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# Monitoring the response to antiretroviral therapy in resource-poor settings: the Malawi model

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**Summary** With assistance from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Malawi is scaling-up the delivery of antiretroviral (ARV) therapy to HIV-positive eligible patients. The country has developed National ARV Treatment Guidelines, which emphasize a structured and standardized approach for all aspects of ARV delivery, including monitoring and evaluation. Using the successful DOTS model adapted by National TB Control Programmes throughout the world, Malawi has developed a system of quarterly ARV cohort and cumulative ARV quarterly analyses. Thyolo district, in the southern region of Malawi, has been using this system since April 2003. This paper describes the standardized ARV treatment regimens and the treatment outcomes used in Thyolo to assess the impact of treatment, the registration and monitoring systems and how the cohort analyses are carried out. Data are presented for case registration and treatment outcome for the first quarterly cohort (April to June) and the combined cohorts (April to June and July to September). Such quarterly analyses may be useful for districts and Ministries of Health in assessing ARV delivery, although the burden of work involved in calculating the numbers may become large once ARV delivery systems have been established for several years.


## 1. Introduction

If disease control programmes are to serve their patients' and their communities' best interests, they

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need a system of regularly monitoring the number of cases identified and the effects of their prevention and treatment strategies. DOTS Tuberculosis Control Programmes provide one of the best examples of how to monitor case burden and treatment outcome by using indicators which are standardized and replicable at district, national and global level (Enarson et al., 2000; WHO, 2003a). There are standardized definitions for the registration of TB cases (for example, type of TB according to pulmonary or extrapulmonary disease and sputum smear status, and category of TB according to new or previously treated disease) and treatment outcome (for example, treatment success, death, default, transfer-out and fail). The case burden and treatment outcomes are monitored at district level using TB registers and treatment cards, and the results reported four times a year. The district quarterly reports on case finding and treatment outcome are compiled regionally and nationally, and used for annual reports on case finding and treatment in all countries of the world which have a DOTS TB programme. The data of national reports are transferred to standardized reporting forms and sent on to the STOP TB Programme of the WHO for their global reports (WHO, 2003b).

Case finding reports enable information on trends in disease to be obtained; this is useful for planning staff needs, resources for diagnosis, drug supplies, stationery, etc. Reports on results of treatment are a key management tool that are used to evaluate the effectiveness of TB control programme delivery. The quarterly reports allow regular assessment of the situation on the ground and enable interventions to be put in place in the event of a deteriorating programme performance.

With assistance from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Malawi is in the process of initiating highly active antiretroviral therapy (HAART) in a number of districts in the country. In order to realize the full benefits to the individual and to minimize drug resistance, the country has adopted a 'public health approach' for the administration and provision of HAART. National Antiretroviral Treatment Guidelines have been produced (Ministry of Health, Malawi, 2003). Adult patients, for example, are eligible for HAART if they are known to be HIV-seropositive, understand the implications of therapy, and are assessed as being in WHO clinical stages III or IV, or have a CD4-lymphocyte count less than 200/mm$^3$. Antiretroviral (ARV) treatment regimens are shown in Table 1. Systems are being worked out to ensure regular procurement and distribution of drugs, good patient management, and monitoring and evaluation. The tools for monitoring and evaluation have been piloted in Thyolo District, in the southern region of Malawi. This paper describes how these tools have been used and the results of patient assessments in the first six months of delivering ARV therapy.

**Table 1** Antiretroviral treatment regimens in Malawi

| |
|---|
| First-line regimen: |
| Stavudine (d4T) + Lamivudine (3TC) + Nevirapine (NVP) |
| Alternative first-line regimen substitutions in case of drug reactions: |
| Severe peripheral neuropathy due to stavudine component |
| Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (NVP) |
| Liver disease such as hepatitis due to nevirapine component |
| Stavudine (d4T) + Lamivudine (3TC) + Efavirenz (EFV) |
| Severe skin reactions due to nevirapine component |
| Stavudine (d4T) + Lamivudine (3TC) + Efavirenz (EFV) |
| Second-line regimen switch in case of failure of first-line regimen: |
| Zidovudine (AZT) + Didanosine (ddI) + Nelfinavir (NFV) |

## 2. Patients and methods

### 2.1. Background

Malawi, a small and impoverished country in central-southern Africa, is experiencing a severe HIV/AIDS epidemic. It has an estimated 900 000 adults and children living with HIV/AIDS (National AIDS Commission, 2003), with the estimated HIV/AIDS prevalence in adults (15—49 years) being 14.4%. AIDS is estimated to account for over 85 000 deaths per year, and up to 170 000 people are thought to be in need of ARV therapy. So far only a small proportion of those in need of ARV therapy actually receive it: for example, by the end of 2002, just under 1400 patients had been started on ARV therapy in three government/mission hospitals in the country (Chimzizi et al., 2003). Since 2002, another two hospitals in the government/mission sector are providing ARV therapy to HIV-positive eligible patients, but the numbers accessing this medication are still small. However, Malawi has

now developed plans for scaling-up ARV therapy country-wide, and it is hoped that many more patients will have access to this life-saving medication by the end of 2004.

## 2.2. Goals and objectives of ARV therapy in Malawi

The main goal of ARV therapy in Malawi is to reduce morbidity and mortality of HIV/AIDS in adults and children. Specific objectives incorporate the following broad themes: (a) to increase the life span of patients with AIDS, (b) to enable adults with AIDS to return to their previous employment or any other productive activity and children with AIDS to return to school, and (c) to reduce the number of new orphans registered each year. For each objective, the Ministry of Health and Population (MOHP) in Malawi is obliged to report regularly to national and international stakeholders, including the GFATM, on a number of output indicators. These indicators were agreed upon by the committee writing the National ARV treatment guidelines and are also explicit in the GFATM proposal. The indicators include: number of patients who start on standardized ARV therapy; proportion of patients who show 95% or more adherence to ARV therapy, as adherence is one of the keys to reducing the development of drug resistance (WHO, 2004); percentage of patients on ARV therapy who are alive at a given time; percentage of patients alive on ARV therapy who are ambulatory or in the case of children engaged in age-related day time activities; and percentage of patients alive on ARV therapy who are engaged in previous work or employment. These indicators address national concerns about the devastating effect which HIV/AIDS is having upon the country, and will be used to measure the effect that HAART may have on improving human and economic development.

## 2.3. Registration and monitoring of patients on HAART in Thyolo district

In Thyolo district, symptomatic HIV-positive patients, who have undergone voluntary counselling and HIV testing in outpatients, the general wards, antenatal clinics or from the community, are referred to a hospital-based ARV clinic, staffed by clinical officers, nurses, counsellors and a clerk. In this clinic, patients are assessed and classified by clinical officers into WHO Clinical Staging categories (WHO, 2004), the main way in which patients are judged eligible for HAART in Malawi. Antiretroviral treatment in Thyolo is provided free (currently from Medicins sans Frontieres-Luxembourg), with tablets issued on a monthly basis to eligible patients from the ARV clinic. Responsibility for patient follow-up lies with the clinic staff. Follow-up is facilitated by the district's network of home-based care groups and volunteers who ensure that patients who do not arrive to collect their monthly treatment are traced to find out what has happened and, if needed, these patients may be provided with assistance for attending follow-up visits.

Each patient who starts ARV therapy is given a unique treatment unit ARV registration number. A patient master card and identity card are completed when the patient starts ARV therapy. The master card contains information on: ARV registration number, name, address, age, gender, weight, name of identifiable guardian, reason for starting ARV therapy, date of starting first-line ARV regimen, and space for either substitutions to alternative first-line regimens in case of drug toxicity or a switch to the second-line regimen in case of drug failure. Identity cards are carried by the patient, and contain the same basic information as the master card.

Once established on ARV therapy, patients are seen every four weeks. At monthly visits, patients have their weight recorded and are asked about general health, ambulatory status, work and drug side effects as listed in the Malawi ARV treatment guidelines. Counts are made of the drugs remaining in the pill containers, and patients are reminded about the importance of strict adherence to therapy. Pill counts are one measure of drug adherence, and, using co-trimoxazole in HIV-positive TB patients, this has been validated in the field (Zachariah et al., 2001). These details and standardized outcomes (see Table 2) are monitored monthly on the master card. The standardized outcomes for ARV use in Malawi are adapted from those used both internationally (Enarson et al., 2000; WHO, 2003a) and nationally (Ministry of Health and Population, Malawi, 2002) for following-up patients on anti-TB treatment. Master cards for all patients registered in a quarter are currently kept in hard-back files. The MOHP has also developed a standardized ARV patient register, which will be placed in ARV clinics and which will facilitate patient registration and follow-up.

## 2.4. Cohort analysis of treatment outcome in Thyolo district

Treatment outcome is monitored by cohort analysis, which is carried out retrospectively every quarter by going through patient master cards, or, in the

**Table 2** Standardized monthly outcomes for patients on antiretroviral (ARV) therapy in Malawi

| | |
|---|---|
| Alive[a] | Patient who is alive and has collected his/her own 30-day supply of drugs |
| Dead | Patient who has died for any reason while on ARV therapy |
| Defaulted | Patient who is not seen at all during a period of 3 months |
| Stopped | Patient who has stopped treatment completely either because of side effects or because of other reasons |
| Transfer-out | Patient who has transferred-out permanently to another treatment unit |

[a] A patient who is alive is further categorized according to the type of regimen he/she is taking: *Start:* the patient has started ARV therapy and takes the first-line regimen. *Substituted:* the patient experienced side effects from ARV therapy and has changed to an alternative first-line regimen. *Switch:* the patient has switched to the second-line regimen because of treatment failure. The patient must have been on first-line ARV therapy for 6 months or more, and have been adhering to treatment, before he/she can be recorded as 'failed'. A patient is deemed to have failed if (a) he/she has developed a new WHO Clinical Stage 4 disease (tuberculosis is an exception because it can occur in immunocompetent persons) or (b) has experienced a significant and sustained drop in CD4-lymphocyte count.

future, the ARV patient register. Cohort analysis is performed in two ways.

#### 2.4.1. Quarterly ARV cohort analysis

All patients who start on ARV therapy during one full quarter (i.e. 1 April to 30 June) form the fixed cohort for this period. Treatment outcome, ambulatory status, work status and drug adherence rates for the last month of that quarter are documented soon after the quarter has finished. Every three months, the outcome data in this particular cohort are analysed. In this way, new events occurring in patients in that cohort are monitored over time, as outcome data will change as patients die, default, transfer-out or stop treatment. The patients who start ARV treatment between 1 July and 30 September form the next cohort of patients, and they are followed-up in a similar way every three months by looking through the treatment cards or ARV patient register. These cohorts then increase in number as more patients over time are started on ARV therapy, and each cohort is analysed as a separate entity.

#### 2.4.2. Cumulative ARV quarterly analysis

When the first two cohorts of patients have started on ARV therapy (i.e. between 1 April and 30 September), it is important to know at a particular moment in time the total number of patients on therapy and the number alive, dead, defaulted and transferred-out. This constitutes the cumulative quarterly analysis, or, in other words, an analysis of all patients who have ever started on treatment. The data are obtained from a combined treatment outcome analysis of the April to June cohort and the July to September cohort. A form for this combined analysis is completed every quarter, and represents a cumulative record of the previous updated quarterly ARV cohort analysis forms.

## 3. Results

### 3.1. Quarterly ARV cohort analysis

The first quarterly cohort analysis of new patients started on ARV therapy between 1 April and 30 June (i.e. second quarter) 2003 in Thyolo District Hospital was carried out in July 2003. The number of cases and the treatment outcomes were collected into a structured proforma (see Table 3). Thus, 104 patients were started on HAART in this period, and when analysed in July, 102 were alive and taking the medications and two patients had died.

Evaluations of this particular cohort are then carried out every three months to record any changes in standardized outcomes over time. The number of patients in the cohort stays the same (i.e. the denominator stays at 104) but their outcomes may change (i.e. deaths may increase from two upwards).

### 3.2. Cumulative ARV quarterly analysis

The first cumulative cohort analysis of two cohorts started on ARV therapy in Thyolo District Hospital is shown in Table 4. Both of these cohorts (the new patients who started on HAART between April to June and the new patients started between July to September) were independently evaluated in October 2003. The number of cases and the treatment outcomes as of October 2003 were then combined to give the cumulative cohort analysis. Thus, 220 patients had been started on HAART between April and September, and when analysed in October, 199 were alive and on medications, 13 had died and eight had stopped treatment.

## 4. Discussion

### 4.1. Usefulness of cohort analysis

The information routinely collected from the quarterly cohort analysis should be an invaluable

**Table 3** Quarterly cohort analysis for patients starting antiretroviral (ARV) therapy in Thyolo District, Malawi

| | | |
|---|---|---|
| ARV Quarterly Cohort Analysis Form | | |
| Treatment Unit: | Thyolo District Hospital Cohort: Year 2003, Quarter 2 (April to June) | |
| Year and quarter in which evaluation is taking place: | 2003 Quarter 3 (July 2003) | |
| Number of patients registered for ARV in the quarter: | 104 | |
| Number alive and on ARV therapy: | 102 | (98%) |
| [Alive and on first-line regimen (Start)]: | [94] | |
| [Alive and on alternative first-line regimen (Substituted)]: | [8] | |
| [Alive and on second-line regimen (Switched)]: | 0 | |
| Dead: | 2 | (2%) |
| Defaulted: | 0 | |
| Stopped: | 0 | |
| Transferred to another treatment unit: | 0 | |
| Of those alive: | | |
| Number who are ambulatory | 102 | |
| Number at work or at school (in case of children) | 91 | |
| Number with side effects | 2 | |
| Number with drug adherence $\geq$95%[a] | 90/90 | (100%) |

[a] Patients are given 30 days supply of ARV tablets (60 tablets) and are reviewed every 28 days. If adherence is 100% there should be four tablets remaining in the container. If there are eight tablets or less in the container, then drug adherence is calculated at 95% or above. This is measured for adults and for those on the first-line regimen only; alternative first-line regimens are not included, as efavirenz, for example, is not available as a fixed-dose combination drug.

**Table 4** Cumulative quarterly analysis for patients starting antiretroviral (ARV) therapy in Thyolo District, Malawi

| | | |
|---|---|---|
| ARV Cumulative Analysis Form | | |
| Treatment Unit: | Thyolo District Hospital | |
| Combined Cohorts: | Year 2003 Quarter 2 (April to June) Year 2003 Quarter 3 (July to September) | |
| Year and quarter in which evaluation is taking place: | 2003, Quarter 4 October 2003 | |
| Total number of patients registered for ARV since start of the ARV programme: | 220 | |
| Number alive and on ARV therapy: | 199 | (90%) |
| [Alive and on first-line regimen (Start)]: | [190] | |
| [Alive and on alternative first-line regimen (Substituted)]: | [9] | |
| Alive and on second-line regimen (Switched)]: | 0 | |
| Dead: | 13 | (6%) |
| Defaulted: | 0 | |
| Stopped: | 8 | (4%) |
| Transferred to another treatment unit: | 0 | |
| Of those alive: | | |
| Number who are ambulatory | 199 | |
| Number at work or at school (in case of children) | 195 | |
| Number with side effects | 27 | (14%) |
| Number with drug adherence $\geq$95%[a] | 151/153 | (99%) |

[a] Patients are given 30 days supply of ARV tablets (60 tablets) and are reviewed every 28 days. If adherence is 100% there should be four tablets remaining in the container. If there are eight tablets or less in the container, then drug adherence is calculated at 95% or above. This is measured for adults and for those on first-line regimen only; alternative first-line regimens are not included as efavirenz for example is not available as a fixed-dose combination drug.

method of assessing whether ARV programme performance is improving or deteriorating.

The individual quarterly cohort analysis allows the district to assess trends over time, and allows, for example, the annual death rate in discrete groups of patients to be monitored. It also allows comparisons of treatment outcomes of cohorts recruited in 2003, 2004 and 2005. Increasing rates of switching from first- to second-line regimens or increasing mortality would point to the development of drug resistance to the first-line regimen. Decreasing rates of death or default would point to improved management of ARV treatment.

The cumulative ARV quarterly analysis allows the district to have regular up to date information on:

- Number of patients ever started on ARV drugs since the programme began (which in the case of Thyolo district was in April 2003).
- Number of patients alive and currently taking ARV drugs (which can be further subdivided into those on first-line regimen, alternative first-line regimens and second-line regimen).
- Number of adults on the first-line regimen with drug adherence rates greater than 95% (as measured by pill counts).
- Number of patients who have died, defaulted, stopped ARV drugs or who were transferred out to another treatment facility since the programme began.
- Number of patients alive on ARV therapy who are ambulant.
- Number of patients alive on ARV therapy who are in employment or in the case of children who are at school.

This information can potentially be collected from all ARV treatment units in the country, collated and used for six-monthly and annual reports. Such data enable the Ministry of Health to assess the effectiveness of ARV treatment in Malawi, and will allow HIV/AIDS officers to identify problems and institute appropriate measures to overcome them. Data on the number of newly registered orphans will require the use of separate forms.

### 4.2. Constraints

The patient master cards, and in the future the ARV patient register, form a continuous patient data set, and quarterly cohort analysis is performed on this data. However, one of the problems for the quarterly form of analysis is the gradual accumulation of cohort analyses, which need to be performed from when ARV delivery began. Five years from the start of delivering ARV therapy in a district hospital, there will be 20 quarterly cohorts, each of which at a particular moment in time will need to be evaluated with the results from each combined into a cumulative analysis record. While the analysis of up to 10 quarterly cohorts can be envisaged on a manual basis, the analysis of large numbers may become problematic.

Solutions are to: (a) perform cohort analysis every 6—12 months at a time when the country has developed experience and feels comfortable with the administration and use of ARV therapy; (b) use electronic data sets which are specially designed for doing cohort analysis as data on each individual patient is continuously entered into the system; or (c) just perform one cumulative cohort analysis every three months to provide a total picture of response to ARV therapy from the time when it was first ever introduced. Accurate, regular and up to date data will be essential to the success or otherwise of any ARV delivery system.

### 4.3. The way forward

Whatever system is used at the start may need modification as the years go on. In addition, some of the parameters being used to monitor response, such as weight or pill counts as a measure of drug adherence, may have to be evaluated and modified as experience is gained with their use. The system described in this paper focuses on patient outcomes, but there are other areas which need careful monitoring, such as drug availability and drug security. Countries which are scaling up and delivering ARV treatment will need to keep abreast of what is happening elsewhere, what works and be flexible in how they adapt to what will become a challenging task over the years.

#### Conflicts of interest statement

The authors have no conflict of interest concerning the work reported in the paper.

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