Patient non-retention, loss to follow-up and death after ART initiation at HIV care and treatment facilities in sub-Saharan Africa: the influence of adherence support and outreach services.

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ABSTRACT

Patient non-retention, loss to follow-up and death after ART initiation at HIV care and treatment facilities in sub-Saharan Africa: the influence of adherence support and outreach services.

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This dissertation uses three types of routinely collected data from HIV care and treatment facilities in sub-Saharan Africa to investigate the association between the availability of adherence support and active outreach services on patient non-retention, loss to follow-up, and measured death after ART initiation. Following a literature review summarizing the state of knowledge concerning the influence of programmatic services on patient retention in care and survival, these relationships are first examined in an aggregate analysis of over 232,000 patients at 349 HIV care and treatment facilities initiating ART between January 2004 and December 2008. Key findings are that several adherence support and outreach services are associated with reduced rates of non-retention, loss to follow-up, and death. Specifically, facilities offering three or more adherence support services, written educational materials promoting ART adherence, one-on-one or group adherence counseling sessions, reminder tools, and food rations to promote ART adherence were associated with reduced non-retention and loss to

follow-up, while facilities offering on-site support groups for HIV+ patients, peer educators, provision of reminder tools, and food rations to promote ART adherence were associated with reduced death rates. In sub-analyses investigating six- and 12-month retention after ART initiation, facilities offering three or more separate adherence support services, routine review of medication pickup and/or dedicated ART pharmacists, and active patient outreach to trace patients missing visits had lower non-retention. Taken together, this analysis provides evidence that program-level services found efficacious in experimental settings are also effective in operational settings.

Next, a sub-analysis is conducted among facilities also providing electronic patient-level data to investigate similarities and differences in the association between adherence support and outreach services and patient non-retention, loss to follow-up, and measured death using aggregate vs. patient-level estimates of these outcomes, and to assess whether adjustment for patient-level differences between facilities change these measures of association. In multivariate analyses, clinics offering active patient outreach had lower rates of non-retention in both the ART cohort analysis and the patient-level analysis, and clinics offering food rations to promote ART adherence were associated with a lower risk of ascertained death in both the facility-level and patient-level analyses, but this association was diminished after adjustment for patient-level covariates. In contrast, various adherence counseling or support services were associated with lower non-retention in the ART cohort analyses but not in the patient-level data analyses. When compared with the results in the first paper, fewer associations were observed, suggesting either that the countries with patient-level

databases are not representative of the entire range of HIV care and treatment facilities assessed in the first paper, and/or the specific facilities with electronic databases are more similar to each other than they are to facilities without electronic databases.

Finally, the dissertation concludes with an investigation into the relationship between loss to follow-up and measured death. For this analysis, estimates of the death probability among patients lost to follow-up are created under varying assumptions (either assuming that the death probability among those lost to follow-up is equivalent to the death probability within various strata of covariates, or assuming that the probability of death is greater among patients lost to follow-up). Key findings from this analysis are that ratio comparisons of death rates between facilities offering different services are robust to changes in the death probability if patients lost to follow-up are assumed to have a similar probability of death, conditioned on covariates, as those not lost to follow-up, but that associations between facility services and death rates are masked under the scenario where the facility service is associated with loss to follow-up and the death probability is assumed to be higher, conditioned on covariates, then the death probability among patients not lost to follow-up.

Table of Contents

List of Tables and Figures

Chapter 3: The relationship of adherence support and active outreach services with rates of patient non-retention, loss to follow-up, and ascertained death in sub-Saharan African HIV care and treatment scale-up clinics

Chapter 4: Investigating the relationship of adherence support and active outreach services with rates of patient non-retention, loss to follow-up, and ascertained death using aggregate and patient-level data from sub-Saharan African HIV care and treatment scale-up clinics

Chapter 5: Loss to follow-up biases measured associations between adherence support and active outreach services and patient survival

Chapter 6: Discussion

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Introduction

The ultimate goal of HIV care and treatment programs is improving patient survival. In sub-Saharan Africa and other settings where resources are limited and future international funding cannot be counted on to expand, identifying specific program services that improve patient survival can inform programmatic decision-making on program design and resource allocation. However, this identification is complicated by a lack of complete patient- and program-level information across these facilities. Information on the cumulative number of patients initiating ART, and the cumulative numbers who have died or become lost to follow-up is routinely available for HIV care and treatment centers supported under the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and overall rates of non-retention, loss to follow-up, and death can be constructed from this information. In addition, HIV care and treatment centers supported under PEPFAR report on the number of patients initiating ART each quarter, and the number of these patients remaining on ART 6 and 12 months after ART initiation. Finally, a subset of facilities also collect electronic patient-level data that can be used to estimate rates of non-retention, loss to follow-up, and death at different time intervals after ART initiation. Combining these outcomes with program-level surveys assessing the availability of adherence support and retention-promoting services can be used to assess whether these services improve patient survival and retention, and whether different estimates of survival and retention result in differing associations between program service availability and patient outcomes.

In any analysis investigating the influence of program service availability on patient survival, loss to follow-up complicates analysis because it causes incomplete

ascertainment of vital status. Additionally, loss to follow-up is both caused by death (if that death is unascertained) and a cause of death (if patients lost to follow-up do not access ART treatment elsewhere). Overall death rates are underestimated when loss to follow-up exists because of this incomplete ascertainment, and relative measures comparing death rates between facilities offering different program services may be biased if the relationship between loss to follow-up and death differs between these facilities.

The purposes of this dissertation are (1)to identify program-level services designed to influence patient adherence to ART and retention in care are associated with improved rates of non-retention, loss to follow-up, and death, (2) to assess whether any observed associations between program-level service availability and estimates of non-retention, loss to follow-up, and death differ by the source of the outcome estimate (overall aggregate, cohort, and patient-level), and (3) to investigate how different estimates of the survival distribution among patients lost to follow-up influence measures of association comparing death rates between facilities offering different services.

The first paper in this dissertation presents an ecologic analysis of over 232,000 patients at 349 HIV care and treatment facilities initiating ART between January 2004 and December 2008. Key findings are that several adherence support and outreach services are associated with reduced rates of non-retention, loss to follow-up, and death. Specifically, facilities offering three or more adherence support services, written educational materials promoting ART adherence, one-on-one or group adherence

counseling sessions, reminder tools, and food rations to promote ART adherence were associated with reduced non-retention and loss to follow-up, while facilities offering on-site support groups for HIV+ patients, peer educators, provision of reminder tools, and food rations to promote ART adherence were associated with reduced death rates. In sub-analyses investigating six- and 12-month retention after ART initiation, facilities offering three or more separate adherence support services, routine review of medication pickup and/or dedicated ART pharmacists, and active patient outreach to trace patients missing visits had lower non-retention. Taken together, this analysis provides evidence that program-level services found efficacious in experimental settings are also effective in operational settings.

The second paper refines the non-retention, loss to follow-up, and death rate estimates by (1) comparing estimates obtained from aggregate vs. patient-level databases and (3) additionally allowing for adjustment for patient-level predictors of loss to follow-up and death. This analysis focuses on a subset of HIV care and treatment facilities in 5 countries that also have electronic patient-level databases. 92,561 patients initiating ART before July 1, 2009 at 92 care and treatment facilities were included in this analysis. A key finding, examined in more detail in Appendix 3, is that estimates of death rates were similar in the aggregate and patient-level analyses, while loss to follow-up rates were higher in analyses using the patient level database. In multivariate analyses, clinics offering active patient outreach had lower rates of non-retention in both the ART cohort analysis and the patient-level analysis, and clinics offering food rations to promote ART adherence were associated with a lower risk of ascertained death in

both the facility-level and patient-level analyses, but this association was diminished after adjustment for patient-level covariates. In contrast, various adherence counseling or support services were associated with lower non-retention in the ART cohort analyses but not in the patient-level data analyses. When compared with the results in the first paper, fewer associations were observed, suggesting either that the countries with patient-level databases are not representative of the entire range of HIV care and treatment facilities assessed in the first paper, and/or the specific facilities with electronic databases are more similar to each other than they are to facilities without electronic databases. The discussion in Paper 2 expands on these conclusions in more detail.

Finally, the third paper focuses on the problem of loss to follow-up in biasing estimates of death rates, and in biasing relative comparisons of death rates between facilities. For this analysis, estimates of the death probability among patients lost to follow-up are created under varying assumptions (either assuming that the death probability among those lost to follow-up is equivalent to the death probability within various strata of covariates, or assuming that the probability of death is greater among patients lost to follow-up). Key findings from this analysis are that ratio comparisons of death rates between facilities offering different services are robust to changes in the death probability if patients lost to follow-up are assumed to have a similar probability of death, conditioned on covariates, as those not lost to follow-up, but that associations between facility services and death rates are masked under the scenario where the facility service is associated with loss to follow-up and the death probability is assumed to be

higher, conditioned on covariates, then the death probability among patients not lost to follow-up.

This dissertation contains six chapters and several appendices. Following this introductory chapter, Chapter 2 presents a literature review on adherence to ART, and retention and survival in care, with a specific focus on the influence of program services on patient non-retention, loss to follow-up, and survival. Chapter three begins the analytic work with an ecologic analysis investigating the relationship between adherence support and outreach services and facility-level rates on non-retention, loss to follow-up, and death. Chapter 4 compares ecologic and patient-level analyses assessing the same research question motivating Chapter 3. Chapter 5 investigates the relationship between loss to follow-up and ascertained death in more detail with a sensitivity analysis investigating the influence of different assumptions of the death likelihood among patients lost to follow-up on the observed relationship between adherence support and outreach services and rates of death. Finally, Chapter 6 summarizes the findings of this dissertation, reviews the process taken to achieve these results, and points toward future areas of related research.

Chapter 2: Background and literature review

Overview of the HIV epidemic in Sub-Saharan Africa

HIV/AIDS continues to be a catastrophic health problem in much of the world, most acutely in the countries of Sub-Saharan Africa. The introduction of highly active antiretroviral therapy (HAART) in 1995-6 drastically reduced the mortality rates, incidence, and overall numbers of deaths from AIDS in low-burden, resource-rich settings [1-3]. However, access to HAART is far from universal, and until recently care and treatment programs in the areas of the world most affected by HIV were rare. Approximately 22.5 million of the 33.2 million individuals living with HIV/AIDS worldwide, 1.7 million of the 2.5 million new cases of HIV, and 1.6 million of the 2.1 million deaths from AIDS were in Sub-Saharan Africa in 2007 [4].

Initiatives aimed at providing care and treatment to HIV-positive individuals in Sub-Saharan Africa have been established through a variety of organizations, both governmental and non-governmental. In contrast to more patient-centered approaches offered in resource-rich areas, sub-Saharan governments have established public health-centered approaches to HIV care and treatment based on WHO guidelines [5]. International and non-governmental initiatives work with each country to interpret these guidelines to meet the needs and constraints of each country. Three of the largest initiatives which have provided funding and/or technical assistance to support the development and maintenance of HIV care and treatment facilities in resource-poor environments are the President's Emergency Plan for AIDS relief (PEPFAR), the Global Fund for AIDS, Tuberculosis, and Malaria, and the World Health Organization's 3x5 initiative [6]. These umbrella initiatives work by developing partnerships with local and

international governmental, non-governmental, and private sector actors to develop infrastructure, recruit and train health care personnel, and provide steady access to HAART medication. While these initiatives all work from the same framework of WHO guidelines for scaling up HIV care and treatment, the implementation of these guidelines differs markedly by country, and by facility, resulting in a heterogeneous mixture of care and treatment programs.

These, and other, treatment initiatives have dramatically increased the number of individuals in care and on ART in developing countries. According to the World Health Organization, there were over 500,000 persons receiving treatment in Sub-Saharan Africa through June 2005 [7]. A more recent WHO report [5] estimates that in sub-Saharan Africa, about 1.3 million (28%) of [1]those needing HAART treatment are receiving it. Although this proportion is still low, it is clear that some progress is being made.

Antiretroviral Treatment Adherence

Definition and overview

Consistent and continual adherence to ART medication drastically improves treatment outcomes for patients living with HIV/AIDS. Adherence is defined as the consistent and regular taking of prescribed ART medication, with 'good adherence' generally classified as correctly taking the prescribed dosage >95% of the time [8]. Maintaining a suppressed viral load and delaying progression to AIDS or death depends on

[1] 'treatment failure' is defined here based on CD4 counts. According to the WHO, guidelines for treatment failure are (1) CD4 count below 100 cells/mm3 after six months of therapy; (2) a return to, or a fall below, the pre-therapy CD4 baseline after six months of therapy; or (3) a 50% decline from the on-treatment peak CD4 value (if known). *Source: WHO 2006*

individuals maintaining high and consistent adherence to ART treatment. Studies both in resource-rich and resource-poor environments have found non-adherence to be associated with lack of viral suppression, accelerated progression to AIDS, and treatment failure* [9-16]. Lack of adherence to HAART has also been associated with increased likelihood of developing drug-resistant mutations [17-19], posing a potential treatment difficulty both to the individual and to any individuals a person with drug-resistant HIV may infect. Modeling studies by Paterson et al [14] and Low-Beer et al [20] suggest that adherence of >95% is optimal for adequate viral suppression and minimizing the development of drug resistant strains of HIV.

What is unknown is how best to optimize consistent and continual adherence in the context of scale-up of HIV care and treatment service delivery in resource-limited settings. Optimal adherence requires two inter-related components: day-to-day adherence and long-term adherence. At the onset of the scale-up of antiretroviral programs in sub-Saharan Africa there was apprehension among researchers and public health practitioners in resource-rich countries about the ability to support and ensure adequate adherence in resource-poor settings [21, 22]. However, early reports on treatment adherence in sub-Saharan Africa were promising, with several suggesting that antiretroviral adherence in the region was higher than was observed in developed countries [13, 23]. More recent reports [9, 10, 13, 16-19, 23-27], including a 2006 meta-analysis comparing reported results of adherence in US and sub-Saharan Africa [28], supported these findings. However, most of these studies were performed on populations participating in trials or research studies with fairly strict inclusion criteria,

such as prior demonstration of adherence to tuberculosis regimens [25], completion of at least 30 days of ART with full adherence [13], or consistent attendance at an HIV clinic [10, 24, 26], all of which may select for higher adherence levels than would be expected in more general populations. Until now there has also been insufficient time to evaluate longer-term adherence, and it is consequently unknown whether the levels of adherence demonstrated in these early studies has been sustained. It is not unexpected, then, that a more thorough investigation of adherence levels indicates a high degree of heterogeneity in reported levels of adherence in resource-poor countries. In the past 5 years, there have been several studies reported in meeting abstracts and journals assessing adherence to antiretroviral medication, with reported adherence levels ranging from 30% “completely adherent” in Burkina Faso [29] to 100% adherent at 3 months in the Democratic Republic of Congo [30] (reviewed in [21]). This suggests that the earliest reports of high adherence in sub-Saharan Africa may not representative of the overall ART adherence picture in the region.

Adherence barriers and enablers

There is little information on the reasons for non-adherence to antiretroviral medication in developing countries, and much of the investigation of barriers to adherence in resource-rich countries have focused on individual-level reasons for non-adherence. A 2000 review of published literature on reasons for nonadherence to ART in developed countries found mostly patient-level factors, such as illicit drug use, forgetfulness, change in one’s daily routine, perceived or real side effects, and lack of belief in benefit of treatment [31, 32], with little published information available on group-level factors. Reasons for non-adherence to antiretroviral medication in developed countries do not seem to be markedly different from reasons for non-adherence to other medications in

the published literature [33]. However, there is reason to expect that barriers to adherence in developing countries differ from those in developed counties. A 2006 qualitative review of barriers to adherence in both resource-rich and resource-poor countries found important differences in reported reasons for non-adherence [34]. Reasons for non-adherence in developing settings were more likely to include issues of consistent access to medication and financial constraints. An extensive literature search has revealed only three published studies formally investigating reasons for non-adherence to antiretroviral medication in developing countries: one in Brazil [35], one in Botswana [19], and one in Botswana, Tanzania and Uganda [36]. In the study conducted in Brazil, which has a nationalized health care system and guaranteed free access to antiretroviral medication, reasons for non-adherence were similar to those found in more developed countries, including forgetfulness and concern over side effects [35]. In contrast, the study in Botswana, where treatment was not free and the health care system is much less developed than it is in Brazil, the most common reasons given for nonadherence were related to inability to pay for treatment, forgetfulness, inconsistent availability of antiretroviral medication, long travel to obtain antiretrovirals, and being 'too busy.' [19] They also estimated that, had medication been given free of charge, the levels of adherence would have risen from 54% to 74% [19]. A 2007 qualitative study in three sub-Saharan African countries focused on reasons for non-adherence to antiretroviral medication in settings where the medicines are offered free of charge to the patients, and found such reasons as high transport costs, long waiting times at the clinic (resulting in lost wages), issues related to hunger (either inability to take drugs more than once a day because they only have food once a day,

or inability to procure sufficient food to combat increased hunger in initial stages of treatment), stigma, and side effects [36].

The qualitative studies on lack of adherence to antiretroviral medications provide an important, if incomplete, starting point for the more central question: how can we improve adherence? As reviewed above, qualitative studies have suggested a plethora of reasons for non-adherence, both in developed and developing settings. However, there have been few studies looking at whether interventions aimed at improving adherence actually do so, with almost all studies being conducted in developed countries. One study in a California population evaluated the impact of an adherence intervention program, combining written information, a verbal discussion with the health care provider on the importance of adherence and suggestions of tools, such as pill boxes and reminder calendars to improve adherence, on adherence. This study found that 91% of individuals who additionally received the adherence intervention reported >95% adherence to medication, compared with 75% of individuals only receiving information on the importance of safer sex [37]. A small randomized trial investigating the impact of an adherence program including an informational component and the availability of various reminder tools found an increase in self-reported adherence during the prior week, but not the prior month, when compared to a control group receiving no additional information on adherence [38]. Similarly, a randomized trial in France found that an intensive informational adherence program improved self-reported adherence levels at 6 months and 12 months, but not at 24 months, when compared with a control arm receiving no intervention [39]. Another French trial found a small but

significant improvement in adherence 6 months after a nurse-provided adherence intervention compared with a control arm (75% vs. 61% adherent) [40]. A randomized trial comparing individual-based cognitive behavioral therapy to standard of care improved adherence at 12 months (70% in intervention arm obtaining >95% adherence measured via electronic monitoring vs 50% in control arm) [41]. Conversely, a study in Texas found no difference in adherence levels or change in viral load between a group receiving an educational adherence intervention and those receiving standard of care [42], and a randomized trial in New York City comparing adherence and HIV viral load suppression between individuals in a peer-support intervention arm to those in a standard of care arm found no effect of the intervention on these outcomes [43].

There have been very few studies attempting to investigate how a facility-level intervention could improve adherence in the context of ART scale-up in resource-poor settings. The study by Weiser et al [19] suggested that, if treatment were offered free of charge in their study population in Botswana, adherence levels would increase from 54% to 74%. A study presented at the 2004 International AIDS conference, in which only 30% of patients reported complete adherence, found that counseling on the importance of adherence helped 75% of those not completely adherent at baseline improve their adherence, although this abstract did not specify how much the improvement was [29]. In a 2005 letter to the editor describing adherence to an antiretroviral treatment program in Rwanda, Demeester et al. reported that counseling and family support were ‘essential’ to their high levels of adherence (87% reporting no missed doses during previous month) [44].

Directly Observed Therapy (DOT), in which patients take their medication in the presence of a health administer, has been shown to effectively improve adherence to antiretroviral medication in Haiti [45, 46]. This method has also shown effectiveness in the treatment of tuberculosis [47], another infectious disease requiring a fairly long treatment regimen. However, the intensive resources needed to scale-up this type of program, the projected numbers of patients, and the fact that ART adherence is required for a lifetime, are likely to limit the applicability of such an intervention on a large scale. Other, less resource-intensive interventions are increasingly available as part of the HIV care and treatment programs in resource-limited countries. However, an extensive literature search has found no evidence of studies which have looked at whether adherence interventions actually improve adherence in resource-poor settings.

Given the heterogeneous nature of the services offered at HIV care and treatment programs in sub-Saharan Africa, the rapid scale up of these programs, and the importance of adherence to improving treatment outcomes, research is urgently needed on how best to optimize adherence in these settings.

Long-term adherence and retention in care and treatment programs

Overview

Optimal HIV care and treatment requires long-term patient follow-up, both to ensure adherence and to provide routine monitoring and treatment of comorbidities. Successful treatment for HIV is a lifelong activity. In the context of Sub-Saharan Africa, patients who are not retained in HIV care and treatment will not receive ART,

dramatically increasing morbidity and mortality risk. Demonstrating this, a study by Mocroft et al. came to the succinct conclusion that individuals with clinical AIDS who discontinue treatment will likely die within a short time [48].

Long-term retention in care in the context of HIV treatment in sub-Saharan African has often been seen as a 'side issue,' with the focus on treatment and outcome evaluation of patients remaining in care [49] and those not retained deemed "lost to follow-up" and treated as a source of potential bias in analysis. This is in part because scale-up of HIV care and treatment centers in sub-Saharan Africa only began in 2004, giving insufficient time for any long-term analysis of retention in care until recently [49]. Published proportions of patients lost to follow-up in clinical settings in Sub-Saharan Africa range from less than 5% [50-52] to over 50% [26]. A recent review [49] gives estimates of patient retention from 33 scale-up programs in sub-Saharan Africa, finding extreme heterogeneity in the amounts of loss to follow-up, with 24-month retention rates ranging from 46% at a fee-for-service facility in Uganda [53] to 85% at a community-based clinic in South Africa [50]. This review was limited by the varying definitions of loss to follow-up across the facilities included in the analysis. A recent study [54] from the ART-LINC collaboration on predictors of loss to follow-up in resource-poor settings in Africa, Asia and Latin America found large variation in follow-up across sites, with facilities serving larger numbers of patients more likely to have higher rates of loss to follow-up. The study found rates of loss to follow-up ranging from no loss in a variety of sites with active follow-up of patients to 45% of patients in a Malawi care and treatment center with no active follow-up [54]. Similarly, a community-based HIV care and treatment

program in South Africa, with active tracing of patients missing scheduled visits, had low rates (2.3%) of loss to follow-up through 4 months of treatment [55].

There have studies investigating the baseline characteristics of patients lost to follow-up in these settings. The ART-LINC collaboration [54] found that, across a range of care and treatment facilities in Africa, Asia, and Latin America, compared to individuals with baseline CD4 counts $\geq$50 cells/μL, individuals with baseline CD4 counts < 25 cells/μL had a higher probability of no follow-up (OR 2.5, 95% CI 1.4-4.3) or loss to follow-up within 4 months (HR = 1.5, 95% CI 1.2-1.8). Since low CD4 count is a strong predictor of mortality, this suggests that individuals with low CD4 counts who are lost to follow-up may actually be unascertained deaths. Facility characteristics associated with loss to follow-up were being a fee-for-service program (OR for no follow-up = 3.7, 95% CI 1.0-16.1). The study also found that loss to follow-up increased substantially from earlier calendar periods (before or during 2000) to more recent periods (2003-2004). The Odds Ratio of no follow-up (OR = 5.1, 95% CI 1.3-20.0) and the Hazard Ratio of loss to follow-up (HR 7.6, 95% CI 4.6-12.8) was significantly higher for the later follow-up period compared with earlier periods, suggesting that sites with increasing numbers of patients, and thus diminishing resources to devote to aspects other than direct patient care, are finding it harder to continue retention. Only one published study in sub-Saharan Africa (Malawi) attempted to identify patients initially lost to follow-up. This study traced patients who had not attended the facility for 3 or more months and found that 50% of the patients classified as lost to follow-up had died [56]. This study highlights the fact that loss to follow-up is an important program outcome in itself, since those lost are at higher risk for treatment failure and death than those retained in

treatment. Taken together, these studies highlight the heterogeneous nature of individuals classified as 'lost to follow-up,' comprising both those individuals whose death prevented them from returning to clinic (a group who would see a benefit in more complete ascertainment, but not reduced risk of death, if exposed to an outreach program) and individuals who, had they been identified through and outreach program may have been re-entered into care.

Methods for improving program retention

It is clear that maximizing patient retention is essential for optimal treatment outcomes. However, there has been little investigation into identifying and evaluating what methods of optimizing retention work best. Methods for improving long-term retention are varied in the context of care and treatment in Sub-Saharan Africa, and the impact of these methods has not been sufficiently assessed. Active outreach programs attempt to locate individuals missing scheduled visitations through mail, telephone, or home visitation. In contrast, facilities describing their outreach programs as 'passive' do not attempt to locate missing individuals, and rely on medical records and death certificates to classify individuals no longer attending the facility as dead, transferred, or unknown. It has been documented that HIV care and treatment centers offering some type of active outreach are likely better able to retain patients in care than are sites offering no outreach [57]. Active outreach programs focused on ART patients have been shown to improve adherence [58] and reduce attrition [57] both in resource-rich and resource-poor environments. However, whether targeting patients for active outreach before they are on ART, in addition to those on ART, improves retention has not been investigated. Active outreach of patients in HIV care, but who do not yet meet ART eligibility criteria,

can provide an indoctrination into the HIV care and treatment process, establish a routine for maintaining contact with medical staff, provide information about the importance of adherence to ARV medications and prompt initiation of treatment when they become clinically eligible. Pre-ART individuals maintaining regular scheduling with their care and treatment facility also have access to a variety of non-ART treatment options, such as opportunistic infection prophylaxis. In addition, the existence of active outreach of pre-ART patients is likely to be indicative of a more comprehensive and/or well-resourced care and treatment program since resources are usually first allocated toward those patients already initiated onto ARV treatment. Interestingly, there has been no systematic evaluation of whether this prioritization of resources is optimal. Thus, comparing treatment outcomes between patients on ART medication attending sites which have active follow-up for both pre-ART and ART patients to those attending sites without such a comprehensive outreach program is thus a useful way to measure the impact of such follow-up, and of comprehensiveness of care in general, on patient outcomes. However, the complication that improved ascertainment of deaths increases a facility's death rate makes assessment of the impact of such outreach programs on actual survival difficult. An approach that can disentangle these effects would thus be beneficial.

Rationale for investigating treatment adherence and retention at the facility/program level.

As discussed above, there are many reasons that an individual patient may fail to adhere on a day-to-day basis to their antiretroviral medication. There are also many reasons why a patient may fail to maintain regular contact with their care and treatment facility. Using a public health approach to treatment scale-up, we are most concerned

with where to potentially intervene in order to best to improve adherence and retention. Thus, even though the act of adherence and retention occurs at the individual-level, the best intervention to improve adherence and retention may occur at the facility/program-level.

As evidenced by the studies of adherence in resource-rich environments, non-adherence to medication is a common problem across all chronic diseases, and we must expect that regardless of the amount of education, adherence reminder tools, and structural interventions, certain individuals will simply not adhere to their medication. There also exist important differences between the reasons for non-adherence given by patients in resource-rich and resource-poor environments, with non-adherence more intimately linked to structural issues of drug availability, cost, and lack of education on the importance of adherence in resource-poor environments [34]. Improving adherence to medication also requires behavioral change, which in turn is intimately tied to questions involving the ability to sustain change and the relationship between this change and social norms surrounding the behavior. In the context of improving adherence to HIV treatment in sub-Saharan Africa, this suggests that programs that have strong adherence support, and active follow-up of patients in care and treatment, may also have better adherence both for individuals participating in the adherence support activities and those not participating, due to information sharing and the overall changing of social norms concerning adherence. This type of 'spillover effect' may be important in evaluating the overall impact of adherence and follow-up programs on treatment outcomes and would be missed in an individual-only assessment.

Conversely, if adherence support activities are found to only benefit those attending, but the proportion of eligible individuals attending such programs is low, there would not be a strong facility and program-level benefit to such an intervention. Finally, from a service delivery perspective, focusing on facility and program-level factors improving treatment adherence and retention is desirable because this level offers the easiest point of intervention, since HIV care and treatment is organized around these facilities.

As highlighted by the findings of studies in resource-poor environments documenting that issues surrounding transportation, cost and drug availability are important determinants of adherence to antiretroviral medication, it follows that interventions targeting more structural issues may have the most impact on improving adherence. Evaluating adherence and retention at the facility/program level offers an opportunity to investigate these more structural interventions on individual-level outcomes. Further, since the number of care and treatment facilities for HIV is exponentially increasing in sub-Saharan Africa, the identification of facility/program-level interventions which improve adherence, or reduce attrition, could potentially be incorporated into new and existing care and treatment facilities. Using an evidence-based approach to investigating which characteristics of care and treatment programs best improve adherence, reduce attrition, and improve treatment outcomes is thus important.

Complexities in assessing program/facility-level factors associated with treatment adherence and patient retention

Individual-level differences between facilities

We must recognize that differences in the characteristics of individuals attending different HIV care and treatment facilities may partially explain observed differences in treatment outcomes between sites. If these individual-level differences are not caused by the programs themselves (such as if patient-level differences in CD4 counts at treatment initiation are caused by differing facility policies on when to initiate treatment), they can provide an alternate explanation for an observed difference in patient outcomes between sites. This potential for individual-level confounding is a threat to the internal validity of any study investigating the causal effect of a facility/program-level intervention. Multilevel methods, which can assess the impact of a facility/program-level characteristic while adjusting for known individual-level differences between sites, have the potential to reduce this limitation, but requires sufficient information to be gathered at the individual level. When individual-level information is not available, it may be possible to adjust for aggregate-level differences in patient populations between facilities using such factors as average CD4 count at treatment initiation and sex and age distribution [59]. This type of analysis, which does not directly evaluate the potential for individual-level differences to drive observed facility-level differences, has not been evaluated for its potential to reduce the threat from individual-level confounding.

Loss to follow-up as a hindrance to evaluation of the impact of facility and program-level services on mortality

A methodological complexity arises when attempting to evaluate the effectiveness of facility/program characteristics on patient mortality rates in settings where there exist non-trivial amounts of censoring. As discussed above, one way in which

facility/program characteristics targeting treatment adherence and patient retention attempt to reduce patient mortality rates is by improving retention in the programs. That is, retention in programs is hypothesized to be in the causal pathway between the exposures of interest (treatment adherence support programs and active outreach programs) and the outcome (death). If we had complete ascertainment of the outcome status of all patients, we would be able to directly measure the relationship between the exposures of interest and patient survival, conceptualizing patient retention as a mediator on this causal pathway. However, in the context of HIV care and treatment facilities in resource-poor environments, there is often a substantial proportion of patients whose outcome status is unknown. These patients may be at higher risk of death than those retained in the program, since program retention is hypothesized as a mediator of the relationship between the facility/program-level characteristics and death. Thus we are left with a situation in which we want to reduce the information bias caused by incomplete outcome ascertainment without adjusting for the causal intermediate of patient retention.

Conventional statistical modeling, such as Cox Proportional Hazards modeling, requires an assumption that, conditioned on the covariates in the model, individuals who are lost to follow-up are missing at random, meaning that they have no greater risk for having the outcome of interest than do individuals retained in the analysis. However, this assumption is clearly untenable since those individuals lost to follow-up are not exposed to the proposed intermediate (patient retention in the care and treatment facility) on the causal pathway between exposure and outcome. More sophisticated statistical

methods, such as marginal structural models [60] and g-estimation techniques, are also ill-suited to adjust for a variable that is both a source of information bias and an intermediate variable. Both of these techniques require that censored observations are 'non-informative' conditioned on measured past exposure and covariate history [61], which does not hold if those censored are at increased risk of death due to their lack of exposure to an intermediate variable.

Methods to separate the effects of an outreach program on (1) death ascertainment and (2) actual death risk are particularly important when evaluating the impact of program-level interventions on survival when the amount of censoring is on the order of, or greater than, the measured death rate. Situations such as this create counterintuitive results that programs having an active outreach service have higher measured death rates than programs not having such services [49, 57]. Patient non-retention and loss to follow-up are often used synonymously in the literature discussed above, but there is an important conceptual distinction between the two concepts. Patients who are not retained in a care and treatment facility may have died, transferred to a different program, or opted out of treatment. These endpoints exist regardless of whether the facility has the information to classify their patients' outcomes. In contrast, patients who are lost to follow-up are those patients whose eventual outcome status is unknown. Thus, loss to follow-up is a source of measurement error that would disappear if we were able to ascertain each individual's outcome status correctly. The distinction between patient non-retention and loss to follow-up is often blurred in studies investigating patient retention, since much of the literature investigating patient retention

in care and treatment facilities defines those individuals whose outcome status is unknown as the pool of patients who have not been retained in the facility. This creates a difficulty in estimating the impact of interventions to improve patient treatment outcomes because the impact of reducing censoring on the measured death rate works in the opposite direction of the hypothesized impact on the actual death rate. This creates seemingly counterintuitive findings in several studies looking at patient survival rates that facilities with active patient outreach programs report substantially higher death rates than facilities without such programs [49, 57].

Conclusion and specific aims

The specific aims investigated in this dissertation stem from gaps in the literature surrounding predictors of non-retention, loss to follow-up, and ascertained death among ART patients in resource-limited settings. Specifically the purposes of this dissertation are (1)to identify whether program-level services designed to influence patient adherence to ART and retention in care are associated with improved rates of non-retention, loss to follow-up, and death, (2) to assess whether any observed associations between program-level service availability and estimates of non-retention, loss to follow-up, and death differ by the source of the outcome estimate (overall aggregate, cohort, and patient-level), and (3) to investigate how different estimates of the survival distribution among patients lost to follow-up influence measures of association comparing death rates between facilities offering different services.

References

1. Mocroft, A., et al., *AIDS across Europe, 1994-98: the EuroSIDA study.* Lancet, 2000. 356(9226): p. 291-6.
2. Palella, F.J., Jr., et al., *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.* N Engl J Med, 1998. 338(13): p. 853-60.
3. Porter, K., et al., *Determinants of survival following HIV-1 seroconversion after the introduction of HAART.* Lancet, 2003. 362(9392): p. 1267-74.
4. Joint United Nations Programme on HIV/AIDS (UNAIDS), W.H.O., *AIDS Epidemic Update: December 2007*. 2007.
5. World Health Organization, U., UNICEF, *Towards universal access : scaling up priority HIV/AIDS interventions in the health sector : progress report, April 2007.* 2007.
6. Nash D, E.B., *The impact of HIV on cities in the era of treatment: A global perspective.* Technology in Society, 2006. 28(1-2): p. 195-223.
7. World Health Organization, *Progress on Global Access to HIV Antiretroviral Therapy: an Update on "3 by 5"*. 2005.
8. Attaran, A., *Adherence to HAART: Africans take medicines more faithfully than North Americans.* PLoS Med, 2007. 4(2): p. e83.
9. Idigbe, E.O., et al., *Management of HIV-1 infection with a combination of nevirapine, stavudine, and lamivudine: a preliminary report on the Nigerian antiretroviral program.* J Acquir Immune Defic Syndr, 2005. 40(1): p. 65-9.
10. Laniece, I., et al., *Adherence to HAART and its principal determinants in a cohort of Senegalese adults.* AIDS, 2003. 17 Suppl 3: p. S103-8.
11. Mannheimer, S., et al., *The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials.* Clin Infect Dis, 2002. 34(8): p. 1115-21.
12. Nachega, J.B., et al., *Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa.* AIDS Res Hum Retroviruses, 2004. 20(10): p. 1053-6.
13. Orrell, C., et al., *Adherence is not a barrier to successful antiretroviral therapy in South Africa.* AIDS, 2003. 17(9): p. 1369-75.
14. Paterson, D.L., et al., *Adherence to protease inhibitor therapy and outcomes in patients with HIV infection.* Ann Intern Med, 2000. 133(1): p. 21-30.
15. Safren, S.A., et al., *ART adherence, demographic variables and CD4 outcome among HIV-positive patients on antiretroviral therapy in Chennai, India.* AIDS Care, 2005. 17(7): p. 853-62.
16. Wools-Kaloustian, K., et al., *Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya.* AIDS, 2006. 20(1): p. 41-8.
17. Rabkin, M., et al., *Antiretroviral treatment in resource-poor settings: clinical research priorities.* Lancet, 2002. 360(9344): p. 1503-5.
18. Stevens, W., S. Kaye, and T. Corrah, *Antiretroviral therapy in Africa.* BMJ, 2004. 328(7434): p. 280-2.
19. Weiser, S., et al., *Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana.* J Acquir Immune Defic Syndr, 2003. 34(3): p. 281-8.
20. Low-Beer, S., et al., *Adherence to triple therapy and viral load response.* J Acquir Immune Defic Syndr, 2000. 23(4): p. 360-1.

21. Gill, C.J., et al., *No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa.* AIDS, 2005. 19(12): p. 1243-9.
22. Harries, A.D., et al., *Preventing antiretroviral anarchy in sub-Saharan Africa.* Lancet, 2001. 358(9279): p. 410-4.
23. Laurent, C., et al., *The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study.* AIDS, 2002. 16(10): p. 1363-70.
24. Coetzee, D., et al., *Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa.* AIDS, 2004. 18 Suppl 3: p. S27-31.
25. Jaffar, S., et al., *Antiretroviral treatment in resource-poor settings: public health research priorities.* Trop Med Int Health, 2005. 10(4): p. 295-9.
26. van Oosterhout, J.J., et al., *Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi.* Trop Med Int Health, 2005. 10(5): p. 464-70.
27. Laurent, C., et al., *Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1-infected adults.* J Acquir Immune Defic Syndr, 2005. 38(1): p. 14-7.
28. Mills, E.J., et al., *Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis.* JAMA, 2006. 296(6): p. 679-90.
29. Traore AA, N.V., McCarrick P, Dhaliwal M, Tioendrebeogo I, Ilboudo A, *Barriers to adherence to ARV therapy in a community-based cohort in Burkina Faso [Abstract]*, in *XV International AIDS Conference*. 2004: Bangkok, Thailand. p. AbstractWePeB5824.
30. Tu D, K.N., Culbert H, Migabo K, Amisi T, *ARV selection criteria and innovative group adherence counseling in Bukavu, Democratic Republic of Congo – Program implementation in the context of chronic war and a failing healthcare system [Abstract]*, in *XV International AIDS Conference*. 2004: Bangkok, Thailand. p. Abstract B12702.
31. Chesney, M.A., *Factors affecting adherence to antiretroviral therapy.* Clin Infect Dis, 2000. 30 Suppl 2: p. S171-6.
32. Chesney, M.A., M. Morin, and L. Sherr, *Adherence to HIV combination therapy.* Soc Sci Med, 2000. 50(11): p. 1599-605.
33. DiMatteo, M.R., *Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research.* Med Care, 2004. 42(3): p. 200-9.
34. Mills, E.J., et al., *Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators.* PLoS Med, 2006. 3(11): p. e438.
35. Brigido, L.F., et al., *Impact of adherence to antiretroviral therapy in HIV-1-infected patients at a university public service in Brazil.* AIDS Patient Care STDS, 2001. 15(11): p. 587-93.
36. Hardon, A.P., et al., *Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa.* AIDS Care, 2007. 19(5): p. 658-65.
37. Milam, J., et al., *Effect of a brief antiretroviral adherence intervention delivered by HIV care providers.* J Acquir Immune Defic Syndr, 2005. 40(3): p. 356-63.
38. Fairley, C.K., et al., *Randomized trial of an adherence programme for clients with HIV.* Int J STD AIDS, 2003. 14(12): p. 805-9.
39. Goujard, C., et al., *Impact of a patient education program on adherence to HIV medication: a randomized clinical trial.* J Acquir Immune Defic Syndr, 2003. 34(2): p. 191-4.
40. Pradier, C., et al., *Efficacy of an educational and counseling intervention on adherence to highly active antiretroviral therapy: French prospective controlled study.* HIV Clin Trials, 2003. 4(2): p. 121-31.

41. Weber, R., et al., *Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial.* Antivir Ther, 2004. 9(1): p. 85-95.
42. Rawlings, M.K., et al., *Impact of an educational program on efficacy and adherence with a twice-daily lamivudine/zidovudine/abacavir regimen in underrepresented HIV-infected patients.* J Acquir Immune Defic Syndr, 2003. 34(2): p. 174-83.
43. Simoni, J.M., et al., *A randomized controlled trial of a peer support intervention targeting antiretroviral medication adherence and depressive symptomatology in HIV-positive men and women.* Health Psychol, 2007. 26(4): p. 488-95.
44. Demeester, R., et al., *Adherence to first-line antiretroviral regimens in Rwanda.* J Acquir Immune Defic Syndr, 2005. 40(1): p. 113-4.
45. Farmer, P., et al., *Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy).* Bull World Health Organ, 2001. 79(12): p. 1145-51.
46. Mitty, J.A., et al., *Directly observed therapy for the treatment of people with human immunodeficiency virus infection: a work in progress.* Clin Infect Dis, 2002. 34(7): p. 984-90.
47. Chaisson, R.E., J.S. Coberly, and K.M. De Cock, *DOTS and drug resistance: a silver lining to a darkening cloud.* Int J Tuberc Lung Dis, 1999. 3(1): p. 1-3.
48. Mocroft, A.J., et al., *Survival of AIDS patients according to type of AIDS-defining event. The AIDS in Europe Study Group.* Int J Epidemiol, 1997. 26(2): p. 400-7.
49. Rosen, S., M.P. Fox, and C.J. Gill, *Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review.* PLoS Med, 2007. 4(10): p. e298.
50. Coetzee, D., et al., *Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa.* AIDS, 2004. 18(6): p. 887-95.
51. Lawn, S.D., et al., *Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation.* Clin Infect Dis, 2006. 43(6): p. 770-6.
52. Tassie, J.M., et al., *Highly active antiretroviral therapy in resource-poor settings: the experience of Medecins Sans Frontieres.* AIDS, 2003. 17(13): p. 1995-7.
53. Kabugo, C., et al., *Long-term experience providing antiretroviral drugs in a fee-for-service HIV clinic in Uganda: evidence of extended virologic and CD4+ cell count responses.* J Acquir Immune Defic Syndr, 2005. 38(5): p. 578-83.
54. Brinkhof, M.D.F.M.L.B.D.B.A., Nash D, Schechter M, Laurent C, Keiser O, May, M, Sprinz, E, Eggar, M, Anglaret, X, *Early loss to program in HIV-infected patients starting potent antiretroviral therapy in lower-income countries.* PLOS Medicine, 2008. in press.
55. Lawn, S.D. and R. Wood, *How can earlier entry of patients into antiretroviral programs in low-income countries be promoted?* Clin Infect Dis, 2006. 42(3): p. 431-2; author reply 432-3.
56. Yu, J.K., et al., *True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi.* Bull World Health Organ, 2007. 85(7): p. 550-4.
57. Braitstein, P., et al., *Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries.* Lancet, 2006. 367(9513): p. 817-24.
58. Tadios, Y. and G. Davey, *Antiretroviral treatment adherence and its correlates in Addis Ababa, Ethiopia.* Ethiop Med J, 2006. 44(3): p. 237-44.
59. King, G., *A Solution to the Ecological Inference Problem*. 1997, Princeton, NJ: Princeton

University Press.
60. Robins, J.M., M.A. Hernan, and B. Brumback, *Marginal structural models and causal inference in epidemiology.* Epidemiology, 2000. 11(5): p. 550-60.
61. Hernan, M.A., et al., *Structural accelerated failure time models for survival analysis in studies with time-varying treatments.* Pharmacoepidemiol Drug Saf, 2005. 14(7): p. 477-91.
62. Greenland, S., J. Pearl, and J.M. Robins, *Causal diagrams for epidemiologic research.* Epidemiology, 1999. 10(1): p. 37-48.
63. Pearl, J., *Causal diagrams for empirical research.* Biometrika, 1995. 82(4).
64. Hernan, M.A., S. Hernandez-Diaz, and J.M. Robins, *A structural approach to selection bias.* Epidemiology, 2004. 15(5): p. 615-25.
65. Rubin, D.B., Schenker, Nathaniel, *Multiple imputation in health-are databases: An overview and some applications.* Statistics in Medicine, 1991. 10(4): p. 585-598.

The relationship of adherence support and active outreach services with rates of patient non-retention, loss to follow-up, and ascertained death in sub-Saharan African HIV care and treatment scale-up clinics

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Abstract

Background:
High rates of loss to follow-up (LTF) and death remain common in HIV care and treatment clinics in sub-Saharan Africa. Few studies have examined the impact of different treatment adherence support strategies and active outreach for patients who miss clinic visits on program retention.

Methods:
Using routinely collected aggregate PEPFAR indicators from 349 HIV care and treatment clinics in 10 sub-Saharan African countries, we investigated the relationship between adherence support and outreach services on patient non-retention in care, LTF, and death among 232,389 patients initiating ART during 2004-2008, and on a subset of ART patients (n=83,389) with 6-month and 12-month follow-up information. Data on adherence support and outreach services were obtained from annual structured site assessments. Multivariate Poisson regression using generalized estimating equations was used to examine differences in mean rates of non-retention, loss to follow-up, and death between clinics with and without adherence support and outreach services.

Results: Among the 232,389 patients included in this analysis, the overall non-retention, LTF, and death rates following ART initiation were 14.1, 9.2, and 4.9 per 100 person-years on ART, respectively. In multivariate analyses lower non-retention rates were observed among sites offering more than two adherence support services (RR_{adj} = 0.59, 95% CI = 0.35-1.0), written educational materials on ART adherence (RR_{adj} = 0.73, 95% CI = 0.63-0.85), one-on-one or group adherence counseling services (RR_{adj} = 0.62, 95% CI = 0.42-0.92), reminder tools (RR_{adj} = 0.79, 95% CI = 0.64-0.97), and food rations to promote ART adherence (RR_{adj} = 0.72, 95%CI = 0.58-0.90) compared with those sites that did not offer such services. Variables associated with non-retention were similarly associated with loss to follow-up. Lower rates of ascertained death were associated with the availability of on-site support groups (RR_{adj} = 0.81, 95% CI = 0.71-0.93) and peer educator programs (RR_{adj}=0.84, 95% CI = 0.74-0.96), along with the provision of reminder tools (RR_{adj} = 0.81, 95% CI = 0.66-0.98) and food support to promote ART adherence (RR_{adj} = 0.83, 95% CI = 0.69-1.0). Six-month non-retention after ART initiation was lower among clinics with more than two adherence support services (RR_{adj}= 0.84, 95% CI = 0.73-0.96), dedicated pharmacists or routine review of medication pickup (RR_{adj}= 0.78, 95% CI = 0.69-0.90), and active patient outreach (RR_{adj}=0.85, 95% CI = 0.73-0.99).

Conclusions: Targeted adherence support services, coupled with active patient outreach, may substantially improve retention and possibly survival among patients initiating ART.

Introduction

The efficacy of antiretroviral therapy (ART) in treating patients with HIV is well-established. However, ART provides optimal outcomes only if patients consistently and continually adhere to their medication, thus requiring both day-to-day adherence to ART medication and retention in care. Although estimates of ART medication adherence among those retained in care in resource-limited settings are thought to be comparable to or better than those in resource rich countries [1-3], little is known about whether services designed to improve retention have an impact on patient outcomes in resource-limited settings. Even less is known about the combined effects of efforts aimed to improve retention in care as well as ART adherence. Identifying factors associated with patient retention in care and survival is a pre-requisite to rolling out and targeting best-practice interventions.

Loss to follow-up results in underestimated survival rates, and is most pronounced where loss to follow-up is substantial. Loss to follow-up is a heterogeneous mixture of undocumented deaths, unascertained transfers, and disengagement from care. However, the distribution of loss to follow-up into these categories is unknown. As a consequence, even though survival is the ultimate outcome of interest, non-retention in care (which combines ascertained deaths and loss to follow-up, but excludes known transfers) has often been used to measure program performance where loss to follow-up is high, implicitly treating death and loss to follow-up as undesirable outcomes when evaluating program performance.

A 2007 review of 33 scale-up clinics in sub-Saharan Africa reported high non-retention at 6 (12%-45%) and 12 (10%-51%) months after ART initiation with substantial variability across clinics [4], and a more recent review provided a pooled estimate of 12-month retention from 39 ART cohorts in resource-limited settings of 20% (range across sites: 7%-45%) [5]. A systematic review of studies where patients lost to follow-up (LTF) were actively traced found high levels of unascertained deaths (nearly 50%) [6], while more recent, smaller studies reported much higher levels of unascertained transfers (up to 50%) [7, 8], together suggesting that undocumented deaths and unascertained transfers both contribute substantially to the LTF population.

Determinants of ART adherence in sub-Saharan Africa likely operate at multiple levels (individual, clinic, structural, societal, etc.). Adherence support services provided by clinics aim to promote ART medication adherence and ideally focus on commonly identified barriers to adherence identified in qualitative studies, including forgetfulness [2, 9-12], lack of knowledge about the importance of adherence [2, 9-14], fear of an increased appetite coupled with food insecurity [12, 14, 15], and issues of stigma [12-15]. Studies in resource-rich settings investigating the impact of adherence support services on improving treatment adherence have reported small, but generally consistent, positive effects on individual patient adherence to medication [16-20], with a few studies showing no effect [21]. The few studies conducted in resource-limited settings have shown small positive effects [22-25].

Services aiming to improve ART adherence may also improve longer-term retention in care by increasing survival and reducing loss to follow-up through influencing a patient's belief in the importance of long-term adherence, or by offering incentives to regularly return to clinic.

Efforts to improve retention in care in resource-limited settings aim to reduce attrition in the first place by reducing travel time or offering non-medical incentives to stay in care (scale-up of clinics in more remote regions, travel reimbursement, food support, etc.) [26], or aim to identify patients missing scheduled visits so that they can be contacted and returned to care ("active patient outreach") [27, 28]. While strategies to improve patient retention in care are understudied in comparison to strategies focusing on adherence, active outreach appears to be associated with lower rates of loss to follow-up and more complete ascertainment of vital status [28, 29].

Two distinct estimates of patient retention after ART initiation are routinely available from HIV care and treatment clinics supported by international governmental initiatives such as the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Both are aggregate measures and have distinct strengths and weaknesses. First, cumulative measures of non-retention, loss to follow-up, and measured survival are available on a quarterly basis, but are limited to tracking changes in cumulative estimates over time at the facility-level, because information on the time each individual is followed is unknown. Because these estimates are cumulative, they are less sensitive to changes in retention rate trajectories over time than estimates from cohorts of individuals initiating ART in a given time period. Second, cohort estimates of the percentage of

patients initiating ART within a given 3-month period that are retained on ART at 6 and 12 months after ART initiation are routinely available, and are more sensitive to identifying changes in retention for a given clinic over time. However, the routinely-collected cohort information does not separate non-retention into loss to follow-up and death.

This paper uses both types of routinely-collected aggregate data, each with strengths and limitations, to investigate whether program-level services designed to improve adherence to ART medication and retention in care are associated with better survival and retention and lower rates of loss to follow-up after ART initiation in HIV care and treatment scale-up programs in a variety of clinics and settings in sub-Saharan Africa.

Methods

Study Population

The study population included all patients initiating ART at HIV care and treatment clinics directly supported by Columbia University's International Center for AIDS Care and Treatment Programs (ICAP; www.columbia.icap.org) in 10 sub-Saharan African countries (Cote d'Ivoire, Ethiopia, Kenya, Lesotho, Mozambique, Nigeria, Rwanda, South Africa, Tanzania, Zambia). Each care and treatment clinic is governed by national guidelines, and all patients attending these clinics are provided free antiretroviral treatment. Care and treatment sites were considered for the analysis if: (1) they reported quarterly care and treatment results for at least 3 consecutive quarters, (2) they completed a survey assessing clinic and facility-level services offered at the site, and (3) they initiated patients on ART medication during the period of observation

(January 2004 through December 2008). Collectively, the 349 (89%) of the 392 clinics supported by ICAP during this time period were included in the analyses, and over 232,000 patients initiated ART at these clinics during the study period.

Data Sources

This analysis uses two aggregate sources of data, each with different strengths and weaknesses. Figure 1 highlights key differences between these two study populations. To obtain estimates of overall non-retention in care, as well as to estimate the proportion of those non-retained that are either lost to follow-up or ascertained deaths, quarterly estimates of person-time were calculated and summed to obtain overall rates of non-retention, loss to follow-up, and death (methodology described below). To examine non-retention in the six- and 12-month period after ART initiation within defined cohorts of patients, non-retention proportions were estimated from cohorts of patients initiating ART within the same quarter (referred to as the "ART cohort population" below).

Cumulative population

ICAP is required to provide aggregate quarterly reports summarizing the patient population at sites it supports under PEPFAR's Track 1.0 agreement [30]. These data are gathered by site staff with technical assistance and oversight by ICAP and focus on key "indicators of care" at each clinic, including the number of patients enrolled in care and initiating ART, disaggregated by sex and age, as well as information on cohorts of patients initiating ART. These data are collected into a web-based database system. A

standard operating procedure on indicator definitions and quality assurance is in place to help ensure consistency of reported indicators across sites and settings.

ART cohort population

A subset of the 232,000 patients in the overall analysis were also included in retrospective cohorts of patients initiating ART within the same quarter. Information on cohorts includes the number of new ART patients in the cohort (cohort size), the number retained at 6 and 12 months after ART initiation, and the number of retained patients who received ART for 6 out of 6 and 12 out of 12 months, respectively. Each quarter, facilities are asked about the number of patients age 6 years and older who initiated ART six and twelve months ago, and the number of these patients remaining in care through the end of the current quarter. This gives two estimates of the baseline population (one at 6 months after ART initiation, and one at 12 months after ART initiation) for each 12-month cohort. For this study, cohorts were excluded if (a) they did not report both 6- and 12-month retention estimates and (b) estimates of the number initiating ART in each cohort from 6- and 12-month follow-up differed by more than 20%. 1,227 cohorts had both 6-month and 12-month follow-up, and 1,097 of these, across 221 clinics, had baseline estimates of the number of patients initiating ART reported at 6 and 12 months of follow-up within 20%. The average of the two reports on the number of patients in the baseline cohort was used in this analysis as the denominator for each cohort's percent non-retention at 6 and 12 months.

Outcome definitions

Overall rates (overall non-retention, Loss to follow-up (LTF), death)

Overall rates of non-retention, loss to follow-up (LTF.), and ascertained death per 100 person-years on ART were estimated from information reported quarterly from each clinic on (1) the cumulative number of patients in care and on ART, (2) the cumulative number of patients lost to program through death, transfer, withdrawal, or loss to follow-up, and (3) the number of patients newly enrolled in care and on ART during each quarter. For rate denominators, the total person-time in care and on ART as of the end of each quarter was calculated, assuming care discontinuations (due to death, transfer, withdrawal, or loss to follow-up) occurred at the midpoint of the quarter. Total person-time on ART for patients at a given clinic was calculated by summing up the estimated person-time from each quarter since the site began reporting on HIV care and ART services. Overall death, loss to follow-up, and non-retention rates were computed for each clinic by dividing the cumulative number reported dead, LTF, or non-retained (dead, stopped ART, or LTF), respectively, by the total person-time. Rates are expressed per 100 person-years on ART, and are through December 2008. It is important to note that the rates calculated in this manner are not cohort-specific, since information on the amount of time a given individual contributes to the denominator is unknown. Appendix 3 to this dissertation provides a description of the methodology used to calculate these rate estimates, and compares these estimates with those obtained in a more traditional manner using patient-level data.

Retention at 6 and 12 months following ART initiation

For the subset of patients in the ART cohorts, retention at 6 and 12 months was calculated as the proportion of patients in each cohort initiating ART during 2004-2008 who remained alive and in care 6 and 12 months after ART initiation.

Probability of receiving all ART regimens for 6 and 12 months after ART initiation

To test whether adherence support services improve patient retention in part by improving adherence to ART medication, a secondary analysis used the proportion of patients receiving ART medication for 6 out of 6, or 12 out of 12 months, as the outcome of interest. This outcome combines retention and ART adherence. Analyses follow the same structure outlined for the 6 and 12 month ART cohorts.

Exposure measures

Clinic-level data, capturing information on clinic characteristics and service availability came from routinely conducted structured site assessments completed by ICAP field staff. This survey focuses on program context (type of clinic, location, size, etc) and the services available to HIV+ patients at the clinic. Rounds of site assessment were conducted in June 2007, December 2007, and July 2008. Test-retest agreement was recently assessed for a subset of survey items at 58 ICAP-supported clinics in seven of the nine countries included in this analysis. For the 31 questions that were assessed, agreement was 83% overall, 79% for the adherence support questions, and 74% for the outreach questions.

Adherence support and related services

Adherence support services offered at HIV clinics can be categorized according to the level of interaction between the patient and staff, and according to the barrier to ART adherence they target. Services are considered to be "directed support services" if they require interaction with site staff and focus on improving adherence to medication. These "directed support services" include the availability of one-on-one or group adherence counseling, on-site support groups for HIV+ patients, and peer educator programs. Services are defined as "informational" if they provide materials to promote ART adherence but do not require interaction with clinic staff, and include the provision of written educational tools providing information on the importance of adherence or reminder tools (such as pill boxes or calendars). "Pharmacy services" include those services intended to make it easier for patients to regularly obtain prescribed ART regimens and to track pharmacy pickups, and include the availability of a dedicated on-site ART pharmacist or routine review of medication pickup. The availability of food rations for adults and/or children to promote ART adherence is in a separate category, as it targets a structural barrier to ART adherence by offering a tangible incentive to consistently return to clinic. Each measured adherence support service (Table 2) was dichotomized according to its reported availability at the time of the survey. In addition, three additional variables were created to examine breadth and scope of adherence support services. First, the total number of adherence support services at a given clinic were summed (range: 0-7), and a dichotomous variable was created comparing clinics offering 3 or more services with those offering two or fewer services to compare clinics in the lowest quintile of the number of services offered with those in the upper four quintiles. Second, the number of "directed ART support services" (defined here as: one-

on-one or group counseling, peer educator programs, and on-site HIV+ support groups) at a clinic were summed to compare clinics offering two or all three directed services to those offering only one service. Third, the frequency with which one-on-one or group adherence counseling services were offered (at least every 3 months vs. less often) was examined based on the cutpoints established in the site assessment.

Active Outreach

Clinics were considered as offering active patient outreach if they reported actively tracing patients who miss visits through telephone calls, letters, or home visits. Clinics reporting active outreach were further classified as to whether outreach activities targeted ART patients only or both pre-ART and ART patients.

Covariates

Factors routinely collected (either from the quarterly form or the semiannual structured site assessment) thought to be plausibly associated with patient outcomes and the exposures of interest examined as potential confounders included clinic size (cumulative number of patients in care), clinic location (urban/rural), facility type (primary, secondary, tertiary), provider-to-patient ratio, year of program start, and calendar time of ART initiation (aggregate cohort population).

Statistical Analyses

Overall rates of non-retention, loss to follow-up, and death, along with 6/12 month non-retention proportions for ART cohorts, were combined with contemporaneous program-level exposure data from the site assessments for analysis and analyzed as follows:

Overall rates of non-retention, LTF, and death

Multivariate Poisson regression using generalized estimating equations was used to estimate non-retention, LTF, and death rate ratios comparing clinics offering a given adherence support or outreach service to those not offering such a service. Both unadjusted and adjusted models were fit, with adjusted models controlling for factors considered *a priori* as potential confounders that appreciably changed the estimate between the exposure and outcome of interest (program location (urban/rural), facility type (primary, secondary, tertiary), and total number of patients enrolled at the site). Next, a "full" model was constructed to assess the joint influence of each treatment adherence and active outreach service found to be associated with the outcome of interest at alpha level of 0.1 or below. Finally, to assess whether the association of adherence support services with non-retention differed depending on whether an outreach program was also present, analyses were repeated, both stratifying by the presence or absence of an active patient outreach program and testing for additive-scale interaction by computing the Interaction Contrast Ratio (ICR) introduced by Rothman [31] and 95% confidence intervals according to methodology outlined by Hosmer and Lemeshow [32].

Retention at 6 and 12 months following ART initiation

To assess whether patients at clinics offering various adherence support or outreach services experienced lower non-retention at 6 and 12 months after ART initiation, information on availability of these services from repeated site assessments was matched to cohorts according to the quarter of ART initiation for each cohort. The mean proportion not retained in ART initiation cohorts within a given clinic at 6 and 12 months were modeled using Poisson regression with repeated measures generalized estimating equations [33], to account for within-site similarity in the retention proportions of cohorts. A secondary model used the proportion of patients not receiving ART medication for 6 out of 6, or 12 out of 12 months, as the outcome of interest. Assessment of potential additive-scale interaction between active outreach and adherence support services was conducted in a manner parallel to that of the overall analysis.

Results

Facility and patient characteristics

There were 349 care and treatment clinics in 10 countries comprising over 232,000 patients who initiated ART, contributing 300,700 person-years of observation on ART. The majority of clinics were housed in primary (47%) or secondary (48%) health facilities, and 57% were located in semi-urban or urban areas (Table 1). Kenya contributed the most clinics to the analysis (71 or 20%), while Mozambique contributed the most patients (53,000, or 23%).

Adherence support and outreach characteristics

Table 2 describes the variation in adherence support and active outreach services across the clinics and cohorts comprising the study population. Almost all clinics (93%)

reported at least one adherence support service, while 53% of the clinics reported that active patient outreach was available. Clinics reported an average of 4 adherence support services, and there was variability in the specific types of adherence support services offered, ranging from 17% offering food rations to adults and/or children for ART adherence to 88% reporting one-on-one or group counseling services.

Outcome characteristics

Of the 232,389 patients comprising the study population, 42,208 (18%) were classified as non-retained (14,678 known to have died; 27,602 lost to follow-up) as of December 2008, for an overall rate of 14.1 per 100 person-years (4.9 deaths per 100 person-years; 9.2 LTF per 100 person-years). Comparing across clinics, the median non-retention rate was 15.1 per 100 person-years (IQR: 6.8-23.6), the median loss to follow-up rate was 5.5 per 100 person-years (IQR: 0.3-12.9), and the median death rate was 6.4 per 100 person-years (IQR: 3.3-10.7).

Among the 1,097 12-month ART cohorts included in this analysis, 82,981 patients had initiated ART, with 80% retained at 6 months and 73% at 12 months. Comparing across cohorts, the median (IQR) proportion retained at 6 and 12 months was 93% (IQR: 80%-98%) and 90% (IQR: 73%-97%), respectively.

Association of adherence support and outreach with overall rates of overall non-retention, LTF, and ascertained death

Non-retention

Table 3 provides the results of the analyses examining whether various adherence support and outreach services are associated with reduced non-retention, loss to follow-up, or measured death. In the unadjusted analyses, clinics offering more than 2 adherence support services had lower non-retention and loss to follow-up than clinics offering fewer services. After adjusting for facility type (primary, secondary, tertiary), location (urban/rural), the year each clinic began offering ART services, and size of program (cumulative number of patients enrolled in care), clinics offering three or more services had significantly lower non-retention rates than those offering 2 or fewer services (RR_{adj} = 0.59, 95% CI: 0.35-1.0). For specific services, the availability of educational materials (RR_{adj} = 0.73, 95% CI = 0.63-0.85), one-on-one or group counseling (RR_{adj} = 0.62, 95% CI = 0.42-0.92), food rations to support ART adherence (RR_{adj} = 0.72, 95% CI = 0.58-0.90) and reminder tools (RR_{adj} = 0.79, 95% CI = 0.64-0.97) were associated with lower non-retention rates.

Loss to follow-up

In both crude and adjusted analyses, a protective effect was observed for clinics offering three or more adherence support services (RR_{adj} = 0.48, 95% CI = 0.25-0.92). For specific adherence services, the availability of educational materials (RR_{adj} = 0.63, 95% CI = 0.52-0.77), directed counseling or support services (RR_{adj} = 0.36, 95%CI = 0.16-0.83), one-on-one or group adherence counseling services (RR_{adj} = 0.55, 95%CI = 0.33-0.89), the availability of a dedicated pharmacist or routine review of medication pickup (RR_{adj} = 0.60, 95%CI = 0.36-1.0), and food support (RR_{adj} = 0.65, 95% CI = 0.47-0.88) were associated with lower LTF compared to clinics that did not offer such

services. Similar associations were observed when using non-retention or loss to follow-up as the outcome of interest for all of the exposures of interest.

Ascertained deaths

Rates of ascertained death were not associated with the total number of adherence support services in this analysis. However, clinics with specific adherence support services were associated with lower death rates. Clinics offering more than one directed counseling or support service were associated with lower measured death rates ($RR_{adj,2vs1}$ = 0.77, 95% CI = 0.63-0.93; $RR_{adj,3vs1}$ = 0.75, 95% CI = 0.64-0.87) than those clinics offering fewer such services. Among the directed adherence services, clinics with on-site support group for HIV+ patients (RR_{adj}= 0.81, 95% CI = 0.70-0.93), peer educators (RR_{adj} = 0.84, 95% CI = 0.74-0.96) had lower ascertained death rates than clinics without such services. Among the informational services, clinics that provided reminder tools (RR_{adj} = 0.81, 95% CI = 0.66-0.98) were associated with lower ascertained death rates compared to those without such tools. Clinics offering food rations to support ART adherence had lower measured death rates (RR_{adj} = 0.69-1.0) compared with those that did not offer food rations. Finally, clinics offering active patient outreach had marginally lower measured death rates than clinics not offering active patient outreach (RR_{adj} = 0.91, 95% CI = 0.79-1.06), with a similar association among clinics offering outreach to all patients, compared with clinics offering to only ART patients (RR_{adj} = 0.86, 95% CI = 0.70-1.06).

In the model including all adherence support or outreach services significant at an alpha level of 0.1 in addition to clinic-level confounders (Table 5a), the provision of

educational materials and food support remained associated with lower non-retention and LTF rates, while all services except for active patient outreach remained associated with lower ascertained death rates.

Association of adherence support and outreach with non-retention at 6 and 12 months after ART initiation

Table 4 presents the results of the analysis investigating whether adherence support and outreach services were associated with lower 6- and 12-month non-retention after ART initiation among cohorts of ART patients. In both the crude and adjusted analyses, clinics offering more than two adherence support services had lower non-retention at 6 months (RR_{adj} = 0.84, 95% CI = 0.73-0.96), though this was not statistically significant at 12 months (RR_{adj} = 0.89, 95% CI = 0.75-1.05). Specifically, clinics offering a dedicated pharmacist or routine review of ART medication pickup had lower non-retention at 6 and 12 months ($RR_{adj,6m}$ = 0.78, 95% CI = 0.69-0.90; $RR_{adj,12m}$ = 0.85, 95% CI = 0.73-1.00). Clinics offering active patient outreach were also associated with lower non-retention at 6 and 12 months ($RR_{adj,6m}$ = 0.86, 95% CI = 0.73-0.99; $RR_{adj,12m}$ = 0.84, 95% CI = 0.74-0.96). In the model including all adherence support or outreach services significant at an alpha level of 0.1 (Table 5b), both services remained significantly associated with lower non-retention.

The percentage of patients retained in each 12-month cohort who received ART medication for 6 out of 6, or 12 out of 12 months was used in a secondary analysis as a proxy for cohort medication adherence to assess whether adherence support services

were associated with this outcome (see Appendix 1.1). In this analysis, cohorts initiating ART at sites with three or more adherence support services had higher proportions of retained patients receiving ART 6 out of 6 months (RR_{adj} = 1.23, 95% CI = 1.05-1.45), with a similar-magnitude but non-significant association with retained patients receiving ART 12 out of 12 months (RR_{adj} = 1.15, 95% CI = 0.87-1.52). Among specific adherence support services, cohorts of patients attending clinics offering a dedicated pharmacist or routine review of medication pickup had higher proportions of retained patients receiving ART 6 out of 6 months (RR_{adj} = 1.25, 95% CI = 1.06-1.47), with marginally significant associations observed for the provision of educational pamphlets, food support to promote ART adherence, and active patient outreach.

Interaction analyses

To investigate whether associations between specific adherence support services and patient outcome measures differed according to whether a given facility also offered active patient outreach services, we (1) stratified associations on the presence/absence of an active outreach program and (2) tested for additive-scale interaction in each adjusted analysis (Figure 2 and Appendix 1.2).

Overall non-retention, LTF, and death rates. The potential for additive-scale interaction was assessed for those adherence support services independently associated with overall rates of non-retention, loss to follow-up, or death in the previous analyses. For non-retention and loss to follow-up as the outcomes of interest, these services were: more than two adherence support services, availability of educational materials

promoting ART adherence, one-on-one or group adherence counseling, availability of reminder tools, the availability of pharmacy services (routine review of ART medication pickup and/or on-site ART pharmacist availability), and food rations to promote ART adherence. For death as the outcome of interest, the services tested for interaction were: more than one directed support or counseling service, on-site support groups for HIV+ patients, peer educators, reminder tool provision, and food rations to promote ART adherence.

In the analyses of potential additive-scale interaction presented in Figure 2a, there was evidence of sub-additive interaction between active outreach and one-on-one or group adherence counseling services in their association with cumulative measures of non-retention and loss to follow-up. The rate ratios comparing rates of non-retention and loss to follow-up between clinics offering both counseling services and active outreach to those offering neither ($RR_{non\text{-}retention}$ = 0.58, 95% CI = 0.39-0.86; RR_{ltf} = 0.50, 95% CI = 0.31-0.82) were closer to the null value than would be expected if the risks of non-retention according to the availability of counseling and outreach services were perfectly additive ($RR_{non\text{-}retention}$ expected if perfectly additive = 0.28; RR_{ltf} expected if perfectly additive = 0.11; Interaction Contrast Ratio (ICR) = 0.67, 95% CI = 0.06-1.28 for non-retention, ICR = 0.94, 95% CI = 0.49-1.38 for loss to follow-up).

With death as the outcome of interest (Figure 2b), there was evidence of super-additivity between having at least three adherence support services and active outreach. Clinics offering at least three adherence support services but not active outreach, and clinics offering both three or more adherence support services and active outreach, had lower cumulative rates of death than did clinics offering neither service,

while clinics offering active outreach but not at least three adherence support services had higher rates of death. The rate ratio for having both at least three adherence support services and active outreach compared to having neither service (RR_{death} = 0.84, 95% CI = 0.70-1.00) was more protective than the expected association if these factors were perfectly additive (RR_{death} expected if perfectly additive = 1.34; ICR = 0.58, 95% CI = 0.13-1.02).

Retention at 6 and 12-months after ART initiation. The potential for additive-scale effect modification was assessed for those adherence support services found to be independently associated with non-retention at 6 or 12 months in the previous analyses. These factors were: three or more adherence support services, on-site support groups for HIV+ patients, and the availability of a dedicated ART pharmacist and/or routine ART medication pickup review.

Evidence of sub-additive interaction was found at both 6 and 12 months between active outreach and the availability of on-site support groups for HIV+ patients (Figure 2c). The risk ratio of non-retention comparing clinics offering both active outreach and on-site support groups to clinics offering neither (RR_{6m}= 0.78, 95% CI = 0.64-0.95; RR_{12m} = 0.78, 95% CI = 0.61-0.95) was less pronounced than would be expected had on-site support groups and active outreach been perfectly additive (RR_{6m} expected if perfectly additive = 0.50, ICR = 0.43, 95% CI = 0.23-0.58; RR_{12m} expected if perfectly additive = 0.58, ICR = 0.30, 95% CI = 0.17-0.44).

Discussion

These analyses suggest that clinic services designed to support patient adherence to medication and retention in care in HIV care and treatment clinics are associated with lower non-retention, loss to follow-up, and death in resource-limited settings. These beneficial effects are consistent with those observed in previous trials examining the effect of adherence support services on patient medication adherence and retention in care [16-20, 22-25]. Our observations, within a programmatic service delivery context, that adherence support and outreach programs may beneficially influence retention, loss to follow-up, and survival are encouraging, given widespread concerns about persistent high rates of non-retention in HIV scale-up [1-5, 34].

Results from both the overall analysis and the 12-month ART cohorts suggest that clinics offering multiple adherence support services have better retention than clinics offering fewer such services. This supports the theory that clinics offering a more comprehensive set of services are better equipped to track and retain ART patients, and may also suggest that overall strengthening and diversification of program services, at least as they pertain to ART adherence, may influence patient outcomes. However, the finding that number of adherence support services was not associated with ascertained death may be due to in part to the likelihood that clinics with lower LTF also have more complete ascertainment of deaths, which would result in an association between clinics with low LTF and increased ascertained death even if the actual death rate (comprised of known and unknown deaths) is not different.

Directed adherence counseling and support groups, including on-site support groups for HIV+ patients and peer educator programs, were associated with lower death rates but not lower loss to follow-up. Crude rates of loss to follow-up were actually higher at clinics offering one or both of these services. It is possible, but unverifiable, that the observed association between these services and lower death rates is due to artifact: namely, that clinics with high loss to follow-up have worse death ascertainment. It is also possible that these directed counseling and support services have an impact on adherence (which we cannot measure) and, subsequently, survival, but do not impact retention. Investigation into the likely outcomes of patients lost to follow-up through sampling or imputation techniques would be necessary to investigate this further.

In contrast, the provision of educational materials promoting ART adherence, provision of one or more directed counseling or support (one-on-one or group counseling, on-site support groups for HIV+ patients, or peer educators), and the availability of a dedicated ART pharmacist or routine review of medication pickup were associated with lower LTF rates but not associated with lower rates of ascertained death in the overall analyses. If these services worked to reduce actual death rates, situations where clinics with high loss to follow-up are differentially underascertaining deaths would mask this relationship by artificially deflating the ascertained death rate among clinics with high loss to follow-up.

In the overall analyses, the provision of food rations to promote ART adherence was alone among those tested in being associated with both reduced loss to follow-up and

reduced ascertained death. Food rations to promote ART adherence was also associated with a lower risk of death 6 months, but not 12 months, after ART initiation in the aggregate ART cohort analysis. This was expected, since food rations target both a potential reason for non-adherence to ART (studies have shown that fear of hunger may be an important cause of non-adherence in resource-limited settings [15]) as well as a more structural barrier to retention in care (e.g., patients attending clinic may be forced to lose a day's wages to attend clinic, and the offer of free food may incentivize their decision to continue in care).

The 12 month ART cohort analyses tested similar hypotheses (namely, an effect of adherence support and outreach service availability on non-retention) as the overall analyses using an overlapping but distinct study population. There were areas of agreement and disagreement when comparing these results to those from the aggregate cumulative analyses. Similar to the aggregate cumulative analyses, we found an association between the availability of more than 2 adherence support services, the availability of a dedicated pharmacists and/or routine medication pickup review, and food rations to promote ART adherence on lower rates of non-retention. In addition to those common factors identified through both study populations, there was an observed association between the presence of active patient outreach and lower rates of non-retention in the ART cohort analysis that was not observed in the overall analysis. This lack of an association in the overall analysis is counterintuitive, since the service is intended to reduce loss to follow-up by improving death ascertainment and returning lapsed patients to care. The finding of a weak protective effect of outreach programs on ascertained death in the overall analysis, without a similar effect on loss to

follow-up, is also counterintuitive since several recent articles have suggested that unascertained deaths represent a substantial proportion of ART patients who become LTF [29, 35]. One explanation is that clinics experiencing high loss to follow-up may be likely to institute active patient outreach. Another explanation is that the rates estimated from the aggregate cumulative population represent the entire history of the clinic through a given quarter, and is less sensitive to the effect of a recent initiation of an outreach program. Cohort analyses, focusing on specific periods of time to estimate retention, can correct for this potential bias, but the lack of death information among cohorts prohibits the partitioning of non-retention into loss to follow-up and death.

Analyses of potential effect modification between adherence support services and active outreach (Figure 2) suggest that different adherence support services may interact with active outreach in different ways. Clinics offering one-on-one or group adherence counseling services had similarly lower rates of non-retention and loss to follow-up regardless of whether they also offered active patient outreach, compared with clinics offering neither counseling nor outreach services, even though clinics offering active outreach but not counseling had the lowest rates of non-retention and death. This finding could be caused by unmeasured differences in patient characteristics between clinics offering both counseling and outreach and clinics offering only outreach. This theory would need patient-level information to test. In addition, clinics offering more than one directed counseling or support service had lower ascertained death rates than clinics offering neither more than one directed counseling or support service nor outreach services only among those clinics also offering active outreach. This finding is

consistent with the theory that directed counseling services improve survival only if steps are taken to reduce loss to follow-up through outreach. However, the potential for differences between clinics due to unmeasured patient-level characteristics cannot be dismissed.

In the ART cohort analysis, clinics offering on-site support groups for HIV positive patients had similarly lower non-retention regardless of whether they also offered outreach services, compared with clinics offering neither counseling nor outreach services, even though clinics offering active outreach but not support groups had the lowest non-retention. This finding could be caused by unmeasured differences in patient characteristics between clinics offering both counseling and outreach and clinics offering only outreach. This theory would need patient-level information to test.

This analysis has a number of strengths. First, it uses routinely collected data from a wide range of HIV care and treatment clinics covering 10 sub-Saharan African countries, allowing us to conduct an analysis with more than 232,000 ART patients. This represents roughly 8% of all patients initiating ART during the time period in sub-Saharan Africa [36]. The use of routine aggregate data also allows us to incorporate clinics, particularly small health centers in rural areas, which do not have electronic patient-level database systems. The large number of clinics and contexts enabled examination of a wide array of relevant program-level factors targeted at improving adherence and retention while also allowing control for potentially confounding variables. Finally, the use of two different types of outcomes (non-retention rates and non-retention at 12 months), each measured somewhat independently, is a strength of

this study. It allows the examination the findings in the context of the different limitations inherent in each approach.

This study also has numerous important limitations. First, the overall analysis suffers from potential misclassification of exposure, since exposure is assigned based on responses to the most recent site assessment. Clinics that have changed their program availability over time will have their adherence support programs misclassified for a portion of the follow-up time contributing to the aggregate outcome rates. It may be reasonable to assume that sites offering adherence support services are not likely to remove them later, but sites originally without such services may have introduced them at some point during program existence. This would bias associations toward the null, since the “exposed” cumulative non-retention rates would include times when patients at a given site were not in fact exposed to the specific adherence support or active counseling service. The cohort analysis corrects this bias by allowing for program availability to change with each followed cohort (i.e., time updated exposure information). Our findings of an association between active outreach in the cohort, but not aggregate cumulative, analysis, are consistent with this logic.

The data used in this analysis were not collected for research purposes. Information on the availability of adherence support and outreach services was based on surveys filled out by clinic staff and may be subject to non-differential misclassification. Further, the site assessment does not investigate the quality of a given service being offered or the proportion of patients taking part in such adherence services. These limitations are

likely to be non-differential, resulting in misclassification of clinics as having a given adherence support or outreach service even if, in reality, the quality or comprehensiveness of the service is poor.

Central limitations of both techniques are that ecologic analyses cannot adjust for between-site differences in patient-level characteristics also associated with risk of non-retention, LTF, or death. Further, the overall analysis cannot estimate the average amount of time a given individual is followed on ART. A more complete analysis would combine patient-level information on program utilization and patient-specific outcomes to adjust for differences in program utilization across sites. However, patient-level data are not widely available in all contexts, and conclusions may not be as generalizable as those using routinely collected aggregate data. An analysis focusing on the subset of clinics also having patient-level information will be the subject of a separate manuscript.

Conclusions

This study based on routinely collected service delivery data provides evidence that adherence support services, and active patient outreach, are associated with lower non-retention, LTF and death rates across a wide array of HIV care and treatment scale-up clinics in sub-Saharan Africa. Additional studies, performed in service settings but using differing tools to measure service offerings, would help reduce the number of non-causal alternate explanations for these findings. However, results for the aggregate cohort analysis are consistent with previous studies suggesting that facilities with active patient outreach services have greater retention in care [29]. It also suggests that at

least some adherence support activities may be responsible for reduced measured death rates, and improved retention through 1 year.

References

1. Attaran, A., *Adherence to HAART: Africans take medicines more faithfully than North Americans.* PLoS Med, 2007. **4**(2): p. e83.
2. Mills, E.J., et al., *Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators.* PLoS Med, 2006. **3**(11): p. e438.
3. Mills, E.J., et al., *Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis.* JAMA, 2006. **296**(6): p. 679-90.
4. Rosen, S., M.P. Fox, and C.J. Gill, *Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review.* PLoS Med, 2007. **4**(10): p. e298.
5. Fox, M.P. and S. Rosen, *Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review.* Trop Med Int Health. **15 Suppl 1**: p. 1-15.
6. Brinkhof, M.W., M. Pujades-Rodriguez, and M. Egger, *Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis.* PLoS One, 2009. **4**(6): p. e5790.
7. Geng, E.H., et al., *Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach.* J Acquir Immune Defic Syndr, 2010. **53**(3): p. 405-11.
8. Geng, E.H., et al., *Tracking a sample of patients lost to follow-up has a major impact on understanding determinants of survival in HIV-infected patients on antiretroviral therapy in Africa.* Trop Med Int Health, 2010. **15 Suppl 1**: p. 63-9.
9. Chesney, M.A., *Factors affecting adherence to antiretroviral therapy.* Clin Infect Dis, 2000. **30 Suppl 2**: p. S171-6.
10. Chesney, M.A., M. Morin, and L. Sherr, *Adherence to HIV combination therapy.* Soc Sci Med, 2000. **50**(11): p. 1599-605.
11. DiMatteo, M.R., *Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research.* Med Care, 2004. **42**(3): p. 200-9.
12. Sanjobo, N., J.C. Frich, and A. Fretheim, *Barriers and facilitators to patients' adherence to antiretroviral treatment in Zambia: a qualitative study.* SAHARA J, 2008. **5**(3): p. 136-43.
13. Kip, E., V.J. Ehlers, and D.M. van der Wal, *Patients' adherence to anti-retroviral therapy in Botswana.* J Nurs Scholarsh, 2009. **41**(2): p. 149-57.
14. Murray, L.K., et al., *Barriers to acceptance and adherence of antiretroviral therapy in urban Zambian women: a qualitative study.* AIDS Care, 2009. **21**(1): p. 78-86.
15. Hardon, A.P., et al., *Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa.* AIDS Care, 2007. **19**(5): p. 658-65.
16. Milam, J., et al., *Effect of a brief antiretroviral adherence intervention delivered by HIV care providers.* J Acquir Immune Defic Syndr, 2005. **40**(3): p. 356-63.
17. Fairley, C.K., et al., *Randomized trial of an adherence programme for clients with HIV.* Int J STD AIDS, 2003. **14**(12): p. 805-9.
18. Goujard, C., et al., *Impact of a patient education program on adherence to HIV medication: a randomized clinical trial.* J Acquir Immune Defic Syndr, 2003. **34**(2): p. 191-4.

19. Pradier, C., et al., *Efficacy of an educational and counseling intervention on adherence to highly active antiretroviral therapy: French prospective controlled study.* HIV Clin Trials, 2003. **4**(2): p. 121-31.
20. Weber, R., et al., *Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial.* Antivir Ther, 2004. **9**(1): p. 85-95.
21. Rawlings, M.K., et al., *Impact of an educational program on efficacy and adherence with a twice-daily lamivudine/zidovudine/abacavir regimen in underrepresented HIV-infected patients.* J Acquir Immune Defic Syndr, 2003. **34**(2): p. 174-83.
22. Traore AA, N.V., McCarrick P, Dhaliwal M, Tioendrebeogo I, Ilboudo A, *Barriers to adherence to ARV therapy in a community-based cohort in Burkina Faso [Abstract]*, in *XV International AIDS Conference*. 2004: Bangkok, Thailand. p. AbstractWePeB5824.
23. Demeester, R., et al., *Adherence to first-line antiretroviral regimens in Rwanda.* J Acquir Immune Defic Syndr, 2005. **40**(1): p. 113-4.
24. Byron, E., S. Gillespie, and M. Nangami, *Integrating nutrition security with treatment of people living with HIV: lessons from Kenya.* Food Nutr Bull, 2008. **29**(2): p. 87-97.
25. Torpey, K.E., et al., *Adherence support workers: a way to address human resource constraints in antiretroviral treatment programs in the public health setting in Zambia.* PLoS One, 2008. **3**(5): p. e2204.
26. Nakanjako, D., et al., *Strategies to optimize HIV treatment outcomes in resource-limited settings.* AIDS Rev, 2009. **11**(4): p. 179-89.
27. Losina, E., et al., *Cost-effectiveness of preventing loss to follow-up in HIV treatment programs: a Cote d'Ivoire appraisal.* PLoS Med, 2009. **6**(10): p. e1000173.
28. Braitstein, P., et al., *Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries.* Lancet, 2006. **367**(9513): p. 817-24.
29. Brinkhof, M.D.F.M.L.B.D.B.A., Nash D, Schechter M, Laurent C, Keiser O, May, M, Sprinz, E, Eggar, M, Anglaret, X, *Early loss to program in HIV-infected patients starting potent antiretroviral therapy in lower-income countries.* PLOS Medicine, 2008. **in press**.
30. PEPFAR, *The President's Emergency Plan for AIDS Relief Indicators Reference Guide*. 2007: Washington, DC.
31. Rothman, K., *Modern Epidemiology*. 1986, Little, Brown: Boston.
32. Hosmer, D.W. and S. Lemeshow, *Confidence interval estimation of interaction.* Epidemiology, 1992. **3**(5): p. 452-6.
33. Park, T., D.W. Shin, and C.G. Park, *A generalized estimating equations approach for testing ordered group effects with repeated measurements.* Biometrics, 1998. **54**(4): p. 1645-53.
34. Fox, M.P., et al., *Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa.* Trop Med Int Health. **15**(4): p. 405-13.
35. Tadios, Y. and G. Davey, *Antiretroviral treatment adherence and its correlates in Addis Ababa, Ethiopia.* Ethiop Med J, 2006. **44**(3): p. 237-44.
36. World Health Organization, U., UNICEF, *Towards universal access : scaling up priority HIV/AIDS interventions in the health sector : progress report 2009*. 2009.
37. Lawn, S.D. and R. Wood, *How can earlier entry of patients into antiretroviral programs in low-income countries be promoted?* Clin Infect Dis, 2006. **42**(3): p. 431-2; author reply 432-3.

38. Coetzee, D., et al., *Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa.* AIDS, 2004. **18**(6): p. 887-95.
39. Lawn, S.D., et al., *Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation.* Clin Infect Dis, 2006. **43**(6): p. 770-6.
40. Tassie, J.M., et al., *Highly active antiretroviral therapy in resource-poor settings: the experience of Medecins Sans Frontieres.* AIDS, 2003. **17**(13): p. 1995-7.
41. van Oosterhout, J.J., et al., *Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi.* Trop Med Int Health, 2005. **10**(5): p. 464-70.
42. Kabugo, C., et al., *Long-term experience providing antiretroviral drugs in a fee-for-service HIV clinic in Uganda: evidence of extended virologic and CD4+ cell count responses.* J Acquir Immune Defic Syndr, 2005. **38**(5): p. 578-83.
43. Brinkhof, M.W., et al., *Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries.* Bull World Health Organ, 2008. **86**(7): p. 559-67.
44. Lawn, S.D., A.D. Harries, and R. Wood, *Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings.* Curr Opin HIV AIDS, 2010. **5**(1): p. 18-26.
45. Brinkhof, M.W., et al., *Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality.* PLoS Med, 2009. **6**(4): p. e1000066.
46. Palombi, L., et al., *Incidence and predictors of death, retention, and switch to second-line regimens in antiretroviral- treated patients in sub-Saharan African Sites with comprehensive monitoring availability.* Clin Infect Dis, 2009. **48**(1): p. 115-122.
47. Anaky, M.F., et al., *Scaling up antiretroviral therapy for HIV-infected children in Cote d'Ivoire: determinants of survival and loss to programme.* Bull World Health Organ. **88**(7): p. 490-9.
48. May, M., et al., *Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes.* Lancet. **376**(9739): p. 449-57.
49. Chang, L.W., et al., *Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial.* PLoS One, 2010. **5**(6): p. e10923.
50. Forster, M., et al., *Electronic medical record systems, data quality and loss to follow-up: survey of antiretroviral therapy programmes in resource-limited settings.* Bull World Health Organ, 2008. **86**(12): p. 939-47.
51. Lawn, S.D., et al., *Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design.* AIDS, 2005. **19**(18): p. 2141-8.
52. Stringer, J.S., et al., *Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes.* JAMA, 2006. **296**(7): p. 782-93.

Tables and Figures, Paper 1

Table 1. Facility and cohort-level characteristics of study population

		Facility-Level Characteristics				12-month Cohort-level Characteristics						
		N (%) Facilities		Cum N (%) patients on ART		N (%) facilities with cohorts		N (%) cohorts		N (%) patients in cohorts		median (q1-q3) patients per cohort per facility
Total		349	(100%)	232,389	(100%)	221	(63%)	1,097	(100%)	83,389	(100%)	48 (21-96)
				213,693	(92%)							
	Adult											
	Adult Female			136,999	(59%)	Median CD4 count at ART initiation:				41 (21-96)		
	Pediatric			18,696	(8%)							
General Facility Characteristics												
	Cote d'Ivoire	9	(2.6%)	980	(0.4%)	.		.		.		.
	Ethiopia	44	(12.6%)	37,374	(16.1%)	38	(17.2%)	244	(22.2%)	20,212	(24.2%)	49 (24-116)
	Kenya	71	(20.3%)	26,001	(11.2%)	33	(14.9%)	113	(10.3%)	6,410	(7.7%)	44 (18-80)
	Lesotho	26	(7.4%)	18,117	(7.8%)	11	(5.0%)	36	(3.3%)	4,362	(5.2%)	103 (52-178)
	Mozambique	39	(11.2%)	53,315	(22.9%)	36	(16.3%)	196	(17.9%)	23,023	(27.6%)	72 (28-186)
	Nigeria	27	(7.7%)	19,478	(8.4%)	12	(5.4%)	36	(3.3%)	5,873	(7%)	124 (88-181)
	Rwanda	44	(12.6%)	19,755	(8.5%)	39	(17.7%)	240	(21.9%)	8,334	(10%)	27 (11-43)
	South Africa	43	(12.3%)	37,620	(16.2%)	31	(14.0%)	148	(13.5%)	8,961	(10.7%)	47 (21-84)
	Tanzania	45	(12.9%)	19,202	(8.3%)	21	(9.5%)	84	(7.7%)	6,217	(7.5%)	56 (32-91)
	Zambia	1	(0.3%)	547	(0.2%)	.	.	.		.		.
Facility Type	Primary	163	(46.7%)	49,434	(21.3%)	85	(38.5%)	354	(32.3%)	14,829	(17.8%)	24 (13-50)
	Secondary	168	(48.1%)	160,020	(68.9%)	122	(55.2%)	646	(58.9%)	56,978	(68.3%)	60 (31-115)
	Tertiary	14	(4.0%)	22,848	(9.8%)	12	(5.4%)	88	(8%)	10,842	(13%)	113 (46-192)
Facility Location	Rural	149	(42.7%)	30,484	(13.1%)	79	(36.0%)	341	(31.1%)	9,850	(11.8%)	24 (15-36)
	Semi-urban	114	(32.7%)	90,409	(38.9%)	75	(34.0%)	333	(30.4%)	23,519	(28.2%)	52 (25-96)
	Urban	80	(22.9%)	111,427	(47.9%)	65	(29.0%)	410	(37.4%)	49,228	(59%)	84 (49-162)
Year site initiated ART care (site-level), or year cohort initiated ART (cohort-level)	2003	7	(2%)	14,583	(6.3%)			--		--		--
	2004	41	(11.7%)	76,924	(33.1%)			--		--		--
	2005	73	(20.9%)	72,391	(31.2%)	n.a		6	(0.5%)	132	(0.2%)	25 (10-32)
	2006	74	(21.2%)	39,457	(17%)	n.a		58	(5.3%)	4,747	(5.7%)	61 (31-100)
	2007	59	(16.9%)	20,042	(8.6%)	n.a		333	(30.4%)	26,145	(31.4%)	48 (20-105)
	2008	94	(26.9%)	8,992	(3.9%)	n.a		700	(63.8%)	52,366	(62.8%)	48 (21-94)

Table 2. Facility and cohort-level exposure characteristics

		Facility-Level Characteristics				Cohort-level Characteristics (N = 221 facilities with cohorts)				
		N (%) of facilities		Cum N (%) patients on ART		Number (%) of cohorts		Number (%) of patients in cohorts		median (q1-q3) patients per cohort per site
Overall		349	(100%)	232,389	(100%)	1,097	(100%)	83,389	(100%)	48 (21-96)
Adherence support and related services										
Any adherence support program	no	15	(4.3%)		(0.2%)	1	(0.1%)	10	(0%)	10 (10-10)
	yes	326	(93.4%)		(99.7%)	1082	(98.6%)	82611	(99.1%)	48 (22-96)
Availability of educational pamphlets, etc	no	150	(43%)	85,929	(37%)	315	(28.7%)	26,578	(31.9%)	49 (18-110)
	yes	199	(57%)	146,460	(63%)	773	(70.5%)	56,070	(67.2%)	47 (23-94)
Number of directed counseling or support services	0	24	(6.9%)	2,225	(1%)	153	(13.9%)	9,272	(11.1%)	40 (16-70)
	1	115	(33%)	53,909	(23.2%)	327	(29.8%)	19,477	(23.4%)	40 (20-81)
	2	97	(27.8%)	60,556	(26.1%)	311	(28.4%)	25,532	(30.6%)	53 (20-110)
	3	113	(32.4%)	115,699	(49.8%)	297	(27.1%)	28,369	(34%)	64 (27-121)
one-on-one or group adherence counseling	no	41	(11.7%)	7,532	(3.2%)	403	(36.7%)	30,947	(37.1%)	48 (21-99)
	yes	308	(88.3%)	224,857	(96.8%)	685	(62.4%)	51,701	(62%)	48 (21-94)
frequency of counseling services	< every 3	32	(9.2%)	31,821	(13.7%)	73	(6.7%)	6,733	(8.1%)	58 (22-127)
	$\geq$ every 3	276	(79.1%)	193,036	(83.1%)	612	(55.8%)	44,969	(53.9%)	48 (21-90)
on-site support group for HIV+ patients	no	159	(45.6%)	62,447	(26.9%)	409	(37.3%)	24,238	(29.1%)	38 (18-74)
	yes	190	(54.4%)	169,942	(73.1%)	679	(61.9%)	58,411	(70%)	59 (25-115)
peer educator program	no	199	(57%)	105,070	(45.2%)	612	(55.8%)	37,115	(44.5%)	39 (19-80)
	yes	150	(43%)	127,319	(54.8%)	476	(43.4%)	45,534	(54.6%)	61 (26-128)
Availability of reminder tools (e.g., clocks, calendars, pill	no	104	(29.8%)	27,522	(11.8%)	110	(10%)	7,844	(9.4%)	33 (17-82)
	yes	245	(70.2%)	204,867	(88.2%)	978	(89.2%)	74,805	(89.7%)	49 (22-99)
Routine medication pickup review, dedicated or team	no	71	(20.3%)	9,253	(4%)	61	(5.6%)	3,220	(3.9%)	24 (12-55)
	yes	278	(79.7%)	223,136	(96%)	1,027	(93.6%)	79,428	(95.3%)	49 (23-99)
Food rations provided to adults or children	no	289	(82.8%)	198,231	(85.3%)	919	(83.8%)	76,078	(91.2%)	53 (23-109)
	yes	60	(17.2%)	34,158	(14.7%)	178	(16.2%)	7,311	(8.8%)	27 (17-57)
Outreach Services										
Active patient outreach	no	164	(47%)	63,969	(27.5%)	363	(33.1%)	25,037	(30%)	44 (21-83)
	yes	185	(53%)	168,420	(72.5%)	725	(66.1%)	57,611	(69.1%)	50 (22-105)
Target population among sites w/ active outreach	ART patients	136	(39%)	108,136	(46.5%)	525	(47.9%)	38,401	(46.1%)	44 (21-90)
	All patients	45	(12.9%)	57,908	(24.9%)	178	(16.2%)	17,564	(21.1%)	74 (24-150)

Table 3. Crude and Adjusted overall rate ratios for non-retention, loss to follow-up, and death

Facility-Level Characteristics		N (yes/no)	Overall Non-retention[1] rate ratio				Overall Loss to Follow-up[2] rate ratio				Overall Death[3] rate ratio			
			Crude (95% CI)		Adjusted[4] (95% CI)		Crude (95% CI)		Adjusted[4] (95% CI)		Crude (95% CI)		Adjusted[4] (95% CI)	
Adherence support services														
Total number of adherence support services provided	> 2 vs ≤ 2	292/57	0.51	(0.31-0.85)	0.59	(0.35-1.0)	0.45	(0.24-0.84)	0.48	(0.25-0.92)	0.7	(0.38-1.28)	0.94	(0.55-1.61)
Availability of educational pamphlets, etc	yes vs. no	199/150	0.83	(0.72-0.96)	0.73	(0.63-0.85)	0.69	(0.57-0.83)	0.63	(0.52-0.77)	1.19	(1.02-1.4)	0.98	(0.85-1.13)
Availability of directed Counseling or support	yes vs. no	325/24	0.44	(0.23-0.86)	0.51	(0.26-1.03)	0.33	(0.16-0.71)	0.36	(0.16-0.83)	1.13	(0.38-3.35)	1.49	(0.57-3.88)
Number of directed counseling or support services	2 vs 1	97/115	0.92	(0.74-1.14)	0.91	(0.72-1.14)	1.04	(0.78-1.39)	1.01	(0.74-1.38)	0.75	(0.61-0.92)	0.77	(0.63-0.93)
	3 vs 1	113/115	1.08	(0.9-1.3)	0.98	(0.82-1.18)	1.27	(0.99-1.62)	1.16	(0.9-1.49)	0.82	(0.69-0.98)	0.75	(0.64-0.87)
One-on-one or group adherence counseling services	yes vs. no	308/41	0.58	(0.4-0.86)	0.62	(0.42-0.92)	0.52	(0.32-0.84)	0.55	(0.33-0.89)	0.75	(0.48-1.17)	0.82	(0.55-1.21)
Frequency of counseling services among sites providing them	≥ every 3 months vs < every 3 months	276/32	1.48	(1.17-1.87)	1.14	(0.88-1.49)	1.43	(1.06-1.94)	1.20	(0.84-1.7)	1.58	(1.24-2.02)	1.05	(0.82-1.33)
On-site support group for HIV+ patients	yes vs. no	190/159	1.06	(0.89-1.25)	1.03	(0.87-1.22)	1.24	(0.99-1.55)	1.20	(0.95-1.52)	0.80	(0.69-0.94)	0.81	(0.7-0.93)
Peer educator program	yes vs. no	150/199	1.10	(0.95-1.27)	0.99	(0.86-1.14)	1.16	(0.96-1.4)	1.08	(0.89-1.32)	0.98	(0.85-1.14)	0.84	(0.74-0.96)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	245/104	0.79	(0.64-0.98)	0.79	(0.64-0.97)	0.79	(0.6-1.05)	0.77	(0.58-1.02)	0.79	(0.63-0.99)	0.81	(0.66-0.98)
Routine medication pickup review, dedicated or team pharmacist	yes vs. no	278/71	0.61	(0.42-0.91)	0.71	(0.48-1.05)	0.59	(0.36-0.96)	0.60	(0.36-1)	0.68	(0.45-1.03)	0.95	(0.66-1.37)
Food rations provided to adults or children	yes vs. no	60/289	0.83	(0.66-1.03)	0.72	(0.58-0.9)	0.66	(0.49-0.9)	0.65	(0.47-0.88)	1.16	(0.95-1.41)	0.83	(0.69-1)
Outreach Services														
Active patient outreach	yes vs. no	185/164	0.97	(0.82-1.14)	1.00	(0.85-1.18)	1.03	(0.83-1.28)	1.05	(0.84-1.32)	0.87	(0.74-1.02)	0.91	(0.79-1.06)
Target population among sites w/ active outreach	All patients vs. ART only	136/45	1.04	(0.85-1.28)	1.01	(0.81-1.27)	1.09	(0.84-1.43)	1.10	(0.81-1.48)	0.95	(0.78-1.16)	0.86	(0.7-1.06)

1. Overall non-retention rates estimated as the cumulative number of patients at a site lost to follow-up, withdrawn, or reported dead, over the total person-years observed on ART at that site
2. Overall loss to follow-up rates estimated as the cumulative number of patients not returning to clinic for > 6 months since last visit, with no known status, over the total person-years observed on ART at that site
3. Overall death rates estimated as the cumulative number of patients reported dead, over the total person-years observed on ART at that site
4. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year facility began providing ART care, and cumulative number of patients seen in care

Table 4. Cohort analysis[4]: Crude and Adjusted risk ratios for non-retention through 6 and 12 months

Facility-Level Characteristics			Non-retention Risk Ratio through 6 months[1]				Non-retention Risk Ratio through 12 months[2]			
		N (yes/no)	Crude	RR (95% CI)	Adjusted[3] RR (95% CI)		Crude	RR (95% CI)	Adjusted[3] RR (95% CI)	
Adherence support services										
Total number of adherence support services provided	> 2 vs ≤ 2	1016/81	0.82	(0.71-0.95)	0.84	(0.73-0.96)	0.9	(0.76-1.07)	0.89	(0.75-1.05)
Availability of educational pamphlets, etc	yes vs. no	773/315	1.01	(0.84-1.21)	0.97	(0.81-1.17)	1.05	(0.91-1.21)	1.02	(0.87-1.19)
Availability of directed Counseling or support	yes vs. no	935/162	1.03	(0.81-1.31)	1.03	(0.84-1.26)	1.14	(0.92-1.4)	1.10	(0.93-1.3)
Number of directed counseling or support services	2 vs 1	311/327	0.96	(0.74-1.24)	0.97	(0.79-1.2)	0.93	(0.74-1.18)	0.90	(0.74-1.1)
	3 vs 1	297/327	0.93	(0.7-1.22)	0.91	(0.74-1.11)	0.99	(0.78-1.25)	0.95	(0.79-1.14)
one-on-one or group adherence counseling services	yes vs. no	685/403	1.13	(1.01-1.26)	1.07	(0.96-1.2)	1.28	(1.12-1.45)	1.22	(1.1-1.36)
Frequency of counseling services among sites providing them	≥ every 3 months vs < every 3 months	612/73	1.34	(0.82-2.17)	1.08	(0.77-1.54)	1.32	(0.89-1.96)	1.22	(0.89-1.67)
on-site support group for HIV+ patients	yes vs. no	679/409	0.91	(0.72-1.14)	0.90	(0.74-1.1)	0.92	(0.77-1.11)	0.89	(0.77-1.03)
peer educator program	yes vs. no	476/612	0.93	(0.74-1.17)	0.93	(0.77-1.12)	0.97	(0.8-1.17)	0.94	(0.81-1.1)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	978/110	1.04	(0.67-1.61)	1.03	(0.7-1.51)	1.03	(0.79-1.36)	1.02	(0.8-1.29)
Routine medication pickup review, dedicated or team pharmacist	yes vs. no	1027/61	0.80	(0.68-0.93)	0.78	(0.69-0.9)	0.89	(0.77-1.03)	0.85	(0.73-1)
Food rations provided to adults or children	yes vs. no	178/919	0.89	(0.7-1.13)	0.82	(0.64-1.05)	1.01	(0.81-1.25)	0.98	(0.78-1.21)
Outreach Services										
Active patient outreach	yes vs. no	725/363	0.83	(0.71-0.96)	0.85	(0.73-0.99)	0.81	(0.71-0.91)	0.84	(0.74-0.96)
Target population among sites w/ active outreach	All patients vs. ART only	525/178	1.18	(0.87-1.59)	1.09	(0.83-1.43)	1.01	(0.78-1.31)	0.94	(0.74-1.21)

1. Cohort non-retention % estimated as 100 - (number of patients on ART through 6 months/number starting cohort at baseline)
2. Cohort non-retention % estimated as 100 - (number of patients on ART through 12 months/number starting cohort at baseline)
3. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, cohort start year, and cumulative number of patients seen in care
4. All analyses adjusting for within-site correlation using generalized estimating equations

Table 5a. Cumulative analyses: Adjusted[1] mean non-retention, LTF, and death rate ratios associated with adherence support: adjusting for other adherence support activities

Adherence support services		Non-retention Rate Ratio	LTF Rate Ratio	Death Rate Ratio
Availability of educational pamphlets, etc	yes vs. no	0.76 (0.66-0.89)	0.67 (0.55-0.81)	not in model
one-on-one or group adherence counseling	yes vs. no	0.77 (0.52-1.14)	0.72 (0.44-1.19)	not in model
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	0.83 (0.67-1.03)	0.83 (0.63-1.11)	0.78 (0.64-0.94)
Dedicated pharmacist, team pharmacist, or routine medication pickup review	yes vs. no	0.92 (0.62-1.38)	0.85 (0.50-1.42)	not in model
Food Support for ART adherence	yes vs. no	0.74 (0.60-0.92)	0.67 (0.49-0.91)	0.86 (0.71-1.04)
on-site support group for HIV+ patients		not in model	not in model	0.82 (0.69-0.99)
peer educator program	yes vs. no	not in model	not in model	0.89 (0.76-1.05)
Active patient outreach program	yes vs. no	not in model	not in model	1.12 (0.93-1.34)

1. All models adjusted for year of ART initiation, facility type (primary, secondary, tertiary), facility location (urban/rural), and cumulative number of patients enrolled in care

2. Rates presented additionally adjusted for other adherence support and active outreach services listed in the above table

Table 5b. ART cohort analyses: Adjusted[1] non-retention risk ratio at 6 and 12 months, adjusting for other adherence support activities

Adherence support services		Non-retention % through 6 months	Non-retention % through 12 months
		RR[2]	RR[2]
Dedicated pharmacist, team pharmacist, or routine medication pickup review	yes vs. no	0.8 (0.7-0.93)	0.88 (0.73-1.05)
Active patient outreach program	yes vs. no	0.86 (0.74-1)	0.84 (0.74-0.96)

1. All models adjusted for year of ART initiation, facility type (primary, secondary, tertiary), facility location (urban/rural), and cumulative number of patients enrolled in care

2. Percent non-retention ratios (RRs) additionally adjusted for other adherence support and active outreach services listed in the above table

Figure 1. Comparison of strengths and weaknesses of aggregate cumulative and cohort data

	Overall (cumulative)	12-month ART cohort
can estimate non-retention proportion		x
ability to separate out non-retention into LTF and death	x	
includes all patients at clinics in study population	x	
can estimate non-retention within 6 months or 1 year after ART initiation		x
sensitive to changes in non-retention rate over time at a given clinic		x
can adjust for clinic-level predictors of non-retention	x	x
can adjust for patient-level predictors of non-retention		

Investigating the relationship of adherence support and active outreach services with rates of patient non-retention, loss to follow-up, and ascertained death using aggregate and patient-level data from sub-Saharan African HIV care and treatment scale-up clinics

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Abstract

Background:
High rates of loss to follow-up and death remain common in HIV care and treatment clinics in sub-Saharan Africa. Examining whether services intended to improve adherence to ART and retention in care are impacting patient outcomes can help identify priority areas of potential intervention, but the ability of using widely available routinely-collected aggregate data to assess this has not been investigated.

Methods:
We used three sources of routinely collected data from 92 HIV care and treatment clinics in 5 sub-Saharan African countries ((1) cumulative facility-level data, (2)12 month ART cohort data, and (3) patient-level data) to investigate whether specific adherence support and active outreach services were associated with measures of non-retention, loss to follow-up, and death among 93,000 patients initiating ART through June 2009. Multivariate Poisson regression using generalized estimating equations was used for the facility-level and 12 month ART cohort analyses, and Proportional Hazards models, which controlled for differences in patient characteristics across clinics, were used for the patient-level analyses. Data on adherence support and outreach services were obtained from annual structured site assessments. We examined whether these three data sources provided similar estimates of the relationship between adherence support and active outreach services and patient non-retention, loss to follow-up, and death.

Results: Overall estimated death rates were similar between the facility-level (4.0 per 100 person-years on ART) and the patient-level (3.4 per 100 person-years on ART) estimations, while the measured rate of loss to follow-up was substantially lower in the facility-level analysis (9.8 per 100 person-years on ART vs. 12.6 per 100 person-years on ART). In multivariate analyses, clinics offering active patient outreach had lower rates of non-retention in both the ART cohort analysis and the patient-level analysis, and clinics offering food rations to promote ART adherence were associated with a lower risk of ascertained death in both the facility-level and patient-level analyses, but this association was diminished after adjustment for patient-level covariates. In contrast, various adherence counseling or support services were associated with lower non-retention in the ART cohort analyses but not in the patient-level data analyses.

Conclusions: Active patient outreach and food rations remained associated with reduced non-retention and measured death, respectively, in both aggregate and patient-level analyses, providing stronger evidence that these two services may influence patient outcomes. However, attenuation of these associations after adjustment for patient-level covariates, and differences in association in the aggregate and patient-level analyses, warrants caution in interpreting these associations as causal.

Introduction

As scale-up of HIV care and treatment services in sub-Saharan Africa reaches maturity, focus has shifted towards identifying factors associated with optimal patient outcomes. We are ultimately interested in identifying modifiable factors improving patient survival so that we can intervene with programs that address these factors. Program-level services within HIV care and treatment clinics, such as outreach and adherence support programs, are intended to maximize patient retention and adherence to ART medications, which in turn is expected to improve survival.

The identification of whether and which types of these services actually have an impact on patient survival in resource-limited settings is complicated by a number of issues. First, high levels of patient loss to follow-up from HIV care and treatment clinics have been observed in these settings [1-9]. Loss to follow-up results in underestimation of death rates, and biases comparisons of death rates between facilities offering different support services if patients lost to follow-up are at higher risk of death than those retained in care [10-12]. Second, routinely-collected data from most HIV care and treatment clinics is usually of limited scope and available only in aggregate. This latter issue creates two related problems. First, routinely-collected cumulative data can be used to estimate overall facility-level rates of non-retention, loss to follow-up, and death, but cannot be used to estimate the average amount of time an individual is retained on ART before reaching one of these endpoints. Second, several studies have found that patient characteristics (e.g., baseline CD4 count and WHO stage, age, and gender, among others) are important predictors of retention in care and survival [13-15], and these differ across sites. This suggests that observed differences in patient retention

and survival across clinics and program types may in part be due to baseline differences in the patient population attending clinics offering different adherence support and retention services. When using aggregate data, the lack of patient-level information on predictors of survival prevents us from assessing this possibility. However, since relatively few clinics have patient-level electronic data available, and since most HIV clinics routinely generate aggregate data, an examination of the situations under which aggregate information can validly be used to assess determinants of patient retention and survival in HIV care and treatment clinics in resource-limited settings is warranted.

Published studies that have investigated the impact of adherence support services on patient survival and retention in care have generally found small but positive associations [16-20]. Similarly, active patient outreach programs, designed to identify patients who miss scheduled visits and return them to care, have been associated with lower rates of loss to follow-up [21]. However, the joint impact of adherence support and active patient outreach on patient retention and survival has not been examined.

This analysis use data from sites where three different sources of information (quarterly estimates of cumulative patient populations, 12-month ART cohorts, and patient-level data) on patient outcome are available to compare estimates of the impact of program-level services designed to improve ART adherence and patient-retention in care after ART initiation: (1) overall facility-level estimates of rates of non-retention, loss to follow-up and death, (2) estimates of non-retention risk 6 and 12 months after ART initiation, and (3) estimates of the rate of non-retention, loss to follow-up, and death from electronic patient-level databases.

Methods

Study Population

Patients initiating ART care between January 2005 and June 2009 at one of 92 HIV care and treatment clinics in the National HIV programs of five sub-Saharan African countries (Kenya, Mozambique, Rwanda, South Africa, Tanzania) directly supported by PEPFAR via Columbia University's International Center for AIDS Care and Treatment Programs (ICAP) that had electronic patient-level databases comprise the study population for this analysis. Clinics with patients initiating ART between January 2005 and June 2009 were included if the clinic (1) routinely reported aggregate data as required under the PEPFAR implementing agreement during this period, (2) completed at least one routine site assessment during this time, and (3) maintained an electronic patient-level database that was available for analysis. Because the aggregate data is not directly derived from electronic patient-level databases in all situations, the analysis therefore had two somewhat independently derived estimates of the total number of patients included in the analysis (one from the aggregate indicator data and one from the patient-level database), with the aggregate database estimating 93,772 patients and the patient-level database estimating 92,651 patients initiating ART during the study period.

Data sources

This analysis uses three sources of data, two available at the aggregate level and one at the patient-level. Figure 1 highlights key differences between these study populations.

Overall facility-level population

ICAP is required to provide aggregate quarterly reports summarizing the patient population at sites it supports under PEPFAR's Track 1.0 agreement [22]. These data are gathered by site staff with technical assistance and oversight by ICAP and focus on key "indicators of care" at each clinic, including the number of patients enrolled in care and initiating ART, disaggregated by sex and age, as well as information on cohorts of patients initiating ART. These data are collected into a web-based database system. A standard operating procedure on indicator definitions and quality assurance is in place to help ensure consistency of reported indicators across sites and settings.

ART cohort population

A subset of the patients comprising the aggregate cumulative study population also had information on the proportion retained in care at six and 12 months after ART initiation. All but one of the 92 clinics in the study reported information on cohorts of patients initiating ART. Cohorts are comprised of patients aged 6 years and above who initiated ART at a given site over a 3-month period. Information on cohorts includes the number of new ART patients in the cohort (cohort size), the number of patients retained at 6 and 12 months after ART initiation, and the number of retained patients receiving ART medication during all months of follow-up. Cohorts were included in this analysis if they reported retention at 6 and 12 months after ART initiation, and if baseline estimates of the proportion of patients initiating ART measured six and 12 months after ART initiation did not differ by more than 20%. 675 cohorts, comprising 53,095 patients, comprise the study population for these analyses.

Patient-level data

All sites used in this analysis had an electronic patient-level database system that was available for analysis. Data clerks at sites with electronic patient-level data directly input information from paper patient records into their database. While each country has a distinct patient-level database, variables of interest from all country databases were combined into a single common-format database for use in this analysis.

Outcome definitions

Facility-level rates (overall non-retention, Loss to follow-up, death)

Facility-level rates of non-retention, LTF, and death per 100 person-years on ART were calculated from aggregate information reported quarterly from each clinic on (1) the cumulative number of patients in care and on ART, (2) the cumulative number of patients lost to program through death, transfer, withdrawal, or loss to follow-up, and (3) the number of patients newly enrolled in care and on ART during each quarter. For rate denominators, the total person-time in care and on ART as of the end of each quarter was calculated, assuming care discontinuations (due to death, transfer, withdrawal, or loss to follow-up) occurred at the midpoint of the quarter. Total person-time on ART for patients at a given facility was calculated by summing up the person-time from each quarter since the site began reporting on HIV care and ART services. Cumulative death, loss to follow-up, and overall non-retention rates were computed for each clinic by dividing the cumulative number reported dead, LTF, or non-retained (dead or LTF), respectively, by the total person-time. Rates are expressed per 100 person-years on ART, and are through June 2009.

Retention at 6 and 12 months following ART initiation

For the subset of patients in the ART cohorts, retention at 6 and 12 months was calculated as the proportion of patients in each cohort of patients initiating ART during 2004-2008 who remained alive and in care at the original site 6 and 12 months after ART initiation.

Patient-level non-retention, LTF, and death rates

Non-retention, LTF, and death rates were also estimated from the patient-level database. Deaths, transfers, and withdrawals from care that were known to clinic staff were recorded in the electronic database, along with the date these events were recorded. Patients were defined as loss to follow-up if they were not documented as deaths or transfers, and if they had not had a visit documented in the electronic database in the 6 months before database closure (June 2009) and were censored at 15 days after their last visit date. ART patients known to have transferred out of an HIV care and treatment facility, or those that withdrew from care, were censored at their transfer or withdrawal date. Per-site LTF, death, and non-retention rates were then calculated as the number of LTF, death, or non-retained (death + LTF) divided by the person-years of observation for a given site as of June, 2009. We expect the estimates of loss to follow-up to be higher in the patient-level analysis than in the aggregate analysis because loss to follow-up is directly inferred from visit dates in the patient-level analysis, while loss to follow-up is based on clinic registry information that requires data clerks to actively mark a patient as “lost” before they are included as lost to follow-up in the aggregate database.

Clinic-level data on adherence support and active outreach

Clinic-level data, capturing information on clinic characteristics and service availability came from routinely conducted structured site assessments completed by ICAP field staff. Rounds of site assessment were conducted in June 2007, December 2007, and July 2008. Test-retest agreement was recently assessed at 58 ICAP-supported clinics in seven countries, including the five included in this analysis, by comparing survey responses to those assessed via repeat survey administration by a supervisory team. For the 31 questions that were assessed, agreement between the two methods was 83% overall, 79% for the adherence support questions, and 74% for the outreach questions.

Adherence support and related services

Adherence support services offered at HIV clinics can be categorized according to the level of interaction between the patient and staff, and according to the barrier to ART adherence they target. Services are considered to be "directed support services" if they require interaction with site staff and focus on improving adherence to medication. These "directed support services" include the availability of one-on-one or group adherence counseling, on-site support groups for HIV+ patients, and peer educator programs. Services are defined as "informational" if they provide materials to promote ART adherence but do not require interaction with clinic staff, and include the provision of written educational tools providing information on the importance of adherence or reminder tools (such as pill boxes or calendars). "Pharmacy services" include those services intended to make it easier for patients to regularly obtain prescribed ART regimens and to track pharmacy pickups, and include the availability of a dedicated on-

site ART pharmacist or routine review of medication pickup. The availability of food rations for adults and/or children to promote ART adherence is in a separate category, as it targets a structural barrier to ART adherence by offering a tangible incentive to consistently return to clinic. Each measured adherence support service (Table 3) was dichotomized according to its reported availability at the time of the survey. In addition, three additional variables were created to examine breadth and scope of adherence support services. First, the total number of adherence support services at a given clinic were summed (range: 0-7), and a dichotomous variable was created comparing clinics offering 3 or more services with those offering 2 or fewer services to compare clinics in the lowest quintile of the number of services offered with those in the upper four quintiles. Second, the number of "directed ART support services" (defined here as: one-on-one or group counseling, peer educator programs, and on-site HIV+ support groups) at a clinic were summed to compare clinics offering 2 or all three directed services to those offering only one service. Third, the frequency with which one-on-one or group adherence counseling services were offered (at least every 3 months vs. less often) was examined based on the cutpoints established in the site assessment.

Active Outreach

Clinics were considered as offering active patient outreach if they reported actively tracing patients who miss visits through telephone calls, letters, or home visits. Clinics reporting active outreach were further classified as to whether outreach activities targeted ART patients only or both pre-ART and ART patients (Table 3).

Covariates

Site-level

Factors routinely collected (either from the quarterly form or the semiannual structured site assessment) thought to be plausibly associated with patient outcomes and the exposures of interest examined as potential confounders included clinic size (cumulative number of patients in care), clinic location (urban/rural), facility type (primary, secondary, tertiary), provider-to-patient ratio, year of program start, and calendar time of ART initiation (12-month retention outcome).

Patient-level

Patient-level factors plausibly associated with patient non-retention, LTF, or death collected from the electronic patient-level database include sex, age, year of ART initiation, and WHO stage and CD4 count at enrollment into care and ART initiation. Several of these variables (WHO stage and CD4 count at ART initiation) are hypothesized to be mediators of the relationship between facility-level adherence support and outreach services and patient non-retention, LTF, and death, since many of these services (such as peer educators and support groups) target patients in the pre-ART phase and may consequently improve health at ART initiation.

Statistical Analyses

Three sets of analyses were performed to assess the association between adherence support and active outreach services and patient retention, LTF, and death, depending on the source of the data (aggregate data, 12-month cohort, and patient-level).

Facility-level analyses

Multivariate Poisson regression using generalized estimating equations was used to estimate non-retention, LTF, and death rate ratios comparing facilities offering a given

adherence support or outreach service to those not offering such a service across the 92 clinics. Both unadjusted and adjusted models were fit, with adjusted models controlling for factors considered *a priori* as potential confounders (urban/rural, facility type, and total number of patients enrolled at the site). Next, a "full" model was constructed to assess the influence of each treatment adherence and active outreach service found to be associated an alpha level of 0.1 or below. Finally, to assess whether the association of adherence support services with non-retention differed depending on whether an outreach program was also present, analyses were repeated, both stratifying by the presence or absence of an active patient outreach program and testing for additive-scale interaction by computing the Interaction Contrast Ratio (ICR) introduced by Rothman [23] and 95% confidence intervals according to methodology outlined by Hosmer and Lemeshow [24].

Retention at 6 and 12 months following ART initiation

Program-level information from repeated site assessments was matched to cohorts according to the quarter of ART initiation for each cohort. The mean proportion not retained in ART initiation cohorts within a given clinic at 6 and 12 months were modeled using Poisson regression with repeated measures generalized estimating equations [25], to account for the correlation in the cohort proportion retained within sites over time. The potential for additive-scale interaction between various adherence support programs and active outreach was investigated in a manner identical to that discussed above for the aggregate cumulative analyses.

Patient-level analysis

Cox Proportional Hazards models, accounting for within-clinic correlation, were used to construct hazard ratios comparing the rate non-retention, LTF, or death at clinics offering a given adherence support or outreach service to those not offering such a service. Proportional hazards modeling, instead of competing risk approaches, were used for loss to follow-up because for this analysis we are interested in differences in the rates of achieving the outcomes of interest, as opposed to the probability (risk) of achieving them. A more thorough explanation of the difference between a competing risk and censoring approaches is provided in Appendix 2.1. Four models were constructed to assess the association between site-level adherence support and active outreach services with non-retention, LTF, and death. The first model, the "crude" model, compared the hazard of non-retention, LTF, and death among patients at sites with differing adherence support and active outreach services, without adjusting for potential confounding variables at the patient- or clinic-levels. A second model adjusted only for patient-level differences as potential confounding variables. Since many of the adherence support and active outreach services are available to patients regardless of their ART status, patient-level characteristics measured after enrollment into care, such as CD4 count, weight, and WHO stage at ART initiation, could plausibly be consequences of exposure to the adherence support and active outreach services. Thus, to avoid over-adjustment for intermediate variables on a pathway between exposure to these services and non-retention, LTF, or death, only variables measured at enrollment were included as patient-level covariates. These included CD4 and WHO stage at enrollment into care, age, sex, and weight at enrollment into care. For the CD4, WHO stage, and weight at enrollment variables, missing values were included as

a separate category in analyses. A third model adjusted only for potential site-level confounding variables used in the aggregate analyses. The final model adjusted for both site- and patient-level factors. Finally, to assess potential interaction between active outreach and adherence support activities, analyses were repeated, both stratifying by the presence or absence of an active patient outreach program and testing for additive-scale interaction following the methods described by Rothman [23] and Hosmer and Lemeshow [24].

Results

92 care and treatment sites, comprised of 93,772 patients initiating ART, were included in the overall facility-level analyses. Six and twelve month aggregate cohort follow-up data were available for 675 cohorts from 91 of these sites, comprising 53,095 patients. Estimations from the patient-level databases were that 92,651 patients across the 92 sites initiated ART during the same time period (Table 1).

Half of the sites were secondary facilities, and the majority of patients in the study population (65%) initiated ART at secondary facilities. Half of patients were seen in urban settings, although only 18% of the clinics were in urban settings. 59% of the study population was adult females, with a median age at ART initiation of 34.5 years (34 years for women, 39 years for men) (Table 1).

The overall non-retention and loss to follow-up rates calculated using the facility-level population were lower than those calculated using patient-level data (NR $Rate_{aggregate}$ = 13.9/100 person-years on ART (PYA); NR $Rate_{patient\text{-}level}$ = 16.0/100 PYA; LTF $Rate_{aggregate}$ = 9.8/100 PYA; LTF $Rate_{patient\text{-}level}$ = 12.6/100 PYA). In contrast, the death rates were very similar (Death Rate: 4.0/100 PYA (aggregate) vs. 3.4/100 PYA (patient-

level)). As discussed earlier, we expected loss to follow-up estimates to be higher in the patient-level analysis compared with the aggregate cumulative analysis. In the ART cohort analysis, the overall non-retention proportion 12 months after ART initiation was 25% (IQR: 14%-36%). Using the patient-level database, mean non-retention, LTF, and death probabilities 12 months after ART initiation were estimated from Kaplan-Meier survival methods to be 21%, 17%, and 5%, respectively (data not shown).

The distribution of adherence support and outreach services is given in Table 3. One-on-one or group adherence counseling services and pharmacy services promoting adherence (e.g., routine review of medication pickup) were offered in one form or another at nearly all sites, preventing analysis investigating differences between sites with and without these services.

Non-retention

Table 4a presents the results of crude and adjusted analyses for the three groups (overall facility-level, 12-month ART cohort, and patient-level).

Non-retention: The number of different adherence support services provided by a given clinic was marginally associated with higher non-retention in the patient-level analyses ($HR_{site\&patient\text{-}level\ adjusted}$ = 1.16, 95% CI = 0.94-1.42), but was not associated with retention in either of the aggregate analyses.

Directed adherence counseling or support services were associated with lower non-retention at 12 months in the ART cohort analysis, but were not associated in the facility-level or patient-level analyses. In the aggregate ART cohort analysis, clinics offering more than 1 directed service (one-on-one or group counseling, on-site support groups, and/or peer educator programs) had lower non-retention at 12 months after

ART initiation (RR_{adj} = 0.84, 95% CI = 0.73-0.96). Among specific directed counseling or support services, clinics offering on-site support groups for HIV+ patients (RR_{adj} = 0.77, 95% CI = 0.68-0.87) and peer educator programs (RR_{adj} =0.87, 95% CI = 0.76-0.98) had lower non-retention.

The provision of food support to promote ART adherence was associated with lower non-retention in the facility-level and ART cohort analyses, but not in the analysis using patient-level data. In adjusted analysis, clinics offering food support had lower non-retention rates (RR_{adj} = 0.67, 95% CI = 0.44-1.03) and lower risk of non-retention 6 and 12 months after ART initiation ($RR_{6m,adj}$ = 0.71, 95% CI = 0.55-0.92; $RR_{12m,adj}$ = 0.78, 95% CI = 0.65-0.95). In patient-level analyses, the hazard of non-retention was marginally lower at clinics offering food support after adjustment for facility-level covariates (HR = 0.84, 95% CI = 0.54-1.31), but this association was diminished after additional adjustment for patient-level factors (HR_{adj} = 0.96, 95% CI = 0.66-1.32).

Active patient outreach was associated with lower non-retention in the 6 and 12 month ART cohorts ($RR_{6m,adj}$ = 0.88, 95% CI = 0.66-0.97; $RR_{12m,adj}$ = 0.86, 95% CI = 0.75-0.98), and in analyses using patient-level data ($HR_{site\&patient\text{-}level\ adjusted}$ = 0.88, 95% CI = 0.78-0.99), but was not associated in the overall facility-level analyses (RR_{adj} = 1.32, 95% CI = 0.87-2.01).

Loss to follow-up. Similar-magnitude associations as those observed using non-retention as the outcome of interest were seen for loss to follow-up in the facility-level and patient-level analyses (Table 4b). Clinics offering food rations to promote ART adherence had marginally lower rates of loss to follow-up in the facility-level analysis (RR_{adj} = 0.61, 95% CI = 0.33-1.14) but not in the patient-level analyses, while active

patient outreach was associated with lower loss to follow-up in the patient-level analysis ($HR_{site\&patient\text{-}level\ adjusted}$ = 0.82, 95% CI = 0.70-0.96) but not in the facility-level analysis (RR_{adj} = 1.50, 95% CI = 0.84-2.67).

Measured Death Table 4c presents the results of the analyses using aggregate and patient-level data investigating the association between the availability of adherence support and outreach services and rates of measured death. In both the facility-level and patient-level analyses, measured death rates were higher among those sites with more adherence support services. Clinics offering more than two different adherence support services had 4.2 times the mortality rate (95% CI = 1.32-13.1) as clinics offering two or fewer services according in the facility-level analysis, while the association observed from the patient-level data was weaker ($HR_{site\&patient\text{-}level\ adjusted}$ = 1.31, 95% CI = 1.01-1.69). Among specific adherence support services, clinics offering educational materials, reminder tools, and/or the availability of an ART pharmacist or routine medication pickup review had higher adjusted death rates in both facility-level and patient-level analyses than clinics not offering these services. In contrast, clinics offering more than one directed counseling or support service had lower measured death rates in the facility-level (RR_{adj} = 0.62, 95% CI = 0.47-0.81) but not the patient-level analysis. Among specific directed counseling or support services, clinics offering on-site HIV+ support groups had lower measured rates of death in the facility-level (RR_{adj} = 0.79, 95% CI = 0.6-1.04) and in the patient-level analyses after adjusting for site-level covariates ($HR_{site\text{-}level\ adjusted}$ = 0.78, 95% CI = 0.58-1.04), but not after additionally adjusting for patient-level covariates ($HR_{site\&patient\text{-}level\ adjusted}$ = 0.88, 95% CI = 0.65-1.19). Clinics offering food support to promote ART adherence had marginally

lower measures of death in both the facility-level analysis (RR_{adj} = 0.76, 95% CI = 0.55-1.04) and in the patient-level analysis after adjusting for site-level covariates ($HR_{site\text{-}level\ adjusted}$ = 0.81, 95% CI = 0.60-1.1), but this association was diminished after adjusting for patient-level differences between sites ($HR_{site\&patient\text{-}level\ adjusted}$ =1.03, 95% CI = 0.81-1.30). Active patient outreach was not associated with measured death in any analysis.

Interaction analyses To investigate whether associations between specific adherence support services and patient outcome measures differed according to whether a given facility also offered active patient outreach services, we tested for additive-scale interaction according to methods outlined in Rothman [23]and Hosmer and Lemeshow [24] (Figure 2). Since active patient outreach was not found to be associated with non-retention, loss to follow-up, or death in the facility-level analysis, this was only examined in the aggregate 12-month cohort and patient-level groups.

12 month ART cohort

Figure 2 presents the results of the interaction analysis using data from the six and twelve month cohort analyses. All services except for food rations were tested for additive-scale interaction, because all clinics offering food rations also offered active outreach. Among the services found to be associated with lower non-retention at six and 12 months (more than one directed counseling or support service, on-site support groups for HIV+ patients, and peer educators), the association between these services and reduced non-retention was similar regardless of whether a clinic also offered active patient outreach, suggesting no additional reduction in risk of non-retention from active patient outreach. One-on-one or group adherence counseling remained associated with higher non-retention among sites both offering and not offering active outreach.

Additionally, the provision of educational materials to promote ART adherence, which was not associated with non-retention in the overall analysis, was associated with lower non-retention only among clinics also offering active patient outreach (RR_{6m} = 0.78, 95% CI = 0.62-1.00, ICR = 0.17, 95% CI = 0.00-0.33; RR_{12m} = 0.88, 95% CI = 0.74-1.05, ICR = 0.03, 95% CI =-0.12-0.19).

Patient-level analyses

There was no evidence of additive-scale interaction between adherence support and active outreach for any of the outcomes (non-retention, loss to follow-up, or death) under investigation (data not shown).

Discussion

This analysis compared three approaches using existing service delivery data, each with some limitations, in testing the hypotheses that program-level services influence risk of non-retention, LTF, and death, and that this influence is modified by the availability of active patient outreach. The approaches used are limited because they rely on routinely-collected data that is often incomplete, unvalidated, and, in the case of the facility-level and 12-month ART cohort analyses, only available at the aggregate-level, and not the patient-level. However, when similar conclusions are reached by these different types of data, it may strengthen inference that these observed associations are plausibly causal, whereas different conclusions reached by these different types of data point to possible limitations in their use.

<u>Areas of internal consistency</u>

Clinics offering food support to promote ART adherence were associated with reduced non-retention in the facility-level analysis, and with reduced non-retention 6 and 12

months after ART initiation in the aggregate cohort analysis. In addition, a similar-magnitude, but non-significant, association, between the availability of food support and lower non-retention was observed in analyses using patient-level data after adjustment for site-level covariates. This association was diminished after further adjustment for patient-level differences. Food support was also associated with reduced measured death in the aggregate analysis, with a similar-magnitude association in the patient-level analysis after adjustment for site-level covariates. This association was again diminished after further adjustment for patient-level covariates. The similarity in inference between these three types of analyses strengthens the likelihood that this association is plausibly causal.

However, the observation of a diminished association after further adjustment for patient-level covariates warrants further discussion. Patients attending clinics offering food support to promote ART adherence have higher average CD4 counts, and less advanced clinical stage at enrollment, than patients attending clinics not offering food support (data not shown). Further, sites offering food support may also be more likely to offer a more comprehensive set of services than sites not offering food support. Adjusting for patient-level covariates may then be adjusting for differences in patient predictors of outcomes through pathways other than the offering of food support. Whether these patient-level differences are confounding the association, or mediating it, depends on whether another factor (such as overall comprehensiveness of care) is associated with both food support and better baseline patient-level measures, or whether food support services are responsible for improved patient-level measures

(such as by access to food support improving pre-art retention or initiating patients on ART earlier).

Active patient outreach was associated with lower non-retention at 6 and 12 months after ART initiation in the cohort analysis, and with lower non-retention and LTF in analyses using patient-level data, but was not associated with non-retention in the overall facility-level analysis. This is likely due to underestimation of loss to follow-up in the facility-level analysis. Specifically, the data used to compute aggregate estimates of non-retention and LTF includes an indicator identifying the cumulative number of patients actively classified as lost to follow-up through a given reporting quarter. Patients are only considered to be LTF if they are identified as such in this indicator. In contrast, the 12-month ART cohort data classified a patient as not retained in care if they did not have a recorded visit in the third quarter after ART initiation, and the patient-level data classify a patient as not retained if they did not have a recorded visit in the last 6 months. This non-differential misclassification of patients will bias the results of the aggregate analysis toward the null.

Non-intuitive associations between the availability of certain adherence support services and *higher* rates of measured death were found in both the aggregate and patient-level analyses. Clinics offering more than 2 adherence support services, as well as clinics offering educational materials and reminder tools promoting ART adherence, had higher measured rates of death than clinics not offering these services. The finding that educational materials and reminder tools were not associated with loss to follow-up weakens support for the theory that the higher observed death rates are in part due to more complete ascertainment of deaths among clinics offering educational materials or

reminder tools. Alternatively, it is possible that clinics observing high death rates instituted adherence support services in efforts to intervene, leading to the observed finding. Analyses examining changes in death rates after a given clinic initiates the provision of educational materials or reminder tools could test this theory, but limitations in our data prevented us from doing so.

Areas of internal inconsistency

This analysis found several differences in the association between adherence support and outreach services and patient non-retention, LTF, and death when using different measures of non-retention, LTF, and death. In analyses using non-retention as the outcome of interest (Table 4a), the availability of more than one directed adherence counseling or support service, as well as on-site support groups for HIV+ patients and peer educator programs were associated with lower non-retention 12 months after ART initiation in the aggregate cohort analysis, but were not associated with non-retention in the overall facility-level or patient-level analysis. Differences between the aggregate cohort results and those from the patient-level data may be in part due to the heterogeneity of follow-up time among individual patients attending clinics. In the cohort analysis, one estimate of non-retention is calculated for each cohort, which dampens within-cohort variability in retention probability. In the patient-level analyses, the variability in non-retention probability between patients within the same cohort is taken into account, which may lead to greater similarity in non-retention rates between patients attending clinics offering a given support service and those not.

The different findings when analyzing the same research question using different data sources from within the same population highlight the difficulty inherent in using

routinely-collected data to infer causal relationships between the availability of adherence support and outreach services on non-retention, loss to follow-up, and death. However, the similar findings of an association between active outreach and food rations to promote ART adherence and reduced non-retention and death provide support for the theory that these two services are having a positive impact. It suggests that on-site support groups for HIV+ patients and food rations to promote ART are associated with lower ascertained death in both aggregate and patient-level analyses, and that active outreach is associated with reduced non-retention. It also suggests that patient-level factors are important determinants of LTF, non-retention, and death (Table 5). This in turn strongly suggests that services geared toward initiating patients on ART at an earlier stage can improve patient outcomes.

This investigation will expand the body of literature investigating the influence of program-level services on patient outcome. Thus far, studies investigating factors associated with patient retention in care and survival in resource-limited settings have focused either on facility-level differences or, more frequently, patient-level characteristics. Studies using routinely-collected data have found associations between the availability and type of active tracing programs and lower risk of loss to follow-up in resource-constrained settings [8, 21, 26], a result also observed in our analysis. In addition, a study in Zambia using patient records to estimate loss to follow-up at 5 HIV care and treatment facilities before and after the introduction of community volunteer adherence support workers found that 12-month retention in care was substantially higher after the introduction of the service (85.4% vs. 100%) [19].

Higher risk of death has been associated with advanced immunodeficiency at ART initiation and male gender in a number of studies in resource-limited settings [3, 8, 27, 28]. A recent study in Zambia found that 71% of the documented deaths among patients initiating ART occurred within 90 days of ART initiation, with mortality associated with low baseline CD4 count, baseline WHO stage III or IV, low baseline BMI, male gender, and poor attendance to scheduled ART pharmacy visits [29]. These factors have also been associated, with lower magnitude, with retention in HIV care, suggesting that patients lost to follow-up represent a heterogeneous population of unascertained deaths and healthy individuals not returning to care [11, 12].

This study has a number of important strengths. First, it is the first study to combine routinely-collected aggregate and patient-level information in analyzing the association between adherence support and related services and patient non-retention, LTF, and death. It was conducted across a diverse range of countries and care and treatment clinics. Second, it used three different types of routinely collected data to address the same hypotheses, so that similar findings using the different data sources would strengthen the plausibility that these findings are not due to artifact.

While the large number of sites and patients, and the clinical settings from which these data derive, provide beneficial evidence of factors associated with non-retention, LTF, and death at typical care and treatment sites, the fact that the data used are for clinical and program tracking purposes, and not designed with these specific research questions in mind, is an important limitation. Although there are standard operating procedures and routine data quality assessments in place to improve the quality of data reported on a routine basis, resource limitations prevent this information from being

independently validated. If errors resulting from the routine nature of the data are random, this will effectively reduce the study's power to detect "true" associations. However, if these errors are related to the adherence support or active outreach services and the outcomes of interest, these can bias the results in unpredictable directions. Thus, caution is warranted when interpreting these results.

Conclusions

This analysis provides evidence that clinics providing food support to promote ART adherence, and active patient outreach, are associated with a lower risk of non-retention than those that do not across a wide range of HIV care and treatment settings in sub-Saharan Africa. However, the fact that all clinics comprising the study population for this analysis had electronic patient-level databases may limit generalizability, as they may be a select group of clinics with more comprehensive services available. A related study investigated the association between adherence support and outreach services on patient non-retention, loss to follow-up, and death at 349 ICAP-supported care and treatment facilities in 10 sub-Saharan African countries, using aggregate data only (Paper 1).

Figures 3a-3c compare the associations observed in that larger study with the current one, and the Discussion section of this dissertation treats this comparison in more detail. With non-retention and loss to follow-up as the outcomes of interest, the larger facility-level study found that facilities offering more than two adherence support services, provision of educational materials promoting adherence, one-on-one or group adherence counseling, reminder tools, or food support to promote ART adherence had lower non-retention and loss to follow-up rates than did facilities not offering these

services (Figures 3a-3b). In the current analysis, only food support to promote ART adherence had similar-magnitude associations in both the larger 10-country and smaller 5-country aggregate analyses, although these associations were diminished when using patient-level data. In addition, active patient outreach, not associated with non-retention or loss to follow-up in the larger aggregate analysis, or in the current aggregate analysis of 92 facilities in 5 countries, was associated with lower non-retention and non-retention in analyses using patient-level data after adjustment for site- and patient-level covariates.

Figure 3c compares the associations between adherence support and outreach services on death rates in the two studies. In the larger 10-country aggregate analysis, facilities offering more than one directed adherence support service, on-site support groups for HIV+ patients, peer educators, reminder tools, or food rations to promote ART adherence had lower measured death rates than facilities not offering such services. Similar-magnitude associations were observed in the smaller 5-country aggregate analysis for having more than one directed adherence support service, on-site support groups for HIV+ patients, and food rations to promote ART adherence, with these associations diminishing after adjustment for patient-level covariates.

Differences in the results of the aggregate analyses between the previous 10-country analysis and the current 5-country analysis that only included facilities with patient-level databases, suggests that the associations between adherence support and non-retention, loss to follow-up, and death, may differ between facilities with and without electronic patient-level databases, and may differ between the subset of countries with electronic patient-level databases and those without. It is likely that facilities with on-site

electronic databases may offer a more comprehensive set of services than facilities without these databases, and this may result in facilities with databases being more similar to each other with respect to services offered than are facilities without such databases. This highlights a potential limitation of the analysis restricted to facilities with electronic patient-level data: they may not be representative of the overall relationship between adherence support and outreach services and patient non-retention, loss to follow-up, and death. However, the finding of similar associations between food support to promote ART adherence and lower rates of non-retention, loss to follow-up, and death in both the larger 10-country and smaller 5-country analyses suggests that this activity may have a more generalizable association. However, the diminished association after adjustment for patient-level differences warrants caution in causal interpretation of this association.

Using three types of routinely-collected data also points to areas of inconsistency in which causal inference should be cautioned. In particular, the underascertainment of vital status due to loss to follow-up provides a barrier to causal inference in examining whether adherence support and outreach services impact patient survival on ART. The availability of patient-level data can improve inference by adjusting for important predictors of loss to follow-up and death, while also improving the measurement of loss to follow-up as an outcome. However, there remains the possibility that observed non-intuitive associations between the availability of adherence support and related services and patient non-retention, LTF, and death are actually a consequence of reverse causality. Namely, it is possible that clinics observing high levels of patient non-retention instituted programs precisely in response to a non-retention problem, and that,

consequently, observed associations between these programs and increased death or non-retention have a different meaning altogether. Before and after analyses restricting to clinics that changed their programs would be able to assess this, but currently our database does not contain a sufficient sample size of clinics to do this.

The general tendency of adjustment for patient-level differences driving observed results toward the null is consistent both with the hypothesis that patient-level differences are confounding the observed association, with the hypothesis that these patient-level factors are in the causal pathway between exposure to the adherence support and related services and risk of non-retention, LTF, and death, and with the hypothesis that patient-level differences at baseline that are related to non-retention and death are themselves causes of a given site instituting a program to improve patient outcomes. Future analyses could focus on sites known to have changed their availability of one or more services to assess whether this change resulted in improvement in patient outcomes. In the absence of randomization, and without definite knowledge of the timing of the effect of the adherence and outreach services on changes in patient-level covariates, caution is warranted in assessing the influence of patient-level characteristics on the observed site-level associations between adherence support and outreach services and patient non-, LTF, and death.

References

1. Lawn, S.D. and R. Wood, *How can earlier entry of patients into antiretroviral programs in low-income countries be promoted?* Clin Infect Dis, 2006. **42**(3): p. 431-2; author reply 432-3.
2. Coetzee, D., et al., *Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa.* AIDS, 2004. **18**(6): p. 887-95.
3. Lawn, S.D., et al., *Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation.* Clin Infect Dis, 2006. **43**(6): p. 770-6.
4. Tassie, J.M., et al., *Highly active antiretroviral therapy in resource-poor settings: the experience of Medecins Sans Frontieres.* AIDS, 2003. **17**(13): p. 1995-7.
5. van Oosterhout, J.J., et al., *Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi.* Trop Med Int Health, 2005. **10**(5): p. 464-70.
6. Kabugo, C., et al., *Long-term experience providing antiretroviral drugs in a fee-for-service HIV clinic in Uganda: evidence of extended virologic and CD4+ cell count responses.* J Acquir Immune Defic Syndr, 2005. **38**(5): p. 578-83.
7. Rosen, S., M.P. Fox, and C.J. Gill, *Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review.* PLoS Med, 2007. **4**(10): p. e298.
8. Brinkhof, M.W., et al., *Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries.* Bull World Health Organ, 2008. **86**(7): p. 559-67.
9. Lawn, S.D., A.D. Harries, and R. Wood, *Strategies to reduce early morbidity and mortality in adults receiving antiretroviral therapy in resource-limited settings.* Curr Opin HIV AIDS, 2010. **5**(1): p. 18-26.
10. Brinkhof, M.W., et al., *Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality.* PLoS Med, 2009. **6**(4): p. e1000066.
11. Geng, E.H., et al., *Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach.* J Acquir Immune Defic Syndr, 2010. **53**(3): p. 405-11.
12. Geng, E.H., et al., *Tracking a sample of patients lost to follow-up has a major impact on understanding determinants of survival in HIV-infected patients on antiretroviral therapy in Africa.* Trop Med Int Health, 2010. **15 Suppl 1**: p. 63-9.
13. Palombi, L., et al., *Incidence and predictors of death, retention, and switch to second-line regimens in antiretroviral- treated patients in sub-Saharan African Sites with comprehensive monitoring availability.* Clin Infect Dis, 2009. **48**(1): p. 115-122.
14. Anaky, M.F., et al., *Scaling up antiretroviral therapy for HIV-infected children in Cote d'Ivoire: determinants of survival and loss to programme.* Bull World Health Organ. **88**(7): p. 490-9.
15. May, M., et al., *Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes.* Lancet. **376**(9739): p. 449-57.

16. Traore AA, N.V., McCarrick P, Dhaliwal M, Tioendrebeogo I, Ilboudo A, *Barriers to adherence to ARV therapy in a community-based cohort in Burkina Faso [Abstract]*, in *XV International AIDS Conference*. 2004: Bangkok, Thailand. p. AbstractWePeB5824.
17. Demeester, R., et al., *Adherence to first-line antiretroviral regimens in Rwanda.* J Acquir Immune Defic Syndr, 2005. **40**(1): p. 113-4.
18. Byron, E., S. Gillespie, and M. Nangami, *Integrating nutrition security with treatment of people living with HIV: lessons from Kenya.* Food Nutr Bull, 2008. **29**(2): p. 87-97.
19. Torpey, K.E., et al., *Adherence support workers: a way to address human resource constraints in antiretroviral treatment programs in the public health setting in Zambia.* PLoS One, 2008. **3**(5): p. e2204.
20. Chang, L.W., et al., *Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial.* PLoS One, 2010. **5**(6): p. e10923.
21. Brinkhof, M.D.F.M.L.B.D.B.A., Nash D, Schechter M, Laurent C, Keiser O, May, M, Sprinz, E, Eggar, M, Anglaret, X, *Early loss to program in HIV-infected patients starting potent antiretroviral therapy in lower-income countries.* PLOS Medicine, 2008. **in press**.
22. PEPFAR, *The President's Emergency Plan for AIDS Relief Indicators Reference Guide*. 2007: Washington, DC.
23. Rothman, K., *Modern Epidemiology*. 1986, Little, Brown: Boston.
24. Hosmer, D.W. and S. Lemeshow, *Confidence interval estimation of interaction.* Epidemiology, 1992. **3**(5): p. 452-6.
25. Park, T., D.W. Shin, and C.G. Park, *A generalized estimating equations approach for testing ordered group effects with repeated measurements.* Biometrics, 1998. **54**(4): p. 1645-53.
26. Forster, M., et al., *Electronic medical record systems, data quality and loss to follow-up: survey of antiretroviral therapy programmes in resource-limited settings.* Bull World Health Organ, 2008. **86**(12): p. 939-47.
27. Brinkhof, M.W., M. Pujades-Rodriguez, and M. Egger, *Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis.* PLoS One, 2009. **4**(6): p. e5790.
28. Lawn, S.D., et al., *Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design.* AIDS, 2005. **19**(18): p. 2141-8.
29. Stringer, J.S., et al., *Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes.* JAMA, 2006. **296**(7): p. 782-93.

Tables and Figures, Paper 2

Table 1. Characteristics of the study population: Facility-level, 12-mohth ART cohort, and patient-level

	Overall facility-level					12-month ART cohort							Patient-level characteristics		
	N (%) sites		Cum N patients on ART (%)		median (q1-q3 patients per site	N (%) sites with cohorts		N (%) cohorts		N (%) patients in cohorts		median (q1-q3) patients per cohort per site	median (q1-q3) patients per site	N (%) patients on ART		median (q1-q3) patients per site
Total	92	(100%)	93,772	(100%)	555 (180-1291)	91	(100%)	675	(100%)	53,095	(100%)	55 (24-102)	291 (87.5-876)	92,651	(100%)	528 (174-1268)
Country																
Kenya	21	(22.8%)	13,730	(14.6%)	183 (41-1254)	20	(22%)	108	(16%)	6,687	(12.6%)	65 (16-87)	89 (8-523)	13,519	(14.6%)	155 (28-1233)
Mozambique	24	(26.1%)	50,047	(53.4%)	1338 (835-3499)	24	(26.4%)	236	(35%)	29,885	(56.3%)	93 (49-188)	816 (466-2005)	48,873	(52.7%)	1214 (865-3284)
Rwanda	27	(29.3%)	15,284	(16.3%)	338 (173-736)	27	(29.7%)	166	(24.6%)	5,950	(11.2%)	27 (13-44)	116 (80-327)	17,991	(19.4%)	427 (186-756)
South Africa	3	(3.3%)	4,283	(4.6%)	1272 (1010-2001)	3	(3.3%)	31	(4.6%)	3,406	(6.4%)	92 (79-136)	1044 (904-1459)	3,719	(4%)	1111 (957-1651)
Tanzania	17	(18.5%)	10,428	(11.1%)	432 (129-698)	17	(18.7%)	134	(19.9%)	7,167	(13.5%)	41 (22-85)	243 (86-722)	8,549	(9.2%)	357 (134-767)
Facility type																
Primary	42	(45.7%)	20,032	(21.4%)	252 (77-577)	41	(45.1%)	214	(31.7%)	10,184	(19.2%)	22 (10-70)	91 (17-211)	19,992	(21.6%)	225 (77-608)
Secondary	46	(50%)	60,628	(64.7%)	911 (435-1619)	46	(50.6%)	421	(62.4%)	37,014	(69.7%)	66 (37-109)	523 (243-1080)	60,279	(65.1%)	871 (363-1553)
Tertiary	4	(4.3%)	13,112	(14%)	3499 (1801-4756)	4	(4.4%)	40	(5.9%)	5,897	(11.1%)	155 (82-220)	1702 (508-2441)	12,380	(13.4%)	3621 (2946-5753)
Facility location																
Rural	39	(42.4%)	13,600	(14.5%)	244 (77-458)	37	(40.7%)	206	(30.5%)	7,865	(14.8%)	30 (16-46)	99 (25-229)	14,024	(15.1%)	265 (77-505)
Semi-urban	35	(38%)	33,315	(35.5%)	698 (183-1554)	35	(38.5%)	271	(40.1%)	18,185	(34.3%)	61 (27-95)	335 (88-876)	30,421	(32.8%)	727 (167-1471)
Urban	18	(19.6%)	46,857	(50%)	2119 (1010-3902)	19	(20.9%)	198	(29.3%)	27,045	(50.9%)	92 (60-218)	986 (614-2419)	47,950	(51.8%)	2465 (1027-4243)
Year of ART initiation[1]																
2003	3	(3.3%)	8,539	(9.1%)	1627 (971-5941)			--		--		--		261	(0.3%)	n.a.
2004	16	(17.4%)	33,614	(35.8%)	1810 (1187-2959)	6	n.a.	8	(1.2%)	254	(0.5%)	21 (16-56)	26 (21-70)	2,304	(2.5%)	n.a.
2005	23	(25%)	28,125	(30%)	885 (551-1307)	25	n.a.	40	(5.9%)	2,867	(5.4%)	44 (17-92)	66 (20-118)	8,759	(9.5%)	n.a.
2006	20	(21.7%)	14,635	(15.6%)	354 (224-989)	46	n.a.	99	(14.7%)	8,293	(15.6%)	68 (34-89)	108 (69-233)	16,390	(17.7%)	n.a.
2007	15	(16.3%)	5,023	(5.4%)	244 (154-435)	69	n.a.	191	(28.3%)	17,803	(33.5%)	66 (29-126)	121 (43-353)	25,789	(27.8%)	n.a.
2008	14	(15.2%)	1,160	(1.2%)	42 (28-107)	86	n.a.	227	(33.6%)	16,310	(30.7%)	44 (19-104)	79 (27-317)	26,726	(28.8%)	n.a.
2009	1	(1.1%)	2,676	(2.9%)	.	72	n.a.	110	(16.3%)	7,569	(14.3%)	42 (18-95)	68 (21-156)	12,422	(13.4%)	

1. Year of ART initiation refers to the year the facility began treating patients (facility-level), the year each specific cohort initiated art (12 month ART cohort), or the year the patient initiated ART (patient-level)

Table 2. Patient-level characteristics of the study population

		Patient-level variables		
		N (%) Patients		median(IQR) patients per site
	Total	92,651	(100%)	528 (174-1268)
Sex	Pediatric*	6853	(7.4%)	42 (12-90)
	Adult Female	54989	(59.4%)	335.5 (98-753)
	Adult Male	30806	(33.2%)	170.5 (57-443.5)
Age at ART initiation	median (IQR)	34.5(28-42.2)		
	0-15	6,802	(7.3%)	44 (13-90)
	15-30	22,900	(24.7%)	105 (37-313)
	30-45	45,549	(49.2%)	277 (81-675)
	45-60	15,435	(16.7%)	102 (30-206)
	> 60	1,914	(2.1%)	14 (5-27)
CD4 count at enrollment into care	median (IQR)	172 (82-285)		
	missing	33,455	(36.1%)	n.a.
	< 100	17,576	(19%)	n.a.
	100-200	16,675	(18%)	n.a.
	200-350	15,325	(16.5%)	n.a.
	> 350	9,620	(10.4%)	n.a.
WHO stage at enrollment into care	missing	22,162	(23.9%)	
	I	11,862	(12.8%)	n.a.
	II	16,241	(17.5%)	n.a.
	III	33,007	(35.6%)	n.a.
	IV	9,379	(10.1%)	n.a.
				n.a.
CD4 count at ART initiation	median (IQR)	159 (78-240)		
	missing	28,443	(30.7%)	n.a.
	< 100	20,095	(21.7%)	n.a.
	100-200	21,344	(23%)	n.a.
	200-350	17,586	(19%)	n.a.
	> 350	5,183	(5.6%)	n.a.
WHO stage at ART initiation	missing	51,290	(55.4%)	n.a.
	I	5,293	(5.7%)	n.a.
	II	8,781	(9.5%)	n.a.
	III	20,153	(21.8%)	n.a.
	IV	7,134	(7.7%)	n.a.

Table 3. Distribution of adherence support and active outreach services

		N (%) Facilities		N (%) 12-month ART cohorts		N(%) patients	
Total		92	(100%)	675	(100%)	92,651	(100%)
Adherence support services							
Total number of adherence support services provided	< three	11	(12%)	82	(12%)	10,095	(11%)
	three or more	81	(88%)	593	(88%)	82,556	(89%)
Availability of educational pamphlets, etc	no	31	(34%)	198	(29%)	27,755	(30%)
	yes	61	(66%)	477	(71%)	64,896	(70%)
Number of separate directed counseling/support services available	0	5	(5%)	165	(24%)	17,692	(19%)
	1	22	(24%)	184	(27%)	29,732	(32%)
	2	24	(26%)	172	(25%)	26,971	(29%)
	3	41	(45%)	154	(23%)	18,256	(20%)
one-on-one or group adherence counseling services	no	5	(5%)	353	(52%)	54,173	(58%)
	yes	87	(95%)	322	(48%)	38,478	(42%)
Frequency of counseling services among sites providing them	< every 3 months	10	(11%)	38	(12%)	8,122	(21%)
	≥ every 3 months	77	(89%)	284	(88%)	30,356	(79%)
on-site support group for HIV+ patients	no	36	(39%)	294	(44%)	30,642	(33%)
	yes	56	(61%)	381	(56%)	62,009	(67%)
peer educator program	no	42	(46%)	388	(57%)	54,696	(59%)
	yes	50	(54%)	287	(43%)	37,955	(41%)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	no	22	(24%)	120	(18%)	15,773	(17%)
	yes	70	(76%)	555	(82%)	76,878	(83%)
Dedicated pharmacist, team pharmacist, or routine medication pickup review	no	14	(15%)	56	(8%)	3,727	(4%)
	yes	78	(85%)	619	(92%)	88,924	(96%)
Food rations provided to adults or children	no	65	(71%)	587	(87%)	86,376	(93%)
	yes	27	(29%)	88	(13%)	6,275	(7%)
Outreach Services							
Active patient outreach	no	31	(34%)	239	(35%)	30,238	(33%)
	yes	61	(66%)	436	(65%)	62,413	(67%)
Target population among sites w/ active outreach	ART patients only	14	(23%)	102	(24%)	22,194	(36%)
	All Patients	47	(77%)	321	(76%)	38,644	(64%)

Table 4a. Rate ratios (Facility-level and Patient-level) and risk ratios (12-month ART cohort) for non-retention by availability of adherence support and active outreach service

		Facility-level analysis: N = 92 sites Non-retention rate ratio[1]				12-month ART cohort analysis Non-retention risk ratio[2]							
						6 months				12 months			
Adherence support services		Crude RR (95% CI)		Adjusted[3] RR (95% CI)		Crude RR (95% CI)		Adjusted[4] RR (95% CI)		Crude RR (95% CI)		Adjusted[4] RR (95% CI)	
Total number of adherence support services offered	>2 vs. ≤ 2	0.91	(0.44-1.86)	1.05	(0.5-2.2)	0.92	(0.73-1.17)	0.9	(0.67-1.2)	1.1	(0.94-1.28)	0.99	(0.83-1.18)
Availability of educational pamphlets, etc	yes vs. no	1.13	(0.85-1.49)	0.99	(0.72-1.34)	1.01	(0.8-1.27)	1.02	(0.82-1.27)	1.01	(0.85-1.2)	1.03	(0.88-1.21)
Number of separate directed counseling services available	2 vs. 1	1.28	(0.86-1.91)	0.86	(0.53-1.38)	0.89	(0.73-1.09)	0.89	(0.74-1.08)	0.87	(0.73-1.03)	0.84	(0.73-0.97)
	3 vs. 1	1.2	(0.85-1.71)	0.81	(0.53-1.22)	1.07	(0.79-1.45)	0.93	(0.67-1.28)	1.04	(0.82-1.3)	0.82	(0.67-1.01)
	more than 1 vs. 1	1.23	(0.89-1.71)	0.82	(0.55-1.22)	0.96	(0.78-1.17)	0.91	(0.74-1.11)	0.93	(0.79-1.1)	0.84	(0.73-0.96)
one-on-one or group adherence counseling services	yes vs. no	0.89	(0.43-1.86)	1.04	(0.49-2.22)	1.17	(0.98-1.39)	1.91	(1.57-2.32)	1.26	(1.12-1.4)	1.46	(1.27-1.68)
Frequency of counseling services among sites providing them	≥ every 3 vs. < every 3 months	1.9	(1.35-2.66)	1.67	(1.16-2.4)	0.74	(0.48-1.13)	0.75	(0.5-1.13)	0.93	(0.73-1.17)	0.93	(0.75-1.15)
on-site support group for HIV+ patients	yes vs. no	1.27	(0.95-1.69)	1	(0.7-1.43)	0.87	(0.68-1.1)	0.82	(0.66-1.01)	0.86	(0.72-1.04)	0.77	(0.68-0.87)
peer educator program	yes vs. no	0.99	(0.76-1.29)	0.81	(0.62-1.07)	0.94	(0.75-1.18)	0.9	(0.74-1.1)	0.93	(0.79-1.1)	0.87	(0.76-0.98)
Availability of reminder tools	yes vs. no	1.15	(0.8-1.66)	1.29	(0.9-1.85)	1.08	(0.84-1.38)	1.11	(0.84-1.47)	1.02	(0.79-1.3)	1.06	(0.83-1.34)
Routine medication pickup review/dedicated pharmacist	yes vs. no	0.88	(0.46-1.67)	1	(0.52-1.93)	1.12	(0.88-1.43)	1.21	(0.94-1.57)	1.13	(0.94-1.36)	1.17	(0.94-1.47)
Food rations provided to promote ART adherence	yes vs. no	0.81	(0.55-1.2)	0.67	(0.44-1.03)	0.82	(0.64-1.04)	0.71	(0.55-0.92)	0.92	(0.77-1.11)	0.78	(0.65-0.95)
Outreach Services													
Active patient outreach	yes vs. no	1.58	(1.11-2.25)	1.32	(0.87-2.01)	0.85	(0.69-1.04)	0.8	(0.66-0.97)	0.92	(0.78-1.08)	0.86	(0.75-0.98)
Target population among sites w/ active outreach	all patients vs ART patients only	1.02	(0.76-1.36)	1.11	(0.75-1.65)	1.21	(0.90-1.63)	1.2	(0.87-1.66)	1.07	(0.84-1.35)	1.01	(0.83-1.23)

Table 4a (continued). Rate ratios (Facility-level and Patient-level) and risk ratios (12-month ART cohort) for non-retention by availability of adherence support and active outreach service

		Patient-level analysis[5]: N = 93,772 patients							
Adherence support services		Crude HR (95% CI)		site-level Adjusted[6] HR (95% CI)		patient-level Adjusted[7] HR (95% CI)		site and patient-level Adjusted[8] HR (95% CI)	
Total number of adherence support services offered	>2 vs. ≤ 2	1.32	(1.06-1.65)	1.09	(0.85-1.39)	1.12	(0.92-1.36)	1.16	(0.94-1.42)
Availability of educational pamphlets, etc	yes vs. no	1.06	(0.89-1.26)	1.05	(0.88-1.24)	1.07	(0.95-1.21)	1.08	(0.95-1.22)
Number of separate directed counseling services available	2 vs. 1	1.14	(0.94-1.38)	1.04	(0.91-1.19)	1.07	(0.94-1.21)	1.07	(0.95-1.21)
	3 vs. 1	1.2	(0.93-1.54)	1.03	(0.75-1.4)	1.06	(0.86-1.3)	1.06	(0.83-1.35)
	more than 1 vs. 1	1.16	(0.96-1.4)	1.04	(0.88-1.22)	1.06	(0.93-1.22)	1.07	(0.93-1.23)
one-on-one or group adherence counseling services	yes vs. no	1.3	(1.19-1.43)	1.67	(1.43-1.96)	1.54	(1.4-1.7)	1.52	(1.36-1.71)
Frequency of counseling services among sites providing them	≥ every 3 months vs. < every 3 months	0.91	(0.63-1.3)	1.01	(0.74-1.38)	1	(0.76-1.31)	1.02	(0.81-1.28)
on-site support group for HIV+ patients	yes vs. no	0.95	(0.77-1.18)	0.95	(0.77-1.17)	1	(0.86-1.17)	1.01	(0.86-1.19)
peer educator program	yes vs. no	1.15	(0.95-1.39)	1.11	(0.91-1.35)	1.1	(0.95-1.26)	1.1	(0.93-1.31)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	1.26	(1-1.58)	1.13	(0.93-1.36)	1.14	(0.96-1.34)	1.15	(0.99-1.32)
Routine medication pickup review/dedicated pharmacist	yes vs. no	1.34	(1.04-1.74)	1.13	(0.88-1.44)	1.13	(0.92-1.39)	1.16	(0.97-1.38)
Food rations provided to promote ART adherence	yes vs. no	0.83	(0.53-1.29)	0.84	(0.54-1.31)	0.94	(0.67-1.34)	0.93	(0.66-1.32)
Outreach Services									
Active patient outreach	yes vs. no	0.89	(0.73-1.08)	0.83	(0.72-0.96)	0.9	(0.79-1.02)	0.88	(0.78-0.99)
Target population among sites w/ active outreach	all patients vs ART patients only	0.96	(0.7-1.31)	1.26	(0.98-1.63)	1.27	(1.04-1.55)	1.28	(1.05-1.56)

1. Facility-level non-retention rates estimated as the cumulative number of patients at a site lost to follow-up, withdrawn, or reported dead, over the total person-years observed on ART at that site
2. 6 and 12 month ART cohort risk ratios estimated as the proportion of patients retained and on ART 6 and 12 months after ART initiation
3. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year facility began providing ART care, and cumulative number of patients seen in care
4. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year cohort initiated ART care, and cumulative number of patients seen in care
5. Patient-level non-retention rate ratios estimated from proportional hazards models
6. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year patient initiated ART care, and cumulative number of patients seen in care
7. Adjusted for CD4 count at enrollment, WHO stage at enrollment, Weight at enrollment, age, and sex
8. Adjusted for facility- and patient-level covariates listed in notes 6 and 7
9. Cohort and patient-level analyses account for within-facility similarity using generalized estimating equations

Table 4b. Rate ratios for loss to follow-up by adherence support and active outreach service availability

Adherence support services		Facility-level analysis: N = 92 sites				Patient-level analysis: N = 93,772 patients							
		LTF rate ratio[1]				LTF rate ratio[2]							
		Crude RR (95% CI)		Adjusted[3] RR (95% CI)		Crude HR (95% CI)		site-level Adjusted[4] HR (95% CI)		patient-level Adjusted[5] HR (95% CI)		site and patient-level Adjusted[6] HR (95% CI)	
Total number of adherence support services offered	>2 vs. ≤ 2	0.7	(0.31-1.54)	0.76	(0.32-1.81)	1.51	(1.12-2.05)	1.08	(0.79-1.46)	1.09	(0.86-1.38)	1.12	(0.86-1.46)
Availability of educational pamphlets, etc	yes vs. no	0.92	(0.65-1.29)	0.83	(0.56-1.24)	1.07	(0.87-1.32)	1.01	(0.81-1.25)	1.04	(0.9-1.21)	1.03	(0.87-1.23)
Number of separate directed counseling services available	2 vs. 1	1.35	(0.82-2.2)	1.07	(0.55-2.08)	1.18	(0.88-1.56)	1.06	(0.9-1.25)	1.09	(0.93-1.27)	1.1	(0.94-1.27)
	3 vs. 1	1.18	(0.76-1.83)	0.92	(0.52-1.63)	1.22	(0.89-1.68)	1.07	(0.75-1.51)	1.08	(0.83-1.4)	1.1	(0.82-1.48)
	more than 1 vs. 1	1.23	(0.82-1.86)	0.95	(0.54-1.66)	1.19	(0.9-1.57)	1.06	(0.88-1.28)	1.08	(0.92-1.28)	1.1	(0.93-1.3)
one-on-one or group adherence counseling services	yes vs. no	0.65	(0.3-1.45)	0.72	(0.3-1.73)	1.4	(1.24-1.58)	1.8	(1.49-2.19)	1.67	(1.49-1.88)	1.65	(1.41-1.92)
Frequency of counseling services among sites providing them	≥ every 3 months vs. < every 3 months	1.77	(1.15-2.72)	1.71	(1.05-2.76)	0.82	(0.55-1.22)	0.95	(0.69-1.32)	0.94	(0.68-1.3)	0.98	(0.76-1.27)
on-site support group for HIV+ patients	yes vs. no	1.3	(0.9-1.87)	1.12	(0.69-1.82)	1.03	(0.8-1.33)	1.02	(0.76-1.36)	1.05	(0.84-1.32)	1.07	(0.84-1.38)
peer educator program	yes vs. no	0.87	(0.63-1.22)	0.75	(0.53-1.07)	1.2	(0.94-1.53)	1.18	(0.94-1.49)	1.14	(0.96-1.36)	1.18	(0.96-1.45)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	1.16	(0.74-1.83)	1.3	(0.81-2.09)	1.33	(1-1.76)	1.08	(0.87-1.35)	1.09	(0.91-1.3)	1.09	(0.91-1.29)
Dedicated pharmacist, team pharmacist, or routine medication pickup review	yes vs. no	0.68	(0.33-1.38)	0.71	(0.32-1.55)	1.56	(1.23-1.98)	1.11	(0.85-1.46)	1.1	(0.88-1.38)	1.12	(0.9-1.39)
Food rations provided to promote ART adherence	yes vs. no	0.66	(0.39-1.11)	0.61	(0.33-1.14)	0.79	(0.45-1.4)	0.87	(0.52-1.46)	0.96	(0.62-1.49)	0.94	(0.61-1.44)
Outreach Services													
Active patient outreach	yes vs. no	1.66	(1.05-2.61)	1.5	(0.84-2.67)	0.87	(0.69-1.1)	0.79	(0.66-0.95)	0.83	(0.71-0.97)	0.82	(0.7-0.96)
Target population among sites w/ active outreach	all patients vs ART patients only	0.92	(0.63-1.35)	1.14	(0.66-1.95)	0.83	(0.57-1.22)	1.22	(0.95-1.57)	1.27	(1.03-1.56)	1.25	(1.02-1.52)

1. Facility-level loss to follow-up rates estimated as the cumulative number of patients at a site lost to follow-up, over the total person-years observed on ART at that site
2. Patient-level loss to follow-up rate ratios estimated from proportional hazards models
3. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year facility began providing ART care, and cumulative number of patients seen in care
4. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year patient initiated ART, and cumulative number of patients seen in care
5. Adjusted for CD4 count at enrollment, WHO stage at enrollment, Weight at enrollment, age, and sex
6. Adjusted for facility- and patient-level covariates listed in notes 4 and 5
7. Patient-level analyses account for within-facility similarity using generalized estimating equations

Table 4c. Rate ratios for ascertained death by adherence support and active outreach service availability

		Facility-level analysis: N = 92 sites Outcome = ascertained death rate ratio[1]				Patient-level analysis: N = 93,772 patients Outcome = ascertained death rate ratio[2]							
Adherence support services		Crude RR (95% CI)		Adjusted[3] RR (95% CI)		Crude HR (95% CI)		site-level Adjusted[4] HR (95% CI)		patient-level Adjusted[5] HR (95% CI)		site and patient-level Adjusted[6] HR (95% CI)	
Total number of adherence support services offered	>2 vs. ≤ 2	3.21	(0.75-13.72)	4.16	(1.32-13.1)	0.88	(0.58-1.34)	1.16	(0.88-1.54)	1.17	(0.87-1.57)	1.31	(1.01-1.69)
Availability of educational pamphlets, etc	yes vs. no	2	(1.45-2.75)	1.59	(1.2-2.11)	1.04	(0.78-1.38)	1.18	(0.95-1.47)	1.17	(0.92-1.49)	1.25	(1.01-1.53)
Number of separate directed counseling services available	2 vs. 1	1.13	(0.73-1.75)	0.55	(0.39-0.77)	1	(0.65-1.54)	0.99	(0.68-1.44)	1.04	(0.74-1.46)	1	(0.72-1.4)
	3 vs. 1	1.27	(0.88-1.83)	0.64	(0.49-0.85)	1.1	(0.68-1.78)	0.94	(0.6-1.46)	1.07	(0.73-1.58)	0.99	(0.68-1.46)
	more than 1 vs. 1	1.22	(0.86-1.73)	0.62	(0.47-0.81)	1.03	(0.67-1.59)	0.97	(0.67-1.43)	1.05	(0.75-1.47)	1	(0.72-1.4)
one-on-one or group adherence counseling services	yes vs. no	6.06	(0.8-45.94)	7.76	(1.63-37.06)	1	(0.8-1.25)	1.32	(1.03-1.67)	1.21	(0.92-1.59)	1.2	(0.92-1.56)
Frequency of counseling services among sites providing them	≥ every 3 months vs. < every 3 months	2.28	(1.57-3.31)	1.56	(1.14-2.12)	1.58	(0.99-2.53)	1.42	(0.91-2.2)	1.39	(0.97-2)	1.4	(1.03-1.9)
on-site support group for HIV+ patients	yes vs. no	1.2	(0.87-1.66)	0.79	(0.6-1.04)	0.73	(0.55-0.95)	0.78	(0.58-1.04)	0.87	(0.65-1.17)	0.88	(0.65-1.19)
peer educator program	yes vs. no	1.34	(1-1.81)	0.99	(0.78-1.26)	0.98	(0.69-1.39)	0.92	(0.65-1.3)	0.99	(0.74-1.31)	0.91	(0.66-1.24)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	1.14	(0.76-1.7)	1.27	(0.93-1.74)	1.04	(0.72-1.5)	1.25	(0.97-1.6)	1.24	(0.95-1.6)	1.33	(1.09-1.62)
Dedicated pharmacist, team pharmacist, or routine medication pickup review	yes vs. no	2.75	(0.82-9.25)	3.66	(1.45-9.24)	0.88	(0.56-1.4)	1.13	(0.79-1.62)	1.19	(0.84-1.69)	1.25	(0.93-1.67)
Food rations provided to promote ART adherence	yes vs. no	1.23	(0.84-1.81)	0.76	(0.55-1.04)	0.96	(0.72-1.28)	0.81	(0.6-1.1)	1	(0.8-1.25)	1.03	(0.81-1.3)
Outreach Services													
Active patient outreach	yes vs. no	1.41	(0.95-2.08)	1.05	(0.75-1.46)	0.94	(0.7-1.27)	0.97	(0.75-1.26)	1.15	(0.91-1.45)	1.15	(0.9-1.46)
Target population among sites w/ active outreach	all patients vs ART patients only	1.34	(1.01-1.78)	1.08	(0.78-1.47)	1.71	(0.95-3.09)	1.69	(1.03-2.77)	1.5	(0.98-2.3)	1.62	(1.07-2.46)

1. Facility-level death rates estimated as the cumulative number of patients at a site ascertained to be dead, over the total person-years observed on ART at that site
2. Patient-level death rate ratios estimated from proportional hazards models
3. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year facility began providing ART care, and cumulative number of patients seen in care
4. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, year patient initiated ART, and cumulative number of patients seen in care
5. Adjusted for CD4 count at enrollment, WHO stage at enrollment, Weight at enrollment, age, and sex
6. Adjusted for facility- and patient-level covariates listed in notes 4 and 5
7. Patient-level analyses account for within-facility similarity using generalized estimating equations

Table 5: Patient-level factors associated with non-retention, loss to follow-up, and measured death

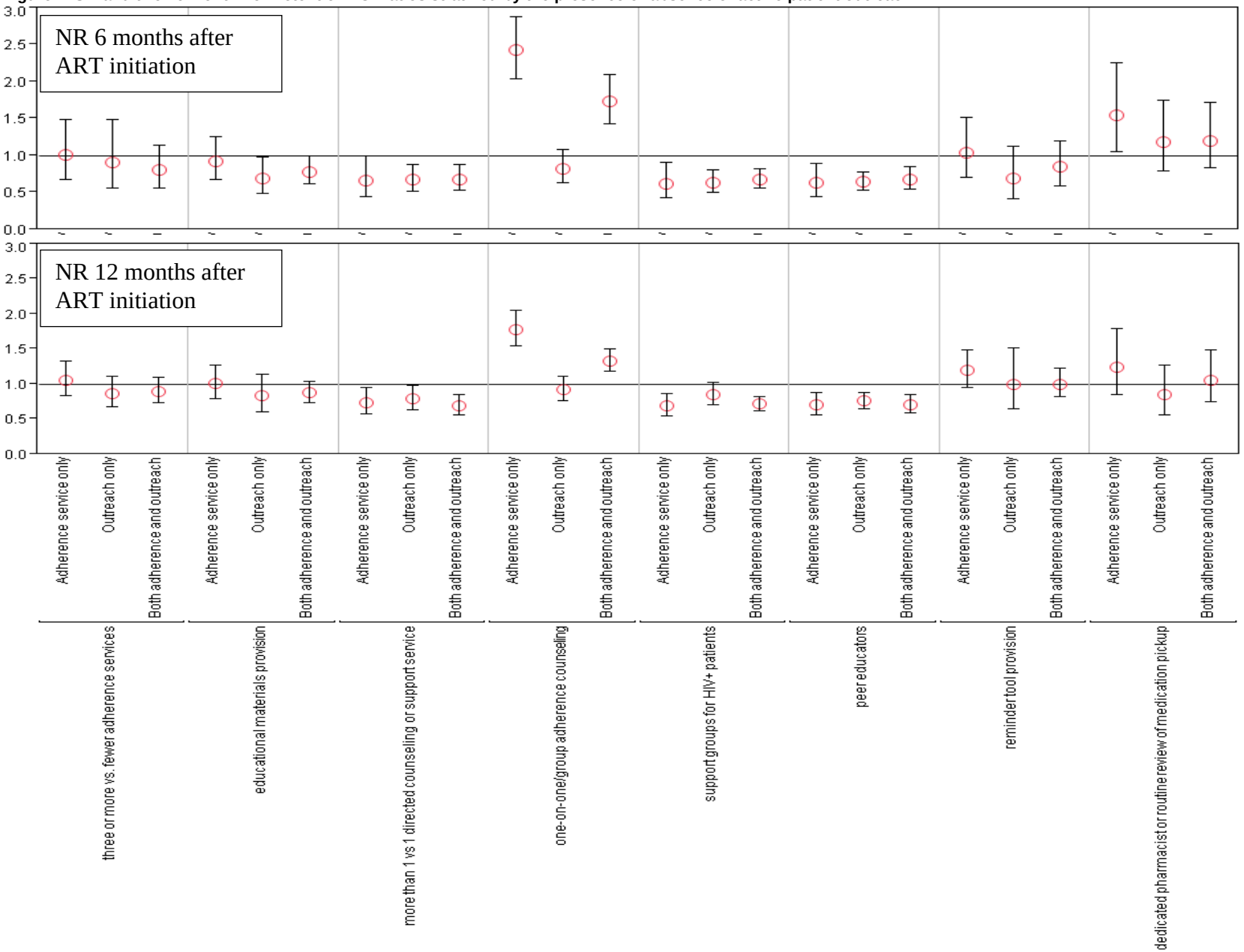
			Rate Ratios and 95% CI		
Variable	**Class**	**N (%)**	**Non-retention**	**LTF**	**Death**
Age at enrollment	< 15	6401 (8%)	0.89 (0.84-0.94)	0.81 (0.76-0.87)	1.15 (1.04-1.27)
	15-30	19761 (24.8%)	1.32 (1.28-1.36)	1.43 (1.38-1.48)	0.95 (0.89-1.03)
	30-45	38766 (48.7%)	1.0 (ref)		
	45-60	13036 (16.4%)	0.98 (0.94-1.02)	0.92 (0.88-0.96)	1.21 (1.12-1.3)
	≥ 60	1614 (2%)	1.21 (1.11-1.33)	1.04 (0.93-1.16)	1.81 (1.55-2.11)
CD4 count (cells/uL) at enrollment	missing	27300 (34.3%)	1.58 (1.51-1.65)	1.52 (1.44-1.59)	1.89 (1.7-2.09)
	< 50	8433 (10.6%)	1.97 (1.87-2.08)	1.67 (1.57-1.77)	3.39 (3.03-3.79)
	50 -100	7115 (8.9%)	1.45 (1.37-1.53)	1.32 (1.23-1.41)	2.05 (1.81-2.33)
	100-150	7136 (9%)	1.26 (1.19-1.34)	1.2 (1.12-1.28)	1.52 (1.33-1.74)
	150-200	7327 (9.2%)	1.13 (1.06-1.20)	1.13 (1.06-1.21)	1.13 (0.98-1.31)
	200-350	9662 (12.1%)	1.04 (0.98-1.10)	1.04 (0.98-1.11)	1.03 (0.89-1.18)
	> 350	12605 (15.8%)	1.0 (ref)		
WHO stage at enrollment	missing	16619 (20.9%)	1.84 (1.75-1.94)	1.83 (1.73-1.94)	1.9 (1.66-2.16)
	1	10595 (13.3%)	1.0 (ref)		
	2	14252 (17.9%)	1.00 (0.94-1.06)	0.92 (0.86-0.98)	1.47 (1.28-1.69)
	3	28789 (36.2%)	1.46 (0.94-1.54)	1.3 (1.23-1.37)	2.38 (2.11-2.69)
	4	9323 (11.7%)	2.55 (2.42-2.69)	2.08 (1.96-2.21)	5.26 (4.63-5.98)
Weight (kg) at enrollment	missing	19586 (24.6%)	1.29 (1.25-1.33)	1.34 (1.3-1.39)	1.09 (1.01-1.18)
	< 25	4585 (5.8%)	1.05 (0.99-1.12)	0.93 (0.87-1.01)	1.5 (1.33-1.69)
	25-50	19529 (24.5%)	1.57 (1.52-1.62)	1.45 (1.39-1.5)	2.07 (1.93-2.21)
	50-100	35743 (44.9%)	1.0 (ref)		
	> 100	135 (0.2%)	0.60 (0.39-0.93)	0.65 (0.41-1.03)	0.44 (0.14-1.38)
Sex	Female	50300 (63.2%)	1.0 (ref)		
	Male	29278 (36.8%)	1.30 (1.27-1.34)	1.22 (1.19-1.26)	1.64 (1.55-1.73)
Year of enrollment	2003	19669 (24.7%)	0.43 (0.37-0.50)	0.43 (0.37-0.51)	0.44 (0.31-0.63)
	2004	6882 (8.6%)	0.53 (0.49-0.57)	0.54 (0.49-0.58)	0.51 (0.43-0.61)
	2005	604 (0.8%)	0.61 (0.58-0.63)	0.55 (0.52-0.58)	0.85 (0.77-0.93)
	2006	2704 (3.4%)	0.69 (0.66-0.72)	0.62 (0.6-0.65)	0.97 (0.89-1.06)
	2007	10119 (12.7%)	0.84 (0.81-0.87)	0.82 (0.79-0.85)	0.92 (0.85-1)
	2008	16542 (20.8%)	1.0 (ref)		
	2009	23058 (29%)	0.83 (0.78-0.88)	0.76 (0.7-0.81)	1.16 (1.02-1.32)

Rate ratios presented obtained from proportional hazards modeling accounting for within-facility similarity using generalized estimating equations. Variables in the table are adjusted for all other variables presented.

Figure 1. Comparison of strengths and weaknesses of Facility-level, ART cohort, and patient-level data

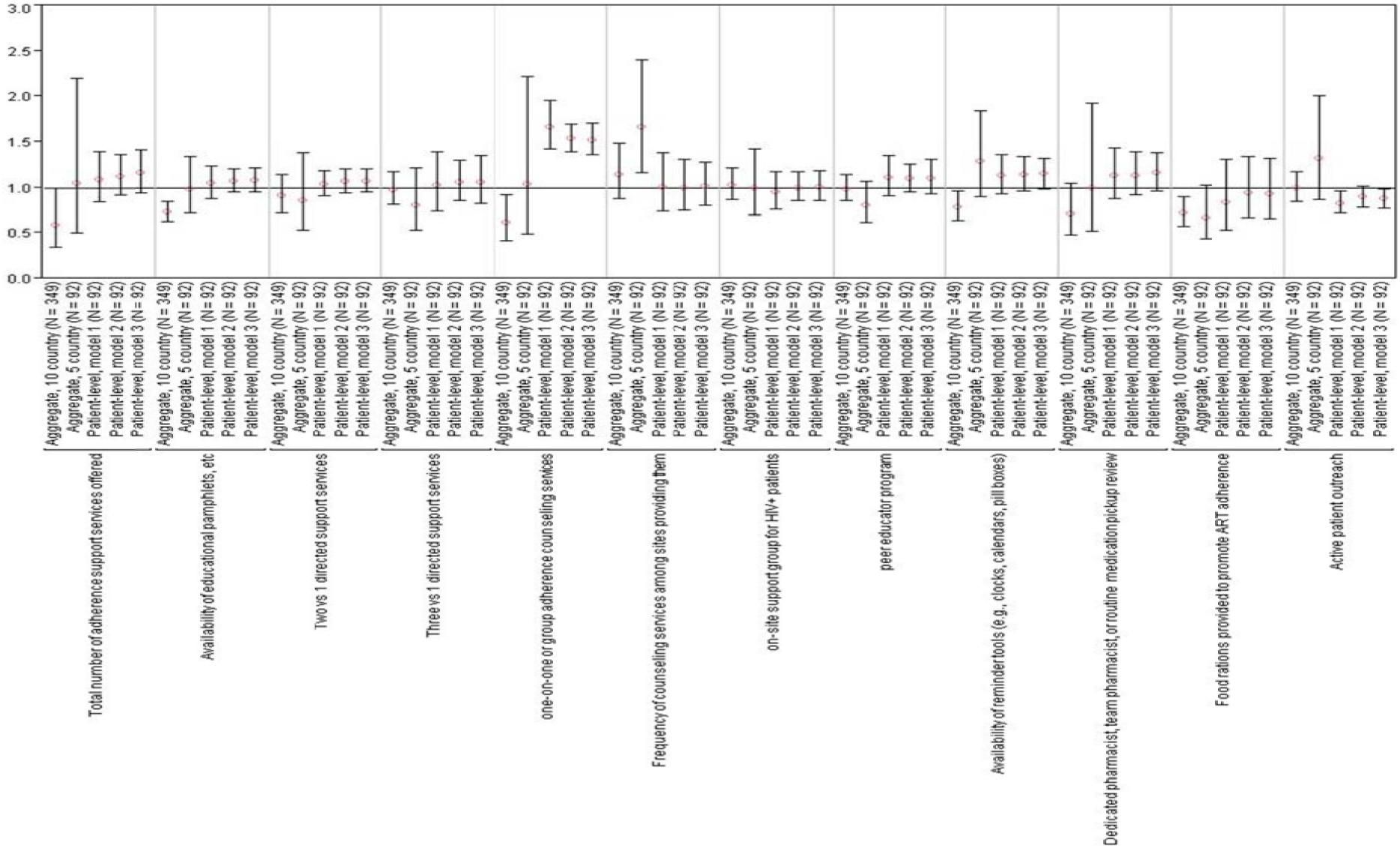
	Overall (cumulative) facility-level	12-month ART cohort	Patient-level
can estimate non-retention proportion		x	x
ability to separate out non-retention into LTF and death	x		x
includes all patients at clinics in study population	x		
can estimate non-retention within 6 months or 1 year after ART initiation		x	x
sensitive to changes in non-retention rate over time at a given clinic		x	x
can adjust for clinic-level predictors of non-retention	x	x	x
can adjust for patient-level predictors of non-retention			x

Figure 2. Six and twelve month non-retention risk ratios stratified by the presence or absence of active patient outreach



Notes: Risk ratios and 95% CIs presented are from the 12 month ART cohort analysis, adjusting for the same site-level factors described in Table 4

Figure 3a. Comparison between Paper 1 and current analysis: Non-retention rate ratios by adherence support and active outreach service



Notes: see notes at the end of Figure 3c

Figure 3b. Comparison between Paper 1 and current analysis: Loss to follow-up rate ratios by adherence support and active outreach service

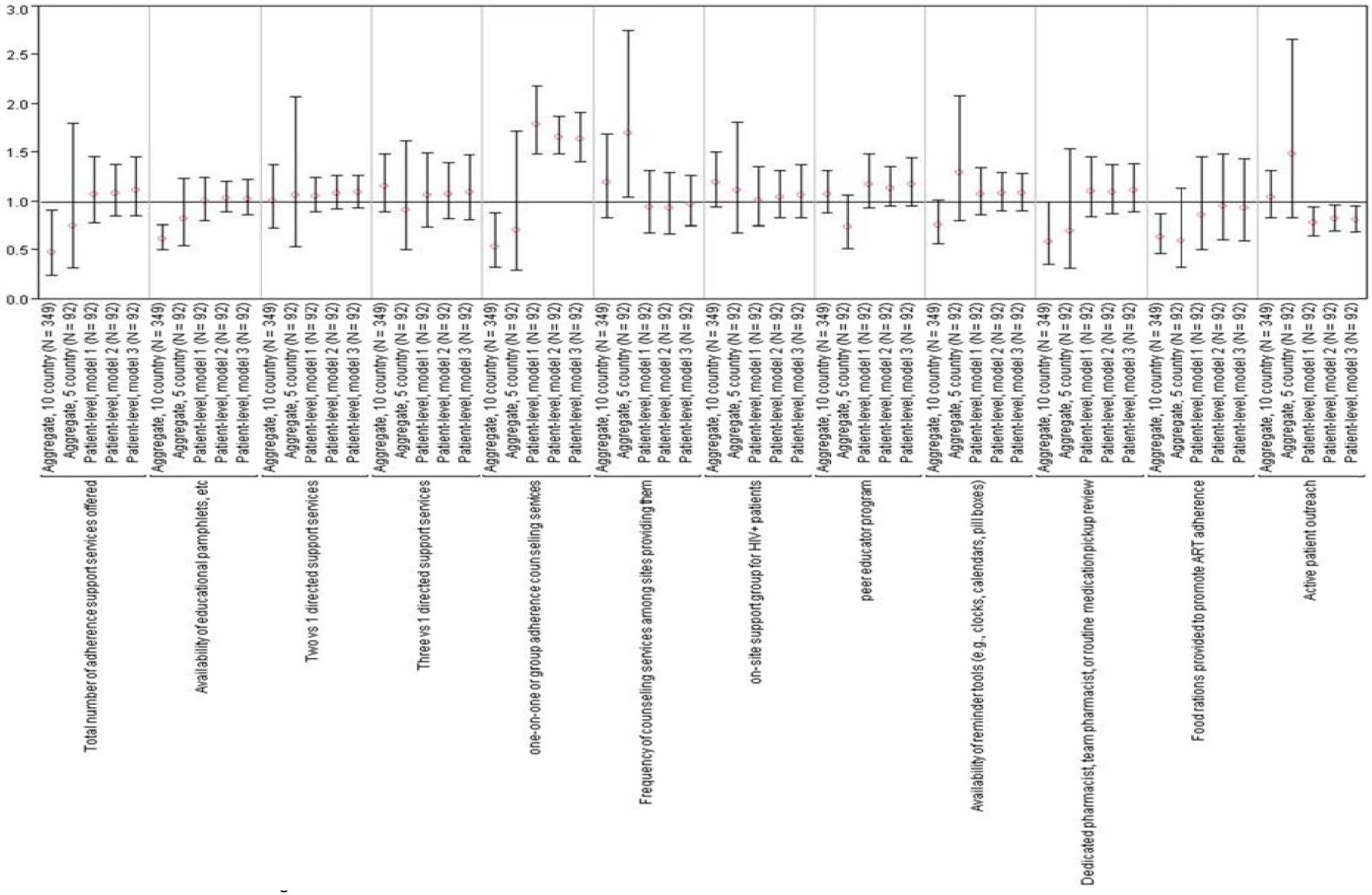
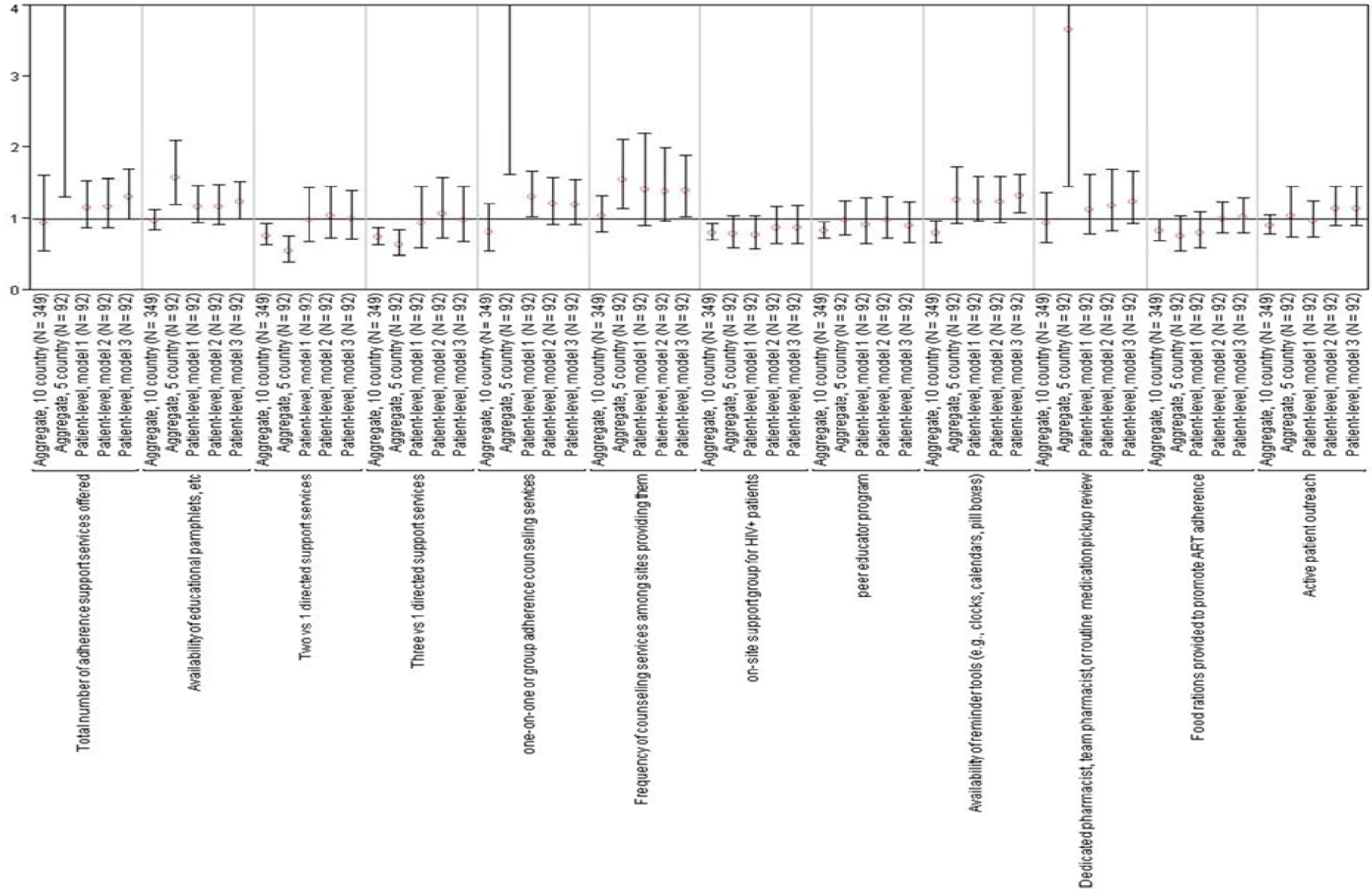


Figure 3c. Comparison between Paper 1 and current analysis: Death rate ratios by adherence support and active outreach service



Notes:

1. Aggregate analyses compare the aggregate cumulative rate ratio, adjusting for facility type (primary, secondary, or tertiary), urban/rural, year facility began providing ART care, and cumulative number of patients seen in care
2. Patient-level model 1 compares rate ratios using patient-level data, adjusting for facility type (primary, secondary, or tertiary), urban/rural, year facility began providing ART care, and cumulative number of patients seen in care
3. Patient-level model 2 compares rate ratio using patient-level data, adjusting for CD4 count at enrollment, WHO stage at enrollment, Weight at enrollment, age, and sex
4. Patient-level model 3 compares rate ratios using patient-level data, adjusting for covariates in model 1 and model 2 in a multi-level model

Loss to follow-up biases measured associations between adherence support and active outreach services and patient survival

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Abstract

Background: High rates of loss to follow-up among patients who initiated ART at HIV care and treatment clinics in sub-Saharan Africa complicate examinations of the potential impact of program-level services on patient survival. Patients lost to follow-up have, by definition, unknown vital status, and routine methods of survival analysis assume that individuals lost to follow-up have the same probability of death as those retained in care, conditioned on predictors of death. This assumption is unrealistic where loss to follow-up is substantial and is itself an important predictor of death. Previous analyses have suggested that loss to follow-up biases measures of individual-level determinants of survival, but whether and how it may bias measures of program-level determinants of survival is unknown. We conducted a sensitivity analysis to adjust estimated mortality rates under differing assumptions concerning the likelihood of death among patients lost to follow-up, to assess whether changes in the estimated survival risk impacted relative comparisons of the mortality rates between patients at clinics offering different ART adherence support and active outreach services.

Methods: The study population included 50,379 patients initiating ART between January 2008 and December 2009 at one of 102 HIV care and treatment clinics in 4 countries (Kenya, Mozambique, Rwanda, Tanzania) with patient-level data available for analysis to investigate whether specific adherence support and active outreach services were associated with measures of non-retention, loss to follow-up, and death. Data on adherence support and outreach services were obtained from annual structured site assessments. We then compared the results from these assessments with 5 sensitivity analyses, using multiple imputation and inverse probability weighting techniques, making different assumptions about the probability of death among patients lost to follow-up. Proportional Hazards models were used to assess the association between adherence support and outreach services on death rates un the baseline and sensitivity analyses.

Results: One-year non-retention, loss to follow-up, and mortality risk in this population was 4%, 17%, and 21%, respectively. Naive analyses comparing rates of non-retention, loss to follow-up and death between clinics offering various adherence support and active outreach services found that clinics offering on-site support groups for HIV+ patients, food rations to promote ART adherence, or active patient outreach had lower rates of non-retention than patients at clinics not offering these services, while patients at clinics offering food rations or ART counseling services had lower rates of ascertained deaths. In the sensitivity analysis active patient outreach became associated with reduced death, and food rations to support ART adherence remained associated with death. Other adherence support services were associated with reduced death in some, but not all, sensitivity analyses.

Conclusions: Adherence support and outreach services, strongly associated with loss to follow-up, also became associated with mortality after imputing the likely death probability among patients lost to follow-up. Findings were robust under a variety of assumptions, suggesting that loss to follow-up is masking real associations between adherence support and active outreach programs and reduced death.

Introduction

Access to antiretroviral therapy in resource-limited settings has increased exponentially in the last five years [1]. Consequently, attention has shifted from scale-up efforts at initiating patients in care to longer-term efforts to optimize patient outcomes in care. Care and treatment facilities offer a range of services intended to improve patient retention in care and on ART, and, ultimately, to improve survival, but the relative effectiveness of different services on these outcomes are not known. Patient survival after ART initiation is the ultimate outcome of interest when examining how HIV care and treatment facilities are performing. Unfortunately, direct comparisons of patient survival after ART initiation are complicated by substantial loss to follow-up, since patients lost to follow-up by definition have unknown vital status.

Patients lost to follow-up can be categorized into three groups based on their actual (but unascertained) status with respect to survival and maintenance of care: (1) transferred and continuing care at another facility, (2) dead (including deaths from both HIV and non-HIV causes), and (3) out of care (withdrawal). The distribution of these three groups is likely context-dependent, but most studies investigating mortality among ART patients lost to follow-up from HIV care and treatment clinics in resource-limited settings have found higher mortality rates among patients lost to follow-up compared to the rates found among those not lost [2]. One study tracing a sample of patients lost to follow-up from a clinic in Uganda estimated that up to 59% of patients lost to follow-up had attended a different clinic for HIV treatment in the last 3 months (unascertained transfers), while 25% were unascertained deaths [3]. Other studies focusing on the proportion of unascertained deaths among patients lost to follow-up ([3-13]; reviewed in [2]) estimate that 20-60% of LTF patients who could be traced had died. Underestimation of mortality due to lost to follow-up does not necessarily imply that relative comparisons of mortality between facilities offering different services will be biased. Studies

investigating predictors of mortality among patients lost to follow-up have found, not surprisingly, that patients with pre-loss indicators of poor health and older age had higher risk of mortality than healthier patients [3, 4, 9]. However, relative comparisons of mortality between different exposure groups will be biased by loss to follow-up only if the effect of these characteristics on mortality differs between patients lost to follow-up and those not lost. A recent study by Geng et al [12] suggests that male gender may be spuriously associated with mortality at an HIV clinic in Uganda if mortality among patients lost to follow-up is not taken into account, while an increasing risk of mortality with increasing age may be masked. Healthier male patients were more likely to be lost, creating a selection bias where the males remaining in care were sicker, and at greater risk of death, than the female population initiating treatment. Similarly, younger patients who were not lost were at higher risk of death than younger patients lost to follow-up, biasing comparisons of mortality by age. We expect that differences in the mortality rate among patients retained in care and lost to follow-up may also impact relations between program-level service availability and mortality. The extent to which this bias exists is unknown and the focus of this paper.

In settings where sampling of those lost to ascertain the true outcome is not possible, other approaches can be used to adjust mortality estimates based on missing vital status information due to loss to follow-up. One approach assumes patients lost to follow-up have the same probability of death as those retained in care, conditioned on measured predictors of death among patients whose vital status is known. A second approach allows for the relationship between these predictors and mortality to differ between patients retained and those lost to follow-up, with predictors of loss to follow-up obtained either from a sampling approach or through use of externally-derived assumptions about predictors of death among patients lost to follow-up. This paper examines the extent to which estimates of the effectiveness of adherence support and active outreach services on improving patient survival are influenced by loss to follow-up.

Methods

Study Population

Patients 5 years old and above initiating ART between January 1, 2008 and December 31, 2009 at one of 102 HIV care and treatment facilities in 4 sub-Saharan African countries (Kenya (N = 25 facilities, 7,147 patients), Mozambique (N =27 facilities, 29,745 patients), Rwanda (N = 31 facilities, 7,325 patients), and Tanzania (N = 21 facilities, 6,162 patients)) comprise the study population. Electronic patient-level databases from each site were anonymized, key variables transformed into a common format, and combined into a single database comprising all sites from these four countries.

Facility Services

Availability of services targeting ART adherence and retention in care was estimated from an annual structured site assessment, completed by facility staff. Two site assessments were completed during the time frame of the study. Patients initiating ART between January and December 2008 were assigned facility-level services based on responses to the first of these assessments (completed in June-August of 2008), while patients initiating ART between January and December 2009 were assigned facility-level services based on responses to the second assessment (completed in June-August of 2009).

Specific facility-level services targeting ART adherence and retention in care examined in this analysis include “directed” services, involving direct consultation with health professionals or support groups (one-on-one or group adherence counseling, peer educator programs, and on-site support groups for HIV+ patients), routine review of ART pharmacy medication pickup, food support services to promote ART adherence, and active outreach services that track patients missing scheduled visits to ascertain vital status and return lapsed patients to care.

Outcomes

The primary outcome in this analysis survival one year after ART initiation. Time from ART initiation until documented death or transfer was calculated as the difference between their ART initiation date

and their date of reported death or transfer in the database. Patients not documented as dead or transferred who have not had a recorded visit in the 6 months before the database close date (June 30, 2010) were classified as lost to follow-up, and their date of LTF was taken as 15 days after their last recorded visit. For all analyses, the measure of association is the hazard rate ratio, comparing the rate of death between sites offering a given service and those not offering such a service.

Analytic Methods

To test the hypothesis that ART patients attending facilities offering specific adherence support and outreach services had lower rates of death than ART patients attending facilities not offering these services, we used Cox Proportional Hazards models, accounting for within-facility correlation, to estimate the measured death rate ratio between facilities with and without such services. We first tested this hypothesis using a naïve approach, assuming that patients lost to follow-up were missing at random and censoring them at their calculated loss to follow-up date. Next, we imputed survival probabilities among patients lost to follow-up in a series of sensitivity analyses (described in detail below). Finally, we compared the results of the naïve analyses with the sensitivity analyses to assess the degree to which measures of association were biased by loss to follow-up.

Baseline ("naïve") analyses

Associations between adherence support and outreach services and measured rates of loss to follow-up, death, and non-retention were first estimated using Cox Proportional Hazards models, accounting for within-clinic correlation. A model using death as the outcome of interest was used as the baseline model against which the sensitivity analyses were compared. The model using loss to follow-up as the outcome of interest was used to examine factors associated with loss to follow-up, which then served to construct key populations used in the sensitivity analyses described below. Finally, a model using non-retention (loss to follow-up + death) as an outcome was used to provide an estimate of the relationship between adherence support and outreach services assuming that loss to follow-up

and death are both undesirable outcomes. For all three outcomes, the first model, the "crude" model, compared the hazard of non-retention, LTF, and death among patients at sites with differing adherence support and active outreach services, without adjusting for potential confounding variables. A second model adjusted for patient-level differences as potential confounding variables, including age, sex, weight at enrollment, CD4 count and WHO stage at enrollment, and status of tuberculosis treatment before ART initiation. Missing values were included as a separate category in analyses. A third model additionally adjusted for potential site-level confounding variables (facility type (primary, secondary, or tertiary), location (urban, semi-urban, or rural), and facility size (cumulative number of patients seen at the clinic))

Sensitivity analyses

The naïve analyses assume that those lost to follow-up are missing completely at random (in the crude analysis) or missing at random (adjusted analyses) conditioned on covariates in the analysis. However, these assumptions are unrealistic. To assess whether relaxation of these assumptions impacts our conclusions about the impact of program services on patient survival, three approaches were used to estimate the mortality rate among patients lost to follow-up, and ultimately to assess whether adjustment of the overall mortality rate based on different assumptions influences observed relationships between the availability of adherence support and outreach services and mortality rates.

Approach #1: Multiple Imputation

The first approach assumes that any differences in the death rate between those lost and those retained is due to a differential distribution of known causes of death between those lost and those not lost. This is equivalent to a missing at random assumption. For this analysis, we assume that predictors of mortality are the same among patients lost to follow-up and those retained in care. Under this approach, we constructed three models. First, a parsimonious model, using a patient's last available CD4 count as the only predictor of mortality was constructed. Second, a model was

constructed controlling for last known CD4 count, and other patient-level factors, including age, sex, and TB infection status, as predictors of mortality. Third, model that controlled only for program-level factors was constructed using country, facility location (urban, peri-urban, or rural), and facility type (primary, secondary, or tertiary) as predictors of mortality. For all analyses under this approach we first calculated the probability of death within one year of ART initiation among patients not lost to follow-up, stratified by one of the three sets of predictor variables described above. These probabilities were then assigned to patients lost to follow-up according to their strata of predictor variables, and a random sample of N*(P(Death|strata)) lost to follow-up patients were re-assigned as dead, where N is the number of patients LTF in a given strata, and (P|Death|strata)) is the probability of death among patients not LTF in that same strata. The entire imputation process was repeated 50 times to create 50 sample populations for analysis to achieve greater than 99.5% efficiency [14]. Proportional Hazards regression was then performed on these 50 sample populations to obtain 50 effect estimates and 50 standard errors of the association between a given adherence support or outreach service and patient survival. Finally, a multiply-imputed Hazard Ratio, which is the average hazard ratio across all 50 imputations, and 95% CI was obtained for each facility-level adherence service exposure category according to formulas given by Rubin [14]:

$$SE = \sqrt{\frac{1}{M}\sum_{k=1}^{M} s_k^2 + \left(\frac{1}{M}\right)\left(\frac{1}{M-1}\right)\sum_{k=1}^{M}\left(b_k - \bar{b}\right)^2}$$

$$\bar{b} = \frac{1}{M}\sum_{k=1}^{M} b_k$$

$$HR = e^{\bar{b}}$$

$$95\%\ CI = e^{\bar{b} \pm 1.96SE}$$

The variables have the following definitions:

b_k = parameter estimate obtained from iteration k
$\bar{b}$ = average parameter estimate
M = number of iterations
s_k = standard error of b_k

Approach #2: Inverse probability of treatment and censoring weights

The second approach also assumes that predictors of survival are the same among patients lost and retained in care, but uses a different approach allowing for simultaneous adjustment for confounding and selection bias due to loss to follow-up. For this analysis, we use both patient-level and facility-level predictors of exposure and loss to follow-up to estimate the probability of loss to follow-up, and the probability of death, given a patient's exposure and covariate stratum. This inverse probability weighting approach [15, 16] calculates two weights: one to adjust for potential confounding, and one to adjust for selection bias due to loss to follow-up. This approach creates a pseudopopulation where exposure (in this case the availability of adherence support or outreach services) is independent of measured confounders and produces effect estimates for a population where no loss to follow-up occurred by creating a pseudopopulation where patients not lost to follow-up are weighted by the inverse of the probability of not being lost to follow-up for a patients exposure status and strata of measured confounders [16]. The hazard ratios and 95% confidence intervals obtained from this approach represent the effect of the exposure of interest on mortality rates assuming (1) correct model specification (i.e., the proportional hazards assumption is correct), (2) no unmeasured confounding, and (3) the mortality rate among patients lost to follow-up is equal to the mortality rate among patients not lost to follow-up, conditioned on exposure and covariate history. For this analysis, patient-level (age, sex, CD4 count and WHO stage at enrollment, tuberculosis treatment status before ART initiation) and clinic-level (facility type (primary, secondary tertiary), facility location (urban, semi-urban, rural), and facility size (the cumulative number of patients seen in care at a given facility)) were included.

Approach #3: Externally derived estimates of mortality among patients lost to follow-up

Both the multiple imputation and inverse probability weighting approaches described above assume that patients lost to follow-up are missing at random within each stratum, meaning that conditioned on

potentially confounding variables the probability of death does not differ between patients lost to follow-up and those not lost. Recent studies that have used sampling approaches to estimate the probability of death among patients lost to follow-up, and factors associated with mortality among this group, suggest that mortality is higher among patients lost to follow-up, and that predictors of mortality differ in their relationship between patients lost to follow-up and those retained [3-5, 8, 12]. To assess the sensitivity of our estimates of the association between availability of adherence support and outreach services and mortality rates under situations where the relationship between predictors of mortality differs between patients lost to follow-up and those retained, we used parameters obtained from a recent study by Fox et al [4] that traced patients lost to follow-up and examined factors associated with mortality among this group to correct for mortality estimates in our study population. This study was chosen because factors it identified as associated with mortality among those lost to follow-up (CD4, tuberculosis diagnosis, age at ART initiation) were those that we could measure from information in our routine patient-level database.

For this analysis, estimates of the probability of death among patients lost to follow-up, conditioned on last known measures of CD4, pre-loss tuberculosis diagnosis, and age were extracted from the Fox et al study [4] and applied to our population. In particular we made the following assumptions:

- Overall probability of death among LTF: 37%
- HR over 40 vs under 40 yrs of age = 1.67
- HR for last CD4 count < 100 vs. > 200: = 3.38
- HR for last CD4 count 100-200 vs. > 200: = 1.8
- HR for diagnosis of TB (yes vs no) = 1.29

Patients missing pre-loss CD4 measures (~18%) were assumed to have a probability of death equal to the average probability of death for the entire subsample within strata of other known measures (tuberculosis diagnosis and age). Random samples of N*P(Death|strata) lost to follow-up patients are re-assigned dead in a manner identical to that used for the multiple imputation analyses, and

statistical analyses were performed using proportional hazards regression in an identical approach to that described above.

For the multiple imputation and externally derived sensitivity analyses, three regression models were tested: an unadjusted model, a model adjusting for site-level differences between facilities --(facility type (primary, secondary tertiary), location characteristics (urban, semi-urban, rural), and the cumulative number of patients seen in care at a given facility (log-transformed and modeled as a linear variable) -- and a model adjusting for both site- and patient-level differences --patient covariates: sex, age at ART initiation, CD4 count at enrollment, WHO stage at enrollment, TB status before ART initiation, and weight at enrollment. For all analyses, repeated-measures techniques were used to cluster patients according to site.

For the inverse probability weighting sensitivity analyses, potential confounding was adjusted for in the weighting process so the models presented are conditional unadjusted models [17].

In total, 6 models (a non-imputation analysis, three internally-derived multiple imputation analyses, one inverse probability weighting analysis, and one externally-derived multiple imputation analysis) were constructed and examined.

Results

Table 1 presents characteristics of the 102 clinics (in 4 countries) comprising the study population for this analysis. The majority of facilities were primary health centers (47%) or secondary facilities such as district hospitals (46%), and they were distributed between large urban areas (32%), peri-urban areas (either population growth areas or business centers serving a large, mostly rural population (26%), and rural areas (42%). All facilities reported offering at least one adherence support service, and nearly all reported offering at least one adherence counseling service (either one-on-one or group adherence counseling services, peer educators, or on-site support groups for HIV+ patients).

There was heterogeneity in the proportion offering specific services, ranging from 35% offering food

support for ART adherence to 86% offering dedicated on-site pharmacists and/or routine review of medication pickup.

Table 2 presents characteristics of the patient population (N = 50,379 patients). 63% of the patients were female, with the majority older than 25 years of age. A substantial proportion of patients initiated ART without a recorded CD4 count (34%) or WHO stage (21%).

Cumulatively, of the 50,379 patients initiating ART in this population between January 2008 and December 2009, 1,961 (4%) were ascertained deaths and 8,669 (17%) were LTF. Using Kaplan-Meier estimates, the risk of ascertained mortality 1 year after ART initiation was 4.5%, and the risk of being lost to follow-up was 18.6%. Table 3 shows how the different sensitivity analyses changed the Kaplan-Meier estimates of loss to follow-up and death proportions in the population. The internally-derived estimates of the death probability increased in all sensitivity analyses, but this increase was relatively modest (0.16%-1.7% absolute increase). Estimates obtained assuming those lost to follow-up had higher risk of death than those retained in care increased the overall death rate substantially (by 6.9%).

Baseline (no imputation) analysis

Table 4 presents the baseline (no imputation) results of the analyses estimating the association between adherence support and outreach services on non-retention, loss to follow-up, and death. For the outcome of death, all patients lost to follow-up are censored at their date of loss, resulting in the assumption that, conditioned on exposure and covariates in the model, patients lost to follow-up have the same probability of death as those retained. Using non-retention as an outcome of interest can be viewed as a “worst case” analysis in which patients lost to follow-up and ascertained to be dead are grouped together as an undesirable outcome (i.e., all patients LTF are assumed to have died). For all analyses, rate ratios obtained from proportional hazards regression are the outcome of interest.

Directed adherence counseling and support services

In crude analyses, clinics offering multiple adherence counseling and support services had lower rates of 1-year non-retention and loss to follow-up than did clinics offering only one such service. This association persisted after adjustment for site-level covariates, but diminished after further adjustment for patient-level differences. After adjustment for site-level differences, facilities offering all three adherence counseling and support services (one-on-one or group adherence counseling, peer educators, and on-site support groups for HIV+ patients) had 0.79 times the rate of loss to follow-up compared to patients offering only one such service (95% CI: 0.69-0.99); after additional adjustment for patient-level differences this association diminished (HR = 0.88, 95% CI: 0.71-1.09). Among specific directed counseling or support services, only the availability of on-site support groups for HIV+ patients was associated with lower non-retention or LTF (HR for non-retention after adjusting for site-level factors: 0.72, 95% CI: 0.51-1.0; after additional adjustment for patient-level factors: HR = 0.79, 95% CI: 0.58-1.06).

Clinics offering one-on-one or group adherence counseling were associated with lower one-year mortality after both site-and patient-level adjustment (HR = 0.58, 95% CI: 0.34-0.98). Neither the availability of more than one directed counseling or support service nor the availability of on-site support groups for HIV+ patients, which were associated with reduced non-retention and loss to follow-up, were associated with 1-year survival in this baseline analysis.

Routine review of ART pharmacy pickup

Routine review of medication pickup was not associated with non-retention, loss to follow-up, or death in this analysis.

Food support for ART adherence

The availability of food support to promote ART adherence was associated with lower non-retention, LTF, and death. After adjustment for site-level covariates, the HRs for non-retention (HR = 0.65,

95% CI: 0.46-0.93), LTF (HR = 0.65, 95% CI: 0.42-0.99), and death (HR = 0.67, 95% CI: 0.53-0.85) were similar, but the HR for death was more diminished after additional adjustment for patient-level covariates ($HR_{non\text{-}retention}$ = 0.74, 95% CI: 0.54-1.01; HR_{LTF} = 0.72, 95% CI: 0.49-1.07; HR_{death} = 0.85, 95% CI: 0.68-1.06).

Active patient outreach

The availability of an active patient outreach program to track patients missing scheduled visits was associated with lower non-retention and LTF, but not death, in the baseline analysis. The associations with non-retention and LTF persisted after adjustment for site- and patient-level covariates ($HR_{non\text{-}retention}$ = 0.68, 95% CI: 0.51-0.90; HR_{LTF} = 0.63, 95% CI: 0.46-0.87), while active patient outreach was not associated with death after adjustment for site-and patient-level covariates (HR_{death} = 0.98, 95% CI: 0.75-1.28).

Based on the results from the non-imputation analysis, we would conclude that food support to promote ART adherence and the availability of one-on-one or group adherence counseling services are associated with lower mortality, with the remaining adherence support services examined not associated with mortality. Further, we would conclude that food rations to promote ART adherence and active outreach are associated with lower loss to follow-up and non-retention.

Sensitivity analyses

To test the hypothesis that differences in mortality between patients lost to follow-up and those retained in care are biasing the observed results in the naïve analyses, we conducted a series of sensitivity analyses. Table 3 presents the changes in the estimated death rates under the different assumptions of the sensitivity analyses. The estimated one-year death risk ranged from 4.5% (no imputation) to 11.4% (imputation based on an assumed increased risk of death among patients lost to follow-up). Figure 1 presents the results of the sensitivity analyses examining the degree to which various imputations of death probability among patients lost to follow-up influences these results.

Figure 1a presents the crude (unadjusted for covariates) analysis, Figure 1b presents the analysis adjusted for site-level covariates (facility type, location (urban,semi-urban,rural), and the cumulative number of patients seen in care at a given facility). Figure 1c presents the analyses adjusted for both site and patient-level (sex, age at enrollment, CD4 and WHO stage at enrollment, enrollment weight, and tuberculosis status). The inverse probability-weighted sensitivity analysis (sensitivity analysis #4) is included only in the Figure 1c because it adjusts for potential site- and patient-level confounding in its calculation of weights. The six models are as follows:

Baseline (naïve): Identical to the results in Table 2, corresponding to the results we would obtain if we did not impute death probabilities among those lost to follow-up.
Internally-derived sensitivity analyses
Sensitivity analysis #1: A parsimonious model using multiple imputation techniques after assuming that patients lost to follow-up have the same death probability as those not lost to follow-up within strata of last known CD4 count.
Sensitivity analysis #2: A parsimonious model using multiple imputation techniques to adjust the mortality rate assuming that patients lost to follow-up have the same death probability as those not lost to follow-up within strata of last known CD4 count, WHO stage at enrollment, sex, age, and tuberculosis status.
Sensitivity analysis #3: Similar to sensitivity analysis #1 and #2, but adjusting for country, clinic type (primary, secondary, tertiary), location (urban, semi-urban, rural), and the cumulative number of patients seen in care.
Sensitivity analysis #4: Uses inverse probability-weighting techniques to simultaneously adjust for potential confounding variables at both the clinic- and patient-level (combines the adjustments in analyses #2 and #3).
Externally-derived sensitivity analyses:
Sensitivity analysis #5: Uses information from Fox et all and assumes that patients lost to follow-up have a mortality rate of 37%, with differences associated with age, CD4 count, and tuberculosis status.

Crude analyses

Figure 1a presents comparisons of the mortality rate ratios in models not adjusting for covariates. The availability of one-on-one or group adherence counseling services, associated with lower mortality in the baseline (no imputation analysis), remained associated in all imputation analyses (sensitivity analyses #1-#4) with very similar-magnitude associations. In addition, the availability of food rations to promote ART adherence and active patient outreach, not associated with mortality in

the crude baseline analysis, was associated after imputation of death among patients lost to follow-up. The associations between food rations and active outreach and reduced death became stronger in magnitude after imputation of death among patients lost to follow-up using the externally-derived risks of death (sensitivity analysis #5). Analyses imputing death probability among patients lost to follow-up using externally-derived estimates also resulted in an observed association between the availability of more than one directed counseling or support service and reduce rate of death (HR = 0.76, 95% CI = 0.61-0.95) that was not present in the non-imputation analyses and when death probabilities were imputed based on the death probabilities among patients not lost to follow-up. Finally, the availability of routine review of ART medication pickup was associated with increased death rate in the sensitivity analysis imputing death rates based on strata of patient-level covariates (sensitivity analysis #2), but not in the other sensitivity analyses.

Site-level adjusted analyses

Figure 1b presents comparisons of the mortality rate ratios in models adjusting for site-level covariates only. The same sensitivity analyses presented in Figure 1a are presented here. There were few differences in the death rate ratio estimates between the baseline (no-imputation) and sensitivity analyses, with the following exceptions. First, the availability of routine review of ART medication pickup was associated with increased death rate in the sensitivity analysis imputing death rates based on strata of patient-level covariates (sensitivity analysis #2), but not in the other sensitivity analyses. Second, while active outreach was not associated with death rate in the non-imputation analysis, it was associated with a lower death in all sensitivity analyses, with the strongest-magnitude association found in the imputation using externally-derived estimates of the death probability among patients lost to follow-up (sensitivity analysis #5).

Site- and patient-level adjusted analyses

Figure 1c presents comparisons of the mortality rate ratios in models adjusting for both site- and patient-level covariates. In these analyses, an additional sensitivity analysis is presented, using inverse probability weights to adjust for both potential confounding and selection bias (sensitivity analysis #4). The graph shows that the first four sensitivity analyses resulted in very little change to the hazard ratios of 1-year death estimated from the baseline analyses, with a few exceptions. First, the availability of any directed counseling or support service, which was not associated with survival in baseline analyses, became marginally associated with higher death rates in sensitivity analysis #2 (assuming the distribution of death among those LTF is the same as that among those not LTF within strata of sex, last known CD4 count, age, and TB treatment status before ART initiation) and sensitivity analysis #5 (using an external estimate of the death proportion among those LTF (37%), with risks associated with age, TB treatment status, and last known CD4 count). After adjustment for site- and patient-level covariates, the HR of death shifted from 1.06 (95% CI: 0.78-1.44) in the baseline analysis to 1.23 (95% CI: 0.94-1.60) in Sensitivity analysis #2, to 1.28 (95% CI: 1.01-1.63) in sensitivity analysis #5.

Second, after adjustment for site- and patient-level covariates, facilities offering active patient outreach were unassociated with hazard of death in the baseline analysis (HR_{death} = 0.98, 95% CI: 0.75-1.28) but significantly associated with a lower hazard of death in those sensitivity analyses after adjustment for site-level covariates, and in sensitivity analysis #5 after adjustment for site- and patient-level covariates (HR_{death} = 0.74, 95% CI: 0.59-0.93).

Discussion

This analysis focuses on an assessment of whether estimations of rates of survival among patients lost to follow-up, both from internally-derived and externally-derived populations, influences assessments of the association between program-level services and hazard of death. We found that, with two exceptions, the sensitivity analyses did not markedly impact our estimation of the association

between the availability of program services and mortality rate. However, the two situations where sensitivity analyses did impact results may serve to highlight both potential drawbacks, and benefits, of this approach.

The sensitivity analysis produced different inference for the association between the availability of any directed adherence counseling or support service and a lower risk of death. In the baseline analysis, there was no evidence of an association, while in the sensitivity analysis using an external distribution of death among patient LTF there was an association observed between the availability of any directed adherence counseling or support service and a *higher* hazard of death (HR= 1.28, 95% CI = 1.01-1.63 after adjustment for site-and patient-level covariates). Looking at Table 1, we see that only 2 facilities in this study reported not offering any of these services. Thus, the small sample from which this group is drawn limits our confidence in the validity of this conclusion, especially since adjustment for site-level characteristics is relatively meaningless when there are only two sites in this exposure group.

The most substantial difference between baseline results and sensitivity analyses comes from the association between active patient outreach and 1-year survival since ART initiation, going from no evidence of an association in the baseline analysis (HR_{death} = 0.98, 95% CI: 0.75-1.28) to evidence of an association between active outreach and lower risk of death in nearly all sensitivity analyses, with the strongest evidence in the sensitivity analysis assuming that patients lost to follow-up had a substantially higher death rate than patients not lost (sensitivity analysis 5). The results from Table 4 show that among the adherence support and outreach services examined, only active patient outreach was associated with lower loss to follow-up in this study population after adjustment for site- and patient-level factors. Patients lost to follow-up consist of unascertained deaths, unascertained transfers, and those truly “lost” from care who are no longer engaged. Facilities with programs in place to track patients missing visits are likely also increasing the proportion of actual deaths that are

ascertained, thereby increasing their measured death rate even if the program is not impacting the actual death rate. This may result in a scenario where, even if an active outreach program reduces the actual death rate, the fact that it is concurrently increasing the measured death rate may result in an inability to detect the true impact on the actual death rate. The sensitivity analyses artificially create parity in death rate ascertainment between facilities by assuming an underlying distribution of actual death among patients lost to follow-up, and allow us to investigate the impact of program services on actual death rate under different assumptions about the distribution of death among patients lost to follow-up. The extent to which these assumptions are reasonable determines the confidence we have in any individual sensitivity analysis.

The aim of these sensitivity analyses is not to establish a single "true" estimate of a given association, but rather to provide a range from plausible assumptions about the distribution of death among patients LTF. Sampling approaches, where a representative sample of patients lost to follow-up are tracked and their vital status ascertained, can help improve the assumptions needed for these sensitivity analyses. The results for non-retention in Table 4 provide the most conservative assumption of the death rate among patients LTF, effectively (if non-retention is taken as a proxy measure for death) assuming that all patients LTF are in actuality unascertained death. Sensitivity analysis #5, which increases the overall death rate from 4% to 12% by assuming that 37% of the patients LTF are in actuality death, allows us to investigate a situation in which being LTF is an independent cause of death, something the other analyses (including the baseline analysis) do not. The fact that two adherence support and retention-promoting services: food support to promote ART adherence and active patient outreach, remain associated with reduced death across the vast majority of these sensitivity analyses, incorporating both patient- and site-level factors, strengthens the evidence that these two services act to improve patient survival.

This analysis has a number of strengths. First, it uses routinely-collected information from a large population in clinical, as opposed to research settings or centers of excellence. It it likely that this population, across four countries and both urban and rural settings, is in many ways typical of HIV care patients and clinics in other areas of sub-Saharan Africa. Second, the sensitivity analysis allows us to examine potential ways in which our lack of complete outcome ascertainment affects our ability to make inference about the ways in which program-level services are improving patient survival. Previous analyses estimating death rates among patients lost to follow-up have focused on its impact on patient survival (e.g, [4, 7-9, 13, 18]), or focused on patient-level factors associated with death among patients lost to follow-up (e.g., [3, 7, 9, 11, 12, 19]). This analysis builds on those by using the information learned about patient characteristics associated with loss to follow-up to assess whether differences in these characteristics between facilities offering various types of adherence support and retention services can influence our ability to assess whether program-level services are associated with patient survival. Thus, even though loss to follow-up may result in a substantial overestimate of patient survival, this overestimate will only influence relative comparisons between survival among facilities with and without various adherence support services if the degree of overestimation also differs by these facility-level services.

Conclusion

This analysis suggests that some associations between adherence support and outreach services and patient survival are masked by loss to follow-up. The results of the sensitivity analyses provide strong evidence that food support services promote ART adherence and active patient outreach improve 1-year survival among ART patients at facilities in 4 countries in sub-Saharan Africa. Outcome imputation for the purposes of sensitivity analysis provides an effective means of assessing the impact of known biases on relative measures of association. Loss to follow-up creates problems in our attempts to assess whether facility-level services are improving patient survival, especially

when the relationship between these factors and mortality risk differs between patients loss to follow-up and those retained in care.

References

1. World Health Organization, U., UNICEF, *Towards universal access : scaling up priority HIV/AIDS interventions in the health sector : progress report 2010*. 2010.
2. Brinkhof, M.W., M. Pujades-Rodriguez, and M. Egger, *Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis.* PLoS One, 2009. 4(6): p. e5790.
3. Geng, E.H., et al., *Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach.* J Acquir Immune Defic Syndr, 2010. 53(3): p. 405-11.
4. Fox, M.P., et al., *Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa.* Trop Med Int Health. 15(4): p. 405-13.
5. Yiannoutsos, C.T., et al., *Sampling-based approaches to improve estimation of mortality among patient dropouts: experience from a large PEPFAR-funded program in Western Kenya.* PLoS One, 2008. 3(12): p. e3843.
6. An, M.W., et al., *The need for double-sampling designs in survival studies: an application to monitor PEPFAR.* Biometrics, 2009. 65(1): p. 301-6.
7. Deribe, K., et al., *Defaulters from antiretroviral treatment in Jimma University Specialized Hospital, Southwest Ethiopia.* Trop Med Int Health, 2008. 13(3): p. 328-33.
8. Bisson, G.P., et al., *Overestimates of survival after HAART: implications for global scale-up efforts.* PLoS One, 2008. 3(3): p. e1725.
9. Dalal, R.P., et al., *Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in johannesburg, South Africa.* J Acquir Immune Defic Syndr, 2008. 47(1): p. 101-7.
10. Maskew, M., et al., *Lost to follow up: contributing factors and challenges in South African patients on antiretroviral therapy.* S Afr Med J, 2007. 97(9): p. 853-7.
11. Yu, J.K., et al., *True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi.* Bull World Health Organ, 2007. 85(7): p. 550-4.
12. Geng, E.H., et al., *Tracking a sample of patients lost to follow-up has a major impact on understanding determinants of survival in HIV-infected patients on antiretroviral therapy in Africa.* Trop Med Int Health, 2010. 15 Suppl 1: p. 63-9.
13. Geng, E.H., et al., *Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa.* JAMA, 2008. 300(5): p. 506-7.
14. Rubin, D.B., *Multiple Imputation for Nonresponse in Surveys*. 1987, New York: J. Wiley & Sons.
15. Cole, S.R. and M.A. Hernan, *Adjusted survival curves with inverse probability weights.* Comput Methods Programs Biomed, 2004. 75(1): p. 45-9.
16. Cole, S.R. and M.A. Hernan, *Constructing inverse probability weights for marginal structural models.* Am J Epidemiol, 2008. 168(6): p. 656-64.
17. Hernan, M.A., S. Hernandez-Diaz, and J.M. Robins, *A structural approach to selection bias.* Epidemiology, 2004. 15(5): p. 615-25.
18. Fox, M.P. and S. Rosen, *Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review.* Trop Med Int Health. 15 Suppl 1: p. 1-15.
19. Massaquoi, M., et al., *Patient retention and attrition on antiretroviral treatment at district level in rural Malawi.* Trans R Soc Trop Med Hyg, 2009. 103(6): p. 594-600.

Tables and Figures, Paper 3

Table 1. Facility-level characteristics of the study population

		Number (%) of sites		Number (%) of patients	
Total		102	100%	50,379	100%
Country	Kenya	25	24.5%	7,147	14.2%
	Mozambique	27	26.5%	29,745	59%
	Rwanda	31	30.4%	7,325	14.5%
	Tanzania	19	18.6%	6,162	12.2%
Facility type*	Primary	48	47.1%	15,753	31.3%
	Secondary	47	46.1%	29,719	59%
	Tertiary	7	6.9%	4,265	8.5%
Facility location	Urban	33	32.4%	25,389	50.4%
	semi-urban	26	25.5%	16,194	32.1%
	rural	43	42.2%	8,796	17.5%
Adherence support and outreach services					
Adherence Counseling	yes	100	98%	49,363	98%
	no	2	2%	1,016	2%
On-site support groups for HIV+ patients	yes	80	78.4%	39,253	77.9%
	no	22	21.6%	11,126	22.1%
Peer Educators	yes	84	82.4%	36,851	73.1%
	no	18	17.6%	13,528	26.9%
Routine medication pickup review/dedicated pharmacist	yes	77	75.5%	37,028	73.5%
	no	25	24.5%	13,351	26.5%
Food support to promote ART adherence	yes	36	35.3%	10,622	21.1%
	no	66	64.7%	39,757	78.9%
Active Outreach	yes	86	84.3%	40,584	80.6%
	no	16	15.7%	9,795	19.4%

Table 2. Patient-level characteristics of the study population

		N	%
Sex	Female	31,944	63.4%
	Male	18,434	36.6%
Age at ART initiaton	5-15 years	1,991	4%
	15-25 years	5,384	10.7%
	25-40 years	26,722	53%
	40-60 years	15,047	29.9%
	> 60 years	1,235	2.5%
Weight at ART initiation (kg)	< 40 kg	25,441	50.5%
	40-50 kg	7,343	14.6%
	50-60 kg	10,554	20.9%
	60-70 kg	5,085	10.1%
	> 70 kg	1,956	3.9%
CD4 at enrollment into care (cells/uL)	missing	17,347	34.4%
	< 50	4,870	9.7%
	50-100	3,972	7.9%
	100-200	8,226	16.3%
	200-350	9,427	18.7%
	> 350	6,537	13%
WHO stage at enrollment into care	missing	10,679	21.2%
	I	8,212	16.3%
	II	9,565	19%
	III	17,092	33.9%
	IV	4,831	9.6%
On tuberculosis treatment before ART initiation	no	47,284	93.9%
	yes	3,095	6.1%

Table 3. Comparison of estimated 1-year mortality under different sensitivity analysis assumptions

Model	Ascertained death risk	LTF risk
Baseline (no sensitivity analysis)	4.46%	18.60%
Multiple imputation analyses		
Model 1: CD4 count	5.99%	17.29%
Model 2: CD4 count, WHO stage, age, weight, sex, tb	6.16%	17.14%
Model 3: site-level	5.43%	17.80%
Inverse probability weighting analyses		
Model 4: site and patient-level	4.62%[1]	*[2]
External weights		
Model 5: probabilities based on Fox et al	11.39%	12.21%

1 inverse probability weighted probabilities of death calculated without adjustment for exposure or covariates

2 Inverse probability weighting creates a pseudopopulation in which there is no loss to follow-up

Table 4a. Baseline (no imputation) analysis: rate ratios of 1-year non-retention by adherence support or outreach service

		Non-retention after 1 year on ART					
		Crude[1]		site adjusted[2]		patient- and site adjusted[3]	
Variable		HR	95% CI	HR	95% CI	HR	95% CI
Availability of directed Counseling or support	yes vs. no	1.39	(1.13-1.71)	1.3	(1.02-1.66)	1.25	(1.05-1.5)
	2 vs 1	0.9	(0.58-1.39)	0.95	(0.63-1.44)	1.08	(0.74-1.58)
	3 vs 1	0.72	(0.59-0.87)	0.79	(0.62-0.99)	0.88	(0.71-1.09)
	more than 1 vs. 1	0.77	(0.62-0.95)	0.84	(0.64-1.11)	0.95	(0.73-1.23)
one-on-one or group adherence counseling services	yes vs. no	0.82	(0.51-1.32)	0.88	(0.61-1.28)	0.85	(0.61-1.17)
Frequency of counseling among sites providing service	> every 3 months vs. < every 3 months	1.05	(0.72-1.51)	1.11	(0.79-1.55)	1.09	(0.82-1.46)
on-site support group for HIV+ patients	yes vs. no	0.69	(0.47-1.02)	0.72	(0.51-1)	0.79	(0.58-1.06)
peer educator program	yes vs. no	0.93	(0.74-1.18)	1	(0.73-1.35)	1.02	(0.78-1.35)
Routine medication pickup review/dedicated pharmacist	yes vs. no	1.11	(0.69-1.77)	1.14	(0.71-1.83)	1.06	(0.70-1.61)
Food rations provided to adults or children	yes vs. no	0.6	(0.44-0.83)	0.65	(0.46-0.93)	0.74	(0.54-1.01)
Outreach Services							
Active patient outreach	yes vs. no	0.6	(0.41-0.89)	0.63	(0.46-0.86)	0.68	(0.51-0.9)
Target population among sites w/ active outreach	all patients vs ART patients only	0.96	(0.79-1.17)	1.22	(0.98-1.51)	1.22	(1.05-1.43)

Table 4b: Baseline (no imputation) analysis: rate ratios of 1-year loss to follow-up by adherence support or outreach service

		Loss to Follow-up after 1 year on ART					
		Crude[1]		site adjusted[2]		patient- and site adjusted[3]	
Variable		HR	95% CI	HR	95% CI	HR	95% CI
	yes vs. no	1.62	(1.29-2.04)	1.44	(1.07-1.93)	1.33	(1.06-1.67)
Availability of directed Counseling or support	2 vs 1	0.87	(0.52-1.47)	0.93	(0.57-1.53)	1.04	(0.66-1.63)
	3 vs 1	0.69	(0.55-0.87)	0.77	(0.57-1.03)	0.85	(0.65-1.11)
	more than 1 vs. 1	0.74	(0.57-0.96)	0.82	(0.59-1.15)	0.92	(0.67-1.26)
one-on-one or group adherence counseling services	yes vs. no	0.9	(0.53-1.53)	0.99	(0.67-1.47)	0.95	(0.7-1.28)
Frequency of counseling services among sites providing them	> every 3 months vs. < every 3 months	1.03	(0.67-1.58)	1.13	(0.76-1.69)	1.13	(0.8-1.6)
on-site support group for HIV+ patients	yes vs. no	0.68	(0.42-1.11)	0.7	(0.46-1.06)	0.76	(0.53-1.1)
peer educator program	yes vs. no	0.92	(0.69-1.21)	0.99	(0.69-1.43)	1.01	(0.73-1.41)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	1.36	(0.97-1.92)	1.34	(0.95-1.91)	1.26	(0.94-1.7)
Routine medication pickup review/ dedicated pharmacist	yes vs. no	1.11	(0.62-1.99)	1.16	(0.65-2.05)	1.08	(0.65-1.79)
Food rations provided to adults or children	yes vs. no	0.55	(0.37-0.83)	0.65	(0.42-0.99)	0.72	(0.49-1.07)
Outreach Services							
Active patient outreach	yes vs. no	0.56	(0.36-0.89)	0.59	(0.41-0.85)	0.63	(0.46-0.87)
Target population among sites w/ active outreach	all patients vs ART patients only	0.89	(0.69-1.14)	1.29	(1.01-1.64)	1.29	(1.07-1.55)

Table 4c: Baseline (no imputation) analysis: rate ratios of 1-year hazard of death by adherence support or outreach service

		Death after 1 year on ART					
		Crude[1]		site adjusted[2]		patient- and site adjusted[3]	
Variable		HR	95% CI	HR	95% CI	HR	95% CI
	yes vs. no	0.84	(0.64-1.09)	0.98	(0.7-1.37)	1.06	(0.78-1.44)
Availability of directed Counseling or support	2 vs 1	1.03	(0.63-1.69)	1.12	(0.72-1.74)	1.39	(0.94-2.06)
	3 vs 1	0.85	(0.55-1.32)	0.9	(0.62-1.29)	1.09	(0.79-1.5)
	more than 1 vs. 1	0.9	(0.59-1.38)	0.96	(0.67-1.36)	1.17	(0.86-1.6)
one-on-one or group adherence counseling services	yes vs. no	0.57	(0.39-0.83)	0.57	(0.36-0.89)	0.58	(0.34-0.98)
Frequency of counseling services among sites providing them	> every 3 months vs. < every 3 months	1.14	(0.72-1.81)	0.93	(0.6-1.45)	0.88	(0.59-1.32)
on-site support group for HIV+ patients	yes vs. no	0.76	(0.53-1.07)	0.8	(0.55-1.17)	0.91	(0.65-1.29)
peer educator program	yes vs. no	1.03	(0.77-1.37)	1.04	(0.82-1.31)	1.13	(0.93-1.36)
Routine medication pickup review/ dedicated pharmacist	yes vs. no	1.08	(0.78-1.49)	1.05	(0.78-1.42)	0.96	(0.72-1.29)
Food rations provided to adults or children	yes vs. no	0.86	(0.66-1.13)	0.67	(0.53-0.85)	0.85	(0.68-1.06)
Outreach Services							
Active patient outreach	yes vs. no	0.87	(0.62-1.23)	0.86	(0.64-1.15)	0.98	(0.75-1.28)
Target population among sites w/ active outreach	all patients vs ART patients only	1.33	(0.94-1.89)	1.03	(0.74-1.43)	1.04	(0.78-1.38)

1. Rate ratios obtained from proportional hazards modeling accounting for within-site similarity using generalized estimating equations
2. Site-level covariates include: facility type (primary, secondary, tertiary), location (urban, semi-urban, rural), and the cumulative number of patients seen in care at a given clinic
3. Patient-level covariates include: age, sex, enrollment weight, enrollment CD4 count, enrollment WHO stage, TB treatment status before ART initiation

Figure1a. Comparison of the association between adherence support and outreach services and measured rate of death 1 year after ART initiation: Crude analysis (no adjustment for covariates)

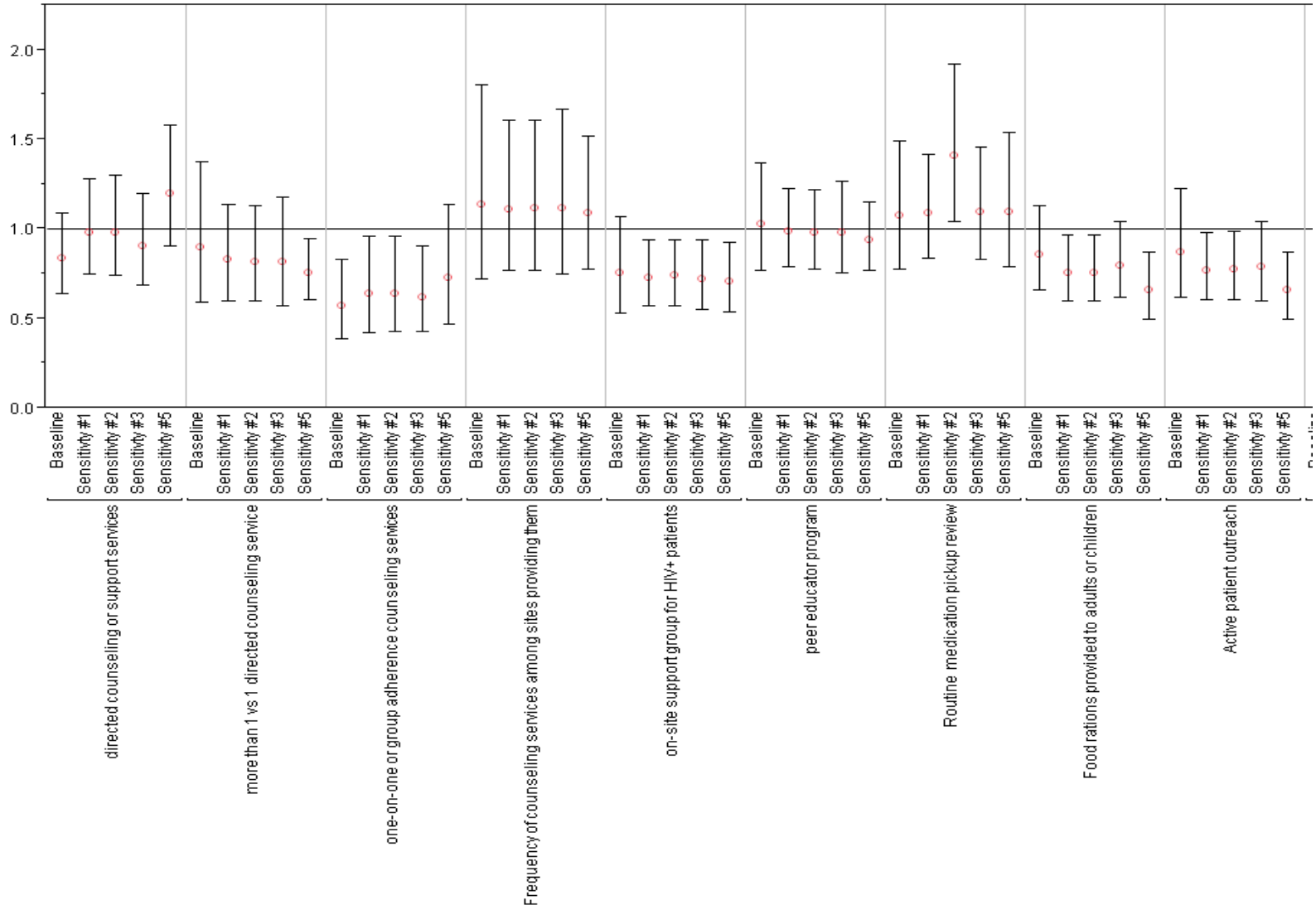


Figure1b. Comparison of the association between adherence support and outreach services and measured rate of death 1 year after ART initiation: Site-level adjusted analysis (no adjustment for patient-level covariates)

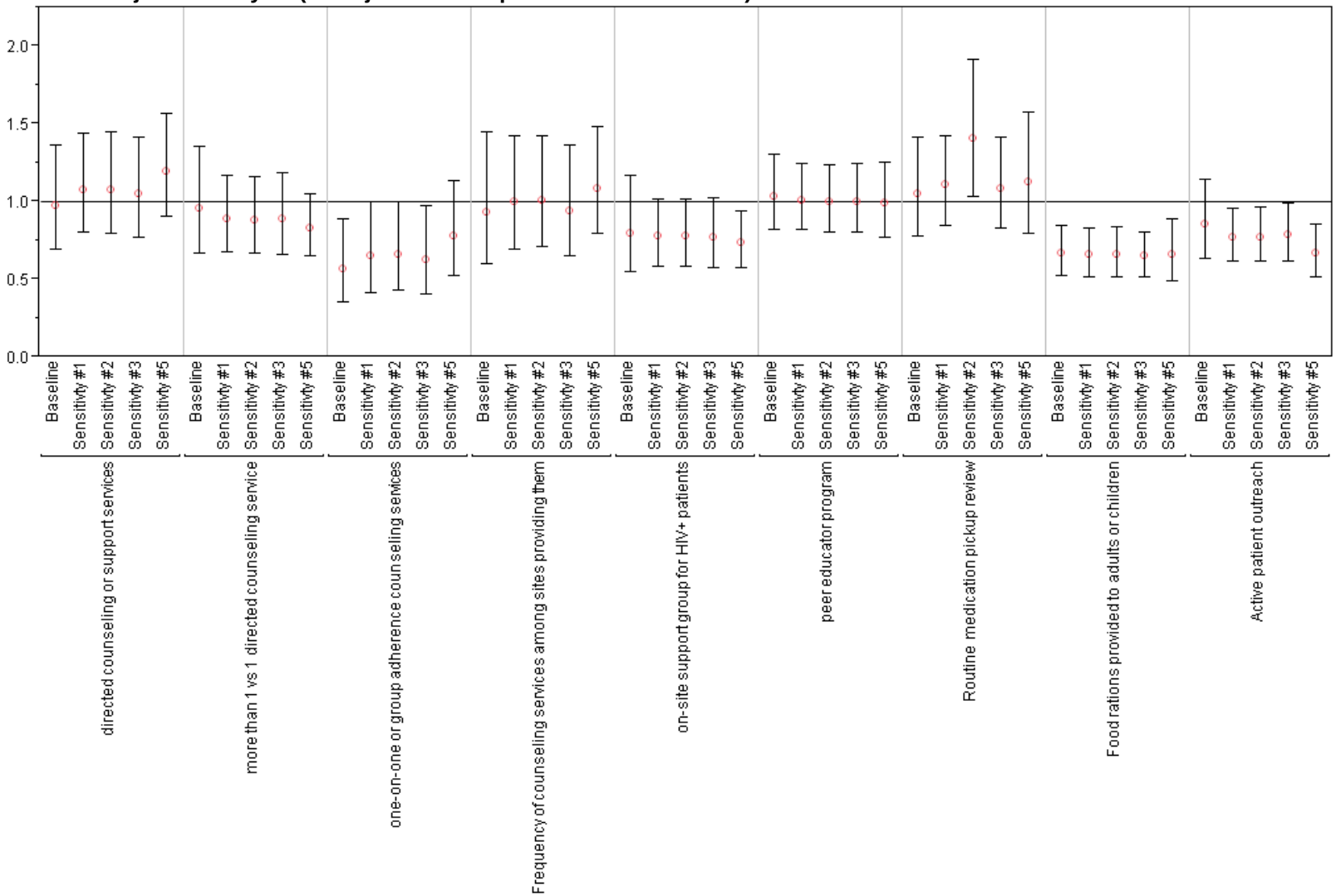
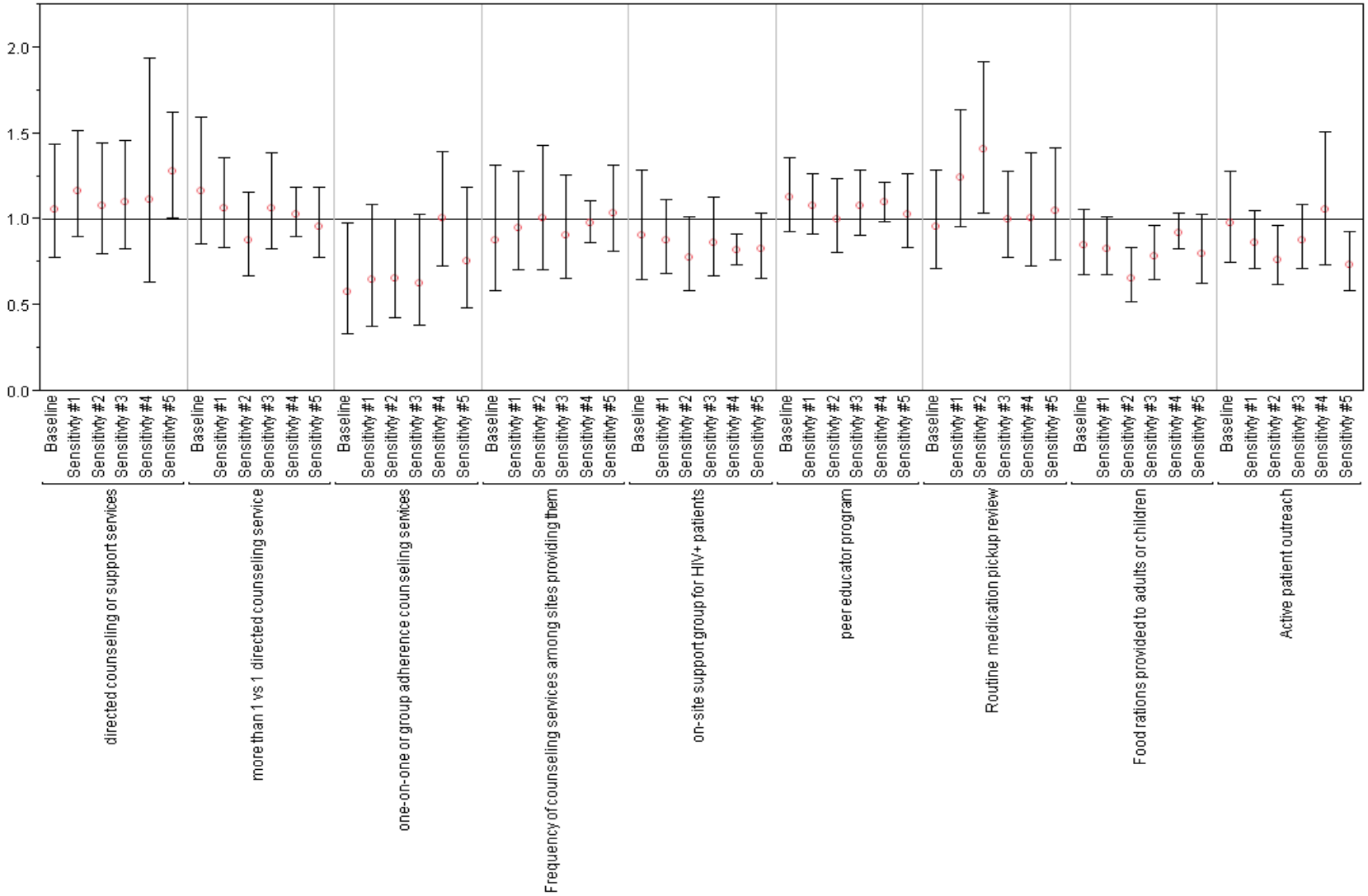


Figure1c. Comparison of the association between adherence support and outreach services and measured rate of death 1 year after ART initiation: Site-level adjusted analysis (adjustment for site- and patient-level covariates)



Notes:
The red circles correspond to the Rate Ratio of mortality 1 year after ART initiation, with 95% Confidence Intervals presented as the range
Baseline analysis: no adjustment for mortality among patients loss to follow-up modeled
Sensitivity #1: Multiple imputation assigning probability of mortality among patients lost to follow-up as equal to the probability of mortality among patients not lost to follow-up within strata of last CD4 count.

Sensitivity #2: Multiple imputation assigning probability of mortality among patients lost to follow-up as equal to the probability of mortality among patients not lost to follow-up within strata of last CD4 count, WHO stage at enrollment, sex, age, and Tuberculosis status.

Sensitivity #3: Multiple imputation assigning probability of mortality among patients lost to follow-up as equal to the probability of mortality among patients not lost to follow-up within strata of country, facility type (primary, secondary, tertiary), facility location (urban, semi-urban, rural)

Sensitivity #4: Inverse-probability weighted estimate of the Hazard ratio of mortality under conditions in which nobody is lost to follow-up. Probability of exposure weights estimated within strata of site- and patient-level potential confounding variables, and probability of not being lost to follow-up weights estimated using same set of covariates.

Sensitivity #5: Multiple imputation assigning probability of mortality among patients lost to follow-up according to estimates obtained from Fox et al study.

Discussion

Introduction

As the scale-up of antiretroviral therapy in sub-Saharan Africa reaches maturity, program evaluation research is shifting from identifying means of scaling up services as rapidly as possible to investigating the outcomes of patients receiving these services. This dissertation was motivated by a simple question: do programmatic services intended to improve patient adherence to ART medication and long-term retention in care improve survival and retention in care? However, due to the vastness and heterogeneity of HIV service scale-up in the region, and limitations in the type and quality of information collected in this setting, a methodologic question became central to evaluating this simple programmatic one. Namely, if programmatic services are influencing patient survival and retention in care, will routinely-collected data be able to reliably identify this association?

Specification of causal hypothesis

The initial motivation for this work came from a series of papers demonstrating levels of adherence to antiretroviral therapy in resource-limited settings similar to, or greater than, those observed in research-rich settings among patients successfully retained in care [1-13], with heterogeneous but generally high rates of loss to follow-up among ART patients in resource-limited settings [14, 15]. A review of the literature on adherence to ART and retention in care in resource-limited settings, included in the proposal for this dissertation (available on request), focused on individual-level, program-level, and

structural determinants of non-adherence to ART, non-retention after ART initiation, and survival. From this review the following conclusions were drawn:

1. Barriers to ART adherence include individual-level, facility-level, and structural factors
    a. Qualitative studies in resource-rich and resource-poor settings have identified forgetfulness, change in life circumstances/routine, and lack of belief in drug effectiveness as reasons for non-adherence [12, 16-21]
    b. In addition to those factors listed above, studies in resource-limited settings have identified more facility-level and structural barriers to adherence, including waiting time, transportation or other opportunity costs, fear of hunger without sufficient food supply, and stigma [12, 20]
    c. Very few studies in resource-limited settings have investigated whether services designed to improve adherence are actually doing so. The studies that have found that adherence counseling and support services improve adherence [22, 23]
2. Barriers to long-term retention in care among ART patients
    a. Low CD4 count at ART initiation was associated with increased probability of early loss to follow-up after ART initiation in a large multi-center study [14], suggesting that loss to follow-up is in part comprised of unascertained deaths.
    b. Facilities actively tracking patients missing scheduled visits had lower rates of loss to follow-up than facilities not actively tracking patients in a study from the same multi-center consortium [24].
    c. There has been almost no published research evaluating the impact of program-level services on patient retention in care in resource-limited settings
3. The relationship between loss to follow-up and mortality
    a. An early study investigating the vital status of patients lost to follow-up, discussed in the proposal to this dissertation found a high proportion of patients lost were unascertained deaths [25]. Papers published since I wrote the proposal have reached similar conclusions [26-33].
    b. Loss to follow-up complicates our ability to assess program-level factors associated with patient survival because a substantial proportion of patients loss to follow-up are unascertained deaths, leading to the finding that facilities with less loss to follow-up will have higher ascertained deaths even if the “true” amount of death is the same.
4. **Research is needed evaluating facility-level factors influencing patient retention in care and survival, especially in resource-limited settings.**

The literature review conducted for my dissertation proposal was then used to create a causal theory hypothesizing what facility-level factors may influence patient retention and survival, the relationship between ascertained death, actual (ascertained plus unascertained) death, and loss to follow-up, and what other predictors of retention in care and survival, at both the facility-level and the patient-level, may bias associations between facility-level services and non-retention, loss to follow-up, and death. Figure 1 presents this causal theory in the form of a Directed Acyclic Graph (DAG) [34].

Key to understanding the complexity involved in identifying factors associated with patient survival is the relationship between non-retention, loss to follow-up, and ascertained death. In Figure 1, non-retention is defined as patients not returning to clinic for a regular appointment without a known transfer to another clinic. There are two reasons why a patient would not return to clinic. Either they died between their last attended visit and their next scheduled visit (represented by the line from NR→D) or they were lost to follow-up (represented by the line from NR→LTF), defined in this DAG as missing scheduled appointments and not known to have died or transferred. However, not all patients who died are ascertained as dead by the facility. This creates the situation where some deaths are ascertained (the line D→D*), while others become lost to follow-up (D → LTF). A further complication is that loss to follow-up reduces the proportion of "true" deaths (D) that are ascertained by the facility to have died (D*), because loss to follow-up causes reduced death ascertainment (LTF→D*).

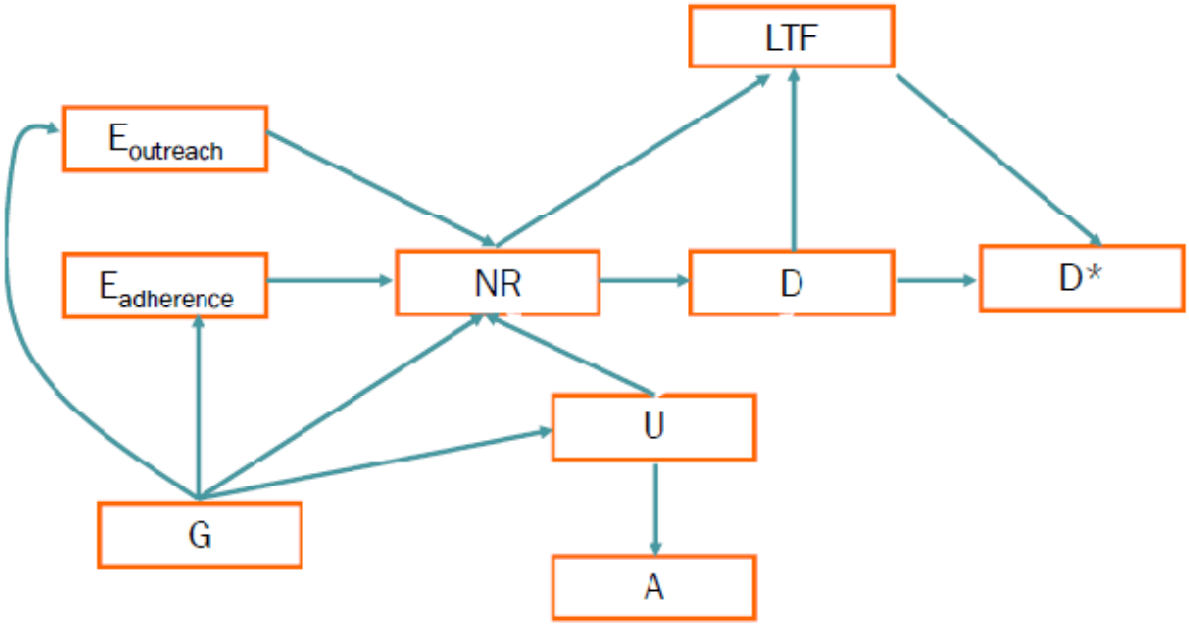
Adherence support services are hypothesized to improve patient survival ($E_{adherence}$ →NR→D) by improving adherence to ART medication. In addition, adherence support services are hypothesized to reduce loss to follow-up through incentivizing return visits

(e.g., offering food support), education on the importance of long-term adherence, and reducing stigma through peer support groups and counseling ($E_{adherence} \rightarrow NR \rightarrow LTF$). Active patient outreach is hypothesized reduce non-retention by identifying patients missing scheduled visits and returning them to care, which in turn is hypothesized to improve patient survival.

Variables G and A represent covariates at the facility-level (G) and patient-level (A) that are hypothesized to be causes of patient non-retention, loss to follow-up, and death that are also associated with our exposures of interest. In the facility-level analyses conducted in Papers 1 and 2, we do not have information at the patient-level do adjust for the potential impact of patient-level causes of non-retention, loss to follow-up and death. The patient-level analysis conducted in Paper 2 can adjust for patient-level differences, but the hypothesized relationship between G and U complicates control of both patient-level and facility-level predictors of non-retention. Specifically, we hypothesize that a set of facility-level services and characteristics (such as program size, overall comprehensiveness of care, location, etc.) influence non-retention independently of their adherence support and outreach service availability. We also hypothesize that patient-level characteristics, such as baseline immunologic and demographic measures, influence non-retention.

Papers 1 and 2 focus on assessing whether adherence support and outreach services, independently and/or synergistically, influence patient non-retention, loss to follow-up, or ascertained death as hypothesized in Figure 1. Paper 3 conducts a sensitivity analysis by estimating the strength of the causal relationship between actual death and loss to follow-up under a range of plausible scenarios.

Figure 1. Causal Diagram of the relationship between adherence support service availability, active outreach, and patient non-retention in care, loss to follow-up, and death.



Key:
$E_{outreach}$ = availability of an active outreach program to track ART patients missing scheduled visits and return them to care or ascertain outcome status (dead, transferred to another facility)
$E_{adherence}$ = availability of one of the tested facility-level services designed to improve patient adherence to ART. For simplicity of the DAG, only one generic example service is given
NR = patient non-retention in care, defined in this DAG as patients missing a clinic visit.
LTF = patient loss to follow-up. One component of non-retention, defined as patients without a clinic visit in 6 months who are not known to have died or transferred to another facility.
D = Patient death. This is comprised of patients known to have died, and those who have died but whose death is unascertained.
D* = ascertained death. This is a patient's vital status as documented by a given clinic.
G = a set of program-level variables associated with both the exposures and outcomes of interest (e.g., clinic size, location, availability of other program services)
U = a set of patient-level variables associated with the outcomes of interest that are also associated (through G) with the program-level exposures of interest.
A = a proxy measure for the set of patient-level variables (e.g., CD4 count and WHO stage at ART initiation, age, sex, tuberculosis status) based on information that is available in the data source.

Methodological questions: can imperfect data be used to test this hypothesis?

Once the causal model was specified, I undertook to identify what sources of data were available to test this model. Since the primary research questions underlying this dissertation are questions of effectiveness (do program-level services improve patient retention in service delivery settings in sub-Saharan Africa), as opposed to questions of efficacy, I believe it is important to test these questions in "real world" settings. Further, since the exposures of interest occur at the facility-level, it was necessary to ensure inclusion of sufficient numbers of facilities, with sufficient heterogeneity in program services availability, in order to be able to test these hypotheses in a statistically meaningful manner. This lead to the prioritization of data sources from HIV care and treatment clinics, as opposed to data sources from trials or other research settings. This allowed the investigation of the association between facility-level services and non-retention, loss to follow-up, and death in a very large and diverse population. However, the information available from this large population is limited in the amount of information collected and often available only in aggregate.

To best utilize available data while identifying how different measures of similar constructs may influence inference about the relationship between program-level service availability and non-retention, loss to follow-up, and death, three different measures of these outcomes were estimated and compared against one another. Each estimation has strengths and weaknesses, and Paper 2 discusses these at some length. Briefly, overall rates of non-retention, loss to follow-up, and ascertained death can be derived from aggregate data sources that are routinely available from care and treatment facilities in sub-Saharan Africa. These estimates are approximately

equivalent to rates calculated from patient-level data sources under a “rolling entry” scenario where patients are allowed entry into the study population during the duration of the observation period, and all patients are censored at the end of the observation period (see Appendix 3). The strength of this measure is its ubiquity, while it suffers from an inability to assess rates of non-retention, loss to follow-up, or death through a given time interval after ART initiation. In addition, the proportion of patients initiating ART in a given reporting quarter who are retained and on ART for 6 and 12 months after ART initiation is routinely available from care and treatment clinics in sub-Saharan Africa, but suffers from an inability to segment non-retention into loss to follow-up and ascertained death. Finally, patient-level data provides the most versatile source for rate estimations, since it can estimate both cumulative rates and endpoint-specific rates (such as the rate through 1 year after ART initiation), but suffers from lack of generalizability because most care and treatment facilities do not have electronic patient-level databases, and those that do may be materially different from those that do not.

This dissertation compares associations between facility-level services and these different measures of non-retention, loss to follow-up, and death, in order to assess which services are associated under all measures of the outcome, and to investigate potential reasons for different inference drawn from use of different outcome measures.

Key Findings

The first paper in this dissertation presents an ecologic analysis of over 232,000 patients at 349 HIV care and treatment facilities in10 countries initiating ART between January 2004 and December 2008 using two ecologic measures of the outcome of

interest: (1) overall non-retention, loss to follow-up and death rates and (2) 6- and 12-month non-retention proportions among cohorts of patients initiating ART within the same reporting quarter. In this analysis, after adjustment for program-level covariates, facilities offering three or more adherence support services, written educational materials promoting ART adherence, one-on-one or group adherence counseling sessions, reminder tools, and food rations to promote ART adherence were associated with reduced non-retention and loss to follow-up, while facilities offering on-site support groups for HIV+ patients, peer educators, provision of reminder tools, and food rations to promote ART adherence were associated with reduced death rates. In sub-analyses investigating six- and 12-month retention after ART initiation, facilities offering three or more separate adherence support services, routine review of medication pickup and/or dedicated ART pharmacists, and active patient outreach to trace patients missing visits had lower non-retention. Taken together, this analysis provides evidence that program-level services found efficacious in experimental settings are also effective in operational settings.

The second paper refines the non-retention, loss to follow-up, and death rate estimates by (1) comparing estimates obtained from aggregate vs. patient-level databases and (3) additionally allowing for adjustment for patient-level predictors of loss to follow-up and death. This analysis focuses on a subset of 92 HIV care and treatment facilities in 5 countries that also have electronic patient-level databases, containing 92,561 ART patients. A key finding, examined in more detail in Appendix 3, is that estimates of death rates were similar in the aggregate and patient-level analyses, while loss to follow-up rates were higher in analyses using the patient level database. In multivariate

analyses, clinics offering active patient outreach had lower rates of non-retention in both the ART cohort analysis and the patient-level analysis, and clinics offering food rations to promote ART adherence were associated with a lower risk of ascertained death in both the facility-level and patient-level analyses, but this association was diminished after adjustment for patient-level covariates. In contrast, various adherence counseling or support services were associated with lower non-retention in the ART cohort analyses but not in the patient-level data analyses.

Comparing the results of the similar analyses conducted in Paper 1 and Paper 2 (as discussed in the conclusion to Paper 2) highlights a common epidemiologic problem: limitations to generalizability. Namely, the study population investigated in Paper 2 is a subset of the population investigated in Paper 1, but the associations between various program-level services and non-retention, loss to follow-up, and death rates differ between the two populations in many cases even when using the same statistical models (see Figures 3a-3c in Paper 2). If facilities having electronic patient-level databases were a true random sample of all of the facilities comprising the study population for the Paper 1 analysis, we would expect similar-magnitude associations between facility-level services and rates of non-retention, loss to follow-up, and death across the two studies.

Tables D1a-D1c of this discussion compare the percentage difference in estimates of the rate ratios for non-retention, loss to follow-up, and death obtained in adjusted analyses in Papers 1 and 2. Of the facility-level services tested, only three (the availability of 2 vs. 1 separate directed counseling services, on-site support groups for HIV+ patients, and food support to promote ART adherence) had similar-magnitude

associations across both study populations, while other facility-level associations were substantially divergent. The findings of similar-magnitude associations in these two overlapping populations for these facility-level services increases our confidence that these associations are plausibly causal because it reduces the likelihood that uncontrolled confounding is responsible for the results. For example, it may be plausible to hypothesize that the association between food support and reduced non-retention is really due to the fact that facilities that offer more comprehensive services are more likely both to offer food support and to have less non-retention. In order for this hypothesis to explain the results from Paper 1 and Paper 2, the effect of comprehensiveness of services on non-retention and the availability of food support would have to be similar among the overall population analyzed in Paper 1 as in the sub-population of clinics in 5 countries with electronic patient-level databases analyzed in Paper 2. However, if this were the case, we would also expect the associations between other facility-level services and non-retention, loss to follow-up, and death rates to be similar between the two populations if we assume that comprehensive clinics are also more likely to offer these other services. Since we have found similar associations in the two analyses for specific facility-level services but not others, the "comprehensiveness of care" hypothesis introduced above would have to be further specified to suggest that "comprehensive" facilities are those that offer food support, more than one directed counseling service, and on-site support groups for HIV+ patients, regardless of whether they offer other services.

The findings of associations between several adherence support and outreach services and rates of non-retention, loss to follow-up, and death in the overall population in

Paper1 but not in the population in Paper 2 is consistent with the theory that these services influence patient outcomes in specified, but unknown, circumstances that do not exist at the clinics in which patient-level databases exist. More thorough examination of specific characteristics of the facilities with and without electronic databases, in order to better understand the reasons for these discrepant findings, is a potentially fruitful next step to this research.

Another finding from the analyses presented in Paper 2 is that adjustment for patient-level predictors of non-retention, loss to follow-up, and death diminishes the observed associations between facility-level services and non-retention, loss to follow-up, and death rates. Whether adjustment for patient-level covariates is appropriate depends on whether these factors are potentially influenced by exposure to the facility-level characteristics under consideration. For example, facilities that offer on-site support groups for HIV+ patients are likely to offer these groups for patients both in pre-ART care and after ART initiation. If these services improve patient retention in the pre-ART phase, a potential consequence would be initiating patients on ART earlier in disease progression. Since the patient-level covariates were based on measures taken at ART initiation, it is possible that these measures could be influenced by exposure to on-site support groups for HIV+ patients during their pre-ART phase, such that adjusting for their ART initiation CD4 measure is in fact adjusting for a consequence of exposure, leading to a bias of effect estimates toward the null. Because we do not have complete information on the timing of exposure compared to the timing of the measures used as “baseline” measures for all patient-level covariates (excepting age and sex), it is conceptually difficult to disentangle the potential confounding and mediating impact of

certain patient-level measures. It is for this reason that both are presented in Paper 2, to allow the reader to reach her own conclusions about the appropriateness of adjustment.

Finally, Paper 3 attempts to investigate the problem of loss to follow-up in limiting our ability to infer influences on patient survival. Loss to follow-up is a mixture of patients who have transferred to other clinics but whose transfer is not known to their initiating clinic, patients who have died but whose death is not known to their clinic, and patients who have withdrawn from care. Loss to follow-up results in underestimates of death incidence because we are missing vital status on those patients who are lost, and because some proportion of them are unascertained death. In analyses investigating whether facility-level services improve patient survival, loss to follow-up is additionally problematic because services that reduce loss to follow-up are likely to improve death ascertainment, such that even if these services do nothing to change the actual death rate, they will increase the ascertained death rate.

Traditional methods of accounting for loss to follow-up treat these patients as "censored" observations, allowing them to contribute person-time to rate denominators up until the time of their loss. Implicit in these methods is the assumption that the reasons for loss to follow-up are non-informative with respect to death likelihood, meaning that, conditioned on covariates, patients who are lost are assumed to have the same likelihood of death as those not lost.

The key finding from this sensitivity analysis is that different assumptions concerning the death probability among patients loss to follow-up impact our estimations of the impact of program-level services on patient survival. Adherence support and outreach

services, strongly associated with loss to follow-up, also became associated with mortality after imputing the likely death probability among patients lost to follow-up. Findings were robust under a variety of assumptions, suggesting that loss to follow-up is masking real associations between adherence support and active outreach programs and reduced death.

Limitations in using facility-level measures of adherence support and outreach service availability

This dissertation has focused on investigating whether the existence of specific facility-level services targeting adherence and retention, as measured by a standardized site assessment tool, influence measures of non-retention, loss to follow-up, and death. It is important to recognize the limitations inherent in assigning exposures in this manner. First, facilities are dichotomized according to whether or not they reported the availability of a given service. No information is available that would allow further categorization based on the overall quality of the service being offered or the number or proportion of patients utilizing the service. While our choice to dichotomize exposure was governed in part by data limitations, it is analogous to the "intention to treat" principle common in randomized clinical trials: every patient who attended a given facility was assumed to be exposed to the facility-level service reported, regardless of whether or not they partook in this service. On the patient-level, this creates misclassification of "true" exposure for patients who attended a facility offering a service that they did not participate in in the same sense that an intent-to-treat analysis creates misclassification of "true" exposure for patients assigned to an active treatment who did

not comply, but does not impact our interpretation of the facility-level effect of having a service available on patient outcomes.

Second, the fact that exposures were classified through questionnaire by in-country staff leaves open the possibility of misclassification. For example, the facility-level characteristic most consistently associated with reduced non-retention, loss to follow-up, and ascertained death in this dissertation was based on results to the following question:

What **food security support** services are provided to patients at this facility? *Please choose all applicable responses.*	Food rations for adults to promote ART adherence (i.e. incentive program)	1
	Food rations for adults to promote household food security (i.e. supplementary feeding program)	2
	Food rations for children <5 yrs to promote ART adherence (i.e. incentive program)	3
	Food rations for children <5 yrs to promote household food security (i.e. supplementary feeding program)	4
	Income generating activities for PLWHAs	5
	Agricultural support (training, materials)	6
	None	7
	Other: _____	8

Facilities responding to option # 1 or #3 were considered to provide food support to promote ART adherence, while those responding to any other option, were considered not to have such a service. It is possible that some facilities responded to options #1 or #3 when the food support service they offered was not specifically designed for ART adherence, but unlikely that a facility would report offering this type of service when it did not offer any food support service. This highlights the fact that the measures we are

using of facility-level services should be interpreted broadly, but does not diminish the associations observed.

Implications and future research

This dissertation is among the first to assess the potential influence of program-level services on patient retention in care and survival in resource-limited settings. Taken together, it provides evidence that program-level services can impact non-retention, loss to follow-up and death rates in this context. Keeping in mind the limitations of routinely-collected observational data, it provides evidence that this data can be used, with appropriate caution, to inform program evaluation. This will add to the small but accumulating body of literature in both resource-rich and resource-poor settings suggesting that adherence support and outreach services improve patient retention and survival [24, 35].

Future research can build on this dissertation by addressing some of its limitations. First, more complete sources of information on facility- and patient-level predictors of loss to follow-up and death are needed to reduce the likelihood that observed associations are due to unmeasured confounding. Second, the influence of loss to follow-up on measures of survival would be much better understood with more studies sampling patients lost to follow-up to ascertain reasons for their loss as well as vital status. Finally, more specific measures of the quality of services offered would allow us to better quantify exactly what aspects of adherence support and outreach services have the most beneficial impact on patient survival and retention in care.

References

1. Coetzee, D., et al., *Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa.* AIDS, 2004. **18 Suppl 3**: p. S27-31.
2. Idigbe, E.O., et al., *Management of HIV-1 infection with a combination of nevirapine, stavudine, and lamivudine: a preliminary report on the Nigerian antiretroviral program.* J Acquir Immune Defic Syndr, 2005. **40**(1): p. 65-9.
3. Jaffar, S., et al., *Antiretroviral treatment in resource-poor settings: public health research priorities.* Trop Med Int Health, 2005. **10**(4): p. 295-9.
4. Laniece, I., et al., *Adherence to HAART and its principal determinants in a cohort of Senegalese adults.* AIDS, 2003. **17 Suppl 3**: p. S103-8.
5. Laurent, C., et al., *The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study.* AIDS, 2002. **16**(10): p. 1363-70.
6. Laurent, C., et al., *Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1-infected adults.* J Acquir Immune Defic Syndr, 2005. **38**(1): p. 14-7.
7. Mills, E.J., et al., *Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis.* JAMA, 2006. **296**(6): p. 679-90.
8. Orrell, C., et al., *Adherence is not a barrier to successful antiretroviral therapy in South Africa.* AIDS, 2003. **17**(9): p. 1369-75.
9. Rabkin, M., et al., *Antiretroviral treatment in resource-poor settings: clinical research priorities.* Lancet, 2002. **360**(9344): p. 1503-5.
10. Stevens, W., S. Kaye, and T. Corrah, *Antiretroviral therapy in Africa.* BMJ, 2004. **328**(7434): p. 280-2.
11. van Oosterhout, J.J., et al., *Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi.* Trop Med Int Health, 2005. **10**(5): p. 464-70.
12. Weiser, S., et al., *Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana.* J Acquir Immune Defic Syndr, 2003. **34**(3): p. 281-8.
13. Wools-Kaloustian, K., et al., *Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya.* AIDS, 2006. **20**(1): p. 41-8.
14. Brinkhof, M.W., et al., *Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries.* Bull World Health Organ, 2008. **86**(7): p. 559-67.
15. Rosen, S., M.P. Fox, and C.J. Gill, *Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review.* PLoS Med, 2007. **4**(10): p. e298.
16. Brigido, L.F., et al., *Impact of adherence to antiretroviral therapy in HIV-1-infected patients at a university public service in Brazil.* AIDS Patient Care STDS, 2001. **15**(11): p. 587-93.
17. Chesney, M.A., *Factors affecting adherence to antiretroviral therapy.* Clin Infect Dis, 2000. **30 Suppl 2**: p. S171-6.

18. Chesney, M.A., M. Morin, and L. Sherr, *Adherence to HIV combination therapy.* Soc Sci Med, 2000. **50**(11): p. 1599-605.
19. DiMatteo, M.R., *Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research.* Med Care, 2004. **42**(3): p. 200-9.
20. Hardon, A.P., et al., *Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa.* AIDS Care, 2007. **19**(5): p. 658-65.
21. Mills, E.J., et al., *Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators.* PLoS Med, 2006. **3**(11): p. e438.
22. Demeester, R., et al., *Adherence to first-line antiretroviral regimens in Rwanda.* J Acquir Immune Defic Syndr, 2005. **40**(1): p. 113-4.
23. Traore AA, N.V., McCarrick P, Dhaliwal M, Tioendrebeogo I, Ilboudo A, *Barriers to adherence to ARV therapy in a community-based cohort in Burkina Faso [Abstract]*, in *XV International AIDS Conference*. 2004: Bangkok, Thailand. p. AbstractWePeB5824.
24. Braitstein, P., et al., *Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries.* Lancet, 2006. **367**(9513): p. 817-24.
25. Yu, J.K., et al., *True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi.* Bull World Health Organ, 2007. **85**(7): p. 550-4.
26. Bisson, G.P., et al., *Overestimates of survival after HAART: implications for global scale-up efforts.* PLoS One, 2008. **3**(3): p. e1725.
27. Brinkhof, M.W., et al., *Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality.* PLoS Med, 2009. **6**(4): p. e1000066.
28. Dalal, R.P., et al., *Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in johannesburg, South Africa.* J Acquir Immune Defic Syndr, 2008. **47**(1): p. 101-7.
29. Deribe, K., et al., *Defaulters from antiretroviral treatment in Jimma University Specialized Hospital, Southwest Ethiopia.* Trop Med Int Health, 2008. **13**(3): p. 328-33.
30. Fox, M.P., et al., *Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa.* Trop Med Int Health. **15**(4): p. 405-13.
31. Geng, E.H., et al., *Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa.* JAMA, 2008. **300**(5): p. 506-7.
32. Geng, E.H., et al., *Tracking a sample of patients lost to follow-up has a major impact on understanding determinants of survival in HIV-infected patients on antiretroviral therapy in Africa.* Trop Med Int Health, 2010. **15 Suppl 1**: p. 63-9.
33. Yiannoutsos, C.T., et al., *Sampling-based approaches to improve estimation of mortality among patient dropouts: experience from a large PEPFAR-funded program in Western Kenya.* PLoS One, 2008. **3**(12): p. e3843.
34. Greenland, S., J. Pearl, and J.M. Robins, *Causal diagrams for epidemiologic research.* Epidemiology, 1999. **10**(1): p. 37-48.

35. Brinkhof, M.D.F.M.L.B.D.B.A., Nash D, Schechter M, Laurent C, Keiser O, May, M, Sprinz, E, Eggar, M, Anglaret, X, *Early loss to program in HIV-infected patients starting potent antiretroviral therapy in lower-income countries.* PLOS Medicine, 2008. **in press**.
36. Milam, J., et al., *Effect of a brief antiretroviral adherence intervention delivered by HIV care providers.* J Acquir Immune Defic Syndr, 2005. **40**(3): p. 356-63.
37. Fairley, C.K., et al., *Randomized trial of an adherence programme for clients with HIV.* Int J STD AIDS, 2003. **14**(12): p. 805-9.
38. Goujard, C., et al., *Impact of a patient education program on adherence to HIV medication: a randomized clinical trial.* J Acquir Immune Defic Syndr, 2003. **34**(2): p. 191-4.
39. Pradier, C., et al., *Efficacy of an educational and counseling intervention on adherence to highly active antiretroviral therapy: French prospective controlled study.* HIV Clin Trials, 2003. **4**(2): p. 121-31.
40. Weber, R., et al., *Effect of individual cognitive behaviour intervention on adherence to antiretroviral therapy: prospective randomized trial.* Antivir Ther, 2004. **9**(1): p. 85-95.
41. Rawlings, M.K., et al., *Impact of an educational program on efficacy and adherence with a twice-daily lamivudine/zidovudine/abacavir regimen in underrepresented HIV-infected patients.* J Acquir Immune Defic Syndr, 2003. **34**(2): p. 174-83.
42. Byron, E., S. Gillespie, and M. Nangami, *Integrating nutrition security with treatment of people living with HIV: lessons from Kenya.* Food Nutr Bull, 2008. **29**(2): p. 87-97.
43. Torpey, K.E., et al., *Adherence support workers: a way to address human resource constraints in antiretroviral treatment programs in the public health setting in Zambia.* PLoS One, 2008. **3**(5): p. e2204.

Dissertation Discussion Tables

Table D1a. Comparison between Paper 1 and Paper2: Covariate-adjusted estimates of the overall non-retention rate ratio

		Paper 1 (N = 349 clinics)			Paper 2 (N = 92 clinics)			
Adherence Support Service		N yes/no	RR	95% CI	N yes/no	RR	95% CI	% difference in Rate Ratio
Total number of adherence support services offered	>2 vs. ≤ 2	292/57	0.59	(0.35-1.0)	81/11	1.05	(0.5-2.2)	78%
Availability of educational pamphlets, etc	yes vs. no	199/150	0.73	(0.63-0.85)	61/31	0.99	(0.72-1.34)	36%
Number of separate directed counseling services available	2 vs. 1	97/115	0.91	(0.72-1.14)	24/22	0.86	(0.53-1.38)	5%
	3 vs. 1	113/115	0.98	(0.82-1.18)	41/22	0.81	(0.53-1.22)	17%
one-on-one or group adherence counseling services	yes vs. no	308/41	0.62	(0.42-0.92)	87/5	1.04	(0.49-2.22)	68%
Frequency of counseling services among sites providing them	≥ every 3 months vs. < every 3 months	276/32	1.14	(0.88-1.49)	77/10	1.67	(1.16-2.4)	46%
on-site support group for HIV+ patients	all patients vs ART patients only	190/159	1.03	(0.87-1.22)	56/36	1	(0.7-1.43)	3%
peer educator program	yes vs. no	150/199	0.99	(0.86-1.14)	50/42	0.81	(0.62-1.07)	18%
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	245/104	0.79	(0.64-0.97)	70/22	1.29	(0.9-1.85)	63%
Dedicated pharmacist, team pharmacist, or routine medication pickup review	yes vs. no	278/71	0.71	(0.48-1.05)	78/14	1	(0.52-1.93)	41%
Food rations provided to promote ART adherence	yes vs. no	60/289	0.72	(0.58-0.9)	27/65	0.67	(0.44-1.03)	7%
Outreach Services								
Active patient outreach	yes vs. no	185/164	1.00	(0.85-1.18)	61/31	1.32	(0.87-2.01)	32%
Target population among sites w/ active outreach	all patients vs ART patients only	136/45	1.01	(0.81-1.27)	47/14	1.11	(0.75-1.65)	10%

Table D1b. Comparison between Paper 1 and Paper2: Covariate-adjusted estimates of the overall loss to follow-up rate ratio

		Paper 1 (N = 349 clinics)			Paper 2 (N = 92 clinics)			% difference in Rate Ratio
Adherence Support Service		N yes/no	RR	95% CI	N yes/no	RR	95% CI	
Total number of adherence support services offered	>2 vs. ≤ 2	292/57	0.48	(0.25-0.92)	81/11	0.76	(0.32-1.81)	58%
Availability of educational pamphlets, etc	yes vs. no	199/150	0.63	(0.52-0.77)	61/31	0.83	(0.56-1.24)	32%
Number of separate directed counseling services available	2 vs. 1	97/115	1.01	(0.74-1.38)	24/22	1.07	(0.55-2.08)	6%
	3 vs. 1	113/115	1.16	(0.9-1.49)	41/22	0.92	(0.52-1.63)	21%
one-on-one or group adherence counseling services	yes vs. no	308/41	0.55	(0.33-0.89)	87/5	0.72	(0.3-1.73)	31%
Frequency of counseling services among sites providing them	≥ every 3 months vs. < every 3 months	276/32	1.20	(0.84-1.7)	77/10	1.71	(1.05-2.76)	43%
on-site support group for HIV+ patients	yes vs. no	190/159	1.20	(0.95-1.52)	56/36	1.12	(0.69-1.82)	7%
peer educator program	yes vs. no	150/199	1.08	(0.89-1.32)	50/42	0.75	(0.53-1.07)	31%
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	245/104	0.77	(0.58-1.02)	70/22	1.3	(0.81-2.09)	69%
Dedicated pharmacist, team pharmacist, or routine medication pickup review	yes vs. no	278/71	0.60	(0.36-1)	78/14	0.71	(0.32-1.55)	18%
Food rations provided to promote ART adherence	yes vs. no	60/289	0.65	(0.47-0.88)	27/65	0.61	(0.33-1.14)	6%
Outreach Services								
Active patient outreach	yes vs. no	185/164	1.05	(0.84-1.32)	61/31	1.5	(0.84-2.67)	43%
Target population among sites w/ active outreach	all patients vs ART patients only	136/45	1.10	(0.81-1.48)	47/14	1.14	(0.66-1.95)	4%

Table D1c. Comparison between Paper 1 and Paper2: Covariate-adjusted estimates of the overall ascertained death rate ratio

		Paper 1 (N = 349 clinics)			Paper 2 (N = 92 clinics)			
Adherence Support Service		N yes/no	RR	95% CI	N yes/no	RR	95% CI	% difference in Rate Ratio
Total number of adherence support services offered	>2 vs. ≤ 2	292/57	0.94	(0.55-1.61)	81/11	4.16	(1.32-13.1)	343%
Availability of educational pamphlets, etc	yes vs. no	199/150	0.98	(0.85-1.13)	61/31	1.59	(1.2-2.11)	62%
Number of separate directed counseling services available	2 vs. 1	97/115	0.77	(0.63-0.93)	24/22	0.55	(0.39-0.77)	29%
	3 vs. 1	113/115	0.75	(0.64-0.87)	41/22	0.64	(0.49-0.85)	15%
one-on-one or group adherence counseling services	yes vs. no	308/41	0.82	(0.55-1.21)	87/5	7.76	(1.63-37.06)	846%
Frequency of counseling services among sites providing them	≥ every 3 months vs. < every 3 months	276/32	1.05	(0.82-1.33)	77/10	1.56	(1.14-2.12)	49%
on-site support group for HIV+ patients	yes vs. no	190/159	0.81	(0.7-0.93)	56/36	0.79	(0.6-1.04)	2%
peer educator program	yes vs. no	150/199	0.84	(0.74-0.96)	50/42	0.99	(0.78-1.26)	18%
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	245/104	0.81	(0.66-0.98)	70/22	1.27	(0.93-1.74)	57%
Dedicated pharmacist, team pharmacist, or routine medication pickup review	yes vs. no	278/71	0.95	(0.66-1.37)	78/14	3.66	(1.45-9.24)	285%
Food rations provided to promote ART adherence	yes vs. no	60/289	0.83	(0.69-1)	27/65	0.76	(0.55-1.04)	8%
Outreach Services								
Active patient outreach	yes vs. no	185/164	0.91	(0.79-1.06)	61/31	1.05	(0.75-1.46)	15%
Target population among sites w/ active outreach	all patients vs ART patients only	136/45	0.86	(0.7-1.06)	47/14	1.08	(0.78-1.47)	26%

Rate ratios presented are for facility-level analyses adjusting for facility type (primary, secondary, tertiary), location (urban, semi-urban, rural), and the cumulative number of patients seen in care at a given clinic

Appendices

Appendix 1.1: Program-level factors associated with retention in care and receiving ART for 6 out of 6, or 12 out of 12 months

Introduction:

To test whether adherence support services improve patient retention in part by improving adherence to ART medication, a secondary analysis used the proportion of patients receiving ART medication for 6 out of 6, or 12 out of 12 months, as the outcome of interest. This outcome combines retention and ART adherence. Analyses follow the same structure outlined for the 6 and 12 month ART cohorts in Paper 1. Results are presented in the table below.

Table A1.1. Association between adherence support and outreach services and the proportion of patients retained and receiving ART for 6 or 12 months

			Non-adherence* Risk Ratio through 6 months[1]			Non-adherence* Risk Ratio through 12 months[2]			
		N (yes/no)	Crude	RR (95% CI)	Adjusted[3] RR (95% CI)		Crude	RR (95% CI)	Adjusted[3] RR (95% CI)	
Adherence support services										
Total number of adherence support services provided	> 2 vs ≤ 2	1016/81	0.83	(0.64-1.07)	0.81	(0.69-0.95)	0.88	(0.66-1.17)	0.87	(0.66-1.15)
Availability of educational pamphlets, etc	yes vs. no	773/315	0.89	(0.74-1.07)	0.87	(0.74-1.02)	0.93	(0.8-1.08)	0.93	(0.8-1.08)
Availability of directed Counseling or support	yes vs. no	935/162	1.04	(0.8-1.36)	1.07	(0.86-1.32)	1.1	(0.81-1.51)	1.10	(0.85-1.41)
Number of directed counseling or support services	2 vs 1	311/327	0.95	(0.73-1.23)	1.04	(0.85-1.26)	0.96	(0.78-1.19)	1.00	(0.84-1.18)
	3 vs 1	297/327	1.07	(0.81-1.42)	1.06	(0.87-1.28)	1.13	(0.9-1.43)	1.09	(0.91-1.3)
one-on-one or group adherence counseling services	yes vs. no	685/403	1.2	(1.06-1.36)	1.10	(0.98-1.24)	1.36	(1.19-1.54)	1.25	(1.1-1.42)
Frequency of counseling services among sites providing them	≥ every 3 months vs < every 3 months	612/73	1.38	(0.77-2.47)	1.07	(0.68-1.7)	1.06	(0.68-1.65)	0.90	(0.63-1.28)
on-site support group for HIV+ patients	yes vs. no	679/409	0.95	(0.76-1.2)	1.01	(0.84-1.22)	0.94	(0.75-1.16)	0.95	(0.8-1.13)
peer educator program	yes vs. no	476/612	1.01	(0.81-1.26)	1.03	(0.88-1.22)	1.05	(0.86-1.28)	1.04	(0.89-1.21)
Availability of reminder tools (e.g., clocks, calendars, pill boxes)	yes vs. no	978/110	1.23	(0.78-1.94)	1.15	(0.78-1.7)	1.2	(0.88-1.63)	1.14	(0.87-1.5)
Routine medication pickup review, dedicated or team pharmacist	yes vs. no	1027/61	0.83	(0.62-1.1)	0.80	(0.68-0.94)	0.85	(0.59-1.2)	0.80	(0.59-1.08)
Food rations provided to adults or children	yes vs. no	178/919	0.85	(0.65-1.11)	0.81	(0.64-1.02)	0.95	(0.76-1.19)	0.93	(0.76-1.13)
Outreach Services										
Active patient outreach	yes vs. no	725/363	0.84	(0.73-0.97)	0.91	(0.79-1.05)	0.83	(0.71-0.96)	0.89	(0.76-1.03)
Target population among sites w/ active outreach	All patients vs. ART only	525/178	1.31	(0.97-1.76)	1.18	(0.91-1.53)	1.14	(0.89-1.46)	1.03	(0.82-1.31)

* Non-Adherence defined as either not being retained in care or not receiving medication for all months

1,2. Cohort non-adherence to care and ART estimates as the proportion of patients receiving ART for 6 out of 6 (or 12 out of 12 months) among those initiating ART in a given 3-month cohort

3. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, cohort start year, and cumulative number of patients seen in care

4. All analyses adjusting for within-site correlation using generalized estimating equations

Appendix 1.2: Results of additive-scale interaction analysis (Paper 1)

Introduction:

This appendix presents the numeric results that are displayed in Figures 2a-2c of Paper 1, and that test for additive-scale interaction between active outreach and adherence support services in influencing rates of non-retention, loss to follow-up, and death.

Table A1.2a. Results of additive-scale interaction analyses: Overall Non-retention, loss to follow-up, and death rate ratios

		Adherence only			Outreach only			Both adherence and outreach			Interaction Contrast Ratio		
Outcome	Exposure	Rate Ratio	LCL	UCL	Rate Ratio	LCL	UCL	Rate Ratio	LCL	UCL	ICR	LCL	UCL
Non-retention	three or more vs. fewer adherence services	0.56	0.33	0.97	0.52	0.04	6.34	0.58	0.34	0.99	0.49	-0.81	1.80
	educational materials provision	0.83	0.62	1.11	1.10	0.85	1.44	0.77	0.60	1.00	-0.16	-0.50	0.18
	one-on-one/group adherence counseling	0.55	0.36	0.83	0.37	0.07	1.91	0.58	0.39	0.86	0.67	0.06	1.28
	reminder tool provision	0.64	0.40	1.02	0.79	0.48	1.29	0.65	0.42	1.02	0.23	-0.17	0.63
	dedicated pharmacist or routine review of medication pickup	0.70	0.42	1.17	0.99	0.46	2.12	0.71	0.43	1.18	0.02	-0.74	0.78
	food rations to promote adherence	0.66	0.32	1.38	1.04	0.88	1.24	0.75	0.58	0.97	0.05	-0.49	0.58
Loss to follow-up	three or more vs. fewer adherence services	0.44	0.22	0.86	0.46	0.02	13.84	0.48	0.24	0.94	0.58	-1.00	2.15
	educational materials provision	0.72	0.49	1.06	1.16	0.83	1.63	0.70	0.50	0.98	-0.18	-0.62	0.26
	one-on-one/group adherence counseling	0.43	0.26	0.73	0.13	0.005	3.69	0.50	0.31	0.82	0.94	0.49	1.38
	reminder tool provision	0.60	0.31	1.14	0.79	0.40	1.56	0.64	0.35	1.20	0.26	-0.27	0.79
	dedicated pharmacist or routine review of medication pickup	0.63	0.32	1.24	1.25	0.47	3.33	0.68	0.35	1.32	-0.21	-1.42	1.00
	food rations to promote adherence	0.46	0.15	1.40	1.09	0.87	1.37	0.71	0.50	1.02	0.16	-0.43	0.75
Ascertained death	more than 1 vs 1 directed counseling or support service	0.93	0.72	1.20	1.48	1.13	1.94	0.84	0.70	1.00	-0.58	-1.02	-0.13
	one-on-one/group adherence counseling	0.88	0.57	1.36	1.10	0.368	3.30	0.81	0.53	1.24	-0.17	-1.40	1.05
	support groups for HIV+ patients	0.94	0.73	1.22	1.21	0.95	1.56	0.86	0.72	1.02	-0.30	-0.67	0.08
	peer educators	1.00	0.72	1.38	1.08	0.89	1.31	0.86	0.73	1.01	-0.22	-0.59	0.16
	reminder tool provision	0.72	0.48	1.06	0.80	0.52	1.22	0.66	0.45	0.97	0.15	-0.22	0.52
	food rations to promote adherence	1.19	0.67	2.10	0.97	0.83	1.13	0.79	0.64	0.98	-0.37	-1.07	0.34

Table A1.2b. Results of additive-scale interaction analyses: 6 and 12 month non-retention risk ratios

ART cohort analysis		Adherence only			Outreach only			Both adherence and outreach			Interaction Contrast Ratio		
Outcome	Exposure	Risk Ratio	LCL	UCL	Risk Ratio	LCL	UCL	Risk Ratio	LCL	UCL	ICR	LCL	UCL
Non-retention through 6 months	three or more vs. fewer adherence services	0.91	0.77	1.08	0.96	0.72	1.28	0.78	0.65	0.94	-0.09	-0.49	0.30
	support groups for HIV+ patients	0.73	0.55	0.96	0.62	0.49	0.78	0.78	0.64	0.95	0.43	0.28	0.58
	dedicated pharmacist or routine review of medication pickup	0.88	0.74	1.04	1.03	0.74	1.43	0.75	0.62	0.90	-0.16	-0.61	0.29
Non-retention through 12 months	three or more vs. fewer adherence services	0.87	0.73	1.04	0.76	0.53	1.09	0.74	0.61	0.89	0.11	-0.18	0.39
	support groups for HIV+ patients	0.79	0.63	0.99	0.68	0.55	0.84	0.78	0.66	0.91	0.30	0.17	0.44
	dedicated pharmacist or routine review of medication pickup	1.01	0.76	1.34	1.10	0.75	1.60	0.84	0.63	1.12	-0.27	-0.70	0.17

1. Overall non-retention rates estimated as the cumulative number of patients at a site lost to follow-up, withdrawn, or reported dead, over the total person-years observed on ART at that site
2. Overall loss to follow-up rates estimated as the cumulative number of patients not returning to clinic for > 6 months since last visit, with no known status, over the total person-years observed on ART at that site
3. Overall death rates estimated as the cumulative number of patients reported dead, over the total person-years observed on ART at that site
4. Overall analyses adjusted for facility type (primary, secondary, or tertiary), urban/rural, year facility began providing ART care, and cumulative number of patients seen in care
5. Cohort non-retention % estimated as 100 - (number of patients on ART through 6 months/number starting cohort at baseline)
6. Cohort non-retention % estimated as 100 - (number of patients on ART through 12 months/number starting cohort at baseline)
7. Adjusted for facility type (primary, secondary, or tertiary), urban/rural, cohort start year, and cumulative number of patients seen in care

Appendix 2.1: Comparing competing risk and censoring methodologies with loss to follow-up as the outcome of interest.

Introduction:

Recent analyses investigating the incidence of loss to follow-up have treated death as a competing risk (e.g., [1-4]), with authors suggesting that traditional time-to-event analyses, such as Kaplan-Meier and Proportional Hazards modeling, overestimate incidence of loss to follow-up in the presence of substantial death. Kaplan-Meier and proportional hazards models censor patients who obtain an outcome that prevents ascertainment of the outcome of interest (e.g., loss to follow-up). For example, when modeling death as an outcome of interest in a population where there is loss to follow-up, Kaplan-Meier methods will allow a patient who is lost to follow-up to contribute person-time until they are lost, after which they are censored. Kaplan-Meier methods can be used to estimate the cumulative incidence of death in the presence of loss to follow-up. However, the implicit assumption in using this approach is that, conditioned on covariates, the incidence of death among patients lost to follow-up is the same as the incidence of death among patients not lost to follow-up (e.g., patients lost to follow-up are missing at random).

Estimating the incidence of loss to follow-up in the presence of death represents a different scenario, because patients known to have died by definition cannot be lost to follow-up. Under this scenario, death is a competing risk for loss to follow-up because it precludes loss to follow-up from occurring. Various investigators (e.g., [1-5]) have correctly pointed out that estimates of the cumulative incidence function using Kaplan-Meier methods (or of using the hazard ratio from proportional hazards modeling as an approximation of the risk ratio) overstates the cumulative incidence of loss to follow-up

in the presence of death as a competing risk because it assumes that patients who died have the same probability of loss to follow-up as those who have not died. Fine and Gray [5] introduced a method of calculating proportional hazards in the presence of competing risk.

This dissertation does not present proportional hazards models using the competing risk approach, instead calculating proportional hazards using Cox Proportional Hazards models. The reasons for this have to do with the interpretation of the proportional hazards ratios obtained from the two methodologies. Under the Cox Proportional Hazards model, incidence rates of loss to follow-up are estimated, allowing persons to contribute person-time until they either achieve the endpoint of interest, achieve a different endpoint (such as death or transfer) that precludes them from achieving the endpoint of interest, or until the end of the follow-up time. If this measure is interpreted as a ratio of rates, rather than as an approximation of a ratio of cumulative incidence, then it is the appropriate measure to use. Specifically, if our research question of interest is how quickly an average person in a cohort under investigation is followed before becoming lost to follow-up, then a rate-based measure appropriately measures this question. On the other hand, if our research question of interest is in the risk of becoming lost to follow-up within a given time frame, rather than how quickly these events occur, then the competing risk measure gives a better approximation of this question.

This dissertation is primarily interested in questions of rate, for several reasons. First, in paper 2, where loss to follow-up is estimated using both aggregate and patient-level data, the only measure available in the aggregate data is a rate measure that is not

interpretable as an estimation of patient-level risk. Thus, patient-level estimates of rate are the appropriate comparison measure. Second, because the programmatic goal is to achieve life-long retention on ART, and because patients will ultimately either become lost to follow-up or die, the question of interest focuses on whether we can take steps to increase the amount of time it takes for this to happen. This question is a question of rate.

To examine whether treating death as a competing risk in patient-level analyses investigating the association between program-level factors and loss to follow-up, the analyses presented in Table 4b were performed treating death as a competing risk. These analyses were performed in R using the computational packages *cmprsk* developed by Fine and Gray. The rate ratio estimations presented in Table 4b were virtually unchanged when assessing using a competing risk framework (average change in point estimate < 1%; data not shown). The reason for this is because competing risk analysis differs from proportional hazards analysis based on (1) the prevalence of the competing risk and (2) the average amount of time a person who obtains the competing risk is followed. If competing risks are of the same order of magnitude AND they disproportionately occur after very little follow-up time, estimates will diverge. In our study, the amount of loss to follow-up is substantially higher than the amount of death, minimizing the influence of competing risk on our hazard ratio estimates.

References

1. Brinkhof, M.W., et al., *Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries.* Bull World Health Organ, 2008. **86**(7): p. 559-67.
2. Graham, S., et al., *Sexual Risk Behavior, Loss to Follow-up, and HIV-1 Acquisition in a Cohort of Female Sex Workers: A 15-Year Study*, in *18th Conference on Retroviruses and Opportunistic Infections*. 2011: Boston, Mass.
3. Schöni-Affolter, F., et al., *Competing Risks: Loss to Follow-up and Mortality in HIV Cohort Studies in Zambia and Switzerland*, in *18th Conference on Retroviruses and Opportunistic Infections*. 2011: Boston, Mass.
4. Szychowski, J.M., et al., *Patient death as a censoring event or competing risk event in models of nursing home placement.* Stat Med, 2009. **29**(3): p. 371-81.
5. Fine, J. and R. Gray, *A proportional hazards model for the subdistribution of a competing risk.* Journal of the American Statistical Association, 1999. **94**(446): p. 13.

Appendix 3: Further explanation of the aggregate non-retention, loss to follow-up, and death rates.

Papers 1 and 2 estimate facility-level non-retention, loss to follow-up, and death rates by calculating the cumulative number of events occurring at a given clinic, and dividing by the cumulative person-time observed at that clinic. This appendix further examines this rate measure, and compares it to incidence rate estimates obtained with patient-level data. It shows that the overall rate estimates obtained from aggregate data are approximately equivalent to patient-level rate estimates under a "rolling entry" scenario, where patients are entered into the study population throughout the observation period, and followed until the end of the observation period, with no minimum follow-up time requirement. The overall rate measure differs from endpoint-specific incidence rate estimates (e.g., death rate through one year after ART initiation) because it cannot estimate average follow-up duration on the patient-level. The extent to which facility-level and patient-level rate measures differ is a function of the distribution of new vs. existing patients in the population, the average time of follow-up until reaching an event, and the minimum follow-up time required for inclusion in the study population.

Methods

First, a sample population was created for heuristic purposes to explain the process of deriving aggregate estimates of person-time and rates of loss to follow-up and death from patient-level data (Table 1). For this sample, the following assumptions were made:

- All patients were enrolled in 2005
- The observation period was January-December 2005

- Patients who died were assumed to do so 90 days after ART initiation
- Patients who were lost to follow-up were assumed to be lost 180 days after ART initiation
- Patients who transferred were assumed to transfer 30 days after ART initiation

From this patient-level study population, quarterly aggregate estimates similar to those used in Papers 1 and 2 were derived as follows. First, all patients are assigned an ART initiation quarter based on their ART start date (orange section in Table 1). Next, patients are assigned a quarterly "status" (dead, transferred, lost to follow-up, active) based on their reported last visit date, reported status, and status date (blue section in Table 1). For each quarter, patients are "currently on ART at the beginning of the quarter" if (1) they initiated ART before the quarter onset and (2) they have not been identified as lost to follow-up, transferred, or dead by the beginning of the quarter (purple section in Table 1). For the aggregate estimates, quarter-specific person time was then calculated as follows:

$$PT_{qi} = Current*3months + New*1.5\ months - Events * 1.5\ months$$
$$PT = \sum PT_{qi}$$

Patient-level estimates of person-time are calculated by taking the time from ART initiation to either the end of the reporting time (December 31, 2005) or the date of an event.

In the example given in Table 1, nearly identical estimates of person-time and rates of death and loss to follow-up are obtained assuming a "rolling entry" scenario where patients are entered into the study population over the duration of the observation time, with no minimum amount of follow-up time required, with observation ending on December 31, 2005 (Table 1, grey columns). This occurs because patients initiating ART and obtaining an endpoint are assumed do so in a random pattern across a

quarter, so assuming patients initiating ART in a given quarter, or achieving an event during a quarter, do so at the midpoint is a reasonable assumption.

However, it is common practice in patient-level analyses to estimate rates of loss to follow-up or death through a given amount of time after ART initiation (e.g., 1 year after ART initiation, black column in Table 1). In this scenario, patients are followed up for a minimum amount of time until they reach the endpoint of interest, are censored, or achieve the outcome of interest. Rates derived from patient-level data will diverge from those derived from aggregate data in certain situations where patients are followed for a set amount of time (say, 1 year after ART initiation) and patient-level estimates of loss to follow-up and death rates through one year of ART treatment are estimated.

Table 2 presents the three different estimates of loss to follow-up and death rates (patient-level rolling entry, patient-level one-year follow-up, aggregate) and shows that in this example, the patient-level rolling and aggregate estimates are nearly identical, while the rolling-entry estimates are larger than the one-year patient-level estimates for both loss to follow-up and death. This is to be expected because, in the one-year follow-up scenario, patients who initiate ART later on in 2005 are followed past the aggregate observation closing date (December 2005), increasing the denominator without equivalent increase in the numerator because events are relatively rare.

To estimate the potential differences in our study population, the study population from the Paper 2 patient-level analysis was used to generate aggregate estimates of loss to follow-up, and death rates in the same manner described in Table 1 of this appendix. Briefly, 92,561 patients initiating ART between January 2005 and June 2009 were considered in this analysis. Quarterly estimates of the number of patients on ART at the

beginning of each quarter, the number of patients newly initiating ART during the quarter, and the number of "events" during each quarter (death, transfer, loss to follow-up) were tallied from the patient-level data to create an aggregate data set. Patient-level estimates of loss to follow-up and death rates were obtained for a "rolling entry scenario" equivalent to the grey cells in Table 1 of this appendix, and for one-year follow-up (equivalent to the black cells in Table 1). Table 3 presents these results. Similar to the simulation study presented in Tables 1 and 2, the aggregate and patient-level data provide similar estimates of the overall loss to follow-up and death rates under a "rolling entry" scenario that does not specify a minimum follow-up period or duration of follow-up time. However, the estimation of one-year loss to follow-up and death rates from the patient-level data are higher in our study population. The reason for this is because most events (loss to follow-up or death) occur within the first year after ART initiation. Restricting follow-up to one year after ART initiation results in lower person-time of observation (less than 50% of the overall person-time occurs in the first year after ART initiation in our population) without a concurrent decrease in the number of events (73% of the events occur in the first year after ART initiation).

This analysis shows that overall rates of loss to follow-up and death are lower than one-year estimates of loss to follow-up and death obtained from patient-level follow-up under the scenario experienced on our patient population. This is to be expected since the rate of loss to follow-up and death are not constant over time after ART initiation. It is therefore improper to interpret aggregate estimates of loss to follow-up and death as equivalent to patient-level estimates of loss to follow-up and death within a defined

follow-up period. However, aggregate estimates are approximately equivalent to the "rolling entry" scenario described above.

Table A4.1. Example calculations: obtaining aggregate person-time from patient-level data

	Patient-level person-time					Aggregate person-time																
						New ART initiation during quarter				Currently on ART at beginning of quarter				Event (LTF, death, transfer) during quarter				Quarter-specific person-time (months)*				
Patient	ART initiation date	Status	Status Date	Person-time (days)	1 year follow-up (days)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Person-time (days)
1	1/1/2005	D	4/1/2005	90	90	1	0	0	0	0	1	0	0	0	1	0	0	1.5	1.5	0	0	91.3
2	2/15/2005			319	365	1	0	0	0	0	1	1	1	0	0	0	0	1.5	3	3	3	319.6
3	3/31/2005	LTF	9/27/2005	180	180	1	0	0	0	0	1	1	0	0	0	1	0	1.5	3	1.5	0	182.6
4	4/1/2005			274	365	0	1	0	0	0	0	1	1	0	0	0	0	0	1.5	3	3	228.3
5	4/5/2005			270	365	0	1	0	0	0	0	1	1	0	0	0	0	0	1.5	3	3	228.3
6	4/8/2005			267	365	0	1	0	0	0	0	1	1	0	0	0	0	0	1.5	3	3	228.3
7	4/12/2005			263	365	0	1	0	0	0	0	1	1	0	0	0	0	0	1.5	3	3	228.3
8	5/1/2005			244	365	0	1	0	0	0	0	1	1	0	0	0	0	0	1.5	3	3	228.3
9	6/5/2005	T	7/5/2005	30	30	0	1	0	0	0	0	1	0	0	0	1	0	0	1.5	1.5	0	91.3
10	6/22/2005	LTF	12/19/2005	180	180	0	1	0	0	0	0	1	1	0	0	0	1	0	1.5	3	1.5	182.6
11	6/30/2005			184	365	0	1	0	0	0	0	1	1	0	0	0	0	0	1.5	3	3	228.3
12	7/5/2005			179	365	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1.5	3	137.0
13	7/15/2005			169	365	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1.5	3	137.0
14	8/5/2005			148	365	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1.5	3	137.0
15	8/30/2005			123	365	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1.5	3	137.0
16	9/30/2005			92	365	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1.5	3	137.0
17	10/15/2005			77	365	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7
18	10/31/2005	LTF	4/29/2006	61	180	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7
19	11/5/2005			56	365	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7
20	11/30/2005			31	365	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7
21	12/1/2005	T	12/31/2005	30	30	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0.0
22	12/5/2005			26	365	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7
23	12/10/2005			21	365	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7
24	12/15/2005			16	365	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7
25	12/25/2005	D	3/25/2006	6	90	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1.5	45.7

Table A4.2: Comparison between patient-level and aggregate estimates of LTF and Death rates, sample data from Table A4.1

	N LTF	N Dead	Person-time	LTF Rate (per 100 person-months)	Death Rate (per 100 person-months)
Patient-level, rolling	2	1	3,336.00	1.82	0.91
Patient-level, 1 year follow-up	3	2	7350.00	1.24	0.83
Aggregate	2	1	3,287.25	1.85	0.93

Table A4.3: Comparison between patient-level and aggregate estimates of LTF and Death rates, patient-level population from Paper 2

	N LTF	N Dead	Person-time	LTF Rate (per 100 person-months)	Death Rate (per 100 person-months)
Patient-level, rolling	19,481	5,284	150,309	12.96	3.5
Patient-level, 1 year follow-up	14,085	3,910	71,410	19.72	5.5
Aggregate	19,481	5,284	143,767	13.55	3.7

*"rolling" estimates refers to the scenario where individuals initiate ART throughout the study period, with no exclusion restrictions on minimum follow-up time

** 1 year follow-up estimates the rate 1 year after ART initiation