

SEA-AIDS-142  
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# Scaling Up Antiretroviral Therapy in Resource-poor Settings

A Selected Annotated Bibliography



**World Health Organization**

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New Delhi

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**“People must know  
that a poor person like  
me living in a shack can  
take these drugs  
properly. They are my  
chance to live”.**

Patient on antiretroviral therapy in Khayelitsha, South Africa  
*[Demystifying antiretroviral therapy in resource-poor settings. Kasper  
T, Coetzee D, Louis F, et al. Essential Drugs Monitor 2003; 32: 20–21.]*

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# Introduction

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This annotated bibliography is intended as a resource for policy makers, programme managers and other personnel working in HIV/AIDS control in developing countries. The aim of this bibliography is to provide representative examples of developing country' experiences on the effectiveness and programmatic challenges for scaling up adult national antiretroviral treatment programmes.

Given that antiretroviral treatment in developing countries is recent, and research in the field is still emerging, the articles for which annotations are presented here not only include examples from original research, but also published viewpoints, research letters, correspondence, etc. Though most articles are from developing countries, some experiences from developed countries that are of significance in the global context are also included. The selections are drawn only from published works in English published between 1999 and December 2003.

This first edition of the bibliography hopes to provide answers to many of the questions faced by country policy planners in developing strategies for widespread access to antiretroviral treatment for HIV/AIDS control in resource-poor settings. The bibliography should prove to be a useful reference in view of the recent WHO declaration of lack of access to antiretroviral treatment as a global emergency and the subsequent launch of the 3 by 5 initiative, i.e. to provide antiretroviral treatment to 3 million by 2005.

Comments and suggestions for improvement of future editions of this bibliography are welcome.

# Programmatic Effectiveness of Antiretroviral Therapy

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## 1. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire.

Djomand G, Roels T, Ellerbrock T, et al. *AIDS* 2003; 17 (suppl 3): S5–S15

The complexity of administering antiretrovirals (ARVs) and their high costs are a deterrent for large-scale implementation of antiretroviral therapy (ART) in resource-poor countries. This two-year pilot project (August 1998–August 2000) was conducted to serve as a model to address challenges to treatment, such as limited health system infrastructure, drug distribution, and training in AIDS treatment for resource-poor countries. In this study, those eligible for treatment were provided with subsidy to pay for medications. Data from 480 HIV-infected patients put on highly active antiretroviral therapy (HAART) in six accredited centres in Abidjan were evaluated for response to treatment. An intention-to-treat analysis of these patients estimated plasma HIV-1 RNA levels to be  $1.9 \log_{10}$  copies/ml (80-fold) lower, and CD4 count to be  $>100$  cells/mm<sup>3</sup> higher than baseline values after one year of therapy. The probability of survival for at least one year was 0.84 (95% confidence interval, 0.80–0.89). The virologic and immunologic outcomes, probability of an adverse event, and estimated survival were similar to those observed from developed settings.

In this study, those eligible for treatment were provided with subsidy to pay for medications. However, with the sharp drop in ARV drug prices and production of generic drugs (which reduces the costs even further) in recent years and the standardized guidelines for treatment published by WHO, scaling up ART in a resource-poor setting should be a definite possibility even in a developing country setting.

The Ministry of Health of Cote d'Ivoire had to address several programmatic challenges. The first included development of clear political and financial commitment

by the national government, the local medical community, donor organizations, and the pharmaceutical industry. The second challenge was to increase laboratory capacity, especially of equipment and trained personnel. The third challenge was enrolment and follow-up of HIV-infected patients in the programme. Large numbers of patients did not return to access treatment (55% of those screened; and 21% of those who initiated therapy) resulting in only one-third of those requiring treatment receiving it. There were no demographic or social differences among those who came regularly for follow-up versus those who did not.

This project proved that ART programmes can be successfully implemented in Africa and that “Increasing community awareness, accessing patients earlier in the course of the disease, and improving patient education and adherence would greatly improve programme efficiency . . .”.

## **2. Dramatic improvement in survival among adult Brazilian AIDS patients**

Marins JRP, Jamal LF, Chen SY, et al. *AIDS* **2003**; 17: 1675–1682

Brazil has led the way among developing countries in providing access to antiretroviral (ARV) drugs for its population through its national health care system since the 1980s. In 1996, a federal law mandated free access to triple antiretroviral treatment.

This large study examined the benefits of ARV in improving the survival and quality of life for AIDS patients on a national scale. The authors conducted a retrospective cohort study of 3930 randomly selected adult AIDS cases diagnosed in 1995 and 1996 from 18 cities in seven states representing all regions of the country. A total of 2821 patients who completely matched the inclusion criteria were analysed. Data from the study of cases diagnosed in 1995–1996 were compared with data from a previous national study on survival among 2135 Brazilian AIDS patients diagnosed in 1982–1989.

Survival time of AIDS patients increased substantially from a median survival of 5 months and 18 months for those diagnosed in the 1980s and 1995, respectively, to 58 months for those diagnosed in 1996. Thus, improvement in survival coincided with the widespread availability of triple ARV therapy in Brazil. Multivariate analysis of the predictors of survival also indicated that ARV was the cause for the increased survival noted. Despite the absence of an effective health care system matching those of developed countries and CD4 and viral load testing not being widely available at the time of the study, Brazil achieved huge gains in survival at the national level.

The study showed that providing access to ARVs at the national level is feasible and can make a tremendous difference in the survival of persons with AIDS in a developing country. Brazil was one of the first countries to provide access to ARVs to its entire population. This was achieved through a combination of political commitment and adoption of bold policies of local generic drug production, aggressive negotiation for discounts in drug prices, development of a national laboratory network, and concerted efforts from governmental and non-governmental sectors.

### **3. Demystifying antiretroviral therapy in resource-poor settings**

Kasper T, Coetzee D, Louis F, et al. *Essential Drugs Monitor* 2003; 32: 20–21

This pilot project was conducted in a poor township, Khayelitsha, close to Cape Town, South Africa. Of 3000 patients who attended the Medecins Sans Frontieres clinics in Khayelitsha, 180 were put on antiretroviral therapy (ART). The median CD4 count of these patients was 43 cells/mm<sup>3</sup>. After nine months of treatment 88% patients were alive with 69% reduction in incidence of opportunistic infections and 85% reduction in incidence of tuberculosis cases. The mean CD4 count increase was 143 cells/mm<sup>3</sup> after six months of treatment. No patient was lost to treatment. There were very few side-effects and no deaths related to drug toxicity.

The important lessons of this project were that ART can be safely and effectively used in resource-poor settings on a wide scale. Patients on ART are easier to manage and follow-up than those who are not. ART bolstered the health system and improved morale of staff because instead of tending to the dying they were providing life saving treatment. The cost of drugs more than offset the drop in hospitalizations and opportunistic infections. A synergy between treatment and prevention activities was created with more people showing the desire to be tested for HIV. “. . . a recent survey of nine sites around South Africa found that Khayelitsha had the highest rates of HIV testing, and desire to be tested among those who had yet to be tested, as well as the highest levels of condom use.”

One of the innovations used in this project was introducing a system by which the community helped in selecting patients for ART (in addition to established biological and clinical criteria) providing equitable treatment to those who needed it the most. Another important innovation was the patient-centered approach. Patients were given easy to take regimens, individualized counselling, peer support in the form of support groups, and educational materials. Patients were the strongest advocates for the programme and were responsible for speaking to the media, politicians, and the public; running

support groups; and educating themselves on adherence and taking responsibility for taking their medications.

The authors attribute the success of any ART programme in resource-poor settings to three key factors: 1. affordable drugs; 2. involvement of the community; and, 3. involvement of patients.

#### **4. Highly active antiretroviral therapy in resource-poor settings: the experience of Medecins Sans Frontieres**

Tassie J-M, Szumilin E, Calmy A, Goemaere E. *AIDS* **2003**; 17: 1995–1997 [Research Letters]

Preliminary results of short-term follow-up at six months of highly active antiretroviral therapy (HAART) programmes in seven resource-poor countries (Malawi, Kenya, South Africa, Cameroon, Cambodia, Thailand, Guatemala) were presented. Only triple-therapy regimen as per World Health Organization guidelines was provided free of cost to 881 patients started on HAART as of May 2002. Results for analysis were available from 743 adults. The probability of survival at six months was very good; 89.5% (95% confidence interval [CI], 86.8–92.1). Among those who survived, the probability of remaining on treatment at six months was 94% (95% CI 91.8–96.1). The median increase in CD4 count among 200 patients was 104 cells/mm<sup>3</sup> (25<sup>th</sup>–75<sup>th</sup> percentiles: 47–163) at six months. A high level of treatment adherence is indicated because patients were regularly coming for treatment and showed good immunological and virological responses similar to those seen in developed countries. The results indicated that ART is feasible and effective in resource-constrained settings.

#### **5. Natural history of human immunodeficiency virus disease in southern India**

Kumaraswamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. *Clinical Infectious Diseases* **2003**; 36: 79–85

Data from 594 patients receiving care at a tertiary referral HIV centre between June 1996 and June 2001 were analysed. Patients were advised to start antiretroviral therapy (ART) when their CD4 count was less than 350 cells/mm<sup>3</sup>, if they could afford to pay for the treatment. Patients receiving ART had a five-fold increased odds of survival (odds ratio=5.37; 95% confidence interval, 1.82–15.83) than those who did not receive ART. Among patients with CD4 count less than 200 cells/mm<sup>3</sup>, the median survival for those who received ART was 45 months compared to 33 months for those who did not

receive ART. The results of the study support benefits of ART in an Indian cohort and are similar to those observed elsewhere.

In this setting only 29% of those eligible for ART and could afford to pay for treatment received it. Unaffordability was a major challenge in India and more persons would have benefited if universal cheaper or subsidized ART was available.

The results of the study support benefits of ART in an Indian cohort and are similar to those observed elsewhere.

## **6. The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study**

Laurent C, Diakhate N, Gueye NFN, et al. *AIDS* 2002; 16: 1363–1370

This prospective observational cohort study evaluated the feasibility, effectiveness, adherence, toxicity and viral resistance of a highly active antiretroviral therapy (HAART) programme in Senegal. Fifty-eight HIV-infected ART-naïve adults in Dakar, most of whom were at an advanced stage of disease (86.2% had AIDS), were enrolled in the study between August 1998 and June 2000. Initial treatment consisted of 2 nucleoside reverse transcriptase inhibitors and one protease inhibitor. Plasma HIV-1 RNA and CD4 cell counts were determined at baseline and every 6 months. The median follow-up period was 19.5 months.

Nearly, 88% of patients reported equal to or more than 80% adherence and treatment was effective in most of them. The two common reasons for non-adherence were reported to be forgetfulness (35%) and financial difficulties (19%). Plasma HIV-1 RNA reached undetectable levels in 80%, 71%, 51%, and 59% of patients at months 1, 6, 12, and 18, respectively. The median viral load was  $-2.5 \log_{10}$  copies/ml. The CD4 count increased by 82, 147 and 180 cells/mm<sup>3</sup> and the cumulative probability of remaining alive (or free of AIDS-related events) was 95%, 85%, and 82%, at 6, 12, and 18 months, respectively. Most adverse effects were mild or moderate. Drug resistance developed in two cases (3.4%) only because of the rationalized use and ensured supply of drugs under the National AIDS Program.

The results of clinical, virological and immunological responses to treatment at 18 months were comparable to those from industrialized countries despite differences in HIV-1 subtype distribution and those enrolled being at an advanced stage of the disease. The authors concluded that HAART was feasible and well tolerated in this cohort of African patients.

## **7. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance**

Weidle PJ, Malamba S, Mwebaze R, et al. *Lancet* **2002**; 360: 34–40

This report summarizes the systematic assessment of a national programme aimed at increasing access to antiretroviral therapy (ART) in Africa. Patients receiving highly active antiretroviral therapy (HAART) at three accredited antiretroviral (ARV) health-care facilities, under the Drug Access Initiative (DAI), between August 1998 and July 2000 were assessed for treatment outcomes. Patients and their families were responsible for paying for all their medical care, drugs, and laboratory tests. Survival probability at six months was found to be 0.82 (95% confidence interval [CI] 0.77–0.86) and at one year was 0.74 (95% CI 0.67–0.79). Adherence to therapy was good at 88%. Non-adherence to therapy was mostly due to financial constraints (33%). The approximate cost of monthly ART at US\$ 708 was too high for Uganda which has a GNP per head of US\$ 26 per month.

The study showed that with modest increases in existing resources, effective drug procurement, distribution and accountability uninterrupted supply of drugs was possible in supporting sustainable management of patients. Results of therapy were similar to those reported from developed countries and patients reported good adherence to treatment. The early success of this programme resulted from important human and financial investment and national commitment with training and capacity building proving to be important components.

## **8. Morbidity and survival in advanced AIDS in Rio de Janeiro, Brazil**

Gadelha AJ, Accacio N, Costa RLB, et al. *Revista do Instituto de Medicina Tropical de Sao Paulo* **2000**; 44: 179–186

This study, conducted in an urban specialized hospital between September 1997 and December 1999, assessed the incidence of opportunistic infections and survival among 79 patients with advanced stage of immunodeficiency. The mean follow-up period was 24 months. Analyses of results showed that with highly active antiretroviral therapy (HAART), survival was prolonged, AIDS-related hospital admissions were reduced and incidence of opportunistic infections was lowered significantly even among AIDS patients at an advanced stage of disease (CD4 count less than 100 cells/mm<sup>3</sup>). These results were similar to those from other parts of the world. There was a 50% reduction in AIDS related hospital admissions and mortality. Patients who had CD4 counts less than 100

cells/mm<sup>3</sup> and were on HAART reported half the incidence rates of opportunistic infections than among those who had CD4 counts more than 100 cells/mm<sup>3</sup> without ART. From the time of AIDS diagnosis mean survival was 7.09 years and median was 7.98 years. Longer survival was found among those whose CD4 counts were restored to above 100 cells/mm<sup>3</sup>.

## Impact on Prevention

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### 9. Access to antiretroviral treatment and sexual behaviours of HIV-infected patients aware of their serostatus in Cote d'Ivoire

Moatti J-P, Prudhomme J, Traore DC, et al. *AIDS* **2003**; 17 (suppl 3): S69–S77

Increase in HIV-related risky sexual behaviours among persons on highly active antiretroviral therapy (HAART) is of concern worldwide because improvements in the quality of life of patients due to access to effective treatment may cause them to continue or resume risky sexual behaviours. In this cross-sectional study, patients who were informed of their serostatus and attending eight health centres involved in HIV care in Abidjan and Bouake in Cote d'Ivoire, between December 1999 and February 2000, were interviewed. Data on sexual behaviour during the previous six months among both antiretroviral (ARV) treated and ARV non-treated patients were compared. Persons on antiretroviral therapy (ART) were significantly less likely to report risky sexual behaviour (19%) than those not on ART (3%) (odds ratio=0.44, 95% confidence intervals 0.26–0.74) and the association was significant even after controlling for co-variables. Only 4% of those on ART reported an occasional irregular partner compared to 13% among those not on ART ( $p=0.02$ ). Patients on ART were significantly more likely to use condoms during their most recent sexual intercourse (80%) than those who were not on ART (59%).

While the authors caution readers about the limitations of the study, it being a cross-sectional design based on patients' self-reported responses with a relatively short follow-up period, they conclude that the results do not support the fears that access to ARVs would increase risky sexual behaviours among African HIV-infected patients on ART. The authors suggested that in this setting, the improvement of care, support and counselling associated with ARV may have been one of the factors responsible for the

lower risky behaviour among those on ART, and recommend that prevention and access to care, including ARV, should mutually reinforce each other in resource-poor settings.

### **10. Predicting the public health impact of antiretrovirals: Preventing HIV in developing countries.**

Blower S and Farmer P. *AIDScience* **2003**; 3. [www.aidsscience.org/articles/aidsscience033.asp](http://www.aidsscience.org/articles/aidsscience033.asp). Accessed 18 Nov 2003

The study used mathematical modelling analysis of the effect of antiretrovirals (ARVs) in developed countries to predict the impact of AIDS treatment in developing countries. Antiretroviral therapy (ART) in developed countries has increased the longevity and quality of life of patients and decreased the rate of transmission of HIV—providing both therapeutic and preventive benefits.

In developing countries, as in developed countries, the epidemic-level impact of ARV usage will depend critically on how widely treatment is made available, and how well it is used. If only a small fraction of HIV-infected individuals receive ARVs, this will have almost no impact on transmission, though levels of drug-resistant strains will be low. Even a moderately high usage of ARV will decrease the transmission rates, but may be accompanied by emergence of drug-resistant HIV. Developing countries need to develop ARV strategies that balance the public health goals of reducing overall transmission and the emergence and transmission of drug-resistant HIV.

“Treatment can act as a prevention tool, but it is an unconventional prevention tool as it is given to the HIV-infected individual rather than to the uninfected individual. Health policy decisions should be made on the basis that ARVs are first and foremost a therapeutic tool, and the effects of ARVs as a prevention tool are secondary. It is essential that access to well-controlled use of ARVs be increased in developing countries. Substantially increased access is likely to significantly reduce both the mortality and the overall transmission of HIV.”

### **11. Highly active antiretroviral treatment does not increase sexual risk behaviour among French HIV infected injecting drug users**

Bouhnik A-D, Moatti JP, Vlahov D, et al. *Journal of Epidemiology and Community Health* **2002**; 56: 349–353

Clinical improvement because of highly active antiretroviral therapy (HAART) has been thought to relate to increased risky sexual behaviours in HIV-infected persons,

especially among specific groups such as injecting drug users (IDUs). This prospective observational MANIF 2000 cohort study was conducted among 188 HIV-infected IDUs in 12 hospitals of south eastern France (Marseilles, Avignon, Nice), between October 1996 and May 1998. Risky sexual behaviour was categorized as being engaged in unprotected sex at least once during the past six months of the visit. Thirty-four of the 188 antiretroviral therapy (ART)-naïve patients were started on HAART. The proportion of patients reporting risky sexual behaviour significantly declined only in the HAART-treated group (47% to 24%,  $p=0.008$ ), but not in the untreated group (44% to 36%,  $p=0.10$ ). Multivariate analyses confirmed that prescription of HAART was associated with reduced risky behaviours.

Three results of this study are of importance to developing countries, especially south-east Asia where the second most important cause of spread of HIV infection is because of IDUs. First, HAART does not increase HIV related risky sexual behaviour in IDUs. Second, because of low adherence suspected among IDUs, physicians tend to delay or not prescribe ART. This study counters this view. Third, factors associated with risky behaviour in general settings were seen in this IDU cohort too, such as depressive symptoms, alcohol consumption, that could be addressed by targeted counselling and interventions as for the general HIV-infected population.

The authors suggested increasing primary and secondary prevention efforts among HIV infected patients to curtail the potential public health threat of infections with viral strains already resistant to the available ART because of possible risky sexual behaviours.

## 12. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics?

Velasco-Hernandez JX, Gershengorn HB, Blower SM. *Lancet Infectious Diseases* 2002; 2: 487–493

The authors used a mathematical model to calculate the probability of high usage of available antiretroviral (ARV) regimens in eradicating the current high prevalence (30%) of HIV. The basic reproduction number ( $R_0$ ) for HIV in a community where ARV is available and both drug-sensitive and drug-resistant strains were co-circulating, i.e.  $R_0^{ARV}$ , was estimated.  $R_0^{ARV}$  is the average number of new infections that one HIV case generates during a lifetime when ARV is available and ARV-resistant strains can evolve and be transmitted. An  $R_0^{ARV}$  of less than one would mean that eradication is possible. Clinical, virological, and behavioural data from a gay community in San Francisco were

used to derive these estimates on the basis of three assumptions: (1) ARV decreases risky sexual behaviour, (2) ARV causes no change in risky sexual behaviour, and (3) ARV increases risky sexual behaviour. The estimates for  $R_0^{ARV}$  were 0.90 (0.85–0.96) if risky sexual behaviour decreased, 1.0 (0.94–1.05) if risky sexual behaviour remained stable, 1.16 (1.05–1.28) if risky sexual behaviour increased. The probability of epidemic eradication was high ( $p=0.85$ ) if risky sexual behaviour decreased, moderate ( $p=0.5$ ) if risky sexual behaviour remained stable, and low ( $p=0.13$ ) if risky sexual behaviour increased. There were four clinical and public health implications of this study.

1. Increasing the percentage of cases receiving ARVs would substantially reduce the severity of the HIV epidemic, even when there are high levels of ARV resistance and risky sexual behaviour.
2. Moderate reductions in the infectivity/transmissibility of treated cases (with development of better drugs or increased use of condoms) can reduce the severity of the HIV epidemic.
3. If highly transmissible ARV-resistant strains emerge, it can reduce the beneficial effect of ARV on the HIV epidemic. Therefore, efforts to prevent cases of acquired resistance are required.
4. The value of  $R_0^{ARV}$  is highly sensitive to changes in risky sexual behaviour. This advocates the need for tightly coupling the usage of ARV with effective prevention strategies.

The study is of relevance to resource-poor settings because the methodology proposed here can be applied to any other geographical location. “Our current quantitative findings imply that widespread usage of ARV in Africa and other developing countries would be extremely beneficial in reducing HIV epidemics.” The authors concluded that a high usage of the currently available combination ARVs, in addition to benefitting the individual patients, would help as an effective HIV-prevention tool even with high levels of drug resistance and risky sexual behaviour.

### **13. Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy)**

Farmer P, Leandre F, Mukherjee J, Gupta R, Tarter L, Kim JY. Bulletin of the World Health Organization **2001**; 79: 1145–1151

The authors describe an early experience of a small community-based demonstration project conducted in collaboration with Haitian community workers

experienced in directly observed antiretroviral (ARV) treatment. Among other results, the study noted a favourable impact on staff morale. The authors believe that the stigma associated with AIDS was reduced because of the dramatic response to therapy. Decrease in stigma increased the demand for HIV testing and reduced patient complaints regarding abusive behaviour from family and neighbours.

“A related consequence of introducing DOT-HAART is an increased use of the clinic’s free HIV testing and counselling services. HIV testing has been available since 1998 but during the past two years its utilization has increased by more than 300%. Thus the provision of AIDS treatment has strengthened AIDS prevention.”

#### **14. Viral load and heterosexual transmission of human immunodeficiency virus type I**

Quinn TC, Wawer MJ, Sewankambo N, et al. *New England Journal of Medicine* 2000; 342: 921–929

Heterosexual contact is the major transmission mode of HIV-1 in Sub-Saharan Africa and other developing countries. This was a community-based randomized trial of 15 127 persons conducted in Rakai, a rural district of Uganda, between November 1994 and October 1998 to study the association between serum HIV-I RNA levels and the risk of heterosexual HIV-I transmission. Condoms were available free of charge and extensive counseling was provided to all subjects; antiretorvirals (ARVs) were not available. The authors identified 415 couples, where one partner was initially HIV-1 positive (228 male and 187 female), who were followed up for 30 months to measure the incidence of HIV infection among the initially seronegative partners.

The authors found that viral load was the chief predictor of heterosexual transmission of HIV-1. The risk of heterosexual transmission decreased significantly with decreasing serum HIV RNA level. The rate of transmission decreased from 23.0 per 100 person-years to 2.2 per 100 person-years as the serum HIV-1 RNA level decreased from >50 000 copies/ml to less than 3500 copies/ml (adjusted rate ratio, 11.87). There were no instances of transmission among the 51 subjects with undetectable viral loads or with serum HIV-1 RNA levels of less than 1500 copies/ml. “This finding raises the possibility that reductions in viral load brought about by the use of antiretroviral drugs could potentially reduce the rate of transmission in this population.”

## Laboratory Diagnosis and Monitoring Methods

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### 15. Simple markers for initiating antiretroviral therapy among HIV-infected Ethiopians

Mekonnen Y, Dukers NHTM, Sanders E, et al. *AIDS* **2003**; 17: 815–819

The standard markers, CD4 cell count and viral load, used to determine the time of start of therapy are too expensive and mostly unavailable in resource-poor settings. This study evaluated the use of simple criteria for initiating antiretroviral (ART) in 1666 individuals from a suburb of Addis Ababa who joined a cohort between 26 February 1997 and 31 August 2001.

Among the 156 individuals who were HIV-positive at intake, simple markers (such as HIV-related symptoms; low body mass index  $<18.5$  kg/m<sup>2</sup>; anaemia; lymphocyte count less than 1500 cells/mm<sup>3</sup>), for predicting death were examined using time-dependent Cox proportional hazards models. Timing of hypothetical treatment was compared between models based on simple markers, guidelines recommended by the United States Department of Health and Human Services (DHHS; based on CD4 cell count and viral load), and guidelines for resource-limited settings recommended by the WHO. All simple markers were found to be significant predictors of death.

The study showed that the management of highly active antiretroviral therapy (HAART) would have been similar for 87% patients whether treated using international guidelines or those based on simple markers. Of the 114 patient hypothetically treated under either the “simple marker” or DHHS guidelines, 91 (80%) would have started HAART at the same time.

In this study the WHO guidelines (without CD4 cell counts) would have resulted in 11 of the patients dying without ever being indicated for treatment.

The authors concluded that simple markers compared well to established laboratory markers and can be used to determine the start of ART in resource-poor settings. They suggested that the findings should be validated in similar settings to test these markers for monitoring of ART.

### **16. Low-cost CD4 enumeration in HIV-infected patients in Thailand**

Pattanapanyasat K, Lerdwana S, Shain H, et al. *Asian Pacific Journal of Allergy and Immunology* **2003**; 21: 105–113

All CD4 cell count enumerations in Thailand are done in accordance with the standard flow cytometric immunophenotyping guidelines recommended by the Centres for Disease Control and Prevention. Since the cost per test is very high at US\$12–24, it is not affordable for monitoring all HIV patients in Thailand. A simpler protocol using fewer lymphocyte markers and cheaper reagents was tried to evaluate the possibility of an affordable yet reliable alternative to the costly standard CD4 cell count enumeration by flow cytometric immunotyping (by 6-tube 2-color or 3-tube 3-color panels).

HIV-infected blood samples were obtained from 142 HIV-seropositive patients and 26 HIV-negative adult blood donors from the Department of Immunology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand. The percentage CD4 values of the whole blood samples generated by just two generic reagents (CD45/CD4) in a 1-tube 2-color panel employing side scatter/CD45 morphospectral gating were compared with those generated from the standard methods. Generic monoclonal antibody reagents were also compared with commercial reagents. The results were comparable with overall correlation coefficient of more than 0.95 for both CD4 and CD8.

The study concluded that the 1-tube 2-color method using two generic antibody reagents and simplified protocol was a more affordable (US\$ 3) yet reliable CD4 testing method and would help increase access to ART for more HIV-infected patients in resource-poor countries.

### **17. Successful implementation of a low-cost method for enumerating CD4+ T lymphocytes in resource-limited settings: the ANRS 12-26 study**

Diagbouga S, Chazallon C, Kazatchkine MD, et al. *AIDS* **2003**; 17: 2201–2208

This multi-center study evaluated the feasibility and effectiveness of an alternative technique to standard flow cytometry. The Dynabeads technique uses

magnetic beads coated with anti-CD4 monoclonal antibodies. Six laboratories and 43 laboratory technicians with little or no experience from Cote d'Ivoire, Mali, Burkina Faso, Togo and Senegal participated in the study. The laboratory technicians received standardized training locally for two days. Blood samples from 657 HIV-infected persons were separated into two aliquots, one each for estimation of CD4 cell counts by Dynabeads and flow cytometry methods. The correlation coefficient for the two methods was 0.89. The overall median difference between Dynabeads and flow cytometry was – 16 cells/mm<sup>3</sup>. Patients were consistently classified at the clinically relevant threshold of 200 cells/mm<sup>3</sup> by both methods in 89% cases. The reproducibility of the Dynabeads methods was high, similar to that of flow cytometry. The epifluorescent microscope used for counting required low maintenance and its cost was half that of the cheapest flow cytometer. The authors concluded that the Dynabeads technique was accurate, consistent, reproducible and easy to use in West Africa. Prior to large-scale implementation, however, the technique would still require rigorous quality control to be set up.

### **18. Use of dried whole blood spots to measure CD4+ lymphocyte counts in HIV-infected patients.**

Mwaba P, Cassol S, Pilon R, et al. *Lancet* **2003**; 362: 1459–1460

The standard flow cytometry method for measuring CD4 cell counts in HIV-infected persons requires fresh anti-coagulated blood and cannot be useful for those who live far away from central laboratory facilities. The authors developed a cheap and practical method to measure CD4 cell counts that has the potential of being used in a rural developing country setting. Whole blood samples collected from 42 HIV-infected persons recruited from the University Teaching Hospital in Lusaka, Zambia were processed and CD4 cell counts done with flow cytometry. In addition, 50 µl of blood from each sample was spotted onto Guthrie card filter paper, dried at room temperature overnight and stored at room temperature for 30 days before analysis by ELISA (modified). The results with the two methods correlated well; mean CD4 count with flow cytometry was 289 cells/mm<sup>3</sup> while that with filter paper ELISA was 347 cells/mm<sup>3</sup>. There was better agreement between results when CD4 counts were greater than 200 cells/mm<sup>3</sup>. This stored filter paper method can be a convenient, reliable, field-friendly option for populations in developing countries and resource-poor settings without immediate access to central laboratories and refrigeration facilities. The method needs further refinement and evaluation on a larger sample in a field-based study.

### **19. Rapid declines in total lymphocyte counts and hemoglobin concentration prior to AIDS among HIV-1-infected men**

Lau B, Gange SJ, Phair JP, et al. *AIDS* **2003**; 17: 2035–2044

The authors studied the potential use of total lymphocyte count (TLC) and haemoglobin (Hb) concentrations as markers to monitor HIV disease progression among persons living in resource-limited settings. This prospective cohort study (Multicentre AIDS Cohort Study) traced the temporal patterns of TLC and Hb concentrations during the course of HIV infection and related these to changes in CD4 cell counts and clinical disease. Patterns of TLC and Hb before and after the estimated inflection point (i.e. the point in time when the change in marker is most likely to have occurred) showed that there were substantial differences after the inflection point for both markers in persons progressing to AIDS than among those remaining free of AIDS. The inflection point for TLC and Hb for those who developed AIDS occurred on an average 0.25 years after CD4 count fell below 350 cells/mm<sup>3</sup> and 0.75 years before CD4 counts fell below 200 cells/mm<sup>3</sup>, 1.6 years before clinically defined AIDS and 2.8–2.9 years before death for this untreated cohort.

“. . . the initial decline in TLC and Hgb generally occurs between an individual's first CD4 cell count of 350 and 200 cells/mm<sup>3</sup>, the time when the current guidelines recommend initiating antiretroviral therapy . . . Until the time of inflection, TLC and Hb markers are stable and provide little information about the risk of disease progression, but late in disease (when CD4 cell counts are generally between 200 and 350 cells/mm<sup>3</sup>) the markers demonstrate rapid decline and thus distinguish those individuals who will soon progress to AIDS or death.”

These results suggest that TLC and Hb, which are inexpensive to measure and do not require sophisticated technology, provide easy and accurate measures to monitor progression to AIDS in HIV-infected persons in resource-poor settings.

### **20. Total lymphocyte count and hemoglobin combined in an algorithm to initiate the use of highly active antiretroviral therapy in resource-limited settings**

Spacek LA, Griswold M, Quinn TC, Moore RD. *AIDS* **2003**; 17: 1311–1317

A retrospective evaluation of combining the surrogate marker total lymphocyte count (TLC) with haemoglobin (Hb) concentrations was done to predict CD4 cell counts in 3269 persons of the John Hopkins HIV observational cohort. The authors developed

clinical algorithms to evaluate the effect of combining TLC and Hb to predict CD4 counts below 200 cells/mm<sup>3</sup> before initiation of highly active antiretroviral therapy (HAART). After adjustment for TLC and Hb levels, sex remained significantly associated with CD4 counts less than 200 cells/mm<sup>3</sup>, and was therefore included in the algorithms. The sensitivity of TLC alone on applying the WHO recommended TLC cutoff of 1200 cells/mm<sup>3</sup> was 70% for men and 72% for women.

The algorithms improved the sensitivity of TLC as a surrogate marker of CD4 cell counts when used in combination with Hb to 79% for men and 88% for women. TLC below 1200 cells/mm<sup>3</sup> and Hb below 12 g/dl significantly predicted CD4 counts below 200 cells/mm<sup>3</sup>. Combining TLC and Hb increased sensitivity, thereby, reducing the risk of false-negative results. The authors caution against directly applying their algorithms to a developing country setting as this study was conducted in patients in an urban clinic in the United States. These algorithms, however, can serve as templates for developing algorithms for resource-limited settings in predicting CD4 counts of less than 200 cells/mm<sup>3</sup> to initiate HAART.

## **21. Total lymphocyte count (TLC) is a useful tool for the timing of opportunistic infection prophylaxis in India and other resource-constrained countries**

Kumaraswamy N, Mahajan AP, Flanigan TP, et al. *Journal of Acquired Immune Deficiency Syndromes* **2002**; 31: 378–383

This study evaluated total lymphocyte count (TLC) as a potential marker of immunosuppression where CD4 cell counts are unavailable. Paired CD4 cell counts and TLC from a total of 405 patients attending an HIV/AIDS clinic (YRG CARE), in south India between 1997 to 2000, were assessed. CD4 cell count was determined by the FACSCount system and TLC was derived from complete blood cell count by multiplying lymphocyte percentage by the white blood cell count. There was a high degree of correlation between CD4 cell counts and TLC;  $r=0.74$ . Sensitivity was maximum at highest TLC ranges. TLC <1400 cells/mm<sup>3</sup> had a sensitivity of 73% and a specificity of 88% for CD4 count <200 cells/mm<sup>3</sup>. For CD4 count <200 cells/mm<sup>3</sup>, the sensitivity and specificity of TLC <1200 cells/mm<sup>3</sup> was 62% and 93%, respectively. The study also showed that TLC can be a cost-effective tool in India for determining a patient's HIV status — while a single CD4 test costed US\$ 30, one TLC test costed only US\$ 0.80. The high correlation of TLC and CD4 cell count in HIV-positive patients in this study confirms the role of TLC in treatment management in resource-poor settings.

## **22. Comparative assessment of five alternative methods for CD4+ T-lymphocyte enumeration for implementation in developing countries**

Didier J-M, Kazatchkine MD, Demouchy C, et al. *Journal of Acquired Immune Deficiency Syndromes* **2001**; 26: 193–195 [Letter to Editor]

The authors compared alternative methods to the expensive standard flow cytometry for enumerating CD4 cell counts for use in developing countries. These included FACSCount (uses flow cytometry), Cytospheres, Dynabeads, Opti-CIM, and Capcellia. Blood samples obtained from 40 HIV-infected persons and 20 healthy adults were tested at the Clinical Immunology Laboratory, Broussais Hospital, Paris by flow cytometry and the above methods as per the manufacturer's instructions. Data were collected for accuracy, the cost, number of samples per series, time to perform the technique, and time of delay for each method.

Correlation coefficients between results obtained by flow cytometry and each of the alternative methods was similar at all ranges of CD4 cells (less or more than 500 cells/mm<sup>3</sup>). Median differences between CD4 cell counts obtained by standard flow cytometry and alternative methods were: 45 for FACSCount, 56 for Dynabeads, 195 for Cytospheres, 134 for Capcellia, and 126 for Opti-CIM. The FACSCount method uses flow cytometry, therefore giving the least median difference and highest correlation ( $r=0.97$ ). The correlation was much lower ( $r=0.45$ ) than obtained in previous studies for cytospheres, and the median difference in counts was high; also this method requires a trained reader. Dynabeads method correlated extremely well ( $r=0.91$ ) with standard flow cytometry irrespective of the CD4 counts, and showed the lowest median difference than by any non-cytofluorometric method. With Opti-CM ( $r=0.72$ ), the CD4 cell counts were overestimated. This method is complex to perform and measures only the percentage and not the absolute CD4 counts. Capcellia showed a low correlation coefficient ( $r=0.42$ ) and the cost of the method is also high.

The authors concluded that FACSCount and Dynabeads methods compared well with standard flow cytometry; of these the Dynabeads method appears less expensive and potentially useful for countries with limited economic resources.

## **23. Affordable CD4+ T cell counts by flow cytometry: II. The use of fixed whole blood in resource-poor settings**

Jani IV, Janossy G, Iqbal A, et al. *Journal of Immunological Methods* **2001**; 257: 145–154

Flow cytometry, the standard method for measuring CD4 cell counts, is expensive and requires high technology with whole blood samples to be tested within 18–24 hours

of collection. In developing countries whole blood samples have to be transported long distances to reach expert laboratories for testing by flow cytometry. The authors tested the feasibility and precision of using TransFix™ (a recently standardized fixative for whole blood) to increase the affordability of flow cytometry. Fresh blood samples collected from HIV-positive and HIV-negative persons were tested in Dar-es-Salaam (Tanzania) and Johannesburg (South Africa) and fixed in TransFix and transported to London (UK) for testing seven days later. The correlation in CD4 cell counts between fresh samples and fixed samples in Tanzania and Johannesburg with the fixed samples tested in UK was high ( $r=0.99$ ). The authors concluded that TransFix allows optimal fixation and transport of whole blood samples in developing countries for flow cytometry to local regional laboratories and for quality assurance testing at international laboratories.

## Cost Analysis

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### **24. Costs of medical services for patients with HIV/AIDS in Khon Kaen, Thailand**

Kitajima T, Kobayashi Y, Chaipah W, Sato H, Chadbunchachai W, Thuennadee R. *AIDS* **2003**; 17: 2375–2381

Providing highly active antiretroviral therapy (HAART) through the public health system in developing countries may be possible only if the cost of antiretrovirals (ARVs) is substantially lowered.

This cost-analysis study was conducted in two referral hospitals in Thailand from December 2001 to February 2002. Data from 522 outpatient visits and 200 inpatients were collected; this included 312 (82%) who were covered under the Universal Coverage plan. The average costs per outpatient/inpatient were US\$ 294.2/US\$ 368.1 and US\$ 26.1/US\$ 43.8, for those on ARV and those not on ARV, respectively.

The maximum expenditure was for ARV drugs; the average HAART cost per visit was US\$ 281. The estimated national annual cost of HAART was US\$ 5 674 629; 20% of the Universal Coverage budget for adults in this province.

Estimates made on the net cost of a new combination drug (GPO-VIR) that was made available after this study showed that the net cost of HAART would reduce from 20% to just 8% by 2006, when the new regimen GPO-VIR is introduced.

Similar analysis for other developing countries will help in testing the feasibility of providing access to HAART through their respective public health systems.

## 25. The most efficient use of resources to identify those in need of antiretroviral treatment in Africa: empirical data from Cote d'Ivoire's Drug Access Initiative

Diomande FVK, Bissangene E, Nkengasong JN, et al. *AIDS* 2003; 17 (suppl 3): S87–S93

Resource scarce settings, such as those in Africa, have huge unmet needs with regard to eligibility screening for antiretroviral therapy (ART). CD4 cell count and viral load tests, usually used for identifying HIV-positive persons in need of ART, are too expensive. In this study, data from the Drug Access Initiative (DAI) in Cote d'Ivoire were used to describe simple cost-effective eligibility screening strategies for initiating ART. The laboratory cost of patient screening using sequential clinical staging, CD4 cell counts, viral load testing, and the proportion of screened patients who were eligible for ART were estimated. Ninety-six percent of the ART naive adults (2057 of 2138) who presented to the DAI between July 1998 and July 2000 were found to be eligible for ART. The median CD4 count was 172 cells/mm<sup>3</sup>. The four algorithms tested, i.e. parallel DAI-CI<sup>1</sup> (clinical criteria plus CD4 count plus viral load) serial DAI-CI (clinical criteria, if not eligible CD4 count, if not eligible viral load), serial US recommendations<sup>2</sup>, and serial WHO model 2002<sup>3</sup>, diagnosed 98%, 98%, 94%, and 87% patients, respectively. The costs were US\$ 2 49 269, US\$ 57 197, US\$ 62 015, and US\$ 48 221, respectively.

With the DAI-CI criteria, the average cost for HIV testing by clinical evaluation was only US\$ 18 per eligible person identified. Inclusion of CD4 cell count to the serial algorithm added an average cost of US\$ 50 per eligible person identified. Inclusion of the viral load criterion added US\$ 108 per eligible person identified. With the US criteria the additional costs were US\$ 62 and 177, respectively for CD4 cell count and viral load. The WHO screening criteria added US\$ 109 for CD4 cell count.

The results showed that majority of HIV-positive persons in need for ART were identified by the low-cost DAI clinical staging criteria. Use of CD4 cell counts identified an additional 15%–18% at moderate cost. Viral load testing identified only 4% additional persons at more than US\$ 100 per person. Viral load testing is very costly and not of much benefit and should not be part of screening algorithms for initiating ART. The authors suggested using clinical staging methods, by training health personnel to

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1 DAI clinical criteria: Clinical staging, CD4 cell count <500 cells/mm<sup>3</sup>, viral load >10 000 copies/ml

2 US recommended criteria: Clinical staging, CD4 cell count <350 cells/mm<sup>3</sup>, viral load >55 000 copies/ml

3 WHO 2002 recommended criteria: Clinical staging, CD4 cell count <200 cells/mm<sup>3</sup>

identify and refer clinically symptomatic persons, for cost-effective and efficient screening for initiating ART in resource-scarce Africa.

## 26. Fighting against AIDS: the Brazilian experience

Levi GC and Vitoria MAA. *AIDS* 2002; 16: 2373–2383 [Editorial Review]

The World Bank had anticipated that the Brazil epidemic would go out of hand by 2000 with 1 200 000 HIV infections per year. However, recent estimates show encouraging results with HIV infections under 600 000 (a 50% reduction). This review described the strategies used by the government for prevention and treatment of HIV and also the costs of providing wide-spread antiretroviral therapy (ART) in Brazil.

Expenditure on AIDS control activities was US\$ 250 million from 1992 to 1998, and US\$ 300 million from 1998 to 2000, partly funded by a loan agreement from the World Bank. Brazil initiated a multipronged approach including preventive, treatment, and community mobilization strategies to counter the AIDS epidemic. The Ministry of Health established procedures for accreditation of public hospitals and expanded the hospital network for the care of HIV-infected patients. As of December 2000, 78% of patients were receiving highly active antiretroviral therapy (HAART). Brazil's initiative to provide full and free access to treatment meant high costs, close to US\$ 200 million in 2001. However, reduction in medication costs has decreased the overall cost of the programme, with 50% of all ART medications being produced within the country; an annual cost reduction of 48% per ART patient, from US\$ 4860 in 1997 to US\$ 2530 in 2001. Cost per patient-day fell from US\$ 13.4 in 1997 to US\$ 8.5 in 2000.

Between 1996 and 2001, the average hospital admissions per patient per year dropped from 1.65 to 0.28, with 358 000 hospitalizations being prevented resulting in savings of more than US\$ 1 billion. Opportunistic infections, mainly tuberculosis, showed a dramatic reduction of 71% between 1996 and 2000, 54% alone in 1996–1997 coinciding with widespread HAART availability. There was also a 61% reduction in costs for *Pneumocystis carinii* infection and 81% for *Mycobacterium avium*. The total ART expenses in 2002 were 1.5% of the total Ministry of Health's budget, less than 0.05% of Brazil's gross domestic product.

The characteristics of the Brazilian response to the AIDS epidemic were early governmental response, strong will, society participation at all decision levels, multisectoral mobilization, balanced prevention and treatment approach and human rights perspective in all strategies and actions. The Brazilian experience shows that

even in countries with constrained and limited resources, ART proves to be a cost-saving approach in controlling the HIV epidemic.

## **27. Country response to HIV/AIDS: National Health Accounts on HIV/AIDS in Brazil, Guatemala, Honduras, Mexico and Uruguay**

Izazola-Licea J-A, Avila-Figueroa C, Aran D, et al. *AIDS* **2002**; 16 (suppl 3): S66–S75

A National HIV/AIDS Accounts system, allowing international comparisons, to quantify all expenditures on HIV/AIDS in five Latin American countries, viz. Brazil, Guatemala, Honduras, Mexico, and Uruguay, is described. The accounting system is based on the National Health Accounts methodology and takes into account the levels of financing and the flow of expenditure. The source of financing may be the government, social security, households, or external corporations. The expenditure was classified by source, use (prevention, care), by object and by type of provider institution. The flow of expenditure is from the source to funds/financing agents to institutions managing the resources. Assessments revealed that health investments varied widely across the 5 countries. Total national HIV/AIDS expenditure estimates for 1998 were US\$PPP<sup>1</sup> 29.5 million in Guatemala, US\$PPP 32.5 million in Uruguay, US\$PPP 257 million in Mexico, US\$PPP 587.4 million in Brazil, and US\$PPP 33.9 million in Honduras (1999 estimate).

The distribution of expenditures was more for care than prevention among all five countries; average estimate of 66% on care and less than 40% on preventive services. Expenditure estimates correlated well with the health policies for HIV/AIDS for each of the countries. Uruguay showed the highest per capita expenditure (unadjusted) with 62% devoted to care because their policy is of universal access to antiretrovirals (ARVs). When adjusted by PPP Uruguay came second to Honduras, because it pays higher prices for technological inputs and has a higher cost of living. Honduras has the adjusted highest per capita expenditure despite not having universal access to ARV as in Uruguay and Brazil, because of its large number of cases, minimal access to ARV, and the significant international financial cooperation. Brazil, Guatemala, and Mexico recorded increased expenditures for HIV/AIDS control between 1997 and 1998, due to condom expenditure, increased hospitalizations and antiretroviral therapy (ART) by the social security system, and mild increase in ARV coverage, respectively.

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<sup>1</sup> *Purchasing power parity (PPP): US\$ adjusted as per standard method set by World Bank Development Reports to allow for international comparison.*

The accounting method described is suited for policy analysis, as it considers even non-health expenditures such as advocacy, food supply, shelters, etc. This methodology is applicable to different countries and since it allows international comparisons, countries can identify their financial indicators and use the results for implementing effective, strategic national AIDS control programmes.

## **28. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence**

Creese A, Floyd K, Alban A, Guinness L. *Lancet* **2002**; 359: 1635–1642

This systematic review analysed 24 studies from Africa on cost and effectiveness of strategies to combat HIV/AIDS. A vast variation in cost-effectiveness of treatment interventions for HIV/AIDS was noted. A case could be prevented for as less as US\$ 11 to as much as US\$ 2000 and a disability-adjusted life-year (DALY) gained for US\$ 1. Though there was not enough data on highly active antiretroviral therapy (HAART) interventions alone, costs were related to other measures such as blood safety which again may cost between US\$ 20 and US\$ 1000 to prevent one HIV case. There were also interventions to prevent mother-to-child transmissions (over US\$ 4000) and sexually transmitted diseases (over US\$ 270). Other associated costs of any HIV/AIDS treatment programme were those for prevention of opportunistic infections, prophylaxis, condom promotion and counselling.

Antiretroviral treatment (ART) for adults cost several thousand dollars per infection prevented. With the recent fall in drug prices costs should go down. However, countries implementing universal access to HAART need to design cost-effective strategies for prevention, care and support as a priority to ensure maximum impact on the epidemic with the available resources.

## Treatment Adherence

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### 29. Adherence to HAART and its principal determinants in a cohort of Senegalese adults

Laniece I, Ciss M, Desclaux A, et al. *AIDS* **2003**; 17 (suppl 3): S103–S108

This was an observational prospective cohort study of 158 patients in an antiretroviral (ARV) access programme in Dakar, Senegal between November 1999 and October 2001 (24 months).

The treatment regimens given in the study were multi-drug combinations of stavudine/didanosine/indinavir and lamivudine/didanosine/efavirenze. Adherence to treatment was self reported (on self-rating questionnaires) by patients on the basis of stated drug intakes and/or unused tablet counts, during regular monthly visits to the dispensary. Ninety-three percent of patients were ARV naïve at inclusion. The mean adherence rate was 91%. Adherence was related to the cost involved in treatment with maximum adherence (92%) among those who received free drugs and the least adherence (66%) among those who had to pay more than US\$ 67. Adherence was better among those on efavirenz-containing regimens than indinavir-containing regimens.

“As expected, viral load was higher in less adherent patients (mean differences of 1.7 and 1.8  $\log_{10}$  copies/ml at months 18 and 24, respectively;  $p < 0.05$ ).” The results observed were similar to those obtained from developed countries. It is concluded that adherence to highly active antiretroviral therapy (HAART) has been very high and similar to those observed from developed countries.

The authors caution that to achieve similar results while scaling up access to ARVs for poor communities around the world, the cost and type of drug regimen must be taken into account.

### **30. Adherence is not a barrier to successful antiretroviral therapy in South Africa**

Orrell C, Bangsberg DR, Badri M, Wood R. *AIDS* **2003**; 17: 1369–1375

Adherence to antiretroviral therapy (ART) was prospectively monitored in a cohort of 289 semi-urban, poor, HIV-infected, ART-naïve South Africans (Cape Town AIDS Cohort [CTAC]) attending a public sector hospital between January 1996 and May 2001 and receiving free ART. Adherence was assessed using clinic-based pill counts.

The median adherence of the cohort up to 48 weeks was 93.5%. Adherence  $\geq 95\%$  to ART significantly predicted reduction in viral load. For those who were  $\geq 95\%$  adherent at 48 weeks, 73% had a viral load of  $<400$  copies/ml compared with only 61% of those whose adherence was  $<95\%$ . On multivariate analyses, increased frequency of dosing was the strongest predictor for both poor adherence and virologic failure. Low socio-economic status was not associated with poor adherence.

The results of this study support that high rates of adherence and viral suppression are achievable in the absence of formal adherence interventions in a Sub-Saharan African cohort, indicating that adherence cannot be a barrier to ART.

### **31. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10<sup>9</sup> cells/L**

Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. *Annals of Internal Medicine* **2003**; 139: 810–816

Besides a high degree of adherence to treatment, the optimal timing of starting highly active antiretroviral therapy (HAART) is considered to be critical to survival of patients. The recommendations on the time of initiating antiretroviral therapy (ART), however, differ. This paper describes a prospective observational follow-up of 1422 HIV-infected patients from the HAART Observational Medical Evaluation and Research (HOMER) study in British Columbia to determine the optimal time to start ART. HIV-infected patients started on HAART between 1 August 1996 and 31 July 2000, were followed through 31 March 2002. Results indicated that there was no increase in mortality when HAART was initiated at a CD4 count of 200 cells/mm<sup>3</sup> or greater for this large cohort of patients within a population-based treatment programme. Mortality rates were statistically similar for adherent patients who started treatment at lower (200 cells/mm<sup>3</sup> to 349 cells/mm<sup>3</sup>) and higher ( $>350$  cells/mm<sup>3</sup>) CD4 counts. Initiating

HAART below 200 cells/mm<sup>3</sup> was not associated with increase in mortality rates. Therefore, HAART can be safely delayed until but not below this level. Mortality rates were higher among non-adherent patients than among adherent patients regardless of the CD4 count of 200 cells/mm<sup>3</sup> or 350 cells/mm<sup>3</sup> or greater. Findings suggested that nonadherence to treatment was associated with faster disease progression even for those who started HAART at baseline CD4 count of 350 cells/mm<sup>3</sup> and greater. The study concludes that in HIV-infected patients with CD4 counts above 200 cells/mm<sup>3</sup>, adherence is the strongest determinant of survival rather than the CD4 cell count when treatment is started.

### **32. Universal access to antiretroviral therapy may be the best approach to 'Do no harm' in developing countries: the Brazilian experience**

Remien RH, Bastos FI, Berkman A, Terto V Jr, Raxach JC, Parker RG. *AIDS* **2003**; 17: 786–787 [Correspondence]

The authors responded to a letter published in an earlier volume of the same journal that suggested addressing systemic and individual obstacles to adherence in developing countries before implementing antiretroviral therapy (ART).<sup>1</sup> Results from their own experience in Rio de Janeiro, Brazil are presented. Data were collected from non-random convenience samples from a wide range of health settings, such as university hospitals and community clinics, of men and women on ART. Adherence to medication, assessed using the AIDS Clinical Trials Group (ACTG) self-report questionnaire, was very high with 82% of persons reporting 90% adherence even with only routine primary care provider adherence counselling.

These results suggested that adherence to antiretrovirals (ARVs) can be as good, if not better, than that seen in developed countries even with little or no counselling regarding adherence to medication. This has important implications for the potential successful outcomes of widespread ART in resource-poor settings. The authors opined that although behavioural interventions to improve adherence would be the ideal strategy, most parts of the developing world have sufficient public health infrastructure and means to benefit from ART. “. . . we must also be careful to do no harm by withholding effective therapies from large groups of individuals who are capable of benefiting from their effectiveness as their peers in the industrialized world.”

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1 Popp D, Fisher JD. *First, do no harm: a call for emphasizing adherence and HIV prevention interventions in active antiretroviral therapy programs in the developing world.* *AIDS* 2002;16:676–678. [Letter]

### **33. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana**

Weiser S, Wolfe W, Bangsberg D, et al. *Journal of Acquired Immune Deficiency Syndrome* **2003**; 34: 281–288

Botswana has the highest rate of HIV infection in the world. In 1997, AIDS patients occupied 60% of the hospital beds in Botswana. Most patients in Botswana did not have access to antiretrovirals (ARVs) because of their unaffordability and the <1% of HIV-infected patients who were on treatment received subsidized antiretroviral therapy (ART).

This cross-sectional study conducted in three private clinics in Botswana between January and July 2000, reported the barriers to and levels of treatment adherence in 109 patients who had at least three months of ART. Patients and health care providers (60) were interviewed separately to obtain information on adherence. In this study, 54% of the patients self-reported adherence. Gaps in treatment (29%) were more frequently reported than day-to-day nonadherence (17%). The main reason for gaps in treatment was inadequate insurance coverage for the expensive medication (69%). For all groups, the other major barriers to adherence were financial constraints (44%), stigma (15%), travel/migration (10%), and side-effects (9%). By logistic regression analysis, when the most important predictor for adherence, i.e. cost, was removed adherence was predicted to increase from 54% to 74%. Health providers, when interviewed separately, estimated 56% adherence among patients. Though the overall proportion was very similar to patient self-reports (54%), there was disagreement about which patients were able to adhere to treatment.

The results of this study indicated that adherence rates in Botswana were comparable to those in most developed countries, despite the large structural and economic barriers to treatment faced by patients in Botswana. The larger gap in treatment, rather than day-to-day missing of doses, reflected the lack of consistency of access to affordable drugs. Therefore, expanding access to ARVs may substantially increase adherence, and thereby treatment outcomes in Botswana and other resource poor settings.

### **34. Compliance to antiretroviral medication as reported by AIDS patients assisted at the University Hospital of the Federal University of Mato Grosso do sul**

Monreal MTFD, da Cunha RV, Trinca LA. *The Brazilian Journal of Infectious Diseases* **2002**; 6: 8–14

This was a small descriptive-analytical study of 139 AIDS patients attending the day clinic of a University Hospital in Brazil between September 1999 and January 2000.

The authors used standard questionnaires to collect data on socio-economic parameters and drug compliance among patients receiving antiretroviral therapy (ART). Those who took 80% or more of their medications were considered compliant. Results showed the average compliance to be 76% with no differences between the sexes. The main reasons given for non-compliance were forgetfulness (68%) and lack of medicines (42%). Compliance was not associated with age, time since diagnosis, number of hospitalizations and employment status. There was more compliance (85%) among those who had most schooling than those who had no or only basic schooling (51%).

The authors concluded that the mean compliance and proportion of compliant patients were similar to that observed from developed countries and further suggested that in this setting health service personnel should use methodologies appropriate to characteristics of the population to improve compliance.

### **35. Impact of adherence to antiretroviral therapy in HIV-1-infected patients at a university public service in Brazil**

Brigido LFM, Rodrigues R, Casseb J, et al. *AIDS Patient Care and STDs* **2001**; 15: 587–593

This was a prospective study in an open cohort of 182 HIV-infected patients, attending the outpatient clinic of Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil, started on or changed to monitored antiretroviral treatment (ART) for a median of 12 months. A simple questionnaire was administered to each patient with mostly closed questions to record patient's perceptions to treatment. All treatments, i.e. double nucleoside reverse transcriptase inhibitors (NRTIs), 2NRTIs and hard-capsule saquinavir, and highly active antiretroviral therapy (HAART) were analysed. The authors evaluated the correlation between adherence to treatment and CD4 cell count and viral load. Patients were categorized according to adherence to treatment as regular (missing no doses), quasi regular (missing up to 4 doses in a month), irregular and ignored (no information). Results available from 90% of patients indicated that less than half reported complete adherence (41%), quasi regular adherence was 19% and irregular was 29%. The main reasons given for non-adherence was forgetfulness in 48% and intolerance in 22%. Significant increase in CD4 cell counts ( $p < 0.001$ ) and decrease in viral load ( $p = 0.04$ ) were observed only in regular and quasi regular categories. AIDS-defining illness and deaths occurred only in the irregular and ignored categories. There was no association between adherence and any risk factors or vulnerable groups. The study found an association between previous treatment and treatment adherence, with treatment-naïve patients more likely to show regular adherence (41%). An interesting

finding was that adherence improved as treatment progressed probably because the monitoring of CD4 cell counts and plasma viral load at regular intervals increased the patient awareness to failure and motivated them to improve adherence.

The authors concluded that though this simple study of adherence was based on self-admittance by patients, it was a reliable indicator correlating well with laboratory and clinical parameters and may be considered in the absence of better methods. The authors also suggested including mechanisms to improve adherence as an important component of any ART programme.

### **36. Factors associated with adherence to antiretroviral therapy in HIV/AIDS patients: a cross-sectional study in Southern Brazil**

Pinheiro CAT, de-Carvalho-Leite JC, Drachler ML, Silveira VL. *Brazilian Journal of Medical and Biological Research* **2002**; 35: 1173–1181

The study investigated associations between adherence to antiretroviral therapy (ART) and sociodemographic, clinical and sociocognitive variables in 195 patients, started on ART between January 1998 and September 2000, at a funded specialist clinic in Pelotas, southern Brazil. Adherence to treatment was assessed by a self-report inventory developed for the study. Results showed that 57% of the patients reported  $\geq 95\%$  adherence to medications on the previous two days. Though this was lower than those reported elsewhere, significant association between viral load below 500 copies/ml and adherence validates the self-report measure used in this study.

Among the sociodemographic variables, schooling of more than eight years was associated with better adherence (odds ratio=2.28, 95% confidence interval [CI] 1.12–4.66). Among the clinical variables, rate of adherence was mostly associated with the number of doses required to be taken per day. Rate of adherence to ART was significantly lower in patients who had to take medications more than four times per day than among those on twice-a-day medication (odds ratio=0.44, 95% CI 0.20–0.94). The results were similar to those observed from the developed world. The study revealed that the strongest association to adherence was of self-efficacy (sociocognitive variable), i.e. the conviction of persons to be successful in executing the required behaviour (odds ratio=3.5, 95% CI 1.9–6.6). The self-efficacy scores among those who were adherent were higher than those who were non-adherent to therapy.

The authors concluded that motivational interventions based on self-efficacy may be useful in increasing treatment adherence. "Patient resources to cope successfully with high-risk situations for nonadherence to treatment can be identified, and those

with low levels of self-efficacy in taking the antiretroviral medication may be supported by interventions in situations in which their ability to adhere is weak.”

### **37. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection**

Paterson DL, Swindells S, Mohr J, et al. *Annals of Internal Medicine* **2000**; 133: 21–30

Although this study was conducted in North America, it underscores the need for high adherence levels for antiretroviral therapy (ART) programmes in all settings. This prospective, observational study was conducted in two HIV clinics between August 1997 and March 1999 with a median follow-up of six months (range, 3 to 15 months). A total of 99 patients (ART naïve and experienced) were prescribed protease inhibitor and their adherence to treatment measured by using a microelectronic monitoring system. The adherence rate was calculated by dividing the number of doses taken by the number prescribed. There was no medication organizer or observation of treatment.

The results from 81 evaluable patients showed that adherence was significantly associated with successful virological outcome ( $p < 0.001$ ) and increase in CD4 cell count ( $p = 0.006$ ). Virological failure occurred in 22% patients with 95% or more adherence; 61% with 80% to 94.9% adherence; and 80% among those with less than 80% adherence. Patients with 95% or more adherence had fewer days in hospital than those with less than 95% adherence; 2.6 days per 1000 days follow-up and 12.9 days per 1000 days follow-up ( $p = 0.001$ ), respectively. The authors concluded that adherence of 95% or more to therapy resulted in good virological outcomes, higher CD4 cell counts, and lower hospitalizations.

## Private Sector and Community Involvement

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### **38. Antiretroviral therapy in the private sector of Nairobi, Kenya: a review of the experience of five physicians**

Macharia DK, Chang LW, Lule DMO, et al. *AIDS* **2003**; 17: 938–939 [Correspondence]

A standardized chart abstraction of 337 patients on antiretroviral therapy (ART) and structured interviews of five best private practitioners in Nairobi providing ART were undertaken to evaluate ART in the private sector. The percentage of patients on highly active antiretroviral therapy (HAART) increased annually from 43% in 1997 to 96% in 2000. Laboratory monitoring was available, however its use was limited because of high costs. Monitoring and evaluation of patients were not done consistently as per international recognized standards because of unaffordability. The probability of a patient remaining on ART at six months was 0.86 (95% confidence interval [CI] 0.81–0.90), at one year was 0.78 (95% CI 0.72–0.83), and at two years was 0.66 (95% CI 0.59–0.74).

Results of the study revealed that antiretroviral (ARV) drugs can be effectively prescribed in the private sector in Nairobi. Patients were able to stay on therapy for an extended period of time and had successful virological and immunological responses similar to those found in developed countries. Any constraints observed with regard to frequency of clinic visits and laboratory monitoring were due lack of patient's finances. The authors advocated the need for simpler and less expensive strategies and technologies for providing and monitoring of ART in resource-poor settings. With the increased demand for ARVs there will be a growing need to tap the potential of private practitioners in providing optimal ART in developing countries. Models of care that provide training and assistance to private practitioners are required as this will prove to be a valuable resource for public programmes within countries.

### **39. Antiretroviral treatment in developing countries: the peril of neglecting private providers**

Brugha R. *British Medical Journal* **2003**; 326: 1382–1384 [Education and Debate]

The main care providers for HIV disease in poor countries are the private physicians and traditional and informal providers. The authors discuss the importance of engaging the private sector in antiretroviral therapy (ART) programmes, citing results from four developing countries. In Zimbabwe in 2000, a quarter of the 68 private physicians and a quarter of the 80 drug pharmacies were prescribing and providing antiretrovirals (ARVs), even though insurance companies did not reimburse their use. “Therapeutic anarchy” was prevalent with prescribers and dispensers using any ARVs they could lay their hands on. Monotherapy drugs were stocked by 82% pharmacies and prescribed to 17% of patients; 92% of the patients believed that ARV drugs would cure them.

A survey of 21 Ugandan private medical clinics reported only four of the 17 facilities prescribing ARVs receiving CD4 cell counts and viral load results in the previous two months, i.e. for 38 of the 340 patients they were monitoring. Test costs per sample were very high (US\$ 150–US\$ 165). Providers had to change patients’ treatment because of differences in drug costs and stock-outs. Alternative sources of ARV drugs were mainly drug donations from relatives abroad and local pharmacies.

In India, of the 200 HIV-positive patients referred to specialist centres because of poor response to ART only 10% adhered to treatment, 50% stopped ART on the advice of traditional healers, and 80% were receiving incorrect doses.

In Senegal in 2002, nine ARV drugs made available through donations from northern countries were on sale in the informal private sector. Monotherapy, dual therapy and intermittent treatment was prevalent. Though patient demands were weak, the marketers in the informal market were trying to develop strategies to encourage the sale of drugs.

The fact that most patients in poor countries prefer and trust private providers (e.g. in India 60%–85% of primary care occurs in the informal private sector), because of confidentiality or easy access, it is important to consider the role of private providers in ART and regulate their behaviour. Rapid increase in distribution has resulted in ARV drugs leaking into the formal and informal private markets. Their uncontrolled use, such as unregulated prescribing and lack of suitable monitoring will lead to the development of resistance. The author suggested that in the regime of increased access to ARVs,

national policies need to account for the role and coverage of these private providers. The public sector needs to work with the private sector in setting up an efficient network and “Trusted private providers, like community health workers, may have greater potential for providing continuity of care and supporting treatment, partly by the economic incentive to retain client loyalty. They are an untapped potential for ensuring long term compliance”, which is an important determinant for the success of ART.

#### **40. Antiretroviral use in Ouagadougou, Burkina Faso**

Nguyen V-K, Grennan T, Peschard K, Tan D, Tiendrebeogo I. *AIDS* **2003**; 17 (suppl 3): S109–S111

This paper describes the role private and local community-based organizations in improving access to antiretroviral (ARV) drugs in Burkina Faso. One of the poorest countries in the world, Burkina Faso has the second highest rates of HIV prevalence in West Africa, estimated at 6.5% of the population.

As in other African countries, in Burkina Faso cost is a major barrier to increased access and adherence.

The authors described three methods for access to ARV drugs:

1. Drug donations through grant-in-aid for purchase of drugs managed by local organizations. However, very few donor agencies commit to grants for lifetime purchase of drugs.
2. Drug donations through the drug recycling programme wherein drugs from developed country donors, patient groups, etc. were sent to their correspondents in Burkina Faso for use by patients. These donations were either on individual-to-individual basis or through local organizations. Because the drug supply was limited, local organizations used informal criteria based on humanitarian grounds as the yardstick for distributing drugs to patients rather than the buying capability of the patient.
3. Purchase from CAMEG, a private company that procures, distributes and promotes essential generic medicines at cost.

Burkina Faso is a successful example of community-driven health-care advocacy and private–public synergies. The authors believe that if adequately financed, private–public synergies can help in increasing equity in countries like Burkina Faso.

#### **41. Community-based approaches to HIV treatment in resource-poor settings**

Farmer P, Leandre F, Mukherjee JS, et al. *Lancet* **2001**; 358: 404–409 [Viewpoint]

The authors report on how HIV treatment programmes can be successful in resource-poor settings. A pilot treatment programme conducted in a poor community in rural Haiti, one of the poorest countries in the western hemisphere, provided directly observed highly active antiretroviral therapy (HAART) to 60 patients free of cost. Since CD4 cell counts and viral load testing were not available in rural Haiti, treatment inclusion depended on simple clinical criteria such as:

- n Absence of active tuberculosis (Patients with active tuberculosis (46%) did not require HAART as they were symptom-free for long periods when put on anti-tuberculosis treatment alone.)
- n Repeated opportunistic infections not responding to antibacterials and antifungals
- n HIV-related wasting conditions such as chronic enteropathies
- n Unexplained or sudden weight loss
- n Severe neurologic complications related to HIV
- n Severe leukopaenia, anaemia or thrombocytopenia

The programme took advantage of the existing tuberculosis-control infrastructure to provide HAART by directly observed therapy to 60 patients. Each patient had a “accompagneur” (usually a community health worker) who observed ingestion of pills and offered moral support. Social support was also provided to patients, such as assistance with children’s school fees, monthly meetings to discuss concerns. This helped boost adherence and thus treatment outcomes. All patients responded very well to HAART with few and readily manageable side-effects.

The authors argued that HIV treatment should not be believed to be reserved only for the wealthy countries with poor countries having to depend solely on prevention. They suggested that directly observed therapy with multidrug regimens can be effective even in resource-poor areas with sustained commitment to provide uninterrupted free care to the patient. And that minor modifications in health infrastructure can improve local capacity to care for the sick with advanced HIV disease. For a successful HIV treatment programme the authors instituted a basic minimum package. This included post-exposure prophylaxis for rape and professional accidents; aggressive AIDS prevention programmes (including barrier methods); maternal–child transmission package (including milk supplements); social assistance to HIV-affected families, including orphans; diagnosis and treatment of opportunistic infections and sexually transmitted diseases; and HAART with directly observed therapy.

# Programmatic Monitoring, Evaluation and Operational Research

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## 42. Global situation of the HIV/AIDS pandemic, end 2003: Part I

World Health Organization. Weekly Epidemiological Record (no. 49) 2003; 78: 417–423

This World Health Organization (WHO) report summarized the magnitude of burden due to HIV/AIDS and the predominant modes of transmission across different regions in the world. The WHO and UNAIDS estimated 40 million adults and children in the world living with HIV/AIDS as of December 2003. An estimated 5 million people were infected in 2003, of whom 700 000 were children, age less than 15 years. HIV/AIDS is the fourth leading cause of death worldwide. During 2003, an estimated 3 million died of HIV/AIDS.

The worst hit is Sub-Saharan Africa among other African regions and accounted for 64% of those infected worldwide in 2003, 66% of people living with HIV/AIDS and 76% AIDS-related deaths. The total number of persons living with HIV/AIDS in Sub-Saharan Africa is 26.6 million.

Asia and the Pacific had an estimated 7.4 million adults and children living with HIV/AIDS in 2003. Though prevalence of HIV in the adult population is relatively low in most Asian countries, sex trade, use of illicit drugs and high-rates of sexually transmitted diseases are high-risk factors for this region.

Latin America and the Caribbean accounted for 2 million cases of HIV/AIDS cases. The epidemic is concentrated among men who have unprotected sex with other men and among injecting drug users.

In Eastern Europe and Central Asia, HIV infection increased and during 2003 there were an estimated 23 000 new infections with a total 1.5 million living with HIV/AIDS. Most infections occurred among injecting drug users.

In North Africa and the Middle East, an estimated 600 000 are living with HIV/AIDS. The biggest risk factor is injecting drug users.

The estimates of HIV/AIDS cases presented in the report provide useful inputs for planning comprehensive services for HIV/AIDS patients including setting up of targets for scaling up of antiretroviral therapy (ART) services. The report concluded that while HIV continues to spread in all regions of the world, there are positive signs that in both industrialized and developing countries people are living longer because of ART.

#### **43. Global situation of the HIV/AIDS pandemic, end 2003: Part II: Estimating ARV global treatment needs (2003–2005)**

World Health Organization. Weekly Epidemiological Record (no. 50) **2003**; 78: 426–430

This report presents data on existing coverage of AIDS patients on antiretroviral therapy (ART) and the strategies to increase access to ART. In 2003, the estimated number of people needing ART was approximately 6 million of whom 400 000 people received it. Coverage is lowest in Africa with a mere 2% having access to ART. To decrease the gap in access to ART, the World Health Organization (WHO) declared lack of access as a global health emergency in September 2003. Along with its partners, WHO launched the 3 by 5 initiative with the aim to provide ART to 3 million by 2005.

The report discussed that the WHO's 3 by 5 Initiative (3 million people on ART by 2005) is a critical, but achievable target and is the first step to the goal of providing ART to all those who require it. The report reiterates that prevention will remain central to HIV interventions, and that universal access to ART will help accelerate prevention in communities who know their HIV status. The guiding principles for the 3 by 5 Initiative are summarized in the report. These include:

- n Urgency in resource mobilization and redeployment and streamlining institutional procedures
- n Keeping the needs and involvement of people with HIV/AIDS central to the programme
- n Ensuring lifelong care for those put on ART
- n Ensuring country ownership of the programme and activities

- n Promoting human rights codified in the Universal Declaration of Human Rights
- n Strengthening partnerships and networks
- n Integrating planning and funding with existing programmes
- n Learning, innovation and sharing for effective scaling up across regions and countries
- n Ensuring ethical approaches to meeting 3 by 5 targets
- n Providing equitable access to ART
- n Developing national accountability among policy makers, providers, people receiving care, and all stakeholders.

#### **44. Once-a-day highly active antiretroviral therapy in treatment-naïve HIV-1-infected adults in Senegal**

Landman R, Schiemann R, Thiam S, et al. *AIDS* **2003**; 17: 1017–1022

This study examined adherence to antiretrovirals (ARVs) among patients treated with a once-a-day regimen. Forty HIV-1 infected patients with no previous antiretroviral therapy (ART) were included in a prospective, open-label one-arm trial. They received three ARV drugs – didanosine, lamivudine, efavirenz – to be taken once a day at bedtime. Patients were examined at screening, on the day of inclusion, at two and four weeks and every month for 15 months. Adherence was assessed by patient questionnaires, plasma drugs concentrations, and immunological and virological efficacy. At each assessment, 95% of patients said they had taken all their tablets in the previous three days. Effective plasma drug concentrations at month six was seen in 83% patients for efavirenz, in 85% for lamivudine, and in 93% patients for didanosine. The CD4 count which was 164 cells/mm<sup>3</sup> at baseline showed a mean increase of 199 cells/mm<sup>3</sup> at month 15. The percentage of patients with plasma HIV-1 RNA below 500 copies/ml at six months was 95% and below 50 copies/ml at 15 months was 69%. No permanent treatment discontinuations occurred because of severe adverse effects; there were no unexpected adverse events.

The virological and immunological efficiency of the regimen was almost as good as those reported from developed countries. The results also compared well with similar triple-drug regimen clinical trials. The efficacy of ART depends on long-term adherence and one psychological factor may be less number of tablets and easy-to-take treatments

adapted to the patient's daily activities. The once-daily regimen used in this study was effective, safe, and easy-to-take for African patients with advanced HIV infection.

#### **45. Brazilian network for HIV Drug Resistance Surveillance (HIV-BresNet): a survey of chronically infected individuals**

Brindeiro RM, Diaz RS, Sabino EC, et al. *AIDS* **2003**; 17: 1063–1069

The authors studied the prevalence of HIV drug resistance mutations and subtype distribution in 535 Brazilian drug-naïve asymptomatic HIV-positive persons from 13 voluntary testing and counselling centres in eight states in 2001. Plasma viral RNA was extracted and sequenced for analysing drug-resistant mutations. Results showed a low prevalence of drug-resistant strains circulating among the diagnosed individuals – 2.36% to nucleoside reverse transcriptase inhibitor, 2.06% to non-nucleoside reverse transcriptase inhibitor and 2.24% to protease inhibitor. The authors concluded that routine genotype testing in drug-naïve populations before initiating highly active antiretroviral therapy (HAART) is not indicated. However, routine epidemiological monitoring of the prevalence of primary resistance must be implemented in countries with widespread availability of HAART.

#### **46. Antiretroviral treatment in resource-poor settings: clinical research priorities**

Rabkin M, El-Sadr W, Katzenstein DA, et al. *Lancet* **2002**; 360: 1503–1505  
[Viewpoint]

This report of a Rockefeller Foundation working group attempted to identify gaps in knowledge and prioritize issues affecting access to treatment for those living with HIV/AIDS in resource-poor settings. The authors listed research priorities along the following four broad areas.

- 1. When to start treatment?** Research questions should include clinical advantages of starting treatment at CD4 count above 200 cells/mm<sup>3</sup>; cheaper and simpler methods for testing viral burden and immune function; laboratory markers other than CD4 cell count and viral load useful in decisions regarding start of treatment; and clinical criteria for start of treatment in the absence of laboratory data.
- 2. How to monitor antiretroviral treatment?** Research questions should include appropriateness of less frequent monitoring than every 3–4 months

suggested by the US guidelines; the minimum laboratory monitoring needed to ensure effectiveness and safety of drug regimens; less expensive methods for measuring immune function and viral load; and whether an algorithm using only clinical variables of weight gain, quality of life, decreased frequency and severity of complications is adequate to assess treatment success or failure.

3. **How to select antiretroviral drugs?** Research questions should include safety and effectiveness of antiretroviral therapy (ART) being prescribed by non-physicians in resource-poor settings using structured clinical algorithms and standard regimens; the most appropriate first-line regimens; definition of treatment failure; when to stop or change ART and whether this decision should be based on clinical, virological, or immunological indices; and the effectiveness and safety of structured treatment interruptions, pulse therapy, or treat-to-safety.
4. **How to improve adherence to ART?** Research questions on adherence to ART should include main determinants and correlates for adherence; predictable barriers to adherence and whether they can be modified; whether fear of disclosure and stigma, or both, are barriers to adherence; effect of traditional healers and parallel health care systems on adherence; and if standard or region-specific adherence interventions are effective.

The report recommended that the need for answers should not delay providing HIV care to those who urgently need it in resource-poor settings. And, that research should be integrated into treatment programmes to facilitate wide use of life-saving ART.



**World Health Organization**

**Regional Office for South-East Asia**

**New Delhi**