western Cape	South Africa <sup>91</sup>
<b>HIV</b>										
#										
<b>Infections</b>	805,879	487,772	1,449,899	1,745,490	600,713	518,156	78,426	582,089	192,946	6,461,372
<b>% Stage 1</b>	62	55	54	50	61	51	62	56	63	55
<b>% Stage 2</b>	18	20	21	21	19	20	18	20	18	20
<b>% Stage 3</b>	15	18	19	21	15	20	15	18	15	18
<b>% Stage 4</b>	5	7	7	8	5	8	5	6	5	7
<b># Stage 1</b>	449,680	241,447	704,651	785,471	329,791	237,834	43,762	293,373	109,400	3,198,379
<b># Stage 2</b>	130,552	87,799	274,031	329,898	102,722	93,268	12,705	104,776	31,257	1,163,047
<b># Stage 3</b>	108,794	79,019	247,933	329,898	81,096	93,268	10,588	94,298	26,048	1,046,742
<b># Stage 4</b>	36,265	30,730	91,344	125,675	27,032	37,307	3,529	31,433	8,683	407,066

Source: Rob Dorrington et al., *HIV/AIDS Profile in the Provinces of South Africa*, (2002) THE CENTRE FOR ACTUARIAL RESEARCH, MEDICAL RESEARCH COUNCIL, & THE ACTUARIAL SOCIETY OF SOUTH AFRICA 6.

<sup>91</sup> “The sum of the provincial projections produced by the ASSA2000 provincial versions does not exactly equal the full projection for the country as a whole.” Dorrington et al. pg. 1

**TABLE 5: Recommendations for First and Second-line Regimens According to Scaling Up: Antiretroviral Therapy In Resource-Limited Settings**

Option	Regimen Structure	First-line Regimen	Second-line Regimen for Treatment Failure	Alternative Second-line Regimen for Treatment Failure
1	2 NRTI + NNRTI	AZT+3TC+EFZ or AZT+3TC+NVP	d4T + ddI + RTV-PI	RTV-PI + ABC + ddI or NFV + ABC + ddI or d4T + ddI + NFV
2	3 NRTI	AZT+3TC+ABC	D4T + ddI + EFZ or d4T + ddI + NVP	d4T + ddI + RTV-PI
2	2 NRTI + PI	AZT+3TC+RTV-PI <sup>92</sup> or AZT+3TC+NFV	D4T + ddI + EFZ or d4T + ddI + NVP	ABC + ddI + EFZ or ABC + ddI + NVP

<sup>92</sup> According to the WHO Guidelines, RTV enhanced PI (IDV/r, LPV/r, SQV/r) is preferred because of the potency of these regimens. World Health Organization, SCALING UP: ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS, 36 (2002).

**TABLE 6: South African HIV Clinicians Society Recommendations For Drug Substitutions by ARV Class**

<b>Active Ingredient</b>		
<b>Nucleoside analogue reverse transcriptase inhibitors (NRTIs)</b>		
zidovudine	AZT	Stavudine
lamivudine	3TC	didanosine or zalcitabine
abacavir	ABC	determined by resistance testing
stavudine	d4T	Zidovudine
didanosine	ddI	lamivudine or zalcitabine
zalcitabine	ddC	abacavir, stavudine or zidovudine or others determined by resistance testing
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</b>		
nevirapine	NVP	There is broad cross-resistance between the currently available NNRTIs. Resistance to one precludes the use of another, unless there is resistance test data to the contrary. Individuals who fail an NNRTI-containing regimen may be candidates for an abacavir-containing triple-nucleoside combination (if viral load is <55 000 RNA copies/mL) or a PI containing regimen. Resistance to one agent of this class effectively results in cross-resistance to all members of drugs in this category (that are currently available in South Africa).
efavirenz	EFZ	Sequential use of these drugs is not recommended. <sup>93</sup>
<b>Protease inhibitors (PIs)</b>		
nelfinavir	NFV	A major reason for regimens that contain protease inhibitors failing is sub-optimal pharmacokinetics and inadequate drug exposure as a result of poor adherence (often due to intolerance). This needs to be considered carefully before deciding to introduce an alternative PI-containing regimen. Second-line protease inhibitors alternatives may exhibit reduced activity due to extensive cross-resistance within this class of drugs. Pharmacologic boosting of protease blood levels can be achieved by combining amprenavir, saquinavir, and indinavir with low doses of ritonavir. Experience with these combinations is limited and advice on dosing should be sought. <sup>94</sup>
indinavir	IDV	
ritonavir	RTV-PI	
saquinavir	SQV	
amprenavir	APV	
lopinavir	LPV/r	

<sup>93</sup> South African HIV Clinicians Society, ANTIRETROVIRAL THERAPY IN ADULTS, SOUTH AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES 11-2 (2002).

<sup>94</sup> South African HIV Clinicians Society, ANTIRETROVIRAL THERAPY IN ADULTS, SOUTH AFRICAN HIV CLINICIANS SOCIETY CLINICAL GUIDELINES 12 (2002).