

SAMPLE PHE CONCEPT PROPOSAL

ESTIMATING MORTALITY AMONG PATIENTS LOSS-TO-FOLLOW-UP

BACKGROUND AND PRELIMINARY DATA

The President's Emergency Plan for AIDS Relief (PEPFAR)¹ is a response by the US government to the unprecedented public health effects of the HIV epidemic in the developing world. Signed in May 2003, 15 billion dollars were committed to fund this program for five years. One of the mandates of the US Leadership against HIV/AIDS, Tuberculosis and Malaria Act of 2003 that established the program was to "harmonize monitoring and evaluation efforts to ensure the most effective and efficient use of resources."² The Act mandated that the program be evaluated within 3 years after its enactment. In fact, the Institute of Medicine has been tasked to carry out an independent PEPFAR evaluation by comparing the success rates of various programs and methods used to treat patients (operations research²).

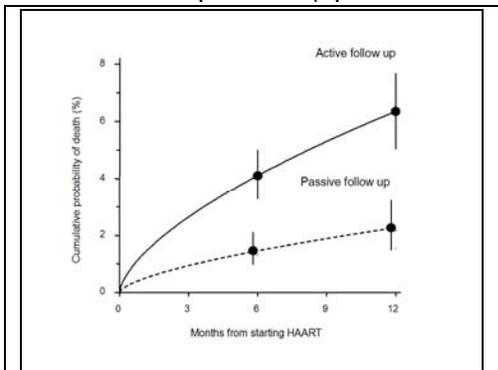


Figure 1. Estimated cumulative probability of death in antiretroviral treatment programs in low-income countries according to methods of follow-up³.

There is a large number of evaluation criteria with which to determine the effectiveness of PEPFAR. One of the most unequivocal and useful is mortality which, given the number of deaths attributable to HIV/AIDS in the target PEPFAR countries, forms a central index of program evaluation. While patient survival and death would appear to be a sufficiently clear outcome, determining mortality rates, in the developing countries targeted by the program is difficult, particularly through the routine passive follow-up HIV/AIDS care programs employ. This is because these passive follow-up systems are only aware of the vital status of the patients who return to follow-up visits or who maintain close

contact with the clinic. This leaves open the distinct possibility that patients who do not return to clinic visits ("losses to follow-up") may have died in the community and this will not be recorded by these passive systems. Indeed, recent data from Antiretroviral Therapy in Low Income Countries (ART-LINC)³ collaboration suggest that deaths among persons who are lost to follow-up may account for the majority of overall mortality. Specifically, the cumulative incidence of death at 1 year following the initiation of therapy was approximately three times higher at clinics which practiced an active form of follow-up surveillance compared to clinics which performed passive follow-up surveillance.

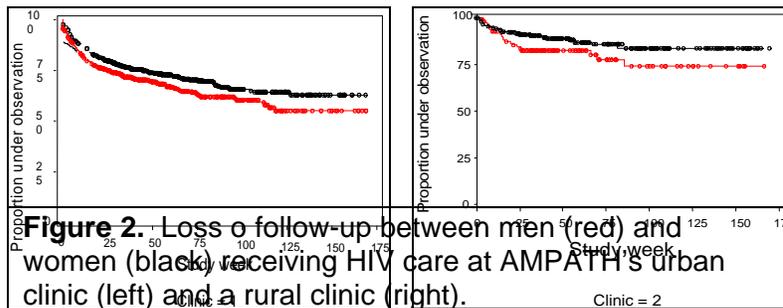


Figure 2. Loss of follow-up between men (red) and women (black) receiving HIV care at AMPATH's urban clinic (left) and a rural clinic (right).

(Figure 1). Data from another site, the Academic Model for Prevention And Treatment of HIV/AIDS (AMPATH), suggest that patients recruited in urban versus rural sites have differential rates of loss to follow-up, while

data from the same source suggest that patients lost to follow-up are more sick and

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	Median CD4	95% CI ¹	p-value ²
Dropouts	80	2-437	<0.001
Non dropouts	111	3-423	

Table 1. CD4 counts at start of ARV among dropouts and non-dropouts

¹Non-parametric (2.5th and 97.5th percentile)
²Wilcoxon two-sample test

have lower CD4 counts at the start of antiretroviral therapy than those that were not lost to follow-up (Table 1). While this is expected to a certain extent, particularly if death is a major cause for patient dropout, these data underline possible significant differences

in mortality rates between patients receiving antiretroviral therapy and those that are lost to follow-up. With annual dropout rates ranging from 20% (Figure 2 and reference # 3) to almost 50%⁴ it is highly probable that mortality estimates derived from observed data alone will be biased, perhaps significantly so. Taken together, these considerations point to an urgent need to address bias in program evaluation introduced by loss to follow-up.

Monitoring and evaluation, patient surveillance and informatics infrastructure.

As part of our monitoring and evaluation (M&E) study, we will formally test the assertion that loss to follow-up introduces bias in mortality estimates (and other indices of program evaluation; see Research Methods below). Even if patient dropout does not materially affect these estimates, we will need to determine the vital status on at least a high percentage of dropouts in order to test this hypothesis in order to test the working (and most likely false) hypothesis that patient dropouts do not affect mortality estimates. A number of methods of dropout recovery can be considered (discussed in detail below). We are basing all this work on a robust informatics infrastructure available to all participating sites is necessary in order to identify, in real time, patients that drop out and electronically record the data necessary contact them, determine their vital status and perform all analyses necessary for program evaluation.

Models of patient surveillance

We describe models of patient vital status ascertainment and dropout recovery that are employed by the participating sites. These programs have been instituted in order to optimize care by increasing patient retention and reinstating into treatment patients that discontinue from care.

The AMPATH model: Complete patient recovery

On the initial visit, each patient completes a tracer card that includes a map to the home, sub-location, and village. When feasible, a mobile phone number for the patient or a contact person is also recorded. If the patient fails to return for a scheduled visit, as determined by the AMPATH Medical Record System (AMRS; <http://www.amrs.iukenya.org/>), an outreach team consisting of HIV infected patients, who receive HAART themselves, try to contact the person by phone or else pursue a home visit to the patient. During that visit, the vital status of the patient is ascertained and, if alive, the patient is encouraged to resume treatment.

The Mbarara model: A stratified sampling approach based on distance from clinic

Every month a list of persons who are lost to follow-up is generated by the AMRS. The

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distance from clinic is determined by tracer cards that have been filled out by patients when they are enrolled in the program. Three strata, based on increasing radius from the clinic (short, medium and large distance) are determined and a progressively smaller number of patients are randomly selected within each stratum up to a maximum number of patients that can be feasibly traced (which, in certain months may include every dropout in that stratum). The proportion of contacted patients will fluctuate from month to month but will otherwise be known based on data derived from the AMPATH Medical Record System, which has been installed to the Mbarara University Clinic. In all cases, the sampling probability for that stratum is known. The Mbarara model will use sophisticated analytic techniques (described below) to overcome lack of resources to trace all patients that discontinue therapy.

SPECIFIC AIMS

The proposed pilot study will be performed in two participating sites in the East Africa region (Mbarara University in Uganda and AMPATH in Kenya; Appendix 1) that are currently following almost 40,000 HIV-infected patients and is providing PEPFAR funded antiviral therapy. The study will have the following aims:

Estimate mortality among HIV-infected patients receiving care in participating sites and assess the impact of loss-to-follow-up on estimates of mortality.

This will be accomplished by comparing four analytical methods:

1. The estimates resulting from observed data only (naïve analysis)
2. Analyses of observed data (i.e., no dropouts) with mortality estimates statistically adjusted for the unobserved vital status of patients lost to follow-up
3. Mortality estimates adjusted after determination of vital status from some or all of patient dropout.
 - a. In the former case (AMPATH model) the analyses in item #1 above will be used using all available data
 - b. In the latter case (Mbarara stratified sampling model) statistical methods will be used to weight the evidence collected by recovering data from a random sample of dropouts

RESEARCH METHODS

Data analyses

A progressively complex analysis of the data collected from the participating sites will be performed, starting with existing approaches based on observed data, attempting to adjust these with statistical approaches and culminating to incorporation of data from vital status from recovered patient dropouts generated from the active follow-up. We briefly describe these here.

The routine “naïve” analysis

The simplest analysis will be based on modeling of patient survival through the usual methods (Kaplan-Meier plots⁵ and Cox proportional hazards models⁶). These methods will focus on the time from study entry until death or end of observation (censoring). All patients that were lost to follow-up will be censored at their last visit. This analysis is considered “naïve” because it assumes (in most cases wrongly) that death rates among those who are lost to follow-up are equal to the rates among those persons who continue to be observed by their clinics (“stay in care”)⁷. Both the ART-LINC data³ and

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the AMPATH baseline CD4 data (Table 1) seem to contradict that the two patient cohorts (drop outs and non-dropouts) are similar types of patients. Consequently, this crucial assumption of analysis of survival data is most likely violated and, more alarmingly, the error in the estimation cannot be estimated. It can thus reasonably be argued that no monitoring and evaluation method that does not account for loss to follow-up can be relied upon.

Analyses adjusted for loss-to-follow-up rates

Mortality rate estimates can in some cases be adjusted by including baseline characteristics and other measures obtained prior to dropout to stratify the patient population into strata where the dropouts and non-dropouts have similar mortality rates⁸.⁹ Strata defining subpopulations in terms of tribal membership, disease progression (e.g., CD4 counts) can be used. While this is an attractive approach, it is handicapped by the fact that the assumptions cannot be tested and there is no guarantee that strata with similar mortality rates will be identified in the patient population. What's more, without vital status known in at least a randomly selected proportion of dropouts, the accuracy of these estimates cannot be estimated. In this regard, this adjusted method shares this fundamental problem with the previously described "naïve" analysis.

Analyses adjusted for dropout vital status ascertainment

One way to derive the correct estimates of mortality, and avoid the biases inherent in analyses that disregard or partially adjust for dropouts, is to determine the vital status in patients that have been lost to follow-up. The capability to determine, *in real time*, who is a "dropout" requires the existence of robust electronic medical record systems in order to determine which patients are due to the clinic to receive care each day and thus quickly identify those that have not shown up for an extended period of time. In cases of program monitoring and evaluation with monthly visits this period can be fixed at two or three months for example (Appendix 2). For programs focused on clinical delivery a much shorter period would be necessary (like the five-day window used at AMPATH). In either case, paper record systems, while able to provide some aggregate data on the volume of patients treated by a specific sites, cannot determine daily lists of patients that have appointments and, by extension, lists of patients lost to follow-up.

If vital status is determined among all dropouts then the mortality estimates generated by an analysis similar to the "naïve" method described above will not be biased. While this vital status ascertainment is feasible in developed countries with death registries, it is resource intensive and extremely difficult in the developing world. However, valid survival estimation for the population, does not require active follow-up on all subjects. Instead, it has been shown, through statistical arguments¹⁰, that ascertaining vital status on a random sample of dropouts (double sampling) can produce reliable estimates of the mortality rates by including, along with patients with observed data, vital status information obtained from randomly sampled dropouts. Current work is underway by Dr. Glidden at UCSF, a co-investigator in this application, for extending this approach to Cox regression. A major limitation of the Frankgakis and Rubin framework¹⁰ is the exclusion of data on dropouts who are not sampled up to the point of loss-to-follow-up. This approach is inefficient and further modeling could allow these data to be further exploited¹¹. We plan to investigate and develop models and methods in this vein. These modeling approaches will be tested by taking a random sample of the recovered AMPATH dropouts (recall that all AMPATH patients that are lost to follow-up will be contacted so a post-hoc analysis including only a random sample of these dropouts is possible).

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Additional considerations for modeling are involved in the Mbarara model, where patients that are lost to follow-up are stratified by distance from the clinic. Once vital status has been ascertained for a proportion of patients, the overall mortality estimates will be adjusted by incorporating the data obtained from recovered patients. Since only a proportion of these will be contacted, data from dropouts will be weighted by the inverse proportion of patients contacted in each stratum (IPW). For example, if 20% of patients were contacted in a specific stratum, vital status data on patients from this stratum will be weighted by a factor of 5¹⁰. A clear distinction will be made between factors that are involved in the modeling of the probability of selection (through a logistic-regression approach¹² and the adjusted (through double sampling) analysis of survival data. We will correct for the increased variability in the estimates due to the inverse probability weighting (IPW) performed by the logistic regression by bootstrapping methods¹³. Other, stabilized estimates of these weights^{14, 15} will be considered as well.

Expected outputs

From this project we expect to generate a more accurate estimate of mortality among HIV-infected patients receiving PEPFAR supported care at the Mbarara Immune Suppression Syndrome Clinic and sites participating in the AMPATH program (see list below). Given experience and preliminary data, we expect that the estimates between passive and active follow-up analyses will be substantial. Such a finding will forcefully argue for incorporation of active follow-up and the attendant informatics and analytical infrastructure into at least some of the PEPFAR-funded sites that will in turn be tasked to evaluate the program.

If, as expected, the differences in the estimates produced by methods adjusted for loss to follow-up, the rather strong suggestion will be that some patient surveillance would need to be included in monitoring and evaluation efforts as part of the routine spectrum of PEPFAR supported care. The viability of active follow-up models will be assessed in terms of the following three criteria:

1. Feasibility: What percentage of persons consent, upon entry into clinic, to be traced if they become lost?
2. Practicability: Of those attempted to be traced, what percentage of persons can be found?
3. Cost effectiveness: What is, for each surveillance model, the cost of each patient contacted?

The success of active follow-up programs will be mainly based on the proportion of dropouts they are able to contact. A tertiary but crucial outcome will also be the determination of the proportion of contacted (and alive) patients that agree to resume treatment. While not explicitly a goal of this proposal, qualitative research into a uniform set of questions to be asked of contacted patients or short questionnaires to determine likely causes of death (such as the so called “verbal autopsies”) will also be piloted with funding obtained from other sources.

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Appendix 1

Participating sites and patient accrual as of July 2006

Participating sites (Adult patients)

	Site	Patients on ART	Total patients
Mbarara	ISS Clinic	3,500	11,000
Total			

AMPATH	Moi University	4,690	7,799
	Mosoriot	1,460	2,734
	Turbo	998	1,904
	Burnt Forest	655	1,049
	Amukura	392	725
	Naitiri	288	558
	Chulaimbo	2,112	3,843
	Webuye	909	1,928
	Teso	324	717
	Kitale	853	1,795
	Kapenguria	134	296
	Mt Elgon	69	195
	Iten	71	119
	Kabernet	174	315
Busia	84	706	
Total		14,296	24,683

Participating sites (Pediatric patients)

	Site	Patients on ART	Total patients
AMPATH	Moi University	425	1,743
	Mosoriot	103	397
	Turbo	77	292
	Burnt Forest	85	193
	Amukura	18	134
	Naitiri	30	119
	Chulaimbo	135	462
	Webuye	58	265
	Teso	20	92
	Kitale	83	370
	Kapenguria	10	54
	Mt Elgon	8	44
	Iten	11	29
	Kabernet	16	43
Busia	4	70	
Total		1,083	4,307

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Appendix 2

Patients on ART that have not attended clinic for over three months (since 5/1/06)

Adult patients

	Site	Total patients
AMPATH	Moi University	1,060
	Mosoriot	300
	Turbo	197
	Burnt Forest	90
	Amukura	41
	Naitiri	57
	Chulaimbo	415
	Webuye	149
	Teso	44
	Kitale	54
	Kapenguria	7
	Mt Elgon	2
	Iten	0
	Kabernet	0
	Busia	0
Total		2,416

Pediatric patients

	Site	Total patients
AMPATH	Moi University	76
	Mosoriot	6
	Turbo	6
	Burnt Forest	5
	Amukura	1
	Naitiri	5
	Chulaimbo	12
	Webuye	9
	Teso	3
	Kitale	5
	Kapenguria	0
	Mt Elgon	0
	Iten	0
	Kabernet	0
	Busia	0
Total		128