Evaluation of Three Sampling Methods to Monitor Outcomes of Antiretroviral Treatment Programmes in Low- and Middle-Income Countries

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Abstract

**Background:** Retention of patients on antiretroviral therapy (ART) over time is a proxy for quality of care and an outcome indicator to monitor ART programs. Using existing databases (Antiretroviral in Lower Income Countries of the International Database to Evaluate AIDS and Médecins Sans Frontières), we evaluated three sampling approaches to simplify the generation of outcome indicators.

**Methods and Findings:** We used individual patient data from 27 ART sites and included 27,201 ART-naive adults (≥15 years) who initiated ART in 2005. For each site, we generated two outcome indicators at 12 months, retention on ART and proportion of patients lost to follow-up (LFU), first using all patient data and then within a smaller group of patients selected using three sampling methods (random, systematic and consecutive sampling). For each method and each site, 500 samples were generated, and the average result was compared with the unsampled value. The 95% sampling distribution (SD) was expressed as the 2.5th and 97.5th percentile values from the 500 samples. Overall, retention on ART was 76.5% (range 58.9–88.6) and the proportion of patients LFU, 13.5% (range 8.8–31.9). Estimates of retention from sampling (n = 5696) were 76.5% (SD 75.4–77.7) for random, 76.5% (75.3–77.5) for systematic and 76.0% (74.1–78.2) for the consecutive method. Estimates for the proportion of patients LFU were 13.5% (12.6–14.5), 13.5% (12.6–14.3) and 14.0% (12.5–13.5), respectively.

**Conclusions:** Our results suggest that random, systematic or consecutive sampling methods are feasible for monitoring ART indicators at national level. However, sampling may not produce precise estimates in some sites.

Introduction

At the end of 2009, more than 5 million people were receiving antiretroviral therapy (ART) in low- and middle-income countries,[1] out of 33.4 million people (estimated range: 31.1 million–35.8 million) living with HIV [2,3]. This represents a 30% increase in one year and a 13-fold increase in ART uptake in six years. Monitoring of ART programmes is critical for understanding when sites are under-performing and estimating the potential impact of treatment, at the population level and for program management at different levels of the health system. In addition, reporting of such indicators helps to sustain national and global commitment to monitor quality of care while expanding access to ART and its growing use.

Many countries are still struggling to report national programme indicators. In 2009, 70 out of 149 low- and middle-income countries (47%) reported statistics on patient retention on ART at 12 months and 30 (20%) at 48 months [4]. This outcome indicator is one of several core indicators recommended to monitor the Declaration of Commitment on HIV/AIDS during the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) [5]. Although some countries have highly automated information systems, many ART sites within countries have difficulty in maintaining the registers/databases necessary to produce these statistics. A number of factors may explain the difficulties in generating good quality information. Many ART programmes are relatively recent, yet facing large and rapid increases in the number of patients starting therapy. They have
thus logically focused their attention on putting new patients into
care and reporting baseline information rather than on follow-up.
In addition to ART, HIV care includes various other components
(e.g. prevention and treatment of opportunistic infections includ-
ing tuberculosis or integration with reproductive health services)
that require regular monitoring. With the rapid expansion of ART
services and decentralisation to peripheral health centres, data
management has to occur at all levels of health service provision
and should be designed to be as simple and user-friendly as
possible in order for it to be adopted universally. Finally, ART
treatment is life-long, leading to continued workload increase due
to inclusion of new patients and continued follow-up.

In this paper we evaluated the performance of three sampling
approaches to produce two clinic and higher level indicators at 12
months: retention on ART [6] and proportion of patients lost to
follow-up, using existing databases from ART programmes in low-
and middle-income countries.

Methods

Sources of data

ART-LINC of IeDEA is a large collaborative network of HIV/
AIDS treatment programmes in low- and middle-income countries
in Africa, South America and Asia, originally funded by the
United States National Institutes of Health (Office of AIDS
Research) and the French Agence Nationale de Recherches sur le
Sida et les hépatites virales (ANRS). It is now part of the
International epidemiological Database to Evaluate AIDS collabor-
ation of the NIH (http://www.iedea-hiv.org). This network was
established in 2003 to characterize the prognosis of HIV-infected
patients treated with ART in resource-limited settings, to compare
the experience between different settings, delivery modes and types
of monitoring; and to compare outcomes with those observed in
industrialized nations [7]. Staff at the sites filled in a detailed
abstraction form using their own medical records, or downloaded
the required data from their own electronic medical records
(EMR) systems. Data were merged anonymously at the University
of Bern, Switzerland and the University of Bordeaux, France [8].

Since 2001, Médécins Sans Frontières (MSF) has provided ART
in 26 countries with a high HIV prevalence, most of them in
Africa and Asia. Basic patient individual clinical, laboratory and
treatment information are routinely collected at every clinic visit
using standardized forms. Data are continuously entered into the
Follow-up and Care of HIV Infection and AIDS (FUCHIA) EMR
software (Epicentre, Paris, France). Capacity building and
maintenance of the databases are funded by MSF and data
centralized anonymously in Epicentre – Paris, France, the
epidemiological support office of MSF [9,10].

Ethics statement

International review boards in each country have approved the
use of routinely collected programme data at all ART-LINC sites.
This study was approved by the research ethics review committee
of the World Health Organisation and the ethics review board of
Médecins Sans Frontières. The data analysed are primarily
collected for patient management and program monitoring, with
the agreement of the ministries of health of the countries. Because
of this reason, patient informed consent is not routinely requested
in all sites. All ethic boards were aware of this and approved the
secondary use of data for this analysis.

Selection of sites and indicators

For this analysis we selected all ART sites with more than 260
ART naïve adults aged ≥15 years old starting ART in the year
2005. All databases were updated more than 12 months after the
inclusion of the last patient in 2005. We analysed the patient status
at 12 months, classified as followed on ART, dead, stopped
 treatment, and lost to follow-up (LFU). Patients LFU were defined
as patients with no recorded visit for ≥90 days from the last visit
within the first year. Patients transferred to another ART
programme within the first 12 months of treatment were excluded
from the analysis (n = 896 or 3% of the overall database).

We studied two indicators measured 12 months after ART
initiation, the proportion of patients LFU and the proportion
retained on ART.

Sampling methods

For each ART site, the required sample size was calculated,
assuming a retention at 12 months of 75% as n ≥ [u² * p * (1-p)]/
(Δ² * (N-1)+u² * p * (1-p)) with n a sample size, N total population of
each site, p expected proportion estimated at 75%, Δ precision
estimated at 0.05 and u₀ estimated at 1.96. We used the sample
required to ensure that the 95% (i.e., 1-alpha) confidence interval
of the 75% proportion had a width at least 2 times Delta where
Delta is the required precision. Three sampling methods were
considered: the random selection, systematic and consecutive
sampling. In random sampling each patient of each clinic database
had an equal probability of selection and each patient was selected
using a random number allocation. In systematic sampling, the
first patient was randomly selected and the others were drawn
from the clinic database according to a sample interval defined as
N/a until achievement of the desired sample size. In consecutive
sampling, the first patient was randomly selected, then patients
consecutively registered were selected until the achievement of the
required sample size.

Statistical analyses

We first compared estimates of the retention on ART at 12
months obtained using Kaplan-Meier methods (taking into
account the exact duration of follow-up of each patient before
treatment discontinuation) with the proportion of patients retained
on ART at 12 months [as recommended by UNGASS [5]]. The
outcomes were either death, stopping ART or LFU within the first
12 months, while for patients alive and on ART follow-up was
censored at 12 months.

Thereafter all estimates were generated as proportions at 12
months as it is the usual method in routine programme
monitoring. We calculated the two indicators using first the
overall dataset and compared the proportions with those resulting
from computation in sub-samples obtained with the three
sampling methods. Indicators obtained using the full dataset are
referred to as “unsampled” values. For each site and for each
sampling method, 500 samples were simulated. We used the mean
of the 500 results and the 2.5th and 97.5th values to determine the
95% sampling distribution (SD) and compared it to the unsampled
site value. Combined indicators for all sites were then generated by
aggregating site specific sampling results; the estimate of the mean
was a weighted average of the proportion at each site weighted by
the sample proportion (i.e., the number of patients selected divided
by the total number of eligible patients at each site). Statistical
analyses were performed using Statistical Analysis System software
(SAS, version 9.1).
Results

Twenty-seven ART sites, 22 located in Africa and five in Asia, were included with a total of 27,201 patients treated. The number of patients per site ranged from 378 to 4111. After 12 months on ART 2,036 (7.5%) patients had died (range 1.9% to 16.7% across sites), 688 (2.5%) had stopped ART (range: 0% to 8.5%) and 13.5% were LFU (range 0.8% to 31.9%) (Table 1). Estimates of retention on ART at 12 months calculated with the proportion and Kaplan-Meier methods were similar, at 75.9% (range 58.7% to 88.6%) and 76.5% (58.9% to 88.6%) respectively. All following results were generated as proportions as it is the usual method in routine programme monitoring.

A total of 5,696 patients (20.9%; range 6.6% to 51.1% across cohorts) were sampled. Estimates for 12-month retention on ART, from random, systematic and consecutive sampling were 76.5% (95% SD 75.4–77.7), 76.5% (95% SD 75.3–77.5) and 76.0% (95% SD 74.1–78.2), respectively, compared to 76.5% for the unsampled value (Figure 1). The sample distribution for the 500 sample iterations varied across sites. Overall, sample distribution was wider when using consecutive sampling; the 2.5th value was within minus 5% of the unsampled value for 14/27 sites (51.8%) and the 97.5th value was within plus 5% for 21/27 sites (78%) and ranged from −10.0% to +10.6%. Variability in sample distribution was independent of cohort size ($P = 0.98$), urban/rural location ($P = 0.99$) or the proportion of patients LFU in the cohort ($P = 0.81$).

Similar results were observed for the proportion of patients LFU indicator (Figure 2). The consecutive sampling method slightly overestimated the estimates (14.0%; 95% SD 12.5–15.5) com-
pared to 13.5% using the full dataset, and the sample distribution was wider than intervals obtained with random (13.5%; 95% SD 12.6–14.5) and systematic sampling (13.5%; 95% SD 12.6–14.3).

Discussion

When paper records are used at ART sites, programme monitoring often relies on transferring key information from patients’ medical records into paper registers or electronic databases and aggregating the information at regular periods for reporting and interpretation of findings at all levels of the health system. Maintaining accurate medical records for all patients at every contact is essential to ensure quality of care and patient management, but the subsequent transfer of information for the purpose of programme monitoring could be limited to a sample of patients rather than the full cohort to reduce workload. Sampling has already been used for HIV/AIDS care program monitoring [11] but precision of the results obtained had not been assessed. Sampling has also been used to determine outcomes among patients LFU by tracing in the community [12,13].

Figure 1. Proportion of patients on ART at 12 months: comparison of estimates according to the sampling technique (median, inter-quartile range, 10–90% deciles and minimum maximum) with the unsampled value (dotted line).

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Figure 2. Proportion of patients lost to follow-up at 12 months: comparison of estimates according to the sampling technique (median, inter-quartile range, 10–90% deciles and minimum maximum) with the unsampled value (dotted line).

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We compared two monitoring indicators, proportions of patients retained on ART and of patients LFU at 12 months. These statistics were obtained first with the overall dataset without sampling, then after applying three sampling strategies. Many international indicators, including the UNAIDS indicators, are indeed calculated only at a national level and do not require exhaustive site-specific data. Our sampling strategies performed well on the dataset combining patient data collected in 27 sites. Overall estimates were similar independently of the sampling method used. Sampling performed particularly well when indicators were calculated in the full dataset while differences in estimates and sample distribution were more variable when analysed at site level. For 12-month retention on ART, the sample distribution obtained by consecutive sampling was wider compared to random and systematic sampling methods with a maximum distribution of ±10% of the unsampled value. Whereas not directly comparable, the cluster sampling method used to monitor immunization coverage in children was developed three decades ago for sampling results to range within ±10% from the population value and has always been recommended since then; although 17% of sampling results fell outside these limits, the method was considered to perform well enough for programmatic purposes [14].

Patient life-long retention on ART is of growing concern in the rapid scale-up of large treatment programmes[4.15–17]. An analysis in South Africa showed a deterioration in retention on ART over time with an increasing proportion of patients LFU among those enrolled during the most recent years. It was in part related to the large increase in patients but the authors also discussed the burden on health informatics systems and administrative errors leading to misclassification in LFU [15]. Improving and maintaining simple and standardised monitoring systems capturing true treatment outcomes is part of the strategies recommended to better document and therefore improve patient retention on ART [17].

The workload required to ensure good quality of ART cohort monitoring is substantial for both paper-based and electronic systems. It also increases with the size and follow-up of the cohort. EMR systems allow the systematic and sometimes automated production of statistical indicators using information from all patients, but they are resource-intensive, as they require data clerks, training, and system maintenance[18]. A review of EMR systems used in 21 ART sites in low- and middle-income countries reported a median proportion of missing data for key information of 10.9% [19]. Missing data declined with training on data-reported a median proportion of missing data for key information clerks, training, and system maintenance [18]. A review of EMR systems. It also increases with the size and follow-up of the cohort. EMR systems allow the systematic and sometimes automated production of statistical indicators using information from all patients, but they are resource-intensive, as they require data clerks, training, and system maintenance [18]. A review of EMR systems used in 21 ART sites in low- and middle-income countries reported a median proportion of missing data for key information of 10.9% [19]. Missing data declined with training on data-

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Author Contributions
Conceived and designed the experiments: JMT KM MPR DB ADH MM MS YS FD. Analyzed the data: KM. Wrote the paper: JMT KM MPR EP DB ADH MM MS YS FD.

References