



Preliminary Report

Uganda Ministry of Health - UNAIDS HIV/AIDS Drug Access Initiative

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Collaborating Institutions:

- **Uganda Ministry of Health**
- **National Advisory Board, HIV/AIDS Drug Access Initiative**
- **Joint Clinical Research Centre**
- **Mengo Hospital**
- **Mildmay Palliative Care Centre**
- **Mulago Hospital**
- **Nsambya Hospital**
- **Medical Access, Ltd.**
- **UNAIDS - Uganda**
- **CDC/Uganda Virus Research Institute Collaboration - Uganda**
- **UNAIDS - Geneva**
- **Centers for Disease Control and Prevention (CDC), U.S.A.**
- **Health Access International**
- **Virco NV, Belgium**
- **Virco, U.K.**

Introduction

With a population of 21 million persons, Uganda has an estimated 1.5 million persons living with HIV/AIDS. The UNAIDS/Ministry of Health HIV/AIDS Drug Access Initiative (DAI) was launched as a pilot project in Uganda in November 1997 and became operational in June 1998. The goal of the initiative was to improve the quality of life of persons living with HIV/AIDS by increasing access to HIV/AIDS drugs.

The purpose of the initiative was to create the proper environment and induce relevant changes in the health care delivery system to improve HIV/AIDS care by:

1. Developing a distribution system to ensure an adequate supply of drugs
2. Implementing mechanisms for improved access to HIV/AIDS drugs without disruption of existing essential drug programs
3. Providing appropriate information and training to health workers and communities and foster the establishment and improvement of an adequate medical information system
4. Ultimately making HIV/AIDS drugs more available in Uganda

To meet these goals, activities of the Initiative have focused on strengthening of infrastructure and capacity-building.

Institutional Framework

The government of Uganda and UNAIDS signed a mutual agreement for implementation of the initiative. In accordance with the terms of agreement, an advisory board, a project coordinator, and a communications consultant were appointed under the Ministry of Health. The government also facilitated the establishment of a nonprofit company, Medical Access Ltd., to promote mechanisms through which drugs could be purchased at a discounted price and distributed to participating treatment centers in the country.

The National Advisory Board

A multidisciplinary advisory board, which was developed in June 1998, now consists of 22 members and has met monthly since its inception. The board reports to the Ministry of Health, with representatives of the Ministry present at every meeting. Also on the board are representatives from the Ministry of Finance and Economic Planning, the Ministry of Gender, Labor, and Social Welfare, and a number of prominent Ugandan HIV/AIDS clinicians and researchers, NGO representatives, and a representative of persons living with HIV/AIDS. The Chairman of the UNAIDS Theme Group, the UNAIDS-funded in-country coordinator of the Initiative, the head of the non-profit company, and the communications consultant serve as ex-officio members. Three subcommittees of the Advisory Board have been formed: Drug Policy and Financing, Care and Practice, and Vertical Transmission.

Among its various activities, the board has served to:

- Recommend to the government HIV-related drug policy on clinical management of HIV/AIDS,
- Develop estimates of the country's needs for HIV/AIDS drugs,
- Recommend to the government a policy on prescription, distribution, and use of HIV/AIDS drugs,
- Recommend minimum requirements for health care centers to be qualified for selection of centers where prescription and use of HIV/AIDS drugs could be assured,
- Recommend objective criteria of patients who may participate in the Initiative,

- Recommend an action plan for the improvement of the health care infrastructure over time in order to make HIV/AIDS drugs more widely accessible,
- Recommend regulations concerning privately-funded purchases and the proper use of HIV-related drugs in Uganda.

Drug Supply, Procurement, and Distribution

A nonprofit company, Medical Access (Uganda) Ltd., is responsible for the procurement of drugs from the participating companies at reduced costs and sale of the products to the accredited centers. With one full-time manager, a pharmacist (who sits on the advisory board) and a part-time administrative assistant, the company receives orders and pays the drug companies on a long-term credit basis. In addition, the company monitors accountability and internal control mechanisms of the Initiative. The manager of Medical Access is in direct contact with treatment centers and participating physicians and has helped with needs estimates and stock management. This has improved the dialogue between the parties and the accuracy of the purchase orders. Four international drug companies are actively involved in the Initiative and are responsible for the operational costs of Medical Access: Glaxo-Wellcome, Bristol Myers Squibb, Roche Products Ltd., and Merck Sharpe and Dhorne. Drug costs include a 6% mark-up to help cover operational costs of Medical Access and the participating centers. Other companies involved with diagnostics have made contributions to the Initiative, including Beckton Dickinson, VIRCO, and TIBOTEC Ltd. (a sister company to VIRCO).

Participating Centers

Standardized criteria for selection of treatment centers were developed and include:

1. Availability of clinical expertise in the management of HIV/AIDS, including appropriate management of opportunistic infections,
2. Adequate laboratory facilities for basic and sophisticated AIDS tests,
3. Adequate psychosocial support and counseling,
4. Good facilities for drug storage, stock management, and accountability.

Assessment of sites was conducted and pilot sites were selected to participate in the Initiative. There are currently five participating treatment centers that prescribe antiretroviral therapy in Uganda -- Nsambya Hospital, Mildmay Palliative Care Center, Mulago Hospital, Joint Clinical Research Center (JCRC), and Mengo Hospital.

Medical Information System

A standardized medical record form has been implemented at multiple sites participating in the Drug Access Initiative for monitoring patients on antiretroviral therapy in Uganda. This system serves as the cornerstone for the evaluation of the UNAIDS DAI in Uganda. Four participating centers have incorporated the standard data collection materials developed by the DAI as part of their antiretroviral patient medical records. An alternative form for patient chart abstraction at one center and corresponding data-entry screen formats were developed to retrospectively abstract information for the DAI database. Technical assistance and support for implementation of the medical information system, data management, and analysis were provided by the U.S. Centers for Disease Control.

Program Evaluation

UNAIDS has prepared a protocol for the evaluation of the Initiative, which includes seven components:

- Economic and pharmaco-economic
- Social and behavioral
- Logistical
- Selection of patients
- The subsidy mechanism
- Clinical, virologic, and immunologic response
- Epidemiologic (adherence and resistance)

This preliminary report, prepared in collaboration with the Uganda Ministry of Health, UNAIDS-Uganda, and the U.S. Centers for Disease Control, will focus primarily on the last two components of the evaluation, that is, the clinical response to treatment and evaluation of drug resistance. In Uganda, patients meet the cost of purchasing antiretroviral medications, visits to the physician, and laboratory testing. For the period of the evaluation of the pilot phase, however, support for viral load and CD4 has been provided by the U.S. Centers for Disease Control and Prevention (CDC). This report will focus on the evaluation of patients accessing antiretroviral therapy during the first 18 months of this pilot Initiative.

Patient population:

Since August of 1998, 905 patients have accessed antiretroviral therapy at the five accredited centers: Nsambya - 233, Joint Clinical Research Center (JCRC) – 543*, Mildmay – 99, Mulago – 18 and Mengo – 12. Of note, JCRC has provided antiretroviral therapy since 1996. Since that time, it is estimated that a total of 934 patients accessed ARV therapy through JCRC, 543 of whom started care after August 1998 when the DAI project started. For this evaluation, JCRC elected to use an alternative data collection system and data extraction is still ongoing. Therefore, for the purpose of this report, the bulk of the data presented will primarily focus on patients from Nysambya, Mildmay, and Mulago.

Median age of patients was 37 years (range 2 – 76). Of interest, 49% of patients were women and 5% were children under 13 years of age.

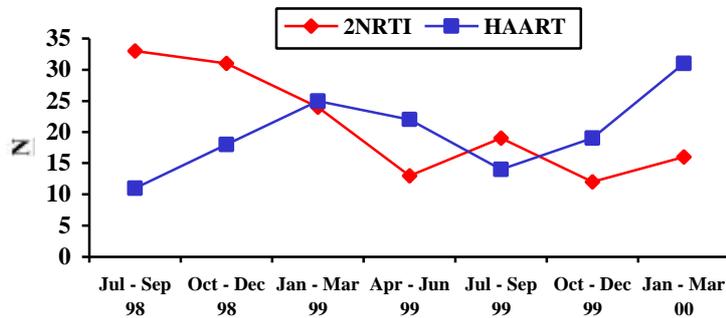
Patients presented at an advanced stage of illness

Of the 207 patients with WHO clinical stage recorded, 40% presented with WHO stage 3 and 34% with Stage 4. Among the 212 patients with a baseline CD4 and viral load measured, median CD4 cell count was 67 cells/mm³ and 80% had CD4+ < 200 cells/mm³. Median viral load was 182,422 copies/ml (interquartile range = 53,384 – 599,401). Nearly two-thirds of the patients had a viral load > 100,000 copies/ml.

Regimens used

In this report, highly active antiretroviral therapy (HAART) will refer to regimens that included 2 nucleoside reverse transcriptase inhibitors (2NRTI) plus either a nonnucleoside RT or a protease inhibitor. The term 2NRTI was used to describe regimens designed to suppress viral load suppression, though not maximally; these regimens included 2NRTI with or without hydroxyurea. Data from Nsambya, Mildmay, and Mulago indicate that 48% of patients were started on HAART as their initial regimen and 52% were started on 2NRTI. More recently, there has been a trend toward increased use of HAART for initial therapy.

**Initial Antiretroviral Therapy by Quarter
at 3 centers - Nsambya, Mildmay, Mulago**



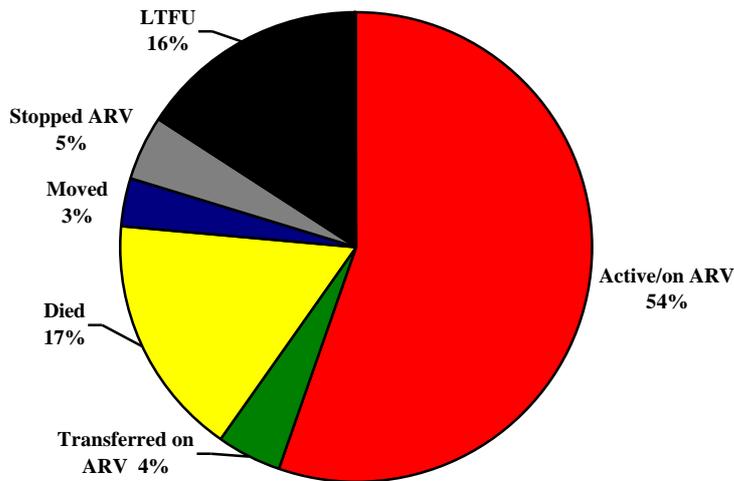
Changes in therapeutic regimens

Changes in antiretroviral therapy were assessed for the 907 follow-up visits recorded in the database from Nsambya, Mildmay, and Mulago. Information was available to assess the need to change antiretroviral therapy for 662 follow-up visits; change in antiretroviral therapy occurred on 15% of these visits. Reasons for changing therapy included toxicity (28%), virologic failure (24%), the patient being unable to afford their current regimen (13%), clinical disease progression (13%), immunologic failure (9%), the patient able to afford better therapy (6%), and other (8%).

Outcome of patients accessing antiretroviral therapy

Information was available for 350 persons who had accessed antiretrovirals through the UNAIDS Initiative at three centers, Nsambya, Mildmay, and Mulago, as of March 31, 2000. Patient status was determined from clinical records and staff at each site and classified as: (1) active/on ARV, (2) known to have died, (3) stopped ARV, (4) transferred care outside DAI/still on ARV, (5) moved from the region, and (6) lost to follow-up (LTFU). Among all patients who accessed ARV therapy since the beginning of the initiative, approximately 58% were alive and in treatment at the time of this evaluation.

Patient Status 31-Mar-2000 (n=350)

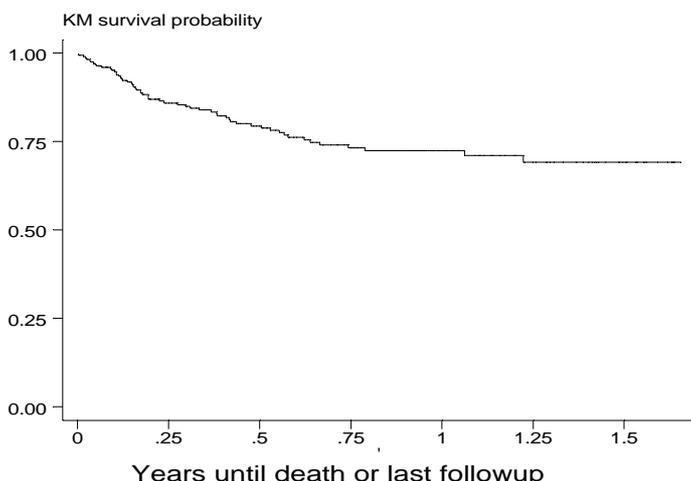


Survival and remaining in care

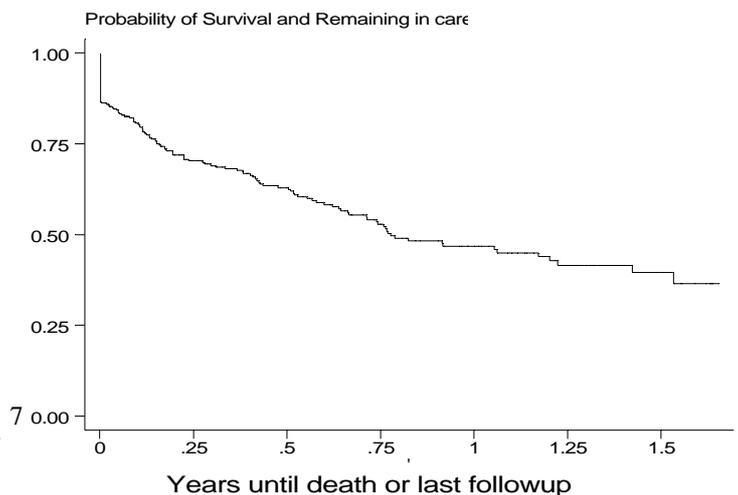
This preliminary analysis of survival included 58 patients who were known to have died as outcome events by 31st March, 2000. This is undoubtedly an underestimate of mortality because home visits were not included in this evaluation and death records are not maintained in Uganda. Patients who stopped ARVs, moved, transferred care, or were lost to follow-up were considered alive up to the last medical visit.

In this analysis, the probability of survival was 79% at six months and 72% at one year. An analysis was also performed that combined patients who died, stopped treatment, moved away, or were lost to follow-up as outcome events. **The probability of surviving and remaining in care was 63% at six months and 48% at one year.** Remaining in care included patients who remained in the Initiative or were transferred on ARVs. Loss to follow-up was similar among patients receiving HAART and 2NRTI regimens. Kaplan-Meier analyses are shown below. Analysis of events occurring after 12 months of follow-up should be interpreted with caution as the number of patients with follow-up for a year or more is very limited at this point.

Overall Survival
(Includes only known deaths as events)



Survival and Remaining in Care
(includes known deaths and lost to follow-up as events)



Rate of death and loss to follow-up were both high early in the course of treatment. The high early death rate is consistent with the fact that most patients accessed antiretroviral therapy at an advanced stage of disease. Seventy-one percent of patients who were lost to follow-up did not return after their initial visit. Some of these patients never initiated therapy and some filled only their first prescription.

Cause of death

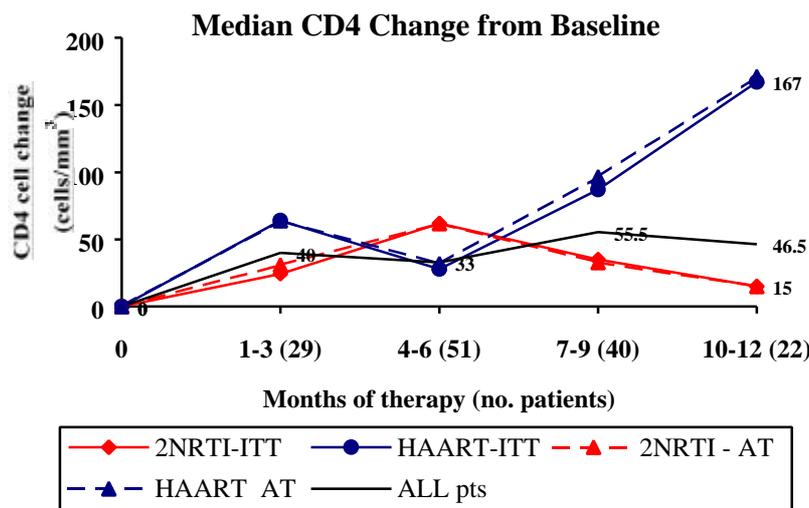
Fifty-eight patients in the initiative were reported to have died, 50 of whom died from AIDS-related causes. Reported cause of death in these 50 patients was similar to that found among AIDS patients in other African settings: severe bacterial infections (24%), cryptococcosis (24%), tuberculosis (15%), *Pneumocystis carinii* pneumonia (7%), Toxoplasmosis (7%), chronic diarrhea (7%), one patient (3%) each with HIV wasting syndrome, HIV encephalopathy, and Kaposi’s sarcoma, and 3 (7%) other/undetermined.

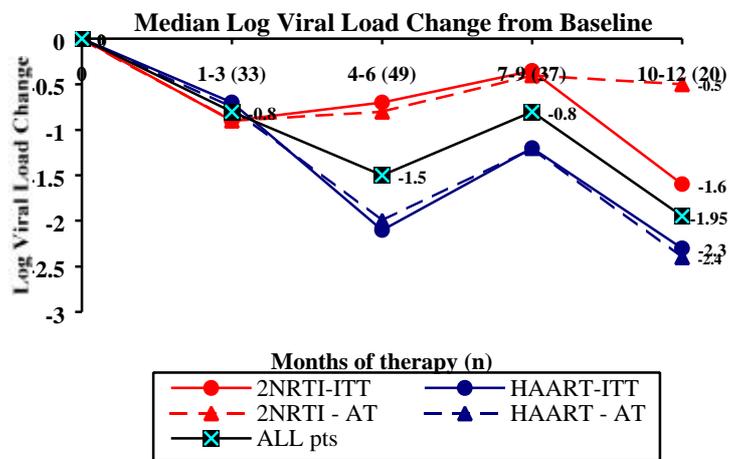
Virologic and immunologic response

An analysis of virologic and immunologic response was performed on the 95 persons who had at least one viral load result while on therapy. Initial ARV therapy was 2NRTI for 50 (53%) and HAART for 45 (47%). Sixteen (32%) of 50 patients started on 2NRTI switched to HAART (median time to switch = 107 days) and 4 (9%) of 45 patients started on HAART switched to 2NRTI (median time to switch = 42.5 days). The graph below indicates response according to the patient’s initial therapeutic regimen or actual treatment received.

“ITT” = intent to treat analysis - patients were coded as 2NRTI or HAART according to the initial regimen, regardless of subsequent changes

“AT” = As Treated – patients were coded according to actual treatment received; patients thus changed category when therapeutic regimens are changed





There are some limitations to this analysis. First, the number of patients with baseline values and an extended follow-up period is limited. The data reflect trends without statistical significance. Second, a survivor effect may occur when the sickest patients may die or stop therapy and the observed data preferentially represent patients who are doing relatively better. Third, an observational analysis such as this tends to observe those patients who return more regularly for care and thus are more likely to have laboratory testing done.

Nonetheless, this evaluation indicates that patients who initially received HAART, or who were switched to HAART regimens, demonstrated continued rise in median CD4 and fall in viral load throughout the follow-up period, suggesting that HAART therapy was successfully implemented in this resource-restricted setting. Among patients on 2NRTI regimens, median CD4 and viral load approached baseline within one year of treatment. The response to 2NRTI was substantially better than what would be expected with no therapy, but the durability of 2NRTI regimens, even in this drug-naïve population, is limited. In this setting, selection of regimens is often constrained by the patient's ability to afford maximally suppressive therapy. As ARV programs expand in Uganda and other countries, selection of drug regimens will need to weigh the costs and benefits to the patient, their families, and the community. The high cost of protease inhibitors and nonnucleoside RTIs continues to limit access to maximally suppressive therapy.

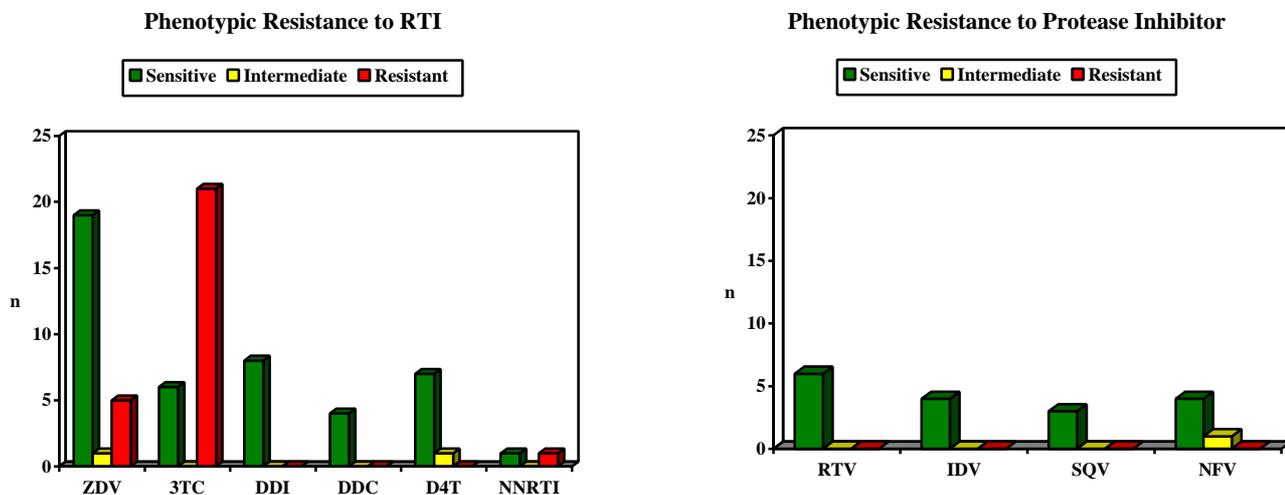
Resistance to antiretroviral drugs

HIV-1 genotypic (VircoGEN) and phenotypic (Antivirogram) resistance testing were performed on specimens from patients who were receiving antiretroviral therapy for ≥ 90 days and had a corresponding viral load of $\geq 1,000$ copies/ml.

Forty-four specimens from 30 patients were selected for analysis; 14 (47%) were on 2NRTI and 16 (53%) were on HAART. Phenotypic resistance testing was completed on 30 specimens and genotypic testing on 37. Phenotypic resistance was found to lamivudine (3TC) for 21 (78%) of 27 specimens from patients on 3TC and was associated with mutations of M184V for 14, M184V/M for 4, M184I for 1 and unknown for 2. Phenotypic resistance was found to zidovudine (ZDV) for 5 (20%) of 25 specimens from patients on ZDV and was

associated with T215Y for 4 and T215F for 1. Other ZDV mutations included M41L, K70R, L210W, and K219E. Coexistent ZDV and 3TC phenotypic resistance was observed in 4 of the above patients and was associated with a G333E mutation for 1. Phenotypic resistance to a nonnucleoside RTI was found in 1 of 2 patients and was associated with a K103N/K. Among 13 specimens from patients on protease inhibitors, only one patient exhibited intermediate phenotypic resistance to nelfinavir. Interestingly, this was associated with an M46I mutation, a mutation usually associated with resistance to indinavir, not nelfinavir.

Phenotypic resistance to 3TC was common when used in 2NRTI therapy or HAART regimens. The predominance of 3TC resistance may be expected as a single genetic mutation confers resistance to 3TC. Similar genotypic mutations for 3TC and ZDV commonly observed in subtype B infections were observed among patients in Uganda, where subtypes A and D predominate.



Summary of resistance findings

Resistance to antiretrovirals is an inevitable consequence to some degree when antiretrovirals are given to patients. As such, the presence of resistance alone is not to be interpreted as a short-coming of the DAI or of providing antiretrovirals to patients in a resource-poor setting. The data presented here cannot be interpreted as the prevalence of resistance within the DAI since only specimens with a viral load > 1000 copies/ml could be tested; an additional 42 patients had viral load < 1000 copies/ml.

These preliminary findings suggest that markers for resistance among non-B subtypes in Uganda are similar to those found in the U.S. and Europe, and methods used for monitoring resistance in the U.S. and Europe can be used in east Africa. The relatively high number of specimens with 3TC resistance serves to underscore the known risks of using 3TC outside of maximally suppressive regimens. It will be important to continue monitoring for emergence and expansion of resistance as this initiative continues and as more patients are followed over time.

The Cost of Antiretroviral Therapy

The current costs of commonly used drug combinations are summarized below. To better represent drug costs in the context of the Ugandan economy, roughly estimated monthly salaries of some government positions and the monthly per capita GNP have been included.

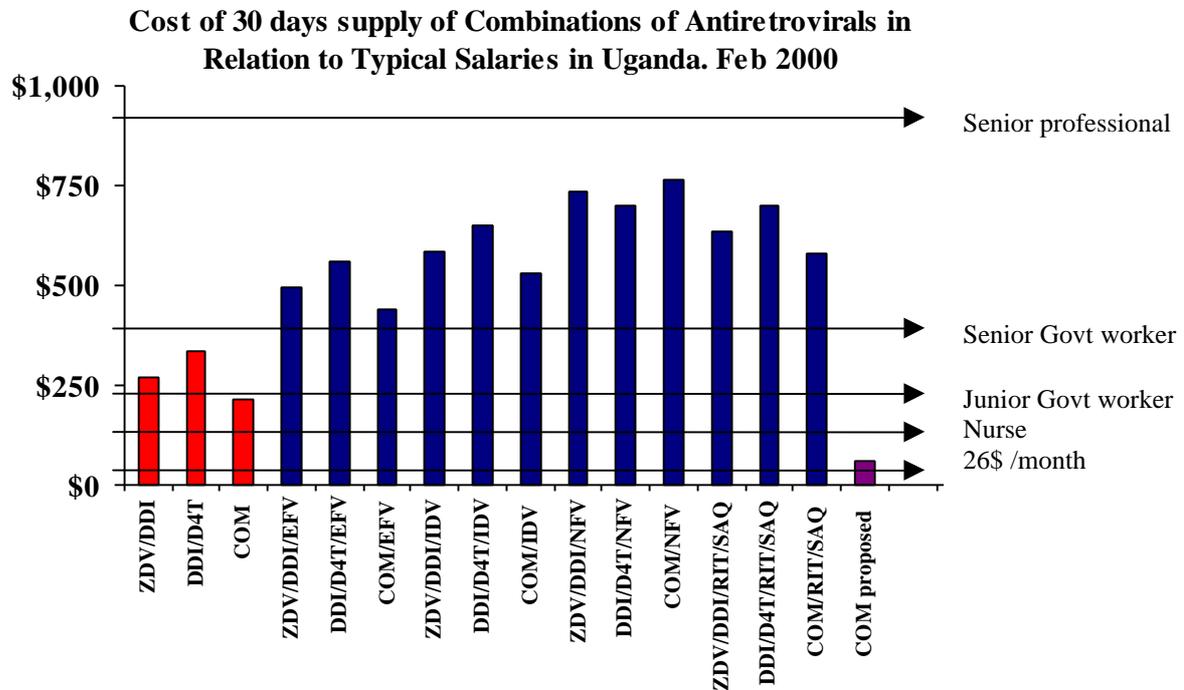
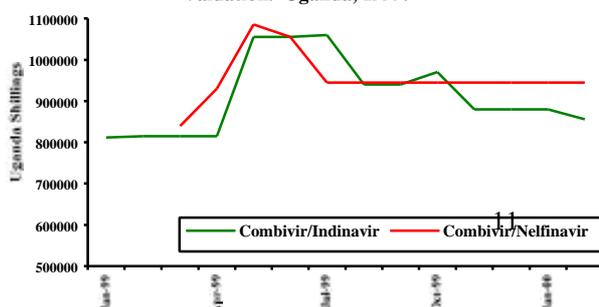


Figure Legend: ZDV = zidovudine (Retrovir), DDI = didanosine (Videx), Com = Zidovudine/Lamivudine (Combivir), D4T = stavudine (Zerit), EFV = efavirenz (Stocrin), IDV = indinavir (Crixivan), NFV = nelfinavir (Viracept), RIT = ritonavir (Norvir), SAQ = saquinavir (Invirase).

Fluctuations in the costs of drugs to the patient

Since the beginning of the initiative, the costs of drugs have changed because 1) new drug products became available, 2) purchase prices from the pharmaceutical manufacturers changed, and 3) the value of the Uganda shilling changed in reference to the major foreign currencies. Six of the first seven price changes occurred due to a currency devaluation, followed by a rise in currency valuation. The rapid currency devaluation resulted in an estimated 20% increase in drug costs to the patient. During this time, some patients were reported to have had treatment interruptions due to their inability to meet the sudden increase in cost in local currency. Changes in drug prices in local currency are summarized below:

Figure 3. Antiretroviral Costs in Response to Currency Valuation. Uganda, 1999.



On an individual patient level, these currency fluctuations may have dramatic short-term or long-term effects on the affordability of drugs and, thus, sustainability of therapy. Regardless, there are many other factors that influence the affordability of drugs by an individual not examined here, including inconsistent income and competing household expenses. The approximate mark-up of 6% at Medical Access Ltd. and the treatment centers is small in comparison to the potential for cost fluctuations due to currency devaluation.

In May 2000, five pharmaceutical firms announced that they will further decrease the prices of antiretroviral drugs. The price of one drug product, Combivir, has been announced to be approximately \$60 for a 30-day supply. This is 28% of the price that was available in Uganda during early 2000. It is expected that these lower prices will enable more patients to access antiretroviral drugs in Uganda. However, these costs need to be considered in the context of typical incomes of Ugandans, where average per capita Gross National Product (GNP) is approximately \$26 per month, making antiretroviral therapy out of reach for the vast majority of persons living with HIV/AIDS in Uganda. It is also important to note that the cost of drugs is only a small component of the health care costs that must be met by the patient. Costs of CD4+ and viral load monitoring, medical visits, and diagnosis, prophylaxis, and treatment of AIDS-related illnesses must also be considered. Costs for training, expansion of laboratory capacity, and other infrastructure needs are additional costs that must also be addressed.

Summary

Initiation of therapy

- A total of 905 patients have accessed the UNAID drug access initiative
- Approximately equal numbers of men and women have begun ARV therapy
- Patients presented at an advanced stage of disease; 80% had CD4+ < 200 cells/mm³
- Approximately half of patients were started on 2NRTI and half on HAART; more recently, there has been an increase in the proportion of patients started on HAART

Response to therapy

- Among all patients started on ARVs to date, 58% are alive and remain in care.
- Kaplan-Meier analysis revealed that the probability of surviving and remaining in care was 48% at one year.
- Patients on both 2NRTI and HAART had virologic and immunologic response to therapy, indicating that antiretroviral therapy programs could be successfully implemented in this developing country setting.
- Patients were often started on 2NRTI due to financial constraints. Although those on 2NRTI demonstrated virologic and immunologic improvement, those on HAART had a greater and more sustained response to therapy.
- Resistance to 3TC was common. Markers for antiretroviral drug resistance in Uganda were found to be similar to those of subtype B viruses in the U.S. and Europe, suggesting that similar methods for monitoring resistance can be used in Uganda.

Lessons learned and future directions

The early successes of the UNAIDS Drug Access Initiative pilot programs have come through an important human and financial investment and national commitment. Training and capacity-building have proved to be important components in a program aimed at expanding access to antiretroviral therapy in Uganda. Access to antiretroviral therapy, however, remains extremely limited, primarily due to the high cost and technical sophistication required for medications and monitoring. To date, nearly 1,000 AIDS patients have started ARV therapy out of an estimated 1.5 million persons living with HIV/AIDS in Uganda. Efforts to expand access to antiretroviral therapies must weigh the benefits and costs to the health sector. Even if patients meet the costs of their medical care, costs of training, development and implementation of treatment guidelines, and expanded access to laboratory diagnostics require substantial investment. Although newly-reduced drug costs have been announced, scaling up of antiretroviral treatment programs will be limited by the rudimentary laboratory infrastructure in the periphery and the median \$300 annual per capita income. In this context, the importance of HIV prevention must remain the cornerstone of programs to prevent AIDS-related morbidity and mortality in Uganda.

That being said, the benefits to patients accessing this initiative are already evident. Although adherence has not yet been evaluated, changes in viral load and CD4 suggest that patients are taking their medications and responding to treatment. In this regard, this pilot program has demonstrated that AIDS patients can be managed successfully with antiretroviral therapy in a developing country setting. Promoting access to therapy earlier in the course of the patients' disease would be expected to further improve patient outcome in this initiative.

To date, approximately half of patients started on antiretrovirals were started on 2NRTIs. The drug costs to the patient are lower, and clearly patients on 2NRTI fared better than what would be expected without therapy. Dual NRTI therapy still bears a substantial cost to the patient in this setting and is associated with a less durable benefit compared to HAART; average CD4 counts and viral load of patients on 2NRTI approached baseline values by one year after initiation of therapy. Extending survival for a matter of months might drain family resources needed for living expenses and education of surviving family members. More information is needed to assess the social and economic impact of this program on patients and their families. Lowering costs of protease inhibitors and nonnucleoside RTIs in this environment would have an important impact on the number of patients who can access HAART and the outcome of patients who are started on antiretroviral therapy.

Resistance to 3TC is conferred by a single drug mutation; emergence of 3TC resistance would be expected to occur, particularly when 3TC is not used as part of a maximally suppressive regimen. With recently reported reductions in the cost of AZT/3TC combination therapy, it is possible that more patients might access this regimen without the ability to afford HAART. It will be important to continue to evaluate clinical practices, patient response, and emergence of resistance as this initiative continues and as new programs develop.

This initiative to date has focused primarily on access to antiretroviral drugs. The initiative has also served to increase awareness of AIDS care and to the fact that patient management, record keeping, laboratory monitoring, and capacity building for the early diagnosis and management of opportunistic infections are all critical to the appropriate care and support of AIDS patients. The medical information system has proved to be an important tool for program evaluation and identification of ways to improve patient care within Initiative. To date, CD4 and viral load monitoring have been supported by outside agencies; the impact of moving this financial burden to the patient is unknown. More work is needed to define if alternative, less expensive monitoring strategies can be developed and implemented in resource-restricted countries. Promotion of AIDS care, and not just AIDS drugs, has been an important component to the success and evolution of this pilot program.

Programs are now underway to expand access to prophylaxis, diagnosis, and treatment of opportunistic illnesses in Uganda. This will benefit both patients who are on antiretroviral therapy and those who are unable to afford or otherwise access antiretrovirals. In addition to clinical training activities, these initiatives will need to address issues of drug procurement and distribution, stock management, and quality control of drugs used for the prophylaxis and treatment of opportunistic illnesses. In these ways, improved AIDS care can be expanded to reach more of those in need.