THE SUCCESSES OF AND BARRIERS TO REACHING AMBITIOUS HIV TREATMENT TARGETS IN RAKAI, UGANDA

by
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Abstract

Objective: The HIV treatment cascade, also referred to as the HIV care continuum, is comprised of the sequential stages of engagement in HIV medical care, from testing to diagnosis to achieving the goal of viral suppression, measured as the proportion of individuals living with HIV who are engaged at each stage. We used clinical data as well as data from the population-based Rakai Community Cohort Study (RCCS), an open HIV surveillance cohort, to characterize the HIV treatment cascade, assess the association between sexual risk behaviors and initiation of antiretroviral therapy (ART), and to explore geospatial patterns of ART treatment facility use and viral suppression, in Rakai District, Uganda.

Methods: Self-reports from the RCCS and clinical records, both collected between 2013-2016, were used to assess the proportions of HIV-positive persons in the cohort achieving each stage in the cascade (n=3,666). Next, we examined HIV risk factors based on sexual behaviors reported for the 12 months prior to the interview, including number of sex partners, non-marital sex partners, sex with partners from outside the community of residence, alcohol use before sex, consistent condom use with non-marital partners, and symptoms of genital ulcer disease. Statistical inference was based on χ^2 tests for categorical variables and modified Poisson regression to estimate prevalence risk ratios (PRRs) and 95% confidence intervals (95%CIs) of enrollment into HIV care and ART use associated with each HIV risk factor, for the whole population and stratified by sex. To explore the geospatial and demographic factors associated with accessing treatment services, we extracted data on the location and type of care services utilized by HIV-positive persons (n = 1670) accessing treatment between February 2015 and September 2016. The distance to facilities offering HIV care in the region was calculated using the open street map road network distance from households to the treatment facilities. Analysis identified independent predictors of distance traveled and, for those bypassing their nearest clinic, the probability of accessing a tertiary care facility.

Results: From September 2013 through December 2015, 3,666 HIV-positive participants were identified, of whom 98% received HIV Counseling and Testing (HCT), 74% were enrolled in HIV care, 63% had initiated ART, 92% of persons on ART were virally suppressed 12 months after initiating ART. Engagement in care and ART use were lower among men than women (enrollment in care: adjPRR 0.84, 95% CI 0.77–0.91; ART initiation: adjPRR 0.75, 95% CI 0.69–0.82), persons aged 15-24 compared with those aged 30-39 (enrollment: adjPRR 0.72, 95% CI 0.63–0.82; ART: adjPRR 0.69, 95%CI 0.60-0.80), unmarried persons (enrollment: adjPRR 0.84, 95% CI 0.71–0.99; ART adjPRR 0.80, 95% CI 0.66–0.95), and new in-migrants (enrollment: adjPRR 0.75, 95% CI 0.67–0.83; ART: adjPRR 0.76, 95% CI 0.67–0.85). We assessed the UNAIDS '90-90-90' targets to be 98%-65%-92% as of 2015, and estimate that 58% of the entire HIV-positive population was virally suppressed. Modest but statistically significant differences in several high-risk sexual behaviors were observed between those who were and were not enrolled in care or on ART. Enrollment into HIV care was lower among persons with non-marital sexual partners (adjPRR 0.92, 95% CI 0.85–1.00) compared to those without 95% CI 0.72–0.99). ART use was also lower in persons with non-marital sexual partners (adjPRR 0.88, 95% CI 0.81–0.96), persons with sexual partners outside the community (adjPRR 0.89, 95% CI 0.80–0.99), and among fisherfolk (adjPRR 0.78, 95% CI 0.64–

0.94). From February 2015 and September 2016, 1554 HIV-positive participants in the RCCS were identified, of whom 1030 (66%) had initiated ART and provided information on where they received treatment services. The median distance from households to the nearest ART facility was 3.10 km (Interquartile range, IQR, 1.65-5.05). However, we found individuals traveled significantly further, traveling a median 5.26 km for ART treatment, p<0.001, (IQR, 3.00-10.03), and 57% of patients (589/1030) chose to travel to a facility further than their nearest facility. Those with higher levels of education and wealth were more likely to travel further and to access higher level services, compare to persons with lower education and affluence. We found the majority 963/1030 (93%) on ART were virally suppressed and found no difference in the distance traveled to an ART facility between those suppressed and the unsuppressed (5.26 km vs. 5.27 km, p=0.650).

Conclusions: We documented important successes in the areas of HIV diagnoses, ART initiation, and viral suppression. However, interventions are needed to promote enrollment of hard to reach and high-risk groups like HIV-positive males, younger individuals, and in-migrants into HIV care. We found substantial heterogeneity in the distance to the nearest treatment facility; however, distance to the nearest treatment factility was not predictive of community ART coverage and found that virologic outcomes among those on ART did not vary by distance traveled for treatment. Our finding that persons with high-risk profiles were less likely to initiate ART suggests one reason why HIV epidemics in some regions have not been substantially mitigated despite scale-up of HIV treatment. Engaging these priority populations will require new resources and strategies in order to meet global targets for ART initiation, retention, and viral suppression.

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DLP	District led program
EMR	Electronic Medical Records
GPS	Global Positioning System
GUD	Genital ulcer disease
HC	Health Center
HCT	HIV counseling and testing
HIV	Human Immunodeficiency Virus
ID	Identification Number
IQR	Interquartile Range
KM	Kilometer
M&E	Monitoring and Evaluation
mL	Milliliter
MOH	Ministry of Health
NGO	Non-governmental Organization
OI	Opportunistic Infection
OpenMRS	Open Medical Record System
OSRM	Open Source Routing Machine

PEPFAR	President's Emergency Program for AIDS Relief
PRR	Prevalence Risk Ratio
RCCS	Rakai Community Cohort Study
RHSP	Rakai Health Sciences Program
UNAIDS	United Nations Progamme on HIV/AIDS
UPI	Unique Patient Identifier
VL	Viral load
WHO	World Health Organization

Chapter 1 Introduction

1.1 Overview and specific aims

The potential benefits of early HIV diagnosis can only be realized if there is successful linkage to and retention in HIV care and treatment. Effective treatment with antiretroviral therapy (ART) results in undetectable viral loads (VL)[1–3] which has benefits both at the individual level (by reducing morbidity and mortality)[4–10] and at the population level by reducing transmission[11–13]. Given these benefits of ART, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has set a '90-90-90' target by 2020 to diagnose and counsel 90% of all HIV-positive individuals, provide ART for 90% of those diagnosed as HIV-positive, and achieve sustained viral suppression for 90% of those treated[14]. This translates to 73% of all HIV-positive individuals being virally suppressed[14].

This dissertation follows the HIV treatment cascade model[15], also referred to as the HIV care continuum[16], the sequential stages of engagement in HIV medical care that people living with HIV go through from testing to diagnosis to achieving the goal of viral suppression, and shows the proportion of individuals living with HIV who are engaged at each stage. The framework provides both an individual and population-based approach to addressing the HIV epidemic, and in the literature, the terms "cascade" and "continuum" are often used interchangeably. However, some have suggested that the term continuum be used only when referring to the dynamic spectrum of HIV care engagement at an individual level, and treatment cascade be used with referring to these steps at a population level[17].

We use data from the Rakai Community Cohort Study (RCCS) and the Rakai Health Science Program (RHSP) clinical data system for the three research studies included in this dissertation. The RCCS is an ongoing longitudinal study of HIV incidence, sexual behaviors, and health service utilization in the Rakai District, Uganda. RHSP provides technical assistance to government-run clinics in the district and collects electronic clinical records on its patients including basic demographics, clinical visits and outcomes, mortality, retention, and adherence information. Together, these data provide information on HIV prevalence in the community, and on the HIV care and treatment cascade: i.e., among those who are HIV-positive, the proportion who accept their HIV results, accept entry into HIV care, accept ART once eligible, achieve HIV viral suppression, and remain in care at each step. Understanding what individual, social, or structural factors are associated with engagement in care is informative for designing and improving existing HIV prevention programs in order to reach treatment targets. Accordingly, the aims of this dissertation were to investigate these areas in Rakai, Uganda.

AIM 1: Characterize the HIV care cascade and examine differences between groups of persons living with HIV by sex, age, and population characteristics at essential steps in the continuum of care.

AIM 2: Assess the association between sexual risk behaviors and acceptance of HIV care and treatment.

AIM 3: Characterize geospatial patterns of treatment facility utilization and to test the impact travel distance has on HIV viral suppression while on ART

It is fundamental that public health programs not only quantify engagement of HIV-positive individuals along the treatment cascade but also acquire an in-depth understanding of the factors that facilitate or hinder this engagement. This understanding will provide public health programs with insights into the influences on health care-seeking behaviors of HIV-positive individuals and how these impact engagement throughout the treatment cascade.

1.2 Organization

This dissertation is organized into seven chapters. The first chapter presents an overview of the dissertation contents and its organization. The second chapter describes the relevant literature on the HIV treatment cascade and potential biases, provides an overview of HIV care delivery in Uganda, The third chapter presents a conceptual framework for the analyses and describes the data sources and unique challenges in the study setting. The next three chapters (4-6) detail the methods and results from our three primary research studies; the fourth chapter summarizes our study on the HIV care cascade among sub-populations, the fifth summarizes findings regarding sexual risk behaviors of persons who accept or decline HIV care and treatment initiation in Rakai, Uganda, and the sixth chapter summarizes findings on geospatial patterns of HIV antiretroviral therapy use and viral suppression. In chapter seven, we close with a synthesis and discussion of our results, including a discussion of the public health significance of the dissertation findings and future studies.

Chapter 2 Background

2.1 Antiretroviral Therapy for Treating and Preventing HIV

Since the advent of effective antiretroviral therapy, studies have demonstrated numerous benefits of treatment at both the individual and population level. Studies have shown that HIV transmission and progression to AIDS or death are associated with viral load (VL)[1–3], and reductions of VL through ART mitigate these outcomes through mechanisms such as the restoration and preservation of immune function, reductions in systemic inflammation and reduced incidence of opportunistic infection[4–6]. ART is the most effective tools to combat the effects of HIV.

For years, HIV experts have debated whether it is better to start ART at diagnosis or defer treatment until later in the course of disease. However, in recent years, there has been a movement toward early initiation given the potency, simplicity, and safety of current regimens, as well as the significant benefit of early therapy in terms of patient health[7,8],survival[9,10], and reduction in the risk of transmission[11–13]. WHO has advanced the timing of ART initiation, raising the threshold CD4 count for treatment from 200 in 2006[18], to 350 in 2010[19], to recommended 500 cells/mL in 2013[20]. HIV care and treatment programs globally have adopted this guidance. In addition, a recent, large trial provided support for the use of a test-and-treat strategy, in which a population is tested for HIV regularly, and those found to be positive are treated immediately, regardless of CD4 count[21]. The WHO's early-release guideline for ART initiation now recommends that treatment starts immediately upon HIV diagnosis[22].

2.2 HIV Treatment Cascade: Framework for HIV Care Engagement

The spectrum of engagement in HIV care spans from HIV acquisition to full engagement in care, receipt of antiretroviral therapy, and achievement of complete viral suppression. Figure 2.1 illustrates a conceptual framework, adapted from previous studies, describing the steps between acquiring HIV infection and engagement in medical care[23].

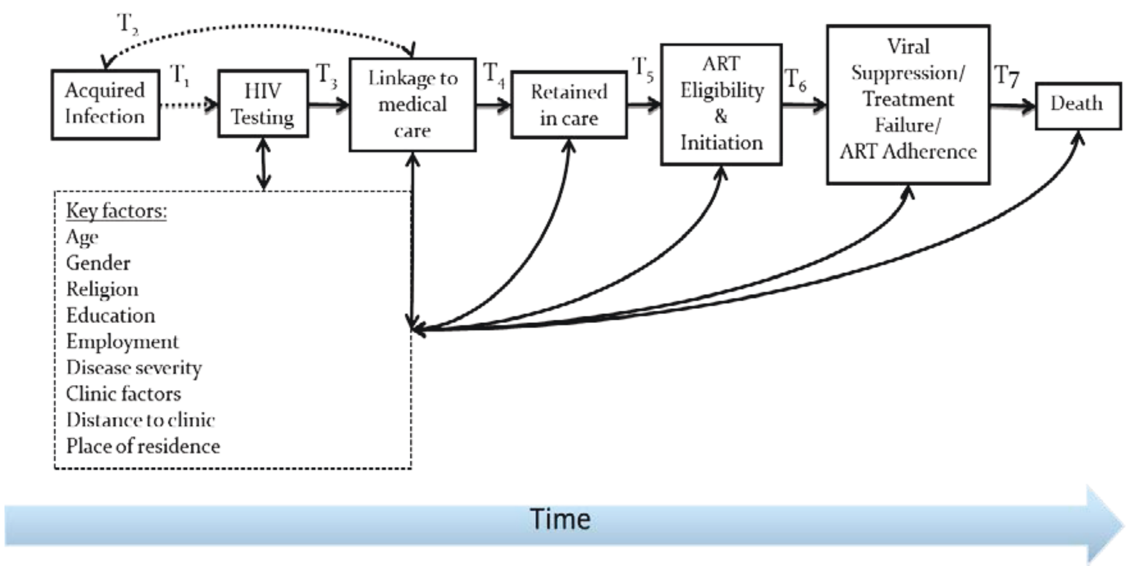

Figure 2.1 Conceptual Framework Engagement in HIV Care. (Adapted from Samet et al., AIDS, 2001).

Specific phases are labeled as time periods 1-7. The process of an HIV-positive individual presenting to care can be divided into two time periods: T1, the time between acquisition of infection and testing/diagnosis; and T2, the time between testing and presentation to care. Period T3 measures the overall delay in linkage to care. The model was expanded to include the time period between presentation to care and maintenance in care (T4); time to ART initiation (T5); time to viral suppression, treatment failure, or discontinuation of care (T6); and time to death (T7). Dates of HIV infection are not available for all persons, so dotted lines are used to represent these time periods.

Ideally, patients transition through the HIV care pathway with minimal disruptions in care; however engagement in care is complex and depends on patient attitudes and behavior, as well as health system resources and coordination. In addition, patients' transitions are bidirectional as they can move from being fully engaged in care to being lost to follow-up[16,24]. Thus, successful HIV programs need to both optimally engage and retain patients.

One useful framework for measuring HIV care engagement is the HIV treatment cascade or care continuum[15]. Beginning with the HIV-positive population, successive bars indicate the proportion in the subsequent stages of HIV diagnosis, linked to care, engaged in continuous care, effectively treated and virally suppressed (Figure 2.2). The treatment cascade how various levels of drop-offs in the early steps of the cascade can affect population rates of viral suppression. In 2011, evaluations of the care cascade for the United States estimated that only 19-28% of individuals were successfully retained and their viral load suppressed on ART[15,25]. The first, by Gardner *et al*., evaluated engagement in care in the 1.16 million people living with HIV in the United States in 2006, they estimated that 60% are not receiving regular HIV care because of lack of diagnosis of infection, inadequate linkage to care, or retention in care[15]. Importantly, the framework illustrates that improvements in a single stage would have little effect on the ultimate goal of viral suppression, underscoring that successful HIV programs require strategic planning and ongoing monitoring throughout the entire process of achieving viral suppression. The cascade can be a useful tool to support these functions by providing a framework with which to evaluate program performance, identify targets for intervention at the individual and population levels, and to provide input data for predictive models of HIV treatment implementation[26].

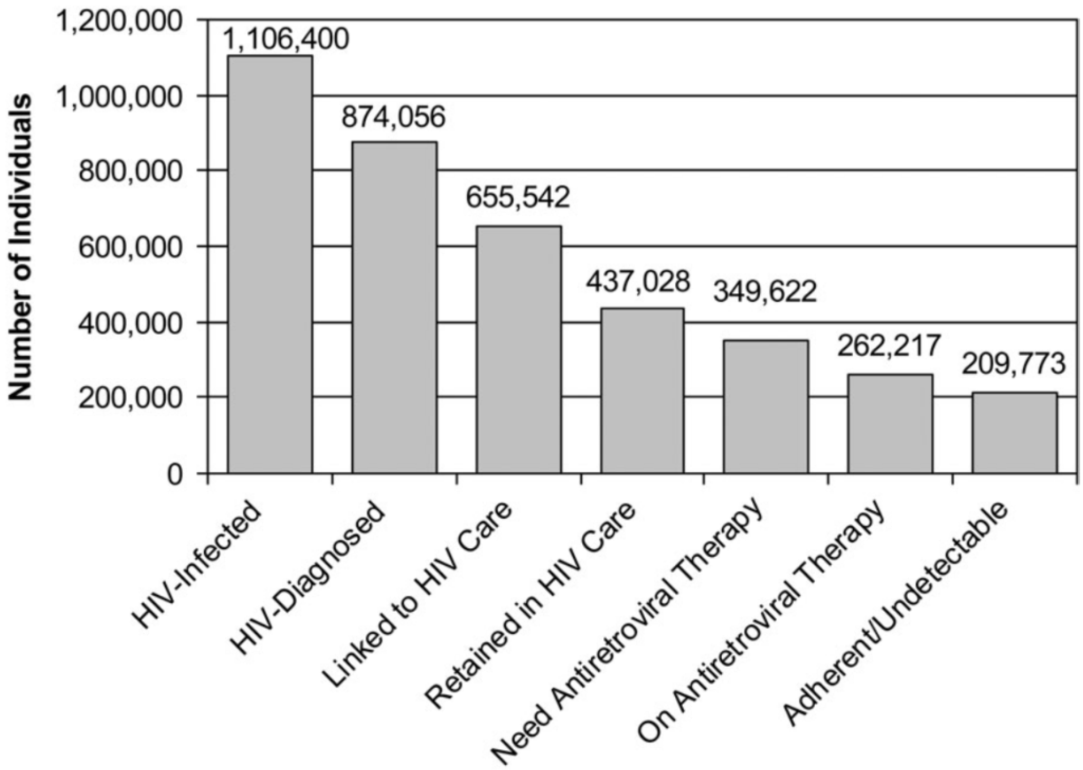

Figure 2.2 Stages of Engagement in HIV Care. The spectrum of engagement in HIV care in the United States spanning from HIV acquisition to full engagement in care, receipt of antiretroviral therapy, and achievement of complete viral suppression. (Reprinted from Gardner *et al.*, *Clinical infectious diseases*, 2011).

2.3 Variability in measurements of treatment cascade stages

There is no standard approach to defining the stages in the HIV treatment cascade, and definitions differ across settings depending on data availability and differences in data-generation[27]. Published estimates continue to employ varying definitions, resulting in incomplete alignment among reported cascades[28–30].

The first stage of the cascade is HIV diagnosis. There have been few attempts to estimate the fraction of the HIV-positive population that is undiagnosed, particularly in developing countries most severely affected by HIV[31]. National surveys the most frequent source of information on HIV counseling and testing (HCT) uptake usually only report whether individuals have been tested for HIV, and not whether they have been diagnosed HIV- positive[32]. Although many national surveys use self-reported HIV testing as a proxy for HIV status, data supporting the validity of this approach are limited. In the 2012 Kenya AIDS Indicator Survey, a nationally-representative household survey including both self-reported and serologic HIV tests, 72% of adults aged 15-64 years reported having ever been tested for HIV and women were more likely to have ever been tested than men (80% vs. 63%)[33]. However, only 47 percent of respondents who were HIV-positive on the HIV test and who reported being tested for HIV prior to the survey reported that they were HIV-positive[33]. It is important to note that there are a number of possible explanations for this finding including recent seroconversion since their last HIV test, failure to understand the test result or untruthful reporting of HIV status. However, another study from sub-Saharan Africa also suggested that HIV-positive individuals may underreport past testing[32]. They found that among all HIV-positive respondents, 40 percent of women and 36 percent of men in Malawi and 32 percent of women and 24 percent of men in Uganda said they had been tested for HIV, had received their test result, and reported that the test result was negative[34].

More consensus exists in defining linkage to care, which is typically measured as having ever attended HIV services[28]. In contrast, defining and measuring retention in care are more complex, as individuals are scheduled for visits at varying time intervals based on clinical and psychosocial factors, and patient preference[35] , and definitions of how much delay in returning for a scheduled visit is classified as a loss to follow-up or inadequate retention .

While the cascade provides a useful framework to depict gaps in the care pathway, the proportions undiagnosed or untreated people living with HIV is limited in the depiction of HIV care as a linear pathway composed of discrete stages[36]. In reality, however, the distinction between some stages may be less discrete, and movement across the stages is a dynamic, non-linear and time-dependent process[37]. For example, engagement in care is both bidirectional, as patients can be non-compliant or drop out of care at multiple points[16,24], and complex, with no standard agreed upon approach to quantify retention in care[28]. Several approaches to measuring retention in care have included recording missed visits, visit adherence and treatment gaps[28]. A comparison of six different commonly used retention measurements found that there is no one best measure of retention in care. Instead, measures should be selected based on the available data, the question of interest, and the study rationale[29].

Eligibility for ART initiation is likewise both person and setting dependent, making a measurement of this stage complex. As treatment guidelines change, ART eligibility expands, as has been recently seen when countries adopted the WHO 2013 guidelines expanding ART eligibility to persons with less than 500 CD4 cells per mL[20]. However, HIV care and treatment programs in resource-poor settings not implementing test-and-treat approaches generally rely on a so-called "deferral strategy." This approach requires that a person is diagnosed, counseled, linked to care and assessed for ART eligibility prior to treatment initiation. If an individual is found not to be eligible for ART initiation, treatment is deferred, and the patient is provided with pre-ART care, and monitored clinically and with CD4 assessments until he/she reaches eligibility[38].

The predominant cascade methodology requires successful performance of an earlier step in the cascade to be ‘‘eligible’’ for a later stage[15,27,39]. In other words, one criticism of the cascade framework is that it does not fully capture current ART programs, as it does not account for the large percentage of patients who initiate treatment at late stages of disease and were not successfully engaged in pre-ART care[40]. Another critique of this approach is that it does not allow for flexibility in patient monitoring. This is problematic as many patients who have been successfully treated for many years may not meet the operational definition for retention in care (i.e., two visits per year) and not counted as being on ART or virally suppressed in these cascades[41].

The last stage of the treatment cascade, successful treatment, and achievement of viral suppression, is often defined as a dichotomous variable, where VL below a threshold of detection, e.g., <400 copies/mL, is defined as suppressed[29,42] or based on WHO criteria, <1000 copies/mL. As with other stages of the cascade, methods differ on the inclusion restrictions for both the numerator and the denominator. One approach is only to include individuals who have a VL measurement within the specified ‘window’ period after ART initiation, for example only those on treatment for more than 6 months and less than one year. This approach can lead to varying estimates depending on whether participants who lacked a VL within the ‘window’ are included in the denominator and treated as non-suppressed[43]. An alternate approach is to use all individuals and their most recent VL measurements, which may be outside the ‘window’ period[43]. With this approach, individuals who have a detectable viral load include both those experiencing treatment failure as well as those that have newly initiated treatment. However, a strength of this approach is that it more accurately reflects the population with unsuppressed viral loads who pose a risk for onward transmission of HIV.

2.4 Challenges and biases of treatment cascade estimates

The utility of the cascade for evaluating the performance of HIV programs often comes in the ability to compare cascades by sub-populations, time, or geographic area. However, a major obstacle to constructing cascades is the availability of data[44], and differences in data sources and methods used to define the outcomes can limit the comparability and introduce biases. While the treatment cascade can be constructed and described using population-based surveys or using clinic-based monitoring data, each approach has unique challenges and limitations.

The first challenge with measuring the HIV treatment cascade is that there is no complete measure to estimate the total population living with HIV, including those who have never been tested[45], and uncertainty in the size of the denominator has downstream effects on the subsequent cascade outcomes. National HIV registries, population-based sampled data, and cohort study data have all been used to estimate or back-calculate the total population living with HIV[45,46]. On the other hand, clinical care databases in which all individuals in care are captured in a single centralized healthcare system have the advantage of allowing for direct measurement of care indicators for patients within those systems[45]. Constructing a cascade based on data from only a single population at all stages improves internal consistency and reduces the risk of biased inference regarding cascade transitions (i.e., proportion who have achieved the next stage or median times to achievement), compared with cascades constructed from multiple data sources[26]. However, in many countries patients receive care in a variety of settings where sharing or pooling of clinical data is not feasible[45]. In addition, the lack of unique patient identifiers and linked clinical data systems impedes the tracking of individuals, making the distinction between persons lost to care or transferring between clinics challenging. Further, most clinic-based monitoring systems capture only those who access services but cannot provide information about those who never enter the continuum of services.

Another challenge with measuring the HIV treatment cascade is that estimates of the number of people diagnosed may be biased by unrecognized deaths, migration out of the population, or incorrect diagnosis. A method to remove these individuals from the denominator is needed to avoid overestimating the size of the population living with diagnosed HIV and subsequently underestimating the rates of retention in care, treatment coverage, and virologic suppression[45]. Because all estimates of stage transitions are conditional on having reached the previous cascade stage, such biases may carry through to all subsequent stages[26].

An additional challenge with measuring the HIV treatment cascade is that the quality of clinic data may vary due to the lack of or suboptimal adherence to data protocols, resulting in incomplete, or inaccurate reporting[47–49]. Additionally, the completeness of laboratory reporting can be heterogeneous across systems, changing rapidly over time due to evolving assays, reporting rules and uneven implementation of electronic laboratory reporting, all of which can dramatically alter estimates of the HIV continuum with the potential for bias due to missing data[50]. Lastly, population-based surveys may be limited by sample size to perform stratified analyses critical for identification of subpopulation disparities in engagement in care[41].

2.5 HIV in Uganda and key populations

Uganda, which was among the first countries in Africa in which HIV was reported in the mid-1980s[51,52], has a mature generalized HIV epidemic. The government is credited with a national campaign to limit sexual partners, use condoms, and abstain from sex, dubbed the ABC approach, and succeeded in reducing the prevalence of HIV from a peak of about 22% in 1991 to around 5% percent in 2000[53]. This decline in HIV prevalence was likely a result of both the high pre-ART mortality and the ABC approach[54]. Subsequently, HIV prevalence increased from 6.7% in 2004-05 to 7.3% in 2011 in national serosurveys, most likely as a result of improved survival due to antiretroviral therapy, but also potentially due to increased risk behaviors[55,56]. HIV remains a significant public health problem in Uganda, with the national HIV prevalence estimated to be 7.4% among the adult population, or 1.5 million people, in 2014[57].

High-risk sub-groups within generalized epidemics can produce concentrated HIV sub-epidemics[58]; as these high-risk sub-groups, known as most-at-risk or key populations, tend to have consistently higher incidence and prevalence rates than the general population[59,60]. Currently, in Uganda, groups that have been identified as key populations include commercial sex workers, uniformed services, fishing communities, truck drivers and men who have sex with men[61]. In addition to these key populations, other sup-populations found to be of importance in Uganda include women, who carry the greater burden of HIV in sub-Saharan Africa[62–65], as well as youth[41,66,67] and migrants[68–70].

Rakai District (area ~2200 km^2, population ~518,000) is in south-central Uganda bordered to the north by Lyantonde, Lwengo and Masaka Districts, to the south by Tanzania, to the west by Isingiro and Kiruhura Districts, and to the east by Lake Victoria

(Figure 2.3). The first AIDS cases in Uganda were identified in this region, and the HIV prevalence remains among the highest in the country at ~13%[71,72]. While the prevalence, estimated among individuals aged 15-49 through the Rakai Community Cohort Study, has remained stable incidence has declined by 42% from 1.17 in 1999 to 0.66/100 person-years in 2016[73].

About 1.2 million people in Uganda directly depend on fisheries industry as their main source of income[74] and the Rakai district has a large population of fisherfolk, fishermen and women who earn their living by fishing[75,76].

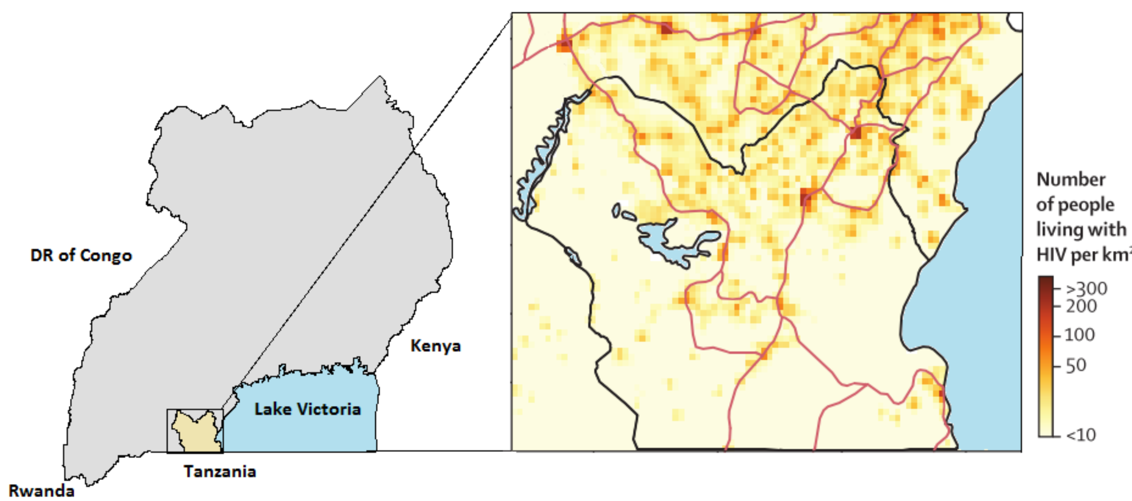

Figure 2.3 Rakai District, Uganda. Rakai District (area ~2200 km^2, population ~518,000) is in south-central Uganda and bordered to the north by Lyantonde, Lwengo, and Masaka Districts, to the south by Tanzania, to the west by Isingiro and Kiruhura Districts, and to the east by Lake Victoria. Interpolated map of the number of people living with HIV 15–49 years in the Rakai region (1 km² resolution). (Reprinted from Chang and Grabowski *et al*., *Lancet HIV*, 2016).

2.6 The Ugandan Health Care System and management of HIV

The Ugandan health care system is organized into two sectors: public and private. While the government operates a national network of public hospitals and clinics, individuals can also access a variety of private providers, including nonprofit hospitals and clinics run by non-governmental organizations (NGO), as well as some for-profit clinics and hospitals[77].

Antiretroviral drugs first became available in Uganda in 2004 through the President's Emergency Fund for AIDS Relief (PEPFAR) and the Ugandan Ministry of Health[78]. Fixed-dose combination ART was initially provided in Rakai District primarily by a non-governmental entity; in this case, the Rakai Health Sciences Program (RHSP). RHSP began providing ART through mobile clinics in 18 non-overlapping catchment areas throughout the district. The mobile clinic model consisted of medical staff traveling from a central facility to designated government health clinics in each catchment area biweekly. Beginning in January 2010, RHSP switched to a static clinic model, establishing 14 Suubi (Hope) clinics to reduce costs of service delivery and increase service access through additional facility hours. Since 2013, the Ugandan PEPFAR program has adopted a policy of increasing government ownership of HIV care and treatment. As a result, HIV services in Rakai, including ART, are provided by Ministry of Health personnel within government clinics with RHSP providing training and oversight through the so-called "District-Led Programming (DLP)" initiative[78].

The public government health care system in Uganda is organized into several levels, and facilities are categorized by the area served and services provided, with each tier providing preventative, curative or rehabilitative services or a combination of the three. The levels are as follows: a) Health Centre II (HC 2) serve parishes with a population ~5,000 and provide outpatient, antenatal, immunization, outreach services and ART primarily for prevention of mother-to-child transmission; b) Health Centre III (HC 3) serve sub-counties and in addition provide fixed-dose combination ART and outpatient care; c) Health Centre IV (HC 4) serve sub-districts and in addition provide surgery, supervision of the lower HCs, data collection and health service planning[77].

Currently, all HIV-positive persons enrolled in HIV care are offered a CD4 test. Eligible individuals are offered ART and monitored clinically, with both CD4 and viral loads[79]. In addition, all-HIV positive persons are provided a basic care package of cotrimoxazole for opportunistic infection prophylaxis, bed nets for malaria prevention, and clean water containers with hypochlorite for prevention of diarrhea[80]. The Ugandan Ministry of health has made an aggressive treatment scale-up effort, including most recently by adopting the 2013 WHO ART guidelines[79], the criteria for ART initiation were raised to a CD4 cell count $\leq$500 cells/mL (from $\leq$350 cells/mL) for the general population and a test-and-treat approach was adopted for pregnant women, HIV-discordant couples, and most-at-risk populations in fishing communities or commercial sex workers[79]. The first-line ART regimen based on WHO and PEPFAR guidelines is one non-nucleoside reverse transcriptase inhibitor (NNRTI, nevirapine or efavirenz) and two nucleoside reverse transcriptase inhibitors (NRTI), most commonly tenofovir or lamivudine)[79]. Second-line regimens most often consist of a boosted protease inhibitor (PI, most commonly lopinavir) with two drugs in the NRTI class[79]. Patients typically receive routine viral load testing, and CD4 counts every 24 to 48 weeks for clinical monitoring[79].

Although it is estimated that 72% of the households in Uganda live within 5km of a health facility; an evaluation of the health sector performance found utilization to be limited due to poor infrastructure, lack of medicines and other supplies, shortage of human resources in the public sector, low salaries, lack of accommodation at health facilities constrain access to quality service delivery[77]. In Uganda, user fees in public health facilities were abolished in 2001; however, they remain in private wings of public hospitals[81]. It is estimated that nationwide enrollment on ART increased from 570,373 in 2013 to 750,896 in 2014[60]. Overall, an estimated 47% of those eligible for ART are currently being treated[56,82].

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Chapter 3 Methods

3.1 Conceptual Framework

The analytic framework (Figure 3.1) used for this research was developed through previous studies in Africa and resource-limited settings[1,2] and draws from established theory, specifically the socio-ecological model[3,4]and the behavioral model of health services use[5].The socio-ecological framework suggests that individuals are dynamic and adapt their behavior (i.e., to engage or disengage with health services) to their social environment and individuals make decisions based on information (e.g. knowledge of the benefits of treatment), influence, and interactions through local social networks, relationships, and institutions[4]. Behavior is influenced by structural factors such as treatment policies, social factors such as partners' use of health services, and program factors such as distance to and quality of care at facilities. Further, social structures and processes are shaped by the collective behavior of individuals, which likely influence each other and shift over time[4]. In addition, the behavioral model posits that usage of health services is determined by three dynamics: predisposing factors (e.g., gender, age), enabling factors (e.g., attitudes and beliefs towards treatment) , and need(e.g., symptoms)[5]. Studies have identified asymptomatic HIV[6], perceptions of disease severity and susceptibility[7] as reasons for failure to utilize health care. Stigma[8], social support[9], as well as perceived barriers to staying on treatment[1] as reasons for failure to utilize health care. In addition, inconvenient clinic hours[8], long lines within clinics[8], and disrespectful treatment from HIV care providers or staff[8,10,11].

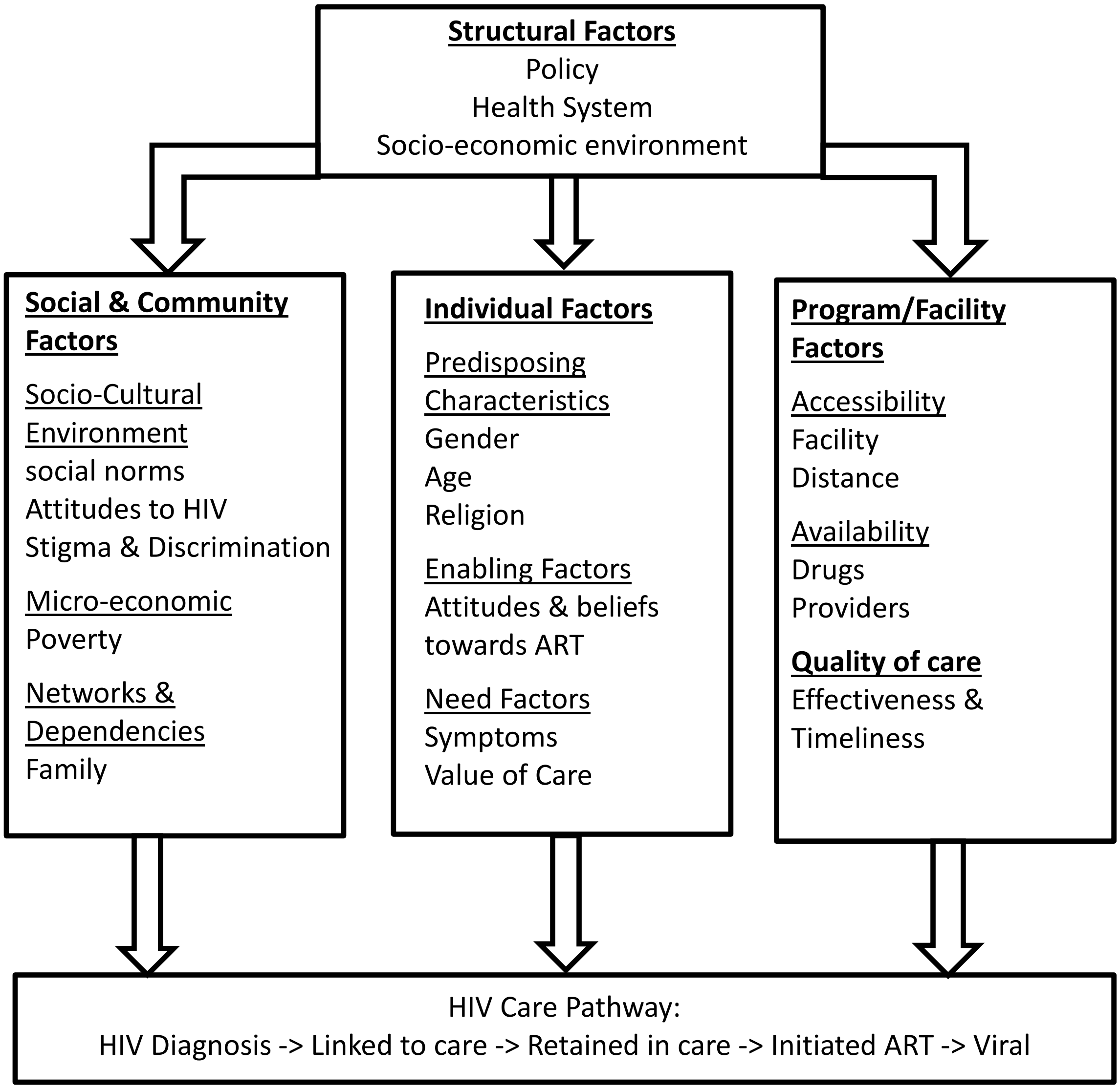

Figure 3.1 Socio-Ecological Framework. Adapted from the social-ecological framework by Roura *et al*., 2009

HIV does not affect a population homogeneously, and factors associated with disparities in HIV incidence may also be associated with disparities in care; subgroups share specific behaviors, and they experience a variety of societal barriers, which may impact how HIV care is both accessed and accepted[12]. Although women carry the greater burden of HIV in sub-Saharan Africa[13–16] studies document lower health care utilization by men in African settings[17–23]. Differences in use of health care may be related to gender-role expectations, traditional perceptions of “masculinity,” differences in symptom perception and health knowledge, and connectedness to social networks which influence symptom interpretation and referral to care[24,25]. In addition, several studies in sub-Saharan Africa have shown that younger age was associated with lower engagement in care[26,21,27], and one reason may be that HIV-positive youth make healthcare decisions for themselves for the first time, often without sufficient knowledge of the importance of sustained engagement with healthcare systems. There is also a growing body of evidence from Uganda, and other sub-Saharan African countries suggesting that fishing communities contribute disproportionately to the national HIV burden, and are at greater risk of infection than the general population, and facilitate HIV transmission to the general population[28–32]. Fishing communities along Lake Victoria have a complex set of factors including poor housing, infrastructure and highly mobile populations[33–35] resulting in high HIV prevalence and hotspots for ongoing transmission[36–39]. Unlike general populations, fishing communities tend to be socially marginalized and often stigmatized. Fishing communities are characterized by a high presence of bars, lodges and entertainment halls, transactional sex (i.e. sex for money and sex for fish) activities, high alcohol consumption and multiple sexual partnerships[28,34,40–42] , but very limited access to health services. Fisherfolk tends to be mobile in search for better fish yields[43], and the daily risk of drowning with immediate death appears to be a bigger concern than the risk of infection with HIV[28].

This dissertation focuses primarily on individual and program factors in order to identify barriers and facilitators to progression through HIV care pathway. Guided by the published literature, we identified key disproportionately affected communities and populations. In our analysis, we performed multiple stratifications, by sex, age, migration status, and among residents of fishing communities along Lake Victoria to explore its heterogeneity and factors associated with engagement in care.

3.2 Description of data sources

The aims of this dissertation were accomplished using data from the Rakai Community Cohort Study (RCCS) and the Rakai Health Science Program (RHSP) clinical data system. The Rakai Community Cohort Study (RCCS) is a well-characterized population-based HIV surveillance cohort in and around the Rakai District, Uganda. All HIV-positive persons identified via the RCCS are referred for care and treatment. Given the free services, the majority of patients in the RCCS use RHSP or Ministry of Health clinics. In addition, RHSP provides technical assistance to government-run clinics in the district, such as data management of electronic clinical records on patients for clinical management, and program monitoring and evaluation purposes.

Methods for the RCCS have been described in detail elsewhere[44]. Briefly, the RCCS is a longitudinal population cohort of approximately 17,000 persons aged 15-49 years residing in 41 agrarian, trading, and fishing communities in the region of Rakai District, south-central Uganda (Appendix Figure 1). RCCS communities are largely representative of rural Uganda (HIV prevalence is ~14% in trading communities, 12% in agrarian communities and ~42% in high-risk fishing communities[39]. Each RCCS survey round occurring every 12–18 months has three activities: 1) census of all households and household residents in the study communities, 2) structured interviews with all consenting newly enrolled and continuing cohort participants, and 3) collection and testing biologic samples of all consenting participants. The RCCS defines households as a group of persons who sleep under one roof and eat communal meals. The RCCS survey collects information on socio-demographic characteristics, health, sexual behaviors, and use of health services (including testing and treatment) using a standardized questionnaire administered by trained same-sex interviewers in central locations using the local language, Luganda. Data obtained on sexual behaviors includes numbers of partners in the past year and lifetime, relationships with partners (marital, non-marital), the location of partners (inside or outside the community), partner characteristics and partner-specific condom use and coital frequency. HIV serostatus is assessed by two enzyme immunoassays, with Western blot confirmation of discordant enzyme immunoassays and for all HIV seroconverters. In addition, data is collected with regard to HCT, long-term medication use including ART and opportunistic infection prophylaxis. All RCCS participants provide written informed consent at enrollment and follow-up. While RCCS has relatively high participation rates compared to other African population-based cohorts, there is substantial mobility which reduces participation and follow-up[45,46]. Between 25-30% of residents in these communities are new in-migrants in any given year, and about 15-20% of prior residents have out-migrated. The mean participation rate among all eligible persons censused is 64% and does not vary substantially between surveys (range: 59-67%), and among those present at the time of the survey, participation rates have steadily increased from 74% to 98%[47].

HIV care in Uganda is monitored through a combination of record keeping tools. Each clinic, hospital and research program has its own means of record keeping, whether paper, electronic or a combination of the two. Regardless of the system, maintaining accurate health records in Uganda can be complicated by a number of factors. Record keeping forms themselves are often completed by hand, and if an electronic system exists, the data are later entered into the system[48]. Paper records are low cost but subject to errors as a result of a lack of data standards (which limit the ability to share data across systems), incomplete reporting and illegible handwriting. They are also difficult to search, sometimes resulting in patient care errors or inadequate application of previous clinical history in decision-making[48]. These paper records also run the risk of being misplaced or destroyed resulting in incomplete patient data[49]. Nevertheless, the use of paper records still persists.

In an effort to modernize its systems and promote uniformity, Uganda has adopted the use of an open source Electronic Medical Record System (OpenMRS)[50]. When a patient is diagnosed with HIV, they are given a patient identification number, a patient appointment card, and a comprehensive care card (also known as the 'Blue Card', Appendix Figure 2) which is updated each time the patient visits the clinic. The OpenMRS was developed by the Regenstrief Institute and Partners in Health to help manage HIV patient care in low-resource settings and to standardize data across settings[51]. However, language translation, reliable electricity, infrastructural funding, and staffing remain challenges to implementing the system[52–55].

This system presents a number of challenges, including incomplete or inaccurate transcription of data between paper and electronic records, patients may not bring their appointment card to every visit, and non-HIV related visits are not captured in this system – all of which can result in incorrect or incomplete data.

An additional challenge is the lack of a universal Patient Identifier. While the patient identification number is unique to the individual clinic, it is not unique throughout the country. Further complicating unique identification, personal attributes (name, age, date of birth, and address) are often not accurate or consistently recorded and are often entered in different formats[56]. First, many patients in rural areas do not know their exact month or date of birth; indeed, in some cases, they only know the year. Next, when street names and/or numbers are not present, the nearest health care facility or landmark is often used to identify a patient's "address."

3.3 Unique data and challenges in this setting

Finally, record linkage, the process of combining records for the same individual contained in two distinct databases[57], is a challenge in the absence of a unique patient identifier. There are three methods used for records linkage of electronic databases: matching-merging, deterministic records linkage, and probabilistic records linkage[57]. Match-merging links records in two files using an exact match of a single unique identifier, and is used where data originate from the same system/agency, or in databases that have a reliable, common identifying numbers (e.g., social security number). Deterministic and probabilistic records linkage methods are used to link records in databases that lack a common unique identifying number and combine various identifying variables to generate a unique identification key[57].

In our study setting, we found records linkage to be challenging because of the large degree of missing information and data entry errors produced falsely matched records. In addition, probabilistic records linkage was problematic because personal attribute keys (name, age, date of birth, address) are not unique to the individual, change over time and can be entered into different systems in different formats. For example, the same individual may at times provide their first name/religious name translated in English and at other times translated in Luganda (e.g. John/Yoana, Charles/Kaloli, Mary/Mere, Bette/Besi). The use of titles posed an additional challenge in our study setting, as they are commonly used but records rarely capture titles as a unique attribute and are recorded incorrectly as first names, middle names, or surnames. In central Uganda titles can also change over time, for example, if a woman becomes the mother of twins she is given the title ‘Nnalongo’, making it challenging to match records for the same individual over time.

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Chapter 4 Human immunodeficiency virus care cascade among sub-populations in Rakai, Uganda.

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4.1 Abstract

Objective: To assess progress towards the UNAIDS targets of HIV counselling and testing (HCT) among 90% of persons living with HIV, 90% enrollment into HIV care/antiretroviral treatment (ART), and 90% virally suppressed among those on ART, by examining the HIV care cascade in the population-based Rakai Community Cohort Study (RCCS) in rural Uganda.

Methods: Self-reports and clinical records were used to assess the proportion achieving each stage in the cascade. The ART initiation criterion was <500 CD4 cells/mL. Statistical inference based on a χ^2 test for categorical variables and modified Poisson regression were used to estimate prevalence risk ratios (PRRs) and 95% confidence interval (CI) in stages of the cascade.

Results: From September 2013 through December 2015, 3,666 HIV-positive participants were identified in the RCCS, of whom 98% received HCT, 74% were enrolled in HIV care, and 63% had initiated ART of whom 92% were virally suppressed after 12 months on ART. Engagement in care was lower among men than women (in care: adjPRR 0.84, 95% CI 0.77–0.91; on ART : adjPRR 0.75, 95% CI 0.69–0.82), persons aged 15-24 compared to those aged 30-39 (care: adjPRR 0.72, 95% CI 0.63–0.82; ART: adjPRR

0.69, 95%CI 0.60-0.80), unmarried persons (care: adjPRR 0.84, 95% CI 0.71–0.99; ART adjPRR 0.80, 95% CI 0.66–0.95), and new in-migrants (care: adjPRR 0.75, 95% CI 0.67–0.83; ART: adjPRR 0.76, 95% CI 0.67–0.85). We achieved 98-65-92 towards the UNAIDS '90-90-90' targets, and estimate that 58% of the entire HIV-positive population was virally suppressed.

Conclusions: We achieved over 90% in both HCT and viral suppression among ART users, but only 65% in enrollment in care/ART stage, due to an ART eligibility criterion of < 500 CD4 cells/mL, and suboptimal entry into care among men, younger individuals, and in-migrants. Interventions are needed to increase enrollment in HIV care.

Key Words: HIV, antiretroviral, HIV care cascade, Rakai, Uganda

4.2 Introduction

Through viral suppression, effective antiretroviral therapy (ART) prevents progression to AIDS[1–3] and death [4,5], and substantially reduces HIV transmission[6,7], thus helping to curtail the HIV epidemic [8,9]. Given these benefits of ART, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has set a '90-90-90' target by 2020 to diagnose and counsel 90% of all HIV-positive individuals, provide ART for 90% of those diagnosed as HIV-positive, and achieve sustained viral suppression for 90% of those treated. This translates to 73% of all HIV-positive individuals being virally suppressed[10].

Reaching the UNAIDS targets requires early diagnosis, effective treatment, and maintaining patients in care[11–13]. However, there is growing evidence that, even among HIV-positive individuals who know their status, substantial proportions do not enroll into HIV care and treatment programs. Delays in diagnosis and entry into care lead to late presentation for ART, with increased risks of HIV-related morbidity and mortality and continued viral transmission[14]. In addition, patients who enroll in HIV care are sometimes non-adherent and do not achieve viral suppression, or are not retained in care[15].

Gardner and colleagues described levels of engagement in HIV care, ranging from 'unaware of HIV infection' to 'fully engaged in HIV care with suppressed viral load, ' i.e., the HIV "care cascade" framework[16]. The framework provides a population-based approach to program monitoring and highlights opportunities for intervention. The Rakai Community Cohort Study (RCCS), a large and long-standing population-based cohort, offers a unique opportunity to study select stages of the HIV care cascade in a rural East African population. Most HIV care programs are clinic-based and do not have population-based data with which to determine the proportion of HIV-positive individuals or selected subgroups who do or do not access care. We assessed the spectrum of engagement in care and examined differences between sub-groups of HIV-positive individuals enrolled in the Rakai Community Cohort Study in Rakai Uganda.

4.3 Methods

Study Population

The study population included HIV-positive residents of the region enrolled in the Rakai Community Cohort Study (RCCS) between September 2013 and December 2015. The RCCS is a longitudinal population cohort of approximately 17,000 persons aged 15-49 years conducted by the Rakai Health Sciences Program (RHSP). The RCCS includes 41 agrarian, trading, and fishing communities in the region of Rakai District, south-central Uganda. RCCS communities are representative of rural Uganda (HIV prevalence is ~14% in trading communities, 12% in agrarian communities and ~42% in high-risk fishing communities [17].

At approximately 18 month intervals, structured confidential RCCS interviews are conducted in Luganda, the local language, by trained same-sex interviewers, in order to collect information on sociodemographic characteristics, health (including the use of HIV care and ART), and sexual risk behaviors. Prior to the interview, pretest counseling and HIV testing are offered free of charge using a validated three rapid test algorithm[18,19], and participant who consents to receive their HIV results receive post-test counseling by on-site counselors.

The RHSP is also a US President's Emergency Plan for AIDS Relief (PEPFAR) implementer, providing HIV counseling and testing (HCT), pre-ART care and ART. Beginning in September 2013 RHSP transitioned from directly delivering care in 19 government health facilities to Ministry of Health (MOH) led the delivery of services (District Lead Programming - DLP) with RHSP assistance. HIV care is provided by

MOH personnel, with supervisory and monitoring support from the RHSP. RHSP staff also collect detailed data to link clinic patients to the RCCS survey participants.

HIV-positive persons identified via the RCCS are referred for care and treatment to the nearest DLP clinic. All RCCS communities are within an hour's walk of a clinic, the majority being within half hour by foot. In the clinics, pre-ART HIV care consists of cotrimoxazole for opportunistic infection prophylaxis, bed nets for malaria prevention, and clean water vessels with hypochlorite to prevent diarrhea, positive prevention education, reproductive health services and treatment of sexually transmitted infections. Six monthly CD4+ cell count monitoring is used to assess ART eligibility. Since January 2014 the criteria for ART initiation were raised to a CD4 cell count ≤500 cells/mL (from ≤350 cells/mL) for the general population, and test and treat for most-at-risk populations in fishing communities[20]. First-line ART consists of standard three-drug regimens approved by the Uganda MOH. HIV-positive individuals on ART are monitored clinically and via six monthly CD4+ cell counts and HIV viral load assays. However, the viral load testing is conducted at a central national laboratory, and there have been delays in the return of results; thus, viral load measurements 12 months after ART initiation were only available for a fraction of ART-patients (20%, 366/1850).

The study was reviewed and approved by the Ugandan Virus Research Institute's Scientific and Ethics Committee, the Uganda Council on Science and Technology, and Western Institutional Review Board, Olympia, WA. Study participants provided written informed consent at each RCCS visit; the consent included an agreement to link participants' RCCS survey results to their clinical data.

Data sources

For this analysis, we linked two longitudinal data sources: the RCCS survey and surveillance data maintained by RHSP and the electronic RHSP clinical data system which uses the Open Medical Record System (OpenMRS) an open source electronic health record[21]. The RHSP clinical data system is derived from the local Ministry of Health clinic-based HIV treatment and care information system, which contains data for all patients enrolled in either pre-ART or ART in each of the 19 clinics within the Rakai district. We linked the OpenMRS data at the individual level to the data in the RCCS study system by using the laboratory identification number utilized in RHSP supported clinics. Together, these data provide information on HIV prevalence in the community, and on the HIV care cascade. The RCCS ascertains the proportion of HIV-positive individuals who accept HCT from RCCS counselors and also collects self-reported data on receipt of HCT from the RCCS or other providers, engagement in pre-ART care and receipt of cotrimoxazole, and use of ART. HIV care status was also assessed from clinic-based patient records. Clinic data included the date of visit; cotrimoxazole and ART dispensed; blood samples for CD4+ cell counts and HIV viral load testing; patient health status and laboratory results when available. Mortality and outmigration prior to December 2015 were ascertained using both the clinical and RCCS study records and individuals who died or out-migrated were removed from the population at risk denominator.

HIV Care Cascade Outcomes

Four stages of the HIV care cascade were included in our framework:

- Awareness of positive HIV status was defined as having received HCT test results through the RCCS counselors and/or self-reported receipt of HCT at a time point after their first positive test identified through the RCCS.
- Enrollment in HIV care was defined as completing at least one clinic visit and/or self-reported use of cotrimoxazole or ART.
- ART status was defined by having a clinically-confirmed ART initiation date and/or self-reported use of ART.
- Viral suppression was defined as a viral load ≤ 1000 copies/mL 12 months after initiation of ART per WHO recommendations[22]. Since viral load testing was not available for participants who self-reported ART from other HIV care providers, the proportion of participants who were virally suppressed was estimated among ART recipients with a viral load measurement 12 months after ART initiation based on RHSP and MOH clinic records.

Statistical Analysis

Participants were categorized into the cascade categories described above. The proportion of HIV-positive persons achieving each stage in the cascade was calculated, and statistical inference was based on a χ^2 test for categorical variables. We also used modified Poisson regression to estimate prevalence risk ratios (PRRs) and 95% confidence intervals (95%CIs) of enrollment into care and initiation of ART. Covariates associated with enrollment into care and initiation of ART in the bivariate analyses with p values <0.05 and potential confounders identified in the literature were included in the multivariable models. In a sensitivity analysis of viral suppression, we used inverse probability weighting to account for potential selection bias associated with having a viral load measurement 12 months after ART initiation. Inverse probability weights were constructed based on established methods[23] using a logistic regression model and data on the age, education level, occupation, socio-economic status, community type, and migration status of participants with and without a viral load measurement 12 months after ART initiation. Weighted PRRs were estimated using Poisson regression assuming independence between individual participant observations and conditional on observed covariates. Migrants were identified through the RCCS community census and defined as persons who moved from another community regardless of distance traveled. For classification of socioeconomic status, we used a household wealth index, based on the building materials of the respondent's home[24]. All statistical analyses were performed in the R statistical software (V3.2.5), and the inverse probability weighted analysis was done using the survey package.

4.4 Results

From September 2013 through December 2015, a total of 3,666 HIV-positive participants were identified in the Rakai Community Cohort (Table 4.1). Sixty-three percent (2308/3666) of HIV-positive participants were female. The median age of all HIV-positive participants was 33 years (Interquartile range, IQR, 27–38). Fifty-nine percent (2166/3666) were currently married, 88% (3207/3666) were Christian, and 92% (3367/3666) had at least some primary education.

Figure 4.1 and Table 4.2 shows the HIV care cascade by participant characteristics. Ninety-eight percent (3577/3666) of all HIV-positive participants were aware of their status; 92% (3386/3666) had consented to and received HIV test counseling, and 5% (191/3666) self-reported receiving their HIV test results and were thus aware of their status. Seventy-four percent (2729/3666) were enrolled in HIV care, and 63% (2312/3666) had initiated ART. We found that 76% (2729/3577) of those who knew their results were in care; the higher rate of those in care compared to those on ART was due in part to the CD4 initiation criteria during this period (CD4 <500 cells/mL). Among 1288 persons who had CD4 measurements available, 96% (1143/1186) of those found to be eligible, given the criteria at the time, were on ART. Among 366 persons who had a viral load measurement 12 months after initiating ART, 92% (336) had a suppressed viral load. Extrapolating to the whole population of HIV-positive RCCS participants, we estimate that 58% (2124/3666) of the overall population of HIV-positive participants were virally suppressed. The inverse probability weighted estimate of viral suppression was 57%.

There was no significant difference by sex in the receipt of HIV test results (p=0.658), but there were significantly lower proportions of males than females in every subsequent stage of the HIV care cascade (p<0.000, Table 4.2). Individuals aged 15-24 were less likely to be aware of their HIV status (p=0.033), to be enrolled in care (p<0.000), on ART (p<0.000) and to have a suppressed viral load (p<0.000), compared to HIV-positive persons aged 30-39 years. In addition, persons who had in-migrated were less likely to be aware of their HIV status (p=0.019), to be enrolled in care (p<0.000), on ART (p<0.000) and less likely to have a suppressed viral load (p<0.000) than long-term residents. We found that the majority (85% [2312/2729]) of those enrolled in care had initiated ART; initiation was 83% [1076/1298] in fishing communities receiving test and treat, which was similar to 86% [680/793] in agrarian communities, and 87% [556/638] in trading communities in which ART was initiated at a CD4 count <500 cells/mL. Despite the fact that fishing community populations were offered ART at the time of diagnosis, we found the same disparities for entry into care and ART initiation by age, sex, marital status, and migration status (Table 4.5).

Table 4.3 shows the unadjusted and adjusted PRR of enrollment into care for all participants. Men were less likely to be enrolled in care compared with women (adjPRR 0.84, 95% CI 0.77–0.91). Enrollment into care by HIV-positive participants aged 15-24 was significantly lower than among older individuals aged 30-39 (adjPRR 0.72, 95% CI 0.63 -0.82). Never married HIV-positive participants, were less likely to be enrolled in care compared with married individuals (adjPRR 0.84, 95% CI 0.71–0.99), and in-migrants had lower enrollment in care than long-term residents (adjPRR 0.75, 95% CI 0.67–0.83). There was no difference in enrollment in care in trading communities (adjPRR 0.98, 95% CI 0.88–1.09) or in fishing communities receiving test and treat (adjPRR 1.08, 95% CI 0.98–1.18) compared to agrarian communities.

Table 4.4 shows the unadjusted and adjusted PRR of initiating ART. Men were less likely to be on ART compared with women (adjPRR 0.75, 95% CI 0.69–0.82). ART use was lower in HIV-positive participants aged 15-24 than those aged 30-39 (adjPRR 0.69, 95% CI 0.60-0.80). Never married HIV-positive participants were less likely to be on ART than married persons (adjPRR 0.80, 95% CI 0.66–0.95), and ART use was lower among in-migrants than long-term residents (adjPRR 0.76, 95% CI 0.67–0.85). There were no differences in ART initiation in trading communities (adjPRR 1.00, 95% CI 0.89–1.12) or fishing communities receiving test and treat (adjPRR 1.00, 95% CI 0.96–1.17) compared to agrarian communities.

We found the UNAIDS ’90-90-90’ treatment targets to be 98-65-92: among HIV-positive RCCS 98% (3577/3666) received HCT, 65% (2312/3577) of HIV-positive participants diagnosed had initiated ART, and 92% (336/366) on ART who had a viral load measurement were virally suppressed at 12 months. We found the ’90-90-90’ treatment targets to be 98-69-93 for women and 97-57-89 for men.

4.5 Discussion

Using the HIV care cascade to identify gaps and opportunities for quality improvement is important for program evaluation. Most HIV care programs are clinic-based and do not have population-based data with which to determine the proportion of the general population who do or do not access care. In contrast, the Rakai Program provides information on patient-level factors affecting HIV care utilization. Our results indicate disparities in engagement in HIV care among several sub-populations.

Diagnosis and receipt of HCT were high as persons in the RCCS are offered immediate HIV results based on a rapid test algorithm. The high uptake of HCT in this population was likely due to the community-based HIV testing strategy, and ongoing health education which strongly recommends receipt of results. However, underutilization of HIV services remains a substantial problem in this setting, despite the availability of free services in close geographic proximity. When comparing our findings to a recent analyses of the HIV care cascade in the Rwanda, we found lower rates of enrollment into care (76% vs. 86%), but higher rates of ART initiation among those enrolled (85% vs. 63%), and higher rates of viral suppression among those who were retained in care (92% vs. 82%)[25]. The majority of persons enrolled in care had initiated ART, and this was similar in communities using a CD4 cell count $\leq$500 for ART initiation as well as in fishing communities using test and treat. These findings are supported by the recent results of the ANRS 12249 treatment as prevention trial that found delayed enrollment into care reduced the potential benefit of early ART initiation[26] suggesting that implementing the new 2015 WHO guidelines, recommending universal access to ART regardless of CD4 count, may not be effective in increasing ART coverage. As treatment for all is implemented in Sub-Saharan Africa, programs will need to focus on enrollment into care the most critical area in the cascade.

Consistent with other studies, we found that men had lower engagement in care than women[27–29] and that younger age was associated with lower engagement in care[27,29], which indicate a need to target interventions for these subpopulations. The lower ART initiation among youth could be a function of earlier stage infection, and lower rates of ART eligibility. However, we found the same disparities by age in the fishing communities where ART eligibility is based on test and treat. The finding that that new in-migrants underutilized care is corroborated with other studies[30–32]. However, it is unclear whether migrants are care-naïve, or whether their care and treatment were interrupted by their migration. Nevertheless, there is a need for interventions to effectively link new in-migrants with HIV care and treatment. These findings support the need for rigorous implementation science, and qualitative studies to discover the underlying reasons why some subpopulations are at higher risk of not linking to care than others and to better understand barriers of service use within these subgroups.

This study has several limitations. First, participants in the cohort might not be fully representative of the regional HIV-positive population. However, the distribution of behaviors in the RCCS is consistent with rates from the Uganda National HIV Serosurvey and the Uganda Demographic and Health Survey[33–36] and participation rates in this study were comparable to similar community cohorts in Africa[37]. The proportion of participants who sought care at other facilities or failed to report care to avoid stigma is not known. In addition, previous studies have shown conflicting results regarding the accuracy of self-reported utilization of health care among HIV-positive individuals[38–41].

However, the use of a combination of data sources is the most effective method for measuring care outcomes[42–44]. Thus the use of both clinic-based records and self-reported information from RCCS surveys likely reduced measurement error. We used self-reported use of ART, but a previous study of self-reported ART use validated by detection of plasma antiretroviral drugs in this population found a high specificity (99%) and sensitivity (76%) for self-reported ART use[45]. Missing data on viral loads among patients 12 months after ART initiation was a further limitation. This was due to programmatic delays in return of results, so we extrapolated available plasma viral load data to the population on ART. Nevertheless, inverse probability weighted analyses to adjust for differences between patients with and without viral load results suggested that this extrapolation was unbiased.

In conclusion, in the four areas of the HIV care cascade we assessed, 98% were aware of their HIV status, however, the remaining three areas were below global targets, likely due to both an ART eligibility criterion of <500 CD4 cells/mL, and suboptimal entry into overall viral suppression in our cohort was below global goals and identified important differences in engagement in HIV care for several sub-populations. Interventions are needed to promote enrollment of HIV-positive males, younger individuals, and in-migrants into HIV care which will require new resources and strategies to meet global targets for ART initiation, retention, and viral suppression.

Table 4.1 Characteristics of 3,666 HIV-positive persons enrolled in the Rakai Community Cohort Study, December 2015

Characteristic	N	(%)
Total	3666	(100.0)
Female	2308	(63.0)
Male	1358	(37.0)
Age, Yrs.‡	33	(27-38)
15-24	542	(14.8)
25-29	776	(21.2)
30-39	1611	(43.9)
40+	737	(20.1)
Marital status		
Married	2166	(59.1)
Never married	282	(7.7)
Previously married	1218	(33.2)
Religion		
Christian	3207	(87.5)
Muslim	429	(11.7)
Other	30	(0.8)
Education		
No education	101	(2.8)
Some primary	3367	(91.8)
Post-primary	198	(5.4)
Occupation		
Agriculture	638	(17.4)
Home/casual/other	1089	(29.7)
Shop/skilled worker	297	(8.1)
Bar/waitress/sex worker	392	(10.7)
Fisherman	551	(15.0)
Trade/truck or motorcycle driver	699	(19.1)
Wealth Index		
High	1631	(44.5)
Middle	723	(19.7)
Low	1312	(35.8)
Long term resident	2888	(78.8)
In migrant	778	(21.2)
Community Type		
Agrarian	1048	(28.6)
Fishing	1743	(47.5)
Trading	875	(23.9)

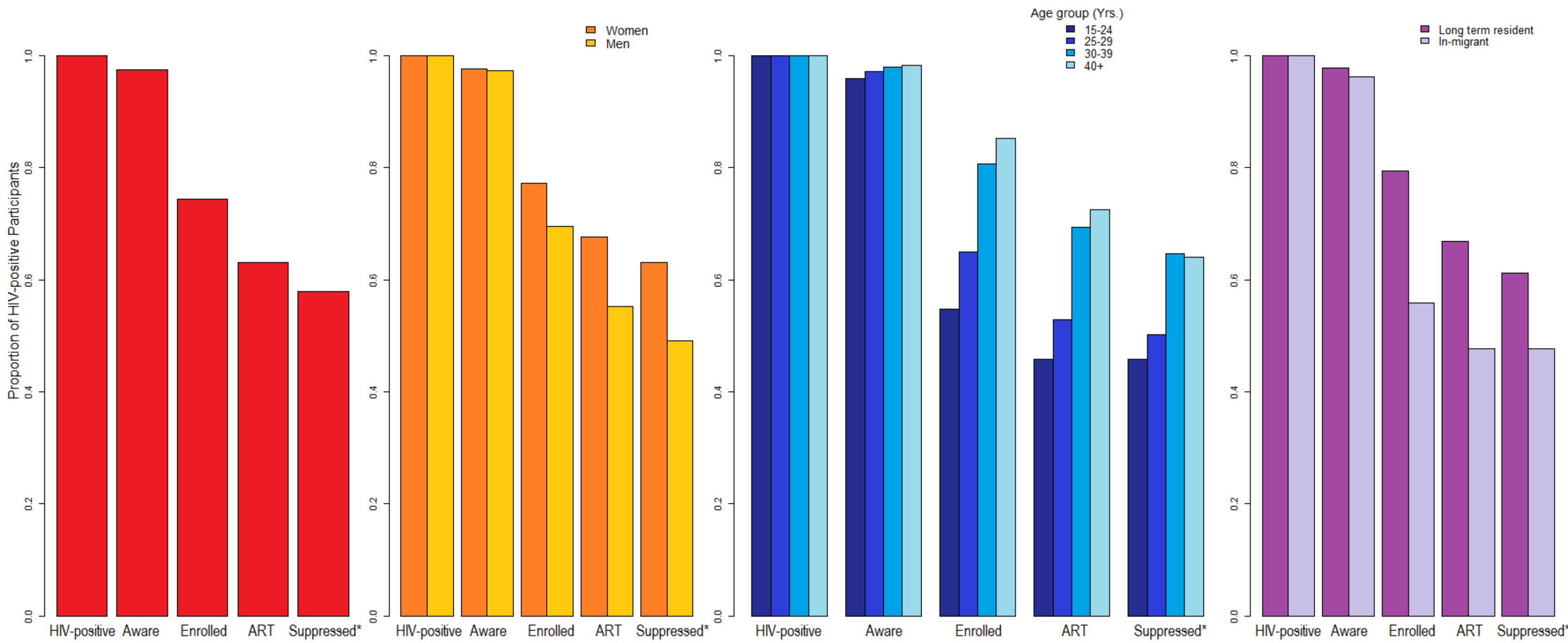
‡ Median (IQR)

Table 4.2 Proportion of Rakai Community Cohort Study population engaged in each of the HIV care cascade stages, Rakai, Uganda

Characteristic	Aware of HIV status			Enrolled in care			Initiated ART			Virally Suppressed		
	n/N	%	P-Value†	n/N	%	P-Value†	n/N	%	P-Value†	n/N	%	P-Value†
Total	3577/3666	97.6		2729/3666	74.3		2312/3666	62.9		2124/3666	57.7	
Female	2254/2308	97.7		1784/2308	77.3		1562/2308	67.7		1458/2308	63.2	
Male	1323/1358	97.4	0.658	945/1358	69.6	**0.000**	750/1358	55.2	**0.000**	666/1358	49.0	**0.000**
Age, Yrs.												
15-24	520/542	95.9		297/542	54.8		248/542	45.8		248/542	45.8	
25-29	754/776	97.2		504/776	64.9		411/776	53.0		390/776	50.3	
30-39	1579/1611	98.0		1300/1611	80.7		1119/1611	69.5		1041/1611	64.6	
40+	724/737	98.2	**0.033**	628/737	85.2	**0.000**	534/737	72.5	**0.000**	472/737	64.0	**0.000**
Marital status												
Married	2115/2166	97.6		1630/2166	75.3		1386/2166	64.0		1265/2166	58.4	
Never married	270/282	95.7		166/282	58.9		133/282	47.2		124/282	44.0	
Previously married	1192/1218	97.9	0.128	933/1218	76.6	**0.000**	793/1218	65.1	**0.000**	734/1218	60.3	**0.000**
Religion												
Christian	3136/3207	97.8		2394/3207	74.6		2024/3207	63.1		1843/3207	57.5	
Muslim	412/429	96.0		314/429	73.2		269/429	62.7		262/429	61.1	
Other	29/30	96.7	0.074	21/30	70.0	0.661	19/30	63.3	0.980	19/30	63.3	0.311
Occupation												
Agriculture	624/638	97.8		481/638	75.4		419/638	65.7		372/638	58.3	
Home/casual/other	1066/1089	97.9		846/1089	77.7		731/1089	67.1		672/1089	61.7	
Shop/skilled worker	282/297	94.9		201/297	67.7		175/297	58.9		156/297	52.5	
Bar/waitress/sex worker	381/392	97.2		302/392	77.0		254/392	64.8		238/392	60.7	
Fisherfolk	540/551	98.0		382/551	69.3		295/551	53.5		268/551	48.6	
Trade/truck or motorcycle driver	684/699	97.9	0.127	517/699	74.0	**0.001**	438/699	62.7	**0.000**	422/699	60.4	**0.000**
Wealth Index												
High	1584/1631	97.1		1211/1631	74.2		1041/1631	63.8		953/1631	58.4	
Middle	705/723	97.5		508/723	70.3		431/723	59.6		389/723	53.8	
Low	1288/1312	98.2	0.188	1010/1312	77.0	**0.002**	840/1312	64.0	0.099	786/1312	59.9	**0.029**
Long term resident	2826/2888	97.9		2294/2888	79.4		1931/2888	66.9		1770/2888	61.3	
In migrant	749/778	96.3	**0.019**	435/778	55.9	**0.000**	371/778	47.7	**0.000**	371/778	47.7	**0.000**
Community Type												
Agrarian	1035/1063	97.4		793/1063	74.6		680/1063	64.0		627/1063	59.0	
Fishing	1688/1721	98.1		1298/1721	75.4		1076/1721	62.5		1048/1721	60.9	
Trading	854/882	96.8	0.110	638/882	72.3	0.241	556/882	63.0	0.762	475/882	53.9	**0.002**

† Fisher's Chi-squared P-Value.

Figure 4.1 Proportion of RCCS participants in December 2015 in each of the HIV care cascade stages **by select participant characteristics**, Rakai, Uganda



* Imputed based on the proportion suppressed with a viral load measurement 12 months after initiating ART.

Table4.3 Unadjusted and adjusted prevalence risk ratio (PRR) for enrollment into care, Rakai, Uganda

Characteristic	Unadjusted			Adjusted		
	PRR	95% CI	P-Value	PRR§	95% CI	P-Value
Female	ref			ref		
Male	0.90	(0.83-0.97)	**0.009**	0.84	(0.77-0.91)	**0.000**
Age, Yrs.						
15-24	0.68	(0.60-0.77)	**0.000**	0.72	(0.63-0.82)	**0.000**
25-29	0.80	(0.73-0.89)	**0.000**	0.83	(0.75-0.92)	**0.001**
30-39	ref			ref		
40+	1.06	(0.96-1.16)	0.263	1.05	(0.96-1.16)	0.290
Marital status						
Married	ref			ref		
Never married	0.78	(0.66-0.91)	**0.003**	0.84	(0.71-0.99)	**0.038**
Previously married	1.02	(0.94-1.10)	0.666	0.96	(0.89-1.05)	0.384
Religion						
Christian	ref			ref		
Muslim	0.98	(0.87-1.10)	0.743	0.98	(0.87-1.11)	0.798
Other	0.94	(0.59-1.40)	0.769	0.96	(0.60-1.43)	0.843
Occupation						
Agriculture	ref			ref		
Home/casual/other	1.03	(0.92-1.15)	0.600	1.03	(0.92-1.16)	0.588
Shop/skilled worker	0.90	(0.76-1.06)	0.199	0.95	(0.81-1.12)	0.575
Bar/waitress/sex worker	1.02	(0.88-1.18)	0.768	1.04	(0.90-1.20)	0.619
Fisherman	0.92	(0.80-1.05)	0.221	1.03	(0.88-1.20)	0.749
Trade/truck or motorcycle driver	0.98	(0.87-1.11)	0.763	1.01	(0.89-1.14)	0.917
Wealth Index						
High	ref			ref		
Middle	0.95	(0.85-1.05)	0.297	0.94	(0.85-1.05)	0.284
Low	1.04	(0.95-1.13)	0.396	1.07	(0.98-1.17)	0.108
Long term resident	ref			ref		
In migrant	0.70	(0.63-0.78)	**0.000**	0.75	(0.67-0.83)	**0.000**
Community Type						
Agrarian	ref			ref		
Fishing	1.02	(0.94-1.12)	0.639	1.08	(0.98-1.18)	0.107
Trading	0.97	(0.88-1.08)	0.626	0.98	(0.88-1.09)	0.700

§Adjusted for variables that were statistically significant in the bivariate analysis and those that were potential confounders (age, sex, marital status and migration status).

Table 4.4 Unadjusted and adjusted prevalence risk ratio (PRR) for initiating ART, Rakai, Uganda

Characteristic	Unadjusted			Adjusted		
	PRR	95% CI	P-Value	PRR§	95% CI	P-Value
Female	ref			ref		
Male	0.81	(0.75-0.89)	**0.000**	0.75	(0.69-0.82)	**0.000**
Age, Yrs.						
15-24	0.66	(0.58-0.76)	**0.000**	0.69	(0.60-0.80)	**0.000**
25-29	0.76	(0.68-0.85)	**0.000**	0.79	(0.70-0.88)	**0.000**
30-39	ref			ref		
40+	1.04	(0.94-1.15)	0.436	1.05	(0.95-1.16)	0.361
Marital status						
Married	ref			ref		
Never married	0.74	(0.62-0.88)	**0.001**	0.80	(0.66-0.95)	**0.014**
Previously married	1.02	(0.93-1.11)	0.645	0.95	(0.87-1.03)	0.230
Religion						
Christian	ref			ref		
Muslim	0.99	(0.87-1.13)	0.923	0.99	(0.87-1.12)	0.849
Other	0.95	(0.58-1.47)	0.844	0.98	(0.59-1.51)	0.930
Occupation						
Agriculture	ref			ref		
Home/casual/other	1.02	(0.90-1.15)	0.777	1.02	(0.91-1.16)	0.698
Shop/skilled worker	0.90	(0.75-1.07)	0.239	0.97	(0.81-1.16)	0.743
Bar/waitress/sex worker	0.99	(0.85-1.15)	0.889	0.99	(0.85-1.16)	0.921
Fisherman	0.81	(0.70-0.94)	**0.006**	0.97	(0.82-1.15)	0.722
Trade/truck or motorcycle driver	0.95	(0.83-1.09)	0.473	0.99	(0.86-1.13)	0.846
Wealth Index						
High	ref			ref		
Middle	0.93	(0.83-1.04)	0.194	0.93	(0.83-1.04)	0.195
Low	1.00	(0.92-1.10)	0.959	1.05	(0.95-1.15)	0.344
Long term resident	ref			ref		
In migrant	0.71	(0.64-0.80)	**0.000**	0.76	(0.67-0.85)	**0.000**
Community Type						
Agrarian	ref			ref		
Fishing	1.00	(0.90-1.10)	0.941	1.06	(0.96-1.17)	0.255
Trading	1.00	(0.89-1.12)	0.880	1.00	(0.89-1.12)	0.965

§Adjusted for variables that were statistically significant in the bivariate analysis and those that were potential confounders (age, sex, marital status and migration status).

Table 4.5 Proportion of Rakai Community Cohort Study population in fishing communities engaged in each of the HIV care cascade stages, Rakai, Uganda

Characteristic	Aware of HIV status			Enrolled in care			Initiated ART			Virally Suppressed		
	n/N	%	P-Value†	n/N	%	P-Value†	n/N	%	P-Value†	n/N	%	P-Value†
Total	1688/1721	98.1		1298/1721	75.3		1076/1721	62.3		1052/1721	60.7	
Female	960/979	98.1		780/979	79.7		674/979	68.8		674/979	68.8	
Male	728/742	98.1	1.000	518/742	69.8	**0.000**	402/742	54.2	**0.000**	378/742	50.9	**0.000**
Age, Yrs.												
15-24	263/273	96.3		163/273	59.7		133/273	48.7		133/273	48.7	
25-29	413/419	98.6		292/419	69.7		235/419	56.1		235/419	56.1	
30-39	767/781	98.2		626/781	80.2		533/781	68.2		508/781	65.0	
40+	245/248	98.8	0.171	217/248	87.5	**0.000**	175/248	70.6	**0.000**	175/248	70.6	**0.000**
Marital status												
Married	1068/1089	98.1		837/1089	76.9		708/1089	65.0		682/1089	62.6	
Never married	72/75	96.0		36/75	48.0		25/75	33.3		25/75	33.3	
Previously married	548/557	98.4	0.286	425/557	76.3	**0.000**	343/557	61.6	**0.000**	343/557	61.6	**0.000**
Religion												
Christian	1440/1462	98.5		1110/1462	75.9		920/1462	62.9		893/1462	61.1	
Muslim	230/241	95.4		173/241	71.8		142/241	58.9		142/241	58.9	
Other	18/18	100.0	**0.017**	15/18	83.3	0.273	14/18	77.8	0.220	14/18	77.8	0.295
Occupation												
Agriculture	99/102	97.1		83/102	81.4		72/102	70.6		72/102	70.6	
Home/casual/other	373/380	98.2		291/380	76.6		253/380	66.6		253/380	66.6	
Shop/skilled worker	68/70	97.1		49/70	70.0		45/70	64.3		45/70	64.3	
Bar/waitress/sex worker	235/241	97.5		190/241	78.8		156/241	64.7		156/241	64.7	
Fisherman	509/520	97.9		360/520	69.2		277/520	53.3		248/520	47.7	
Trade/truck or motorcycle driver	404/408	99.0	0.462	325/408	79.7	**0.004**	273/408	66.9	**0.000**	273/408	66.9	**0.000**
Wealth Index												
High	476/487	97.7		371/487	76.2		313/487	64.3		313/487	64.3	
Middle	136/137	99.3		87/137	63.5		70/137	51.1		70/137	51.1	
Low	1076/1097	98.1	0.616	840/1097	76.6	**0.004**	693/1097	63.2	**0.019**	667/1097	60.8	**0.015**
Long term resident	1303/1324	98.4		1072/1324	81.0		885/1324	66.8		863/1324	65.2	
In migrant	407/419	97.1	**0.101**	248/419	59.2	**0.000**	207/419	49.4	**0.000**	207/419	49.4	**0.000**

† Fisher's Chi-squared P-Value.

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Chapter 5 Sexual risk behaviors of persons who accept or decline HIV care and treatment initiation in Rakai, Uganda.

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5.1 Abstract

Data from a population-based HIV surveillance cohort were used to assess the association between characteristics and sexual behaviors of HIV-positive persons and their enrollment in HIV care and initiation of antiretroviral therapy (ART) using Poisson multivariate regression to estimate adjusted prevalence ratios (adjPRR). Of 3,666 HIV-positive persons interviewed between 2013 and 2015, 74% were enrolled in HIV care, and 63% had initiated ART. Modest but statistically significant differences in enrollment in care were observed between those with and without several high-risk sexual behaviors. ART use was also lower in persons with non-marital sexual partners (adjPRR 0.88, 95% CI 0.81–0.96) compared to those without such partners, among persons with sexual partners outside the community (adjPRR 0.89, 95% CI 0.80–0.99), and among fishermen compared to lower risk occupations (adjPRR 0.78, 95% CI 0.64–0.94). Persons with high-risk profiles were less likely to enroll in care and initiate ART and are likely to sustain ongoing transmission, a potential reason why some HIV epidemics have not been substantially mitigated despite scale-up of ART.

Key Words: Antiretroviral therapy (ART); People living with HIV/AIDS; Sexual behavior; Rakai, Uganda.

5.2 Introduction

Effective antiretroviral therapy (ART) substantially reduces HIV transmission [1–3] and is the basis for the treatment as prevention strategy and for the promotion of HIV test-and-treat programs which rely on early identification and initiation of ART for all HIV-positive individuals [4]. Mathematical models of the potential impact of ART on HIV incidence [5–7] have suggested that if high-risk individuals do not initiate ART, heterogeneity in sexual behaviors can attenuate the impact of test-and-treat [8–10]. These models highlight the need to better quantify HIV care-seeking and ART initiation among those with behaviors which may lead to increased risks of onward transmission.

To date, most empirical research on ART and risk behaviors have used HIV clinic-based data which exclude individuals not enrolled in HIV care and therefore do not fully reflect behaviors within the general HIV-positive population [11–23]. The Rakai Community Cohort Study (RCCS), a cohort of agrarian, trading, and fishing communities in and around Rakai District, south-central Uganda, offers an opportunity to study the association between sexual risk behaviors engagement in HIV care, and initiation of ART at the population-level.

5.3 Methods

Study Population

The study population included all HIV-positive residents who participated in the RCCS between September 2013 and December 2015. The RCCS is a longitudinal population cohort of approximately 17,000 persons aged 15-49 years, resident in 41 communities, conducted by the Rakai Health Sciences Program (RHSP). The 41 RCCS communities are largely representative of rural Uganda (HIV prevalence is ~14% in trading communities, 12% in agrarian communities and ~42% in high-risk fishing communities [24]). At approximately 18 month intervals, the RHSP conducts a detailed census of all households in the cohort, followed by structured confidential interviews conducted in the local language Luganda by trained same-sex interviewers. Participation rates among those present in the communities at the time of the survey is over 90%. Prior to the interview, pretest counseling and HIV testing using a validated three rapid test algorithm [25,26] are offered free of charge, and consenting participants receive post-test counseling by on-site counselors. HIV-positive persons identified via the RCCS are immediately referred for care and treatment. All RCCS communities are within an hour's walk of an HIV clinic, the majority being within a half hour walk.

HIV care is provided by Ministry of Health (MOH) personnel, with supervisory and monitoring support from RHSP staff; the latter also collects detailed data to enable linkage of clinic records to RCCS data. In the clinics, pre-ART HIV care consists of cotrimoxazole for opportunistic infection prophylaxis, bed nets for malaria prevention, clean water vessels with hypochlorite to prevent diarrhea, positive prevention education, reproductive health services and treatment of sexually transmitted infections. Six monthly

CD4+ cell count monitoring is used to assess ART eligibility. Between September 2013 and January 2014, the Ugandan MOH criterion for ART initiation in the general population was a CD4+ cell count <350 cells/mL; in early 2014, the criterion was raised to a CD4+ cell count ≤500 cells/mL. Most-at-risk populations in fishing communities were eligible for test-and-start throughout the period of analysis [27]. First-line ART consisted of standard three-drug regimens approved by the Uganda MOH. Individuals on ART are monitored clinically and via six monthly CD4+ cell counts and annual HIV viral load assays.

The study was reviewed and approved by the Ugandan Virus Research Institute's Scientific and Ethics Committee, the Uganda National Council on Science and Technology, the Johns Hopkins School of Medicine, and Western Institutional Review Board, Olympia, WA. Study participants provided written informed consent at each RCCS visit; the consent included agreement to link participants' RCCS survey results to their clinic data.

Data sources and definition of variables

The analysis used data from two sources: the RCCS surveys and the RHSP clinic data system which uses the Open Medical Record System (OpenMRS) an open source electronic health record [28]. The RCCS surveys collect self-reported information on sociodemographic characteristics, health (including engagement in pre-ART care, receipt of cotrimoxazole; and use of ART), and sexual risk behaviors. Enrollment in HIV care was defined as completing at least 1 documented clinic visit and/or self-reported use of cotrimoxazole or ART in the RCCS survey. ART status was determined through clinic data and/or self-reported use of ART in the RCCS.

HIV risk factors were based on sexual behaviors reported for the 12 months prior to the interview, including number of sex partners, non-marital sex partners, sex with partners from outside the community of residence, alcohol use before sex, consistent condom use with non-marital partners, and symptoms of genital ulcer disease. Variables for condom- and sex-associated alcohol use were evaluated on the basis of partner-specific information, including partner type. Previous studies have highlighted sex with partners outside the community and having multiple partners as risk factors for HIV transmission [24,29–33]. Other variables considered were occupation, and community type (fishing and general population; the latter included agrarian and trading communities). Occupation was collapsed into four categories. Occupations previously found to have high HIV prevalence include commercial sex work; working in bars and restaurants; fishing; and driving trucks or motorcycles [34–37]. The remaining occupational categories classified as non-high risk included work in agriculture, shop attendants and laborers, professional and clerical workers, students, and `others.'

Statistical Methods

Descriptive statistics were used to summarize sociodemographic characteristics of participants by HIV care and ART status. We used modified Poisson regression to estimate prevalence risk ratios (PRRs) and 95% confidence intervals (95%CIs) of enrollment into HIV care and ART use associated with each HIV risk factor, for the whole population and stratified by sex. Since CD4+ cell counts were not available for individuals not enrolled in HIV care, we were unable to assess ART eligibility. However, we examined ART initiation restricted to high-risk fishing communities in which test and treat had been implemented. In addition, we examined ART initiation restricted to younger persons aged 15-29 who are likely to be at a similar stage of infection and ART eligibility. All statistical analyses were performed in the R statistical software (V3.2.5).

5.4 Results

From September 2013 through December 2015, a total of 3,666 HIV-positive participants were surveyed in the RCCS (Table 5.1). Sixty-three percent (2308/3666) of HIV-positive participants were female. The median age of all HIV-positive participants was 33 years (Interquartile range, IQR, 27–38). Fifty-nine percent (2166/3666) were currently married, 88% (3207/3666) were Christian, 92% (3367/3666) had at least some primary education, and 48% (1749/3666) were living in fishing communities. Seventy-four percent (2729/3666) were enrolled in HIV care, and 63% (2312/3666) had initiated ART. Forty-five percent (567/1253) of sexually active men and 79% (1584/2004) of women reported only one sexual partner in the past year ($p<0.000$). 697 (56%) of 1253 sexually active men reported a non-marital partner in the past year compared with 952 (48%) of 2004 women ($p<0.000$); and 59% (742/1253) of 1253 sexually active men and 36% (721/2004) of women reported alcohol use before sex ($p<0.000$).

Enrollment in HIV care

We found modest but statistically significant differences in enrollment of HIV care among persons reporting several high-risk sexual behaviors (Table 5.2, Figure 5.1, and Figure 5.2). Enrollment in care was lower among persons who reported a non-marital partner in the last 12 months (adjPRR 0.92, 95% CI 0.85–1.00) and among fisherfolk (PRR 0.84, 95% CI 0.72–0.99). Persons from fishing communities were more likely to be enrolled in care compared to those in other communities (adjPRR 1.10, 95% CI 1.02–1.19). Women were less likely to be enrolled in care if they reported sexual partners from outside the community (PRR 0.84, 95% CI 0.73–0.96, Figure 5.2). The associations with sexual risk behaviors were similar when restricted to high-risk fishing communities (Table 5.4) and among young persons aged 15-29 (Table 5.5).

We found no difference in enrollment in care between those who reported consistent condom use with non-marital partners compared to inconsistent/no condom use with non-marital partners, or between those who reported symptoms of GUD in the past 12 months, compared to those not reporting symptoms.

ART initiation

As with enrollment in care, we found modest but statistically significant differences in ART initiation among persons reporting several high-risk characteristics and/or sexual behaviors compared to those not reporting such characteristics or behaviors (Table 5.3, Figure 5.3, and Figure 5.4). ART initiation was lower among persons reporting non-marital partners (adjPRR 0.88, 95%CI 0.81-0.96), sex partners outside the community (adjPRR 0.89, 95%CI 0.80-0.99) and fisherman (adjPRR 0.78, 95%CI 0.64-0.94). Findings were similar when analyses were restricted to fishing communities where test and treat had been initiated (Table 5.4). Differences in ART initiation in relation to sexual behaviors were more pronounced among younger age groups than among older age groups (Table 5.5). In particular, young women aged 15-29 were less likely to be on ART if they reported 2 sexual partners in the past 12 months (PRR 0.75, 95% CI 0.57–0.96), non-marital sexual partners (PRR 0.77, 95% CI 0.64–0.92), or sexual partners outside the community (PRR 0.76, 95% CI 0.60–0.95). In addition, young men aged 15-29 with non-marital sexual partners were 37% less likely to be on ART (PRR 0.63, 95% CI 0.45–0.90). We found no difference in ART initiation between those reporting consistent condom use with non-marital partners compared to inconsistent/no condom use with non-marital partners, or between those reporting or not reporting symptoms of GUD in the past 12 months.

5.5 Discussion

In this population-based study of HIV-positive adults in Rakai, Uganda we found modest, but significantly lower levels of enrollment in HIV care and ART initiation among persons with risky sexual behaviors, particularly among non-monogamous youth (<30 years) and fisherfolk. In this analysis, we were unable to assess ART eligibility but included a sub-analysis restricted to younger persons aged 15-29 who are likely to be at a similar stage of infection and ART eligibility [38]. Therefore, the lower use of ART among men and women aged 15-29 with non-marital partners is unlikely to be due to ART eligibility and probably reflects more risky profiles among those, not on ART who are potential sources of HIV transmission. Approaches to reach such individuals with ART and promotion of sexual risk reduction are needed to curb the HIV epidemic.

Models of treatment as prevention have shown that the potential for treatment to eliminate HIV is dependent on patterns of sexual mixing in the population and high-risk behaviors of persons not on ART can substantially attenuate the impact of treatment as prevention on HIV incidence [8,10]. There have been limited population-based studies of sexual behavior and ART use with conflicting results [39–43]. Our findings of reduced treatment uptake among individuals with non-marital partners and partners residing outside the community of residence suggests this may dilute the effectiveness of treatment as prevention efforts.

Previous studies have shown that fishing communities have higher rates of risk behaviors, large gaps in treatment coverage [24,34,44,45], complex socio-economic conditions and a large influx of migrants [35,46,47]. Persons in fishing communities were more likely to be enrolled in care, possibly due to recent outreach efforts, but were not more likely to have initiated ART despite eligibility for test and treat. Additional research is needed to understand the scale-up of HIV prevention and treatment services in these high-risk communities and their role in the evolving HIV epidemic.

This study has limitations. Prior studies have shown conflicting results regarding the accuracy of self-reported utilization of HIV care [48–51], and the proportion of participants who sought care at other facilities or failed to report care and ART use to avoid stigma is not known. However, we used both clinic-based records and self-reported information to measure care [52–54]. In addition, we previously validated self-reports of ART use by detection of plasma antiretroviral drugs and found 99% specificity and 76% sensitivity for self-reported ART use [55]. Another potential limitation is that sexual behavior was ascertained through self-report which is subject to recall error and could reflect a social desirability bias. However, since we found no difference in the reported condom use between individuals engaged or not engaged in HIV care, it is unlikely that all observed differences in sexual behavior were due to social desirability bias.

Our finding that persons with high sexual risk profiles were less likely to enroll in care and initiate ART, suggests one reason why HIV epidemics in some regions have not been substantially mitigated despite scale-up of HIV treatment [56], and that effective treatment as prevention will depend in part on enrolling and retaining these individuals on ART.

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Table 5.1 Population characteristics

Characteristic	N	(%)
Total	3666	(100.0)
Female	2308	(63.0)
Male	1358	(37.0)
Age, Yrs. ‡	33	(27-38)
15-24	542	(14.8)
25-29	776	(21.2)
30-39	1611	(43.9)
40+	737	(20.1)
Marital status		
Married	2166	(59.1)
Never married	282	(7.7)
Previously married	1218	(33.2)
Religion		
Christian	3207	(87.5)
Muslim	429	(11.7)
Other	30	(0.8)
Education		
No education	101	(2.8)
Some primary	3367	(91.8)
Post-primary	198	(5.4)
Occupation		
Not high risk	2646	(72.2)
Bar/waitress/sex worker	388	(10.6)
Fisherman	580	(15.8)
Trade/truck or motorcycle driver	52	(1.4)
Community Type		
General population: Agrarian & Trading communities	1917	(52.3)
Fishing communities	1749	(47.7)
Sexual partners in last 12 mo. ‡	1	(1-2)
None	413	(11.3)
1 partner	2151	(58.7)
2 partners	693	(18.9)
3+ partners	409	(11.2)

‡ Median IQR

Table 5.2 Unadjusted and adjusted prevalence risk ratios (PRR) of enrollment in care by HIV risk factors

			Univariate			Adjusted		
	n/N	%	PRR	95% CI	P-Value	PRR§	95% CI	P-Value
One sexual partner	1630/2151	75.8	1.00			1.00		
2 partners	478/693	69.0	0.91	(0.82-1.01)	0.071	0.95	(0.86-1.06)	0.345
3+ partners	272/409	66.5	0.88	(0.77-1.00)	0.046	0.95	(0.83-1.08)	0.426
Not sexually active	349/413	84.5	1.12	(0.99-1.25)	0.065	1.02	(0.91-1.15)	0.714
No non-marital partner*	1284/1671	76.8	1.00			1.00		
At least one non-marital partner*	1147/1649	69.6	0.91	(0.84-0.98)	**0.014**	0.92	(0.85-1.00)	**0.044**
No sex with partner outside the community*	1855/2470	75.1	1.00			1.00		
Sex with partner outside the community*	576/850	67.8	0.90	(0.82-0.99)	**0.031**	0.91	(0.83-1.00)	0.050
No alcohol before sex*	1366/1830	74.6	1.00			1.00		
Used alcohol before sex*	1064/1488	71.5	0.84	(0.68-1.04)	0.119	0.91	(0.73-1.12)	0.373
Consistent condom use with non-marital partners†	302/408	74.0	1.00			1.00		
Inconsistent condom use†	837/1228	68.2	0.92	(0.81-1.05)	0.219	0.95	(0.83-1.08)	0.421
No symptoms of genital ulcer disease	2233/2976	75.0	1.00			1.00		
Symptoms of genital ulcer disease	494/684	72.2	0.96	(0.87-1.06)	0.442	1.01	(0.91-1.11)	0.898
Non-high risk occupation	2380/3121	76.3	1.00			1.00		
Bar/waitress/sex worker	160/221	72.4	0.95	(0.81-1.11)	0.525	0.94	(0.79-1.10)	0.435
Fisherman	177/298	59.4	0.78	(0.67-0.90)	**0.001**	0.84	(0.72-0.99)	**0.043**
Truck or motorcycle driver	12/26	46.2	0.61	(0.32-1.02)	0.083	0.68	(0.36-1.14)	0.181
General population communities	1404/1917	73.2	1.00			1.00		
Fishing communities	1325/1749	75.8	1.03	(0.96-1.12)	0.377	1.10	(1.02-1.19)	**0.011**

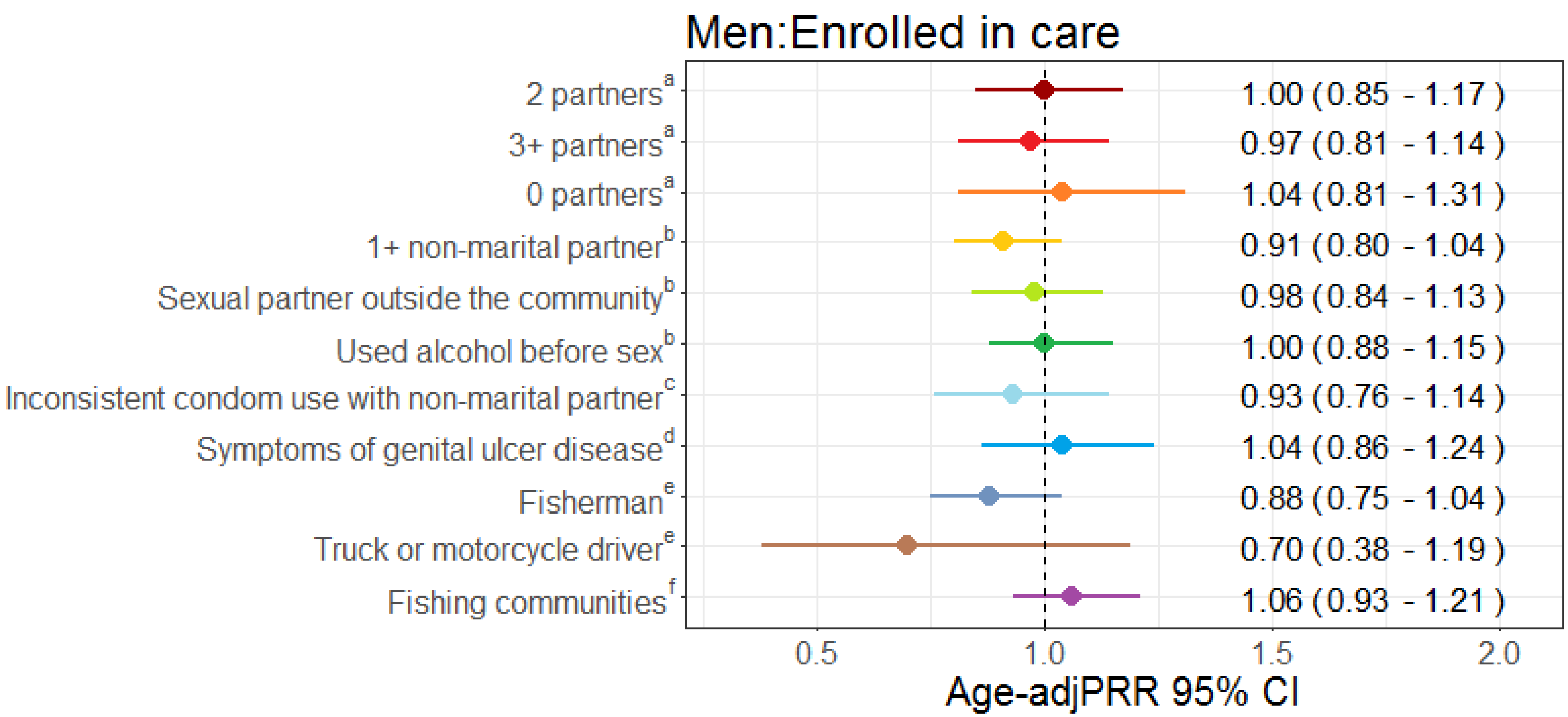
§Adjusted for variables identified as potential confounders (age & sex) *among sexually active; †among sexually active and reporting sex with a non-marital partner.

Table 5.3 Unadjusted and adjusted prevalence risk ratios (PRR) of ART initiation by HIV risk factors

			Univariate			**Adjusted**		
	n/N	%	PRR	95% CI	P-Value	PRR[§]	95% CI	P-Value
One sexual partner	1394/2151	64.8	1.00			1.00		
2 partners	383/693	55.3	0.85	(0.76-0.95)	**0.006**	0.91	(0.81-1.03)	0.133
3+ partners	214/409	52.3	0.81	(0.70-0.93)	**0.004**	0.91	(0.78-1.06)	0.229
Not sexually active	311/413	75.3	1.16	(1.03-1.31)	**0.017**	1.05	(0.93-1.19)	0.410
No non-marital partner*	1100/1671	65.8	1.00			1.00		
At least one non-marital partner*	933/1649	56.6	0.86	(0.79-0.94)	**0.001**	0.88	(0.81-0.96)	**0.004**
No sex with partner outside the community*	1562/2470	63.2	1.00			1.00		
Sex with partner outside the community*	471/850	55.4	0.88	(0.79-0.97)	**0.012**	0.89	(0.80-0.99)	**0.033**
No alcohol before sex*	1181/1830	64.5	1.00			1.00		
Used alcohol before sex*	852/1488	57.3	0.80	(0.63-1.01)	0.071	0.91	(0.71-1.14)	0.427
Consistent condom use with non-marital partners[†]	251/408	61.5	1.00			1.00		
Inconsistent condom use[†]	674/1228	54.9	0.89	(0.77-1.03)	0.123	0.91	(0.79-1.06)	0.230
No symptoms of genital ulcer disease	1888/2976	63.4	1.00			1.00		
Symptoms of genital ulcer disease	413/684	60.4	0.95	(0.85-1.06)	0.363	0.99	(0.89-1.10)	0.894
Non-high risk occupation	2037/3121	65.3	1.00			1.00		
Bar/waitress/sex worker	125/221	56.6	0.87	(0.72-1.03)	0.120	0.83	(0.69-1.00)	0.052
Fisherman	131/298	44.0	0.67	(0.56-0.80)	**0.000**	0.78	(0.64-0.94)	**0.010**
Truck or motorcycle driver	9/26	34.6	0.53	(0.25-0.96)	0.058	0.64	(0.31-1.16)	0.182
General population communities	1206/1917	62.9	1.00			1.00		
Fishing communities	1096/1749	62.7	1.00	(0.92-1.08)	0.925	1.08	(0.99-1.18)	0.068

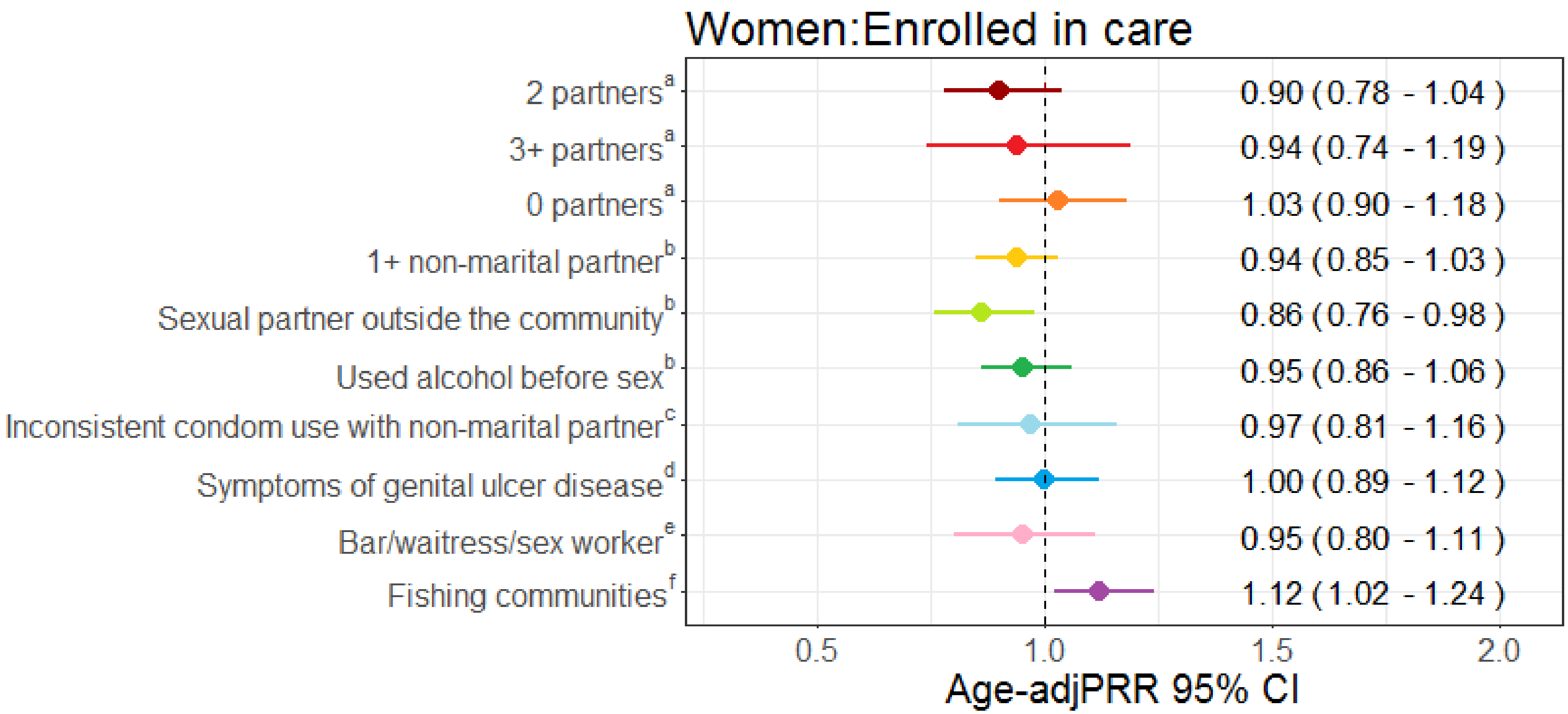
§Adjusted for variables identified as potential confounders (age & sex) *among sexually active; †among sexually active and reporting sex with a non-marital partner.

Figure 5.1 Prevalence Risk Ratios (PRR) Enrollment into care, Men



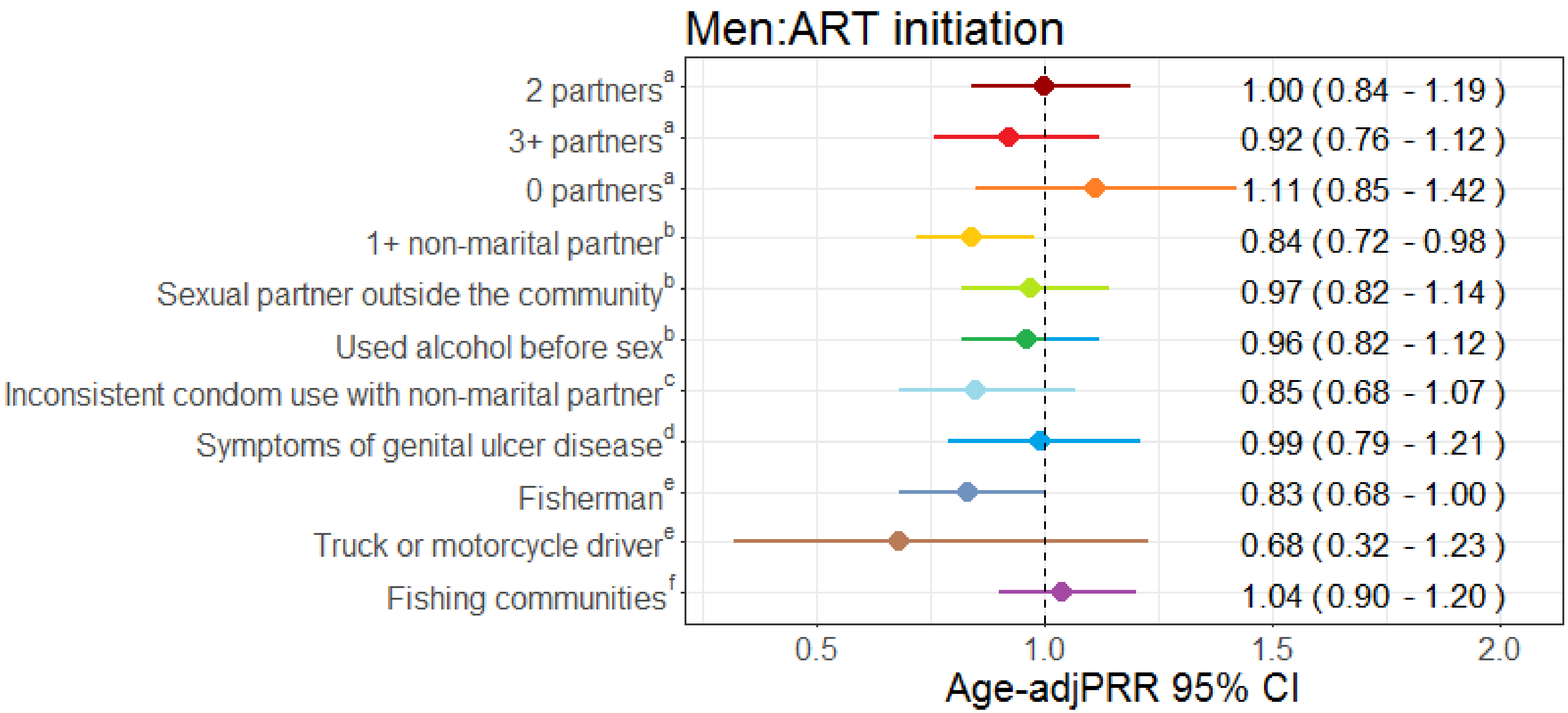
[a]number of sexual partners vs. one in the last 12 months; [b]among sexually active: Yes/No; [c]among sexually active and report sex with a non-marital partner: Yes/No; [d]Yes/No; [e]occupation/non-high risk occupation; [f]fishing communities/general population.

Figure 5.2 Prevalence Risk Ratios (PRR) Enrollment into care, Women



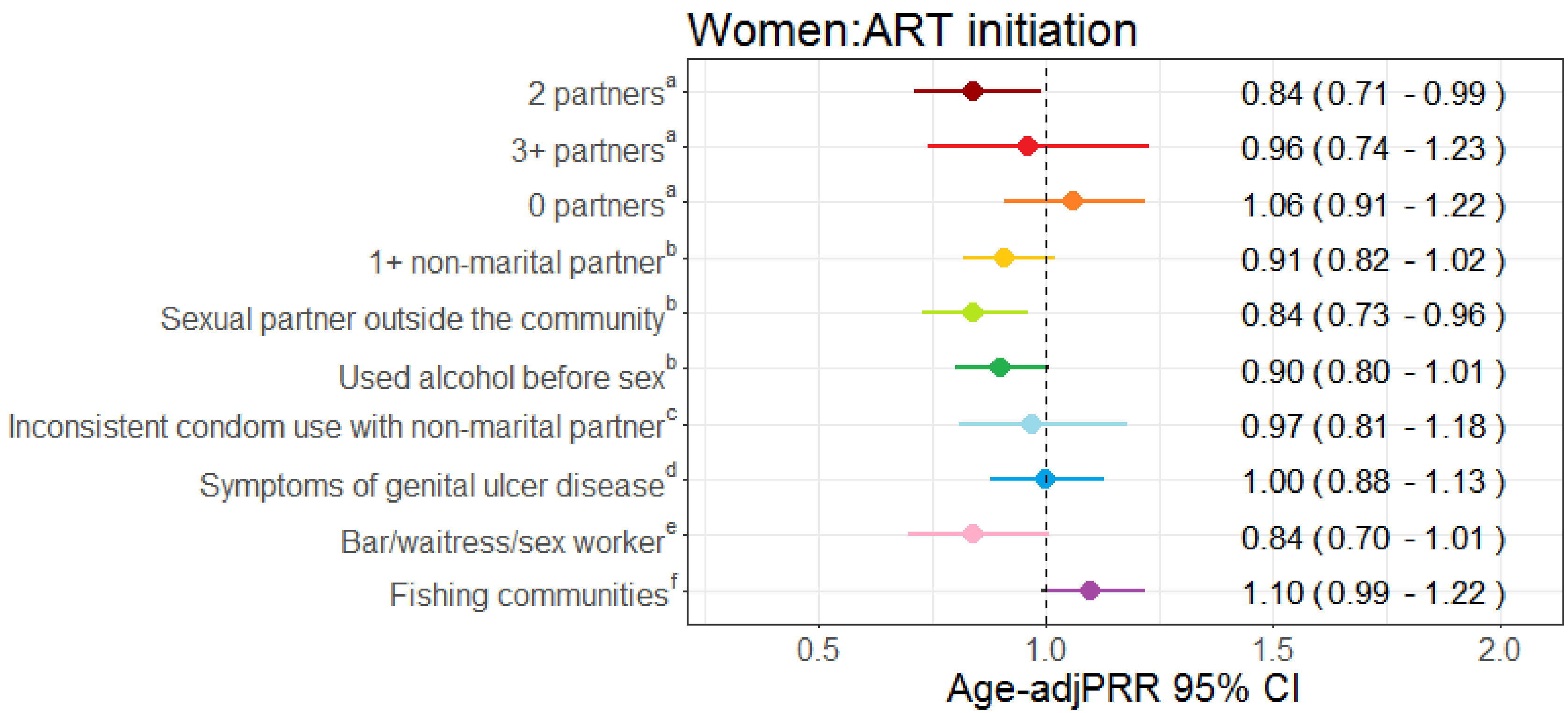
[a]number of sexual partners vs. one in the last 12 months; [b]among sexually active: Yes/No; [c]among sexually active and report sex with a non-marital partner: Yes/No; [d]Yes/No; [e]occupation/non-high risk occupation; [f]fishing communities/general population.

Figure 5.3 Prevalence Risk Ratios (PRR) ART initiation, Men



[a]number of sexual partners vs. one in the last 12 months; [b]among sexually active: Yes/No; [c]among sexually active and report sex with a non-marital partner: Yes/No; [d]Yes/No; [e]occupation/non-high risk occupation; [f]fishing communities/general population.

Figure 5.4 Prevalence Risk Ratios (PRR) ART initiation, Women



[a]number of sexual partners vs. one in the last 12 months; [b]among sexually active: Yes/No; [c]among sexually active and report sex with a non-marital partner: Yes/No; [d]Yes/No; [e]occupation/non-high risk occupation; [f]fishing communities/general population.

Table 5.4 Prevalence risk ratios (PRR) of enrollment in care and ART initiation in fishing community

			Enrolled in care					Initiated ART		
	n/N	%	PRR§	95% CI	P-Value	n/N	%	PRR§	95% CI	P-Value
One sexual partner	762/961	79.3	1.00			646/961	67.2	1.00		
2 partners	277/385	71.9	0.95	(0.82-1.09)	0.477	222/385	57.7	0.92	(0.79-1.08)	0.309
3+ partners	201/300	67.0	0.92	(0.78-1.09)	0.332	156/300	52.0	0.88	(0.73-1.06)	0.188
Not sexually active	85/103	82.5	0.93	(0.74-1.16)	0.536	72/103	69.9	0.92	(0.71-1.17)	0.514
No non-marital partner*	619/779	79.5	1.00			532/779	68.3	1.00		
At least one non-marital partner*	621/867	71.6	0.93	(0.83-1.04)	0.191	492/867	56.7	0.87	(0.77-0.98)	**0.027**
No sex with partner outside the community*	929/1216	76.4	1.00			779/1216	64.1	1.00		
Sex with partner outside the community*	311/430	72.3	0.95	(0.84-1.09)	0.478	245/430	57.0	0.91	(0.79-1.05)	0.213
No alcohol before sex*	612/798	76.7	1.00			520/798	65.2	1.00		
Used alcohol before sex*	628/848	74.1	0.87	(0.69-1.09)	0.248	504/848	59.4	0.87	(0.66-1.12)	0.287
Consistent condom use with non-marital partners†	171/225	76.0	1.00			137/225	60.9	1.00		
Inconsistent condom use†	445/634	70.2	0.93	(0.78-1.11)	0.427	350/634	55.2	0.91	(0.75-1.11)	0.344
No symptoms of genital ulcer disease	1037/1366	75.9	1.00			863/1366	63.2	1.00		
Symptoms of genital ulcer disease	288/383	75.2	1.01	(0.89-1.16)	0.829	233/383	60.8	0.98	(0.84-1.13)	0.755
Non-high risk occupation	1038/1312	79.1	1.00			882/1312	67.2	1.00		
Bar/waitress/sex worker	115/148	77.7	0.95	(0.78-1.15)	0.616	86/148	58.1	0.81	(0.64-1.01)	0.068
Fisherman	168/284	59.2	0.79	(0.66-0.94)	**0.010**	125/284	44.0	0.74	(0.60-0.91)	**0.004**
Truck or motorcycle driver	4/5	80.0	1.07	(0.33-2.51)	0.887	3/5	60.0	1.02	(0.25-2.66)	0.977

§Adjusted for variables identified as potential confounders (age & sex) *among sexually active; †among sexually active and reporting sex with a non-marital partner.

Table 5.5 Prevalence risk ratios (PRR) of enrollment in care among those 15-29 years of age, stratified by gender

Men:	**n/N**	**%**	**PRR**	**95% CI**	**P-Value**
One sexual partner	84/161	52.2	1.00		
2 partners	47/103	45.6	0.84	(0.57-1.23)	0.389
3+ partners	47/95	49.5	0.93	(0.63-1.35)	0.712
Not sexually active	15/25	60.0	1.15	(0.62-1.97)	0.628
No non-marital partner*	79/132	59.8	1.00		
At least one non-marital partner*	104/236	44.1	0.74	(0.55-0.99)	**0.040**
No sex with partner outside the community*	132/267	49.4	1.00		
Sex with partner outside the community*	51/101	50.5	1.02	(0.73-1.40)	0.898
No alcohol before sex*	88/179	49.2	1.00		
Used alcohol before sex*	95/189	50.3	0.92	(0.54-1.47)	0.740
Consistent condom use with non-marital partners†	31/63	49.2	1.00		
Inconsistent condom use†	72/172	41.9	0.85	(0.56-1.31)	0.452
No symptoms of genital ulcer disease	151/302	50.0	1.00		
Symptoms of genital ulcer disease	42/81	51.9	1.04	(0.73-1.45)	0.835
Non-high risk occupation	139/275	50.5	1.00		
Fisherman	50/99	50.5	1.00	(0.72-1.37)	0.996
Truck or motorcycle driver	4/9	44.4	0.88	(0.27-2.08)	0.800
General population communities	64/151	42.4	1.00		
Fishing communities	129/233	55.4	1.31	(0.97-1.77)	0.081
Women:	n/N	%	PRR	95% CI	P-Value
One sexual partner	438/656	66.8	1.00		
2 partners	92/162	56.8	0.86	(0.68-1.08)	0.212
3+ partners	35/58	60.3	0.91	(0.63-1.28)	0.619
Not sexually active	43/58	74.1	1.12	(0.80-1.53)	0.479
No non-marital partner*	333/483	68.9	1.00		
At least one non-marital partner*	242/408	59.3	0.86	(0.73-1.01)	0.075
No sex with partner outside the community*	463/685	67.6	1.00		
Sex with partner outside the community*	112/206	54.4	0.80	(0.65-0.98)	**0.039**
No alcohol before sex*	375/581	64.5	1.00		
Used alcohol before sex*	200/310	64.5	0.84	(0.33-1.72)	0.680
Consistent condom use with non-marital partners†	51/80	63.7	1.00		
Inconsistent condom use†	189/324	58.3	0.92	(0.68-1.26)	0.574
No symptoms of genital ulcer disease	454/694	65.4	1.00		
Symptoms of genital ulcer disease	154/239	64.4	0.98	(0.82-1.18)	0.871
Non-high risk occupation	559/848	65.9	1.00		
Bar/waitress/sex worker	49/85	57.6	1.00	(0.80-1.24)	0.988
General population communities	278/470	59.1	1.00		
Fishing communities	330/464	71.1	1.20	(1.03-1.41)	**0.024**

*among sexually active; †among sexually active and reporting sex with a non-marital partner.

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Chapter 6 Geospatial patterns of HIV antiretroviral therapy treatment facility use and viral suppression in Rakai, Uganda.

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6.1 Abstract

Objective: We assessed geospatial patterns of HIV antiretroviral therapy (ART) treatment facility use and viral load (VL) suppression.

Methods: We extracted data on the location and type of care services utilized by HIV-positive persons accessing ART in south-central Uganda between February 2015 and September 2016 using data from the Rakai Community Cohort Study (RCCS). The distance from RCCS households to all facilities offering HIV care in the region was calculated using travel distance along the open street map road network. Modified Poisson regression was used to identify predictors of distance traveled and, for those traveling beyond their nearest facility, the probability of accessing services from a tertiary care facility.

Results: 1554 HIV-positive RCCS participants were identified, of whom 1076 (68%) had initiated ART. The median distance from households to the nearest facility offering ART was 3.10 km (Interquartile range, IQR, 1.65-5.05). However, median distance traveled to facility was 5.26 km, $p<0.001$, (IQR, 3.00-10.03), and 57% of individuals (589/1030) chose to travel to a facility further than their nearest facility. Those with higher levels of education and wealth were more likely to travel further than their nearest ART facility, and those with additional health needs such as hypertension were more likely to access tertiary care services. 93% of persons on ART (1002/1076) were virally suppressed, and there was no difference in the distance traveled to an ART facility between those with suppressed and unsuppressed VLs (5.26 km vs. 5.27 km, p=0.650).

Conclusions: Distance traveled and type of HIV services used, were associated with socioeconomic status, suggesting that relatively wealthier individuals exercise greater choice of where they receive HIV treatment. However, viral suppression did not vary by distance traveled for treatment regardless of ART source.

6.2 Introduction

Persons living with HIV are most in need of high quality accessible healthcare[1] and geographic distance from residence to health facility is an important factor affecting health service utilization in sub-Saharan Africa[2]. Distance-decay implies that persons who must travel greater distances may delay seeking health care and have worse outcomes, a number of studies have shown associations between transportation barriers and HIV-related outcomes including lower rates of ART adherence, lower rates of patient retention, and increased mortality[3–5]. However, the dynamics of health-care utilization are complex, and several other studies have failed to show an association between transport barriers and HIV outcomes[6–11]. One possibility for this discrepancy is the inconsistent measurement of transportation barriers across studies, which have include self-reported travel distance[9,10,12,13], self-reported travel time[6,13–16], self-reported travel cost[13,14], cost surface distance[17], linear travel distance[13,14,18], and calculated travel distance[13,14]. Choice in healthcare adds additional complexity to the relationship with health outcomes. In sub-Saharan Africa, a diverse marketplace of public and private providers allows HIV-positive individuals a choice of health care facilities. Many individuals reside far from a treatment facility and have no choice but to travel a significant distance for treatment[19–21]; while others have considerable flexibility as to where they access ART[22] and may choose to travel for treatment at distant facilities[23]. Moreover, the extent to which individuals exercise service choice is likely to depend on the perceived quality of services offered, but the reasons why HIV-positive individuals may travel additional distances for care are not well understood, and willingness to travel beyond local services has important implications for both health systems and HIV treatment programs.

The Rakai Community Cohort Study (RCCS), a population-based cohort of HIV incidence and risk behaviors in communities in and around Rakai District, Uganda provides a unique opportunity to characterize geospatial patterns of ART treatment facility use and the effect on virologic outcome. In this study, we test the hypothesis that communities with larger geographic distance to the nearest ART treatment facilities will have lower ART coverage and viral suppression and that demographic and health characteristics have an impact on facility choice.

6.3 Methods

Study setting and population

The first AIDS cases in east Africa were identified in Rakai District, Uganda[24] and communities in and around Rakai continue to have among the highest HIV prevalence in Uganda[25]. We used data from the Rakai Community Cohort Study (RCCS), an open population-based census and HIV surveillance cohort. The RCCS currently includes all consenting residents aged 15-49 in 38 communities in and near Rakai District. Written informed consent is provided at each visit. The RCCS conducts a household census and subsequently interviews consenting individuals aged 15-49 using structured questionnaires in the local language (Luganda). Data collected include sociodemographic, behavioral information, and health service use. HIV-positive persons utilizing care were asked the location of their care provider. Venous blood is collected for HIV testing using a validated three rapid test algorithm[26], and viral loads are performed using the Amplicor Monitor Assay, version 1.5 (Roche Diagnostics, Branchburg, NJ, USA, or Abbott Real Time assay) with lower limits of detection of <400 copies/mL. (Viral suppression was defined as <400 copies/mL.) HIV-positive persons identified through the RCCS were immediately offered free HIV counseling and testing and referred for care and treatment. ART was initiated at CD4 counts <500 cells/mL, or at the time of diagnosis for HIV discordant couples, pregnant/lactating women and key populations (sex workers, fishing communities).

For this study, we used data collected from all HIV-positive persons (n=1152) residing in 30 communities serviced by static (i.e., non-mobile) clinics between February

2015 and September 2016 (n = 2543). 76 persons were missing treatment facility information and were excluded from the facility choice analysis.

The study was reviewed and approved by the Ugandan Virus Research Institute's Scientific and Ethics Committee (HS540), the Uganda Council on Science and Technology (GC/127/15/11/137), and Western Institutional Review Board, Olympia WA (20031318).

Geographic methods

With each head of household's consent and the approval of Institutional Review Boards, RCCS households were individually identified with handheld GPS units by the RCCS Census team. GPS locations were also obtained for all of the fixed-location HIV care providers in the study region. Health facilities and clinics were classified by level of care (primary or tertiary), managing authority (Government, private, non-governmental organization (NGO), and HIV and general health services offered. The health-care facilities which provide ART in the study region include public hospitals and facilities as well as a variety of private providers, including nonprofit hospitals and facilities run by NGOs as well as some for-profit clinics and hospitals[27]. Public health facilities were categorized by the area served and services provided. Government Health Centers II & III (public facilities) provide outpatient care and ART treatment. Government Health Centers IV (Hospitals) provide inpatient and outpatient care, tertiary services, and ART. A total of 31 ART treatment facilities were identified in the study region, 2 (6%) were Government Health Centers II, 20 (65%) were Government Health Centers III, 6 (19%) were private or NGO health facilities, and 3 (10%) were HC4 providing tertiary care (Figure 6.1). Five additional tertiary care facilities outside the study region were reported by study participants. Locations for these facilities were identified on a map and geocoded using Google Earth by Ugandan co-investigators with local expertise. The distance from the participant's home to all facilities offering HIV care in the region was calculated by estimating the travel distance along the open street map road network from households to the facilities (Appendix Figure 3). The Open Source Routing Machine (osrm) package in R was used to query driving distances between locations from the OpenStreetMaps API. The nearest facility was also calculated to determine how far each person would have needed to travel to the nearest facility compared to how far they traveled to the facility actually utilized.

Statistical analysis

Variables of interest included distance traveled in kilometers; whether or not persons traveled further than their closest ART treatment facility; and the level of service accessed. For classification of socioeconomic status, we used a household wealth index, based on household building materials[28]. Demographic characteristics were compared between individuals attending the nearest facility and those traveling beyond the nearest facility. Cumulative distribution functions and medians and interquartile ranges were used to summarize distances traveled between the household and facility location, and significant differences in travel distance between sub-groups were assessed by Wilcoxon-rank sum tests. RCCS data were aggregated into 11 sub-counties. For those traveling beyond the nearest ART facility, unadjusted and adjusted modified Poisson regression models were used to estimate prevalence risk ratios (PRR) with 95% CI of attending a Health Center Level 4 for tertiary care versus lower level facilities. All statistical analyses were performed in the R statistical software (V3.2).

6.4 Results

From February 2015 and September 2016, a total of 1554 HIV-positive persons were identified in the RCCS. Of these persons, 1076/1554 (69%) were on ART, and 1002/1076 (93%) of those on ART were virally suppressed (<400 copies/mL.)

Demographics of ART-treated and virally suppressed populations

Table 6.1 shows the demographics of the 1554 HIV-infected persons, 1076 on ART (and 1002 virally suppressed participants. Men were less likely to be on ART compared to women ($p<0.001$). Individuals aged 15-24 were less likely to be on ART ($p<0.001$) and to have a suppressed viral load ($p<0.001$), compared to older HIV-positive persons. Previously married individuals and those in non-high risk occupations were more likely to be on ART.

Distance to ART treatment facility

The median distance from households to the nearest ART facility was 3.10 km (Interquartile range, IQR, 1.65-5.05), Figure 6.2. However, individuals traveled significantly further than their nearest clinic, traveling a median of 5.26 km for ART treatment, $p<0.001$, (IQR, 3.00-10.03, Table 6.2, Figure 6.4), and 57% of patients (589/1030) chose to travel to a facility further than their nearest facility (Table 6.3). Figure 6.3 presents distributions of ART coverage and distance to nearest treatment facility in the 30 communities. It shows substantial variability in coverage and distances across communities. However, no associations between community ART coverage and distance to the nearest ART facility were found when distance was considered as a linear or as a categorical variable. There was considerable variation in distance to the nearest clinic, the distance ranged from a median of 1.41 km to 6.45 km across sub-counties, and in all but two sub-counties, individuals traveled significantly further than their nearest ART treatment facility, the distance traveled ranged from a median of 2.76 km to 10.97 km across sub-counties, (Figure 6.5). Figure 6.6, shows the cumulative proportion who traveled specific distances for ART treatment by sociodemographic characteristics and type of facility. The travel distance to a treatment facility was longer among those with a post-primary school education (6.56 km vs 5.09 km, $p<0.001$), those whose higher socioeconomic status (6.43 km vs 4.87 km, $p=0.001$), and by those attending a HC4 tertiary care facilities (9.02 km), compared to HC3 (4.76 km), HC2 (6.97km) or Private/NGO run facilities (4.39 km, $p=0.001$). Table 6.3 shows the PRRs of attending the nearest facility. Traveling beyond the nearest ART facility was associated with having higher wealth ($P = 0.038$).

Virologic and health outcomes

We found 963/1030 (94%) of persons on ART were virally suppressed and found no difference in the distance traveled to an ART facility between those with suppressed (5.26 km) compared to those with a detectable viral load (5.27 km, $p=0.650$). We found no difference in viral suppression between those who choose their nearest facility and those who traveled beyond (adjPRR 0.99, 95% CI 0.70–1.37, Table 6.3). In addition, there was no difference in viral suppression by type of treatment facility. Forty-one percent (241/589) of those not attending their nearest ART facility obtained treatment from a tertiary care facility (Table 6.4). Obtaining treatment from a HC4 was higher among those aged 15-24 (adjPRR 1.55, 95% CI 1.01–2.29), among those who reported prolonged fever lasting more than a month (adjPRR 1.84, 95% CI 1.02–3.06) or diagnosed with hypertension (adjPRR 1.75, 95% CI 1.00–2.87).

6.5 Discussion

Multiple studies measuring the effects of transportation on HIV outcomes, have reported negative[3–5], null[6–8,13], and positive[9–11] effects of self- reported transportation barriers on HIV-associated outcomes. The few studies which utilized GPS measurements found both null effects on adherence measured through pill counts[14] and negative effects on visit attendance[13,17,18]. In south-central Uganda, we found substantial heterogeneity in the distance to the nearest treatment facility, however, our main finding was that this distance was not predictive of community ART coverage or viral suppression. In addition, more than half of the individuals in our study traveled beyond their nearest facility, which corroborates a recent study in Uganda which found that people living with HIV bypassed nearer ART sites and sought care at higher-tiered ART sites[22]. While we did not have data to assess this in our study, excess travel for treatment may be attributable to the stigma associated with HIV reported in other studies[20] and should be explored in future studies.

We found that the extent to which individuals exercise choice in treatment facilities is associated with severity of illness and economic status. Those with lower levels of education and wealth were less likely to travel further than their nearest ART facility, whereas persons of higher education and wealth exercised greater choice about where they received their HIV treatment. Those with coexisting health conditions such as hypertension were more likely to travel further to access tertiary care services.

HIV-positive persons on ART in rural Uganda can achieve good virologic outcomes, despite economic and geographic barriers[4,6,10]. Most patients traveled 5 or more km each way, a burdensome distance by foot; yet, most were able to achieve viral suppression; suggesting that individuals on ART are likely to be highly motivated and adherent. This study used road network analysis as a more accurate way to estimate travel distance[21,22] compared to Euclidean distance[3,8,23] and road distance has been found to be more strongly associated use of health services[24].

This analysis has several limitations. First, we did not directly measure travel distances or travel times, and the road network analysis approach may overestimate the actual travel distance. However, the shortest-route is a reasonable conservative distance estimate. The analysis excluded regions with mobile HIV treatment outreach, so findings may not be generalizable to areas with mobile services. Our study was restricted to individuals engaged in the local healthcare system and did not capture the extent to which geospatial barriers limit access to all HIV care or ART initiation.

In conclusion, we find that access to health care cannot be explained solely by the distance to services, but that viral suppression rates did no vary by distance traveled for treatment. Distance traveled, and type of services used was associated with higher socioeconomic status, so travel costs may provide a selective to advantage those with higher relative wealth and remain a barrier to those of lower socioeconomic status. Our findings have implications for improving access to care in rural resource-limited settings. Ministry of Health and health system planners must account for location as well as service type, and individual preferences when seeking to expand access to treatment services.

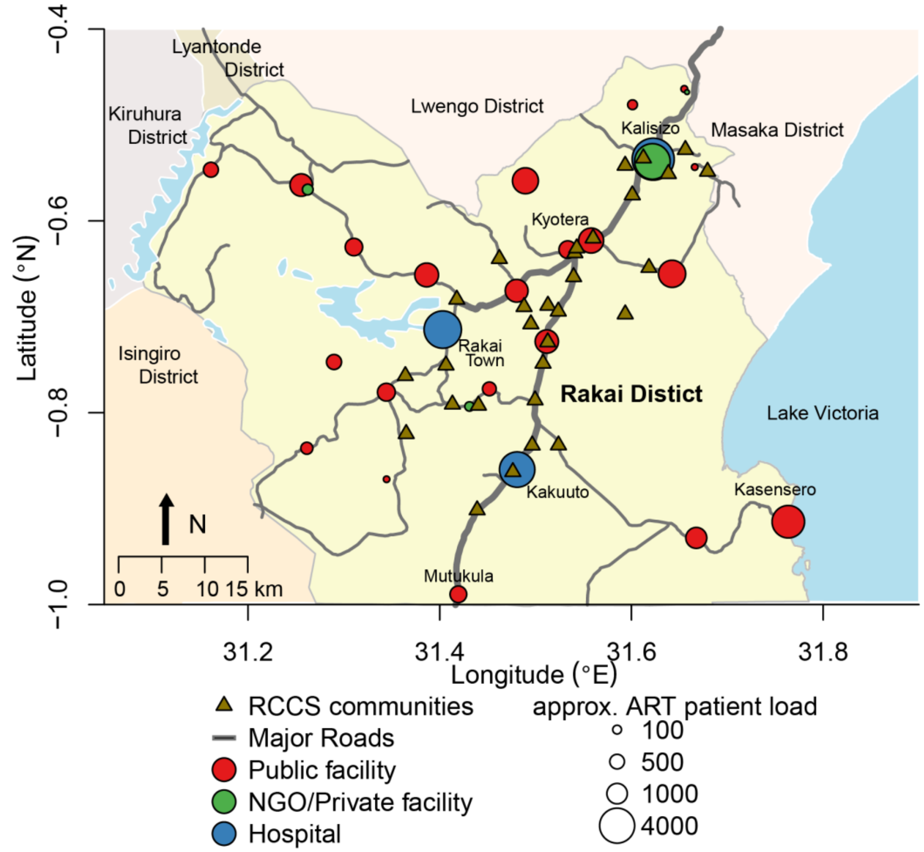

Figure 6.1 HIV treatment facilities, in the Rakai region. Map of the Rakai region showing the location of ART treatment facilities, major towns, and RCCS communities; red circles represent public ART treatment facilities, green circles represent private, or NGO-run facilities and blue circles represent Hospitals or tertiary care facilities.

Table 6.1 Demographic characteristics of HIV-positive Rakai Community Cohort Study (RCCS) participants from February 2015 and September 2016, by ART and viral suppression status

	Initiated ART			Suppressed§		
	n/N	**%**	**p-value‡**	**n/N**	**%**	**p-value‡**
Overall	1076/1554	68.7	-	1002/1076	93.1	-
Female	781/1075	72.7		728/781	93.2	
Male	295/479	61.7	**<0.001**	274/295	93.2	1.0
Age, Yrs.						
15-24	105/198	53.3		85/105	81.0	
25-29	155/270	57.4		143/155	92.3	
30-39	441/610	72.3		415/441	94.1	
40+	375/476	78.8	**<0.001**	359/375	96.0	**<0.001**
Marital status						
Married	596/879	67.8		555/596	93.3	
Previously Married	381/519	73.4		358/381	93.4	
Never Married	99/155	63.9	**0.022**	89/99	89.9	0.362
Educational status						
Some primary	817/1167	70.1		760/817	93.1	
Post Primary	259/387	66.9	0.253	242/259	93.4	1.0
Occupation						
Non-high risk occupation	986/1407	70.1		917/986	93.1	
Bar/waitress/sex worker/Truck or motorcycle driver/Fisherfolk	90/147	61.2	**0.030**	85/90	94.4	0.827
Distance from household to nearest ART facility (km)						
<0.5	87/126	69.0		84/87	96.6	
0.5-2	224/310	72.3		207/224	92.4	
2-5	481/688	70.0		440/481	91.7	
5+	284/430	66.0	0.319	271/284	95.4	0.121
Wealth Index						
High wealth	673/987	68.3		629/673	93.5	
Low wealth	403/567	71.1	0.254	373/403	92.8	0.708
Vehicle ownership						
None	865/1255	69.0		806/865	93.2	
Car or Motorcycle	211/299	70.6	0.626	196/211	93.3	1.0
ART treatment facility type						
Health center II (HC2) or Health center III (HC3)	-	-	-	533/570	93.5	
Private or NGO	-	-	-	133/142	93.7	
Health center IV (HC4)	-	-	-	297/318	93.4	
Missing				39/46	84.7	0.190

§ defined as viral load <400 copies/mL
‡ Chi-square p-values

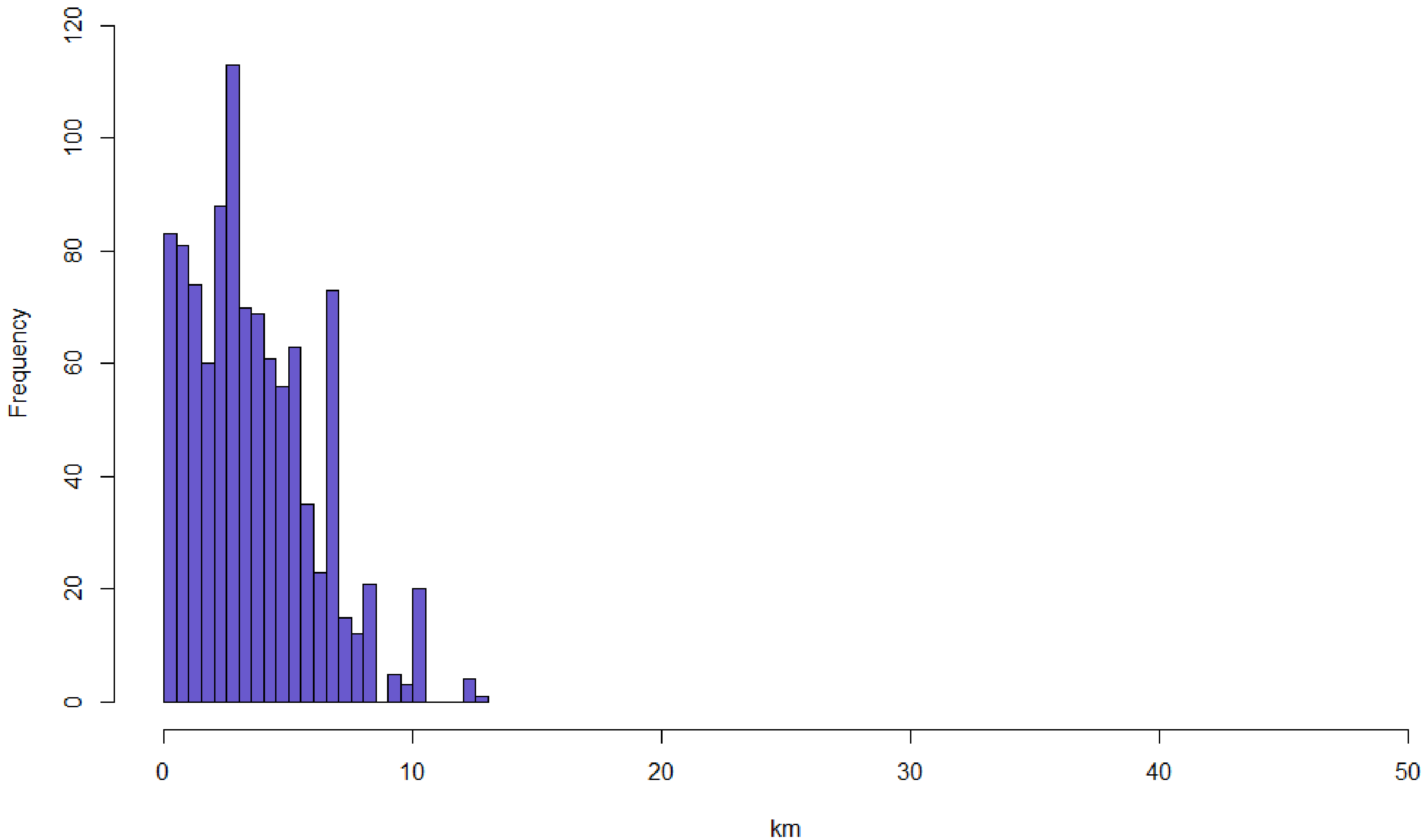

Figure 6.2 Distance to nearest treatment facility. Distances are from household to their treatment facility in kilometers.

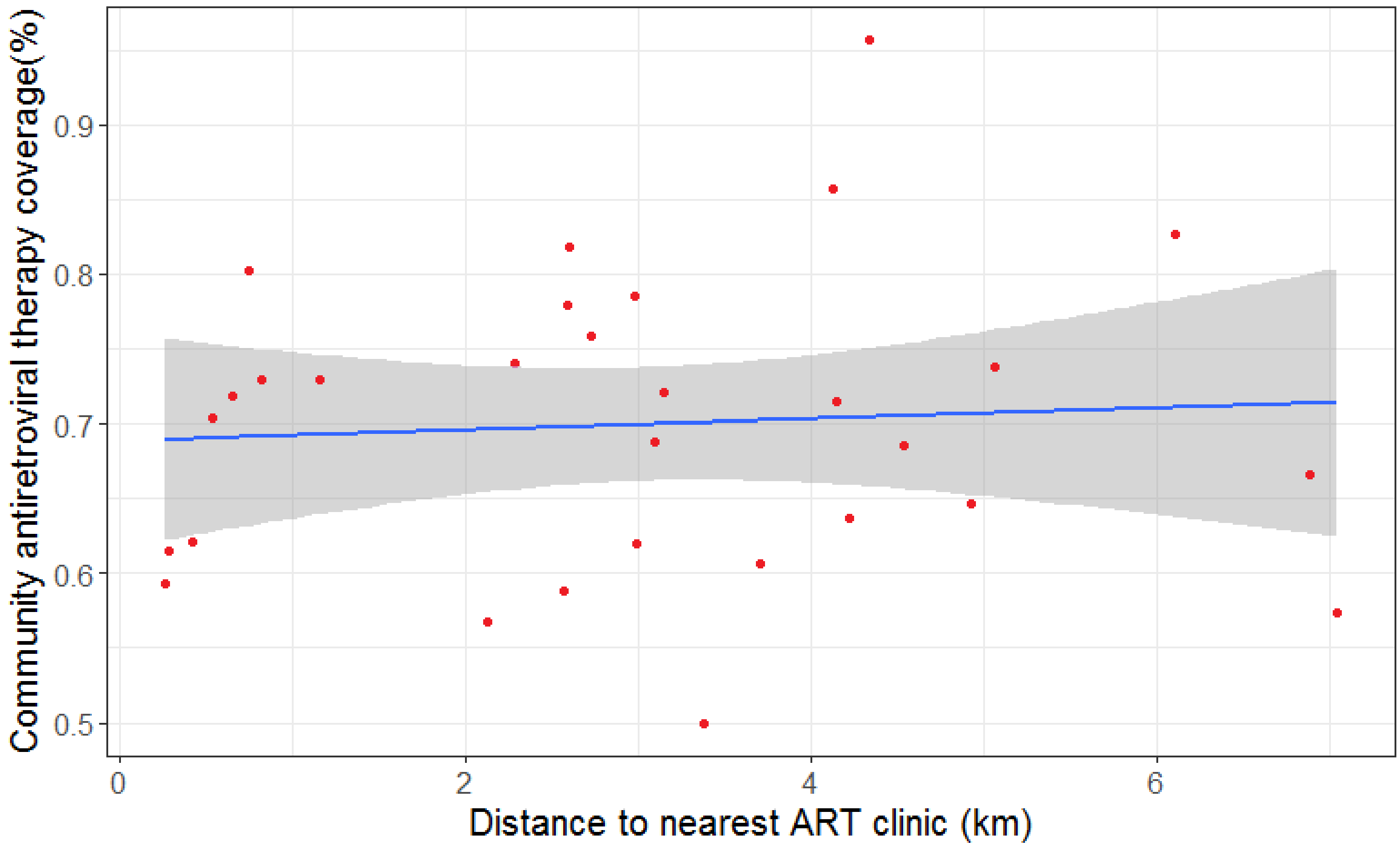

Figure 6.3 Community antiretroviral therapy coverage and distance to nearest treatment facility. Distances are from household to their treatment facility in kilometers.

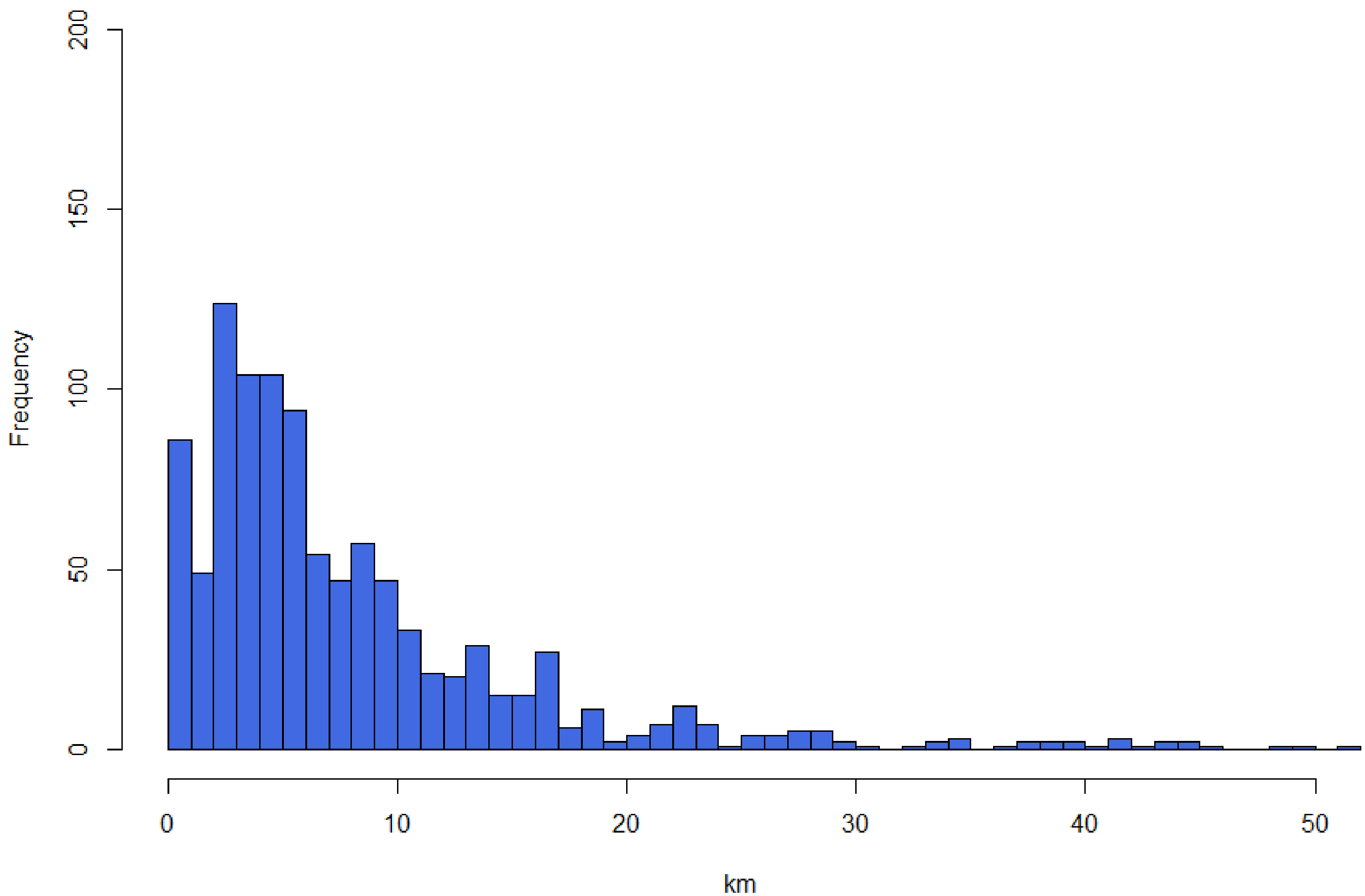

Figure 6.4 Distance traveled to treatment facility. Distances are from household to their treatment facility in kilometers.

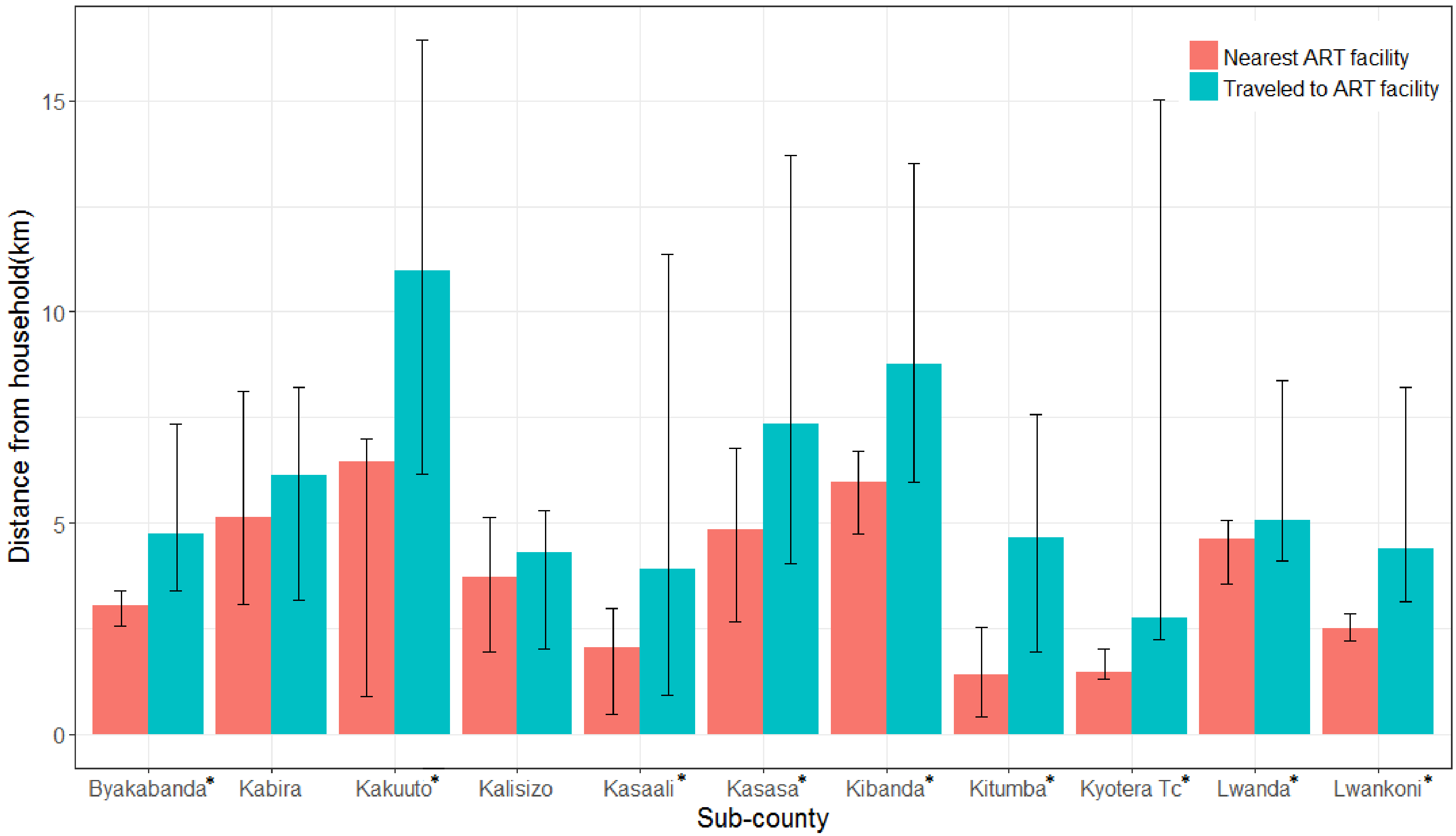

Figure 6.5 Distance to nearest treatment facility and distance traveled to treatment facility by sub-county. Plot show medians and IQRs of distances from household to treatment facility in kilometers.

Table 6.2 Regional & sub-county differences in distance to nearest ART facility and distance traveled for ART

		Distance to nearest ART facility (km)	Distance traveled to ART facility (km)	P-value	Number of ART facilities
	N	Median (IQR)	Median (IQR)		
Overall	1030	3.10 (1.65-5.05)	5.26 (3.00-10.03)	<0.001	29
Sub-County					
Byakabanda	48	3.05 (2.56-3.40)	4.74 (3.39-7.33)	<0.001	4
Kabira	60	5.12 (3.08-8.13)	6.12 (3.16-8.20)	0.161	9
Kakuuto	148	6.45 (0.89-7.01)	10.97 (6.14-16.42)	<0.001	12
Kalisizo	84	3.70 (1.97-5.13)	4.31 (2.02-5.28)	0.151	9
Kasaali	53	2.06 (0.46-2.98)	3.92 (0.92-11.36)	<0.001	11
Kasasa	126	4.84 (2.65-6.76)	7.35 (4.02-13.71)	<0.001	14
Kibanda	28	5.95 (4.73-6.72)	8.77 (5.95-13.52)	<0.001	5
Kitumba	107	1.41 (0.41-2.53)	4.64 (1.94-7.57)	<0.001	7
Kyotera Tc	109	1.47 (1.31-2.03)	2.76 (2.23-15.01)	<0.001	15
Lwanda	183	4.62 (3.55-5.05)	5.05 (4.10-8.39)	<0.001	10
Lwankoni	84	2.49 (2.20-2.84)	4.39 (3.14-8.22)	<0.001	4

Wilcoxon-rank p-values comparing distance traveled and distance to nearest facility

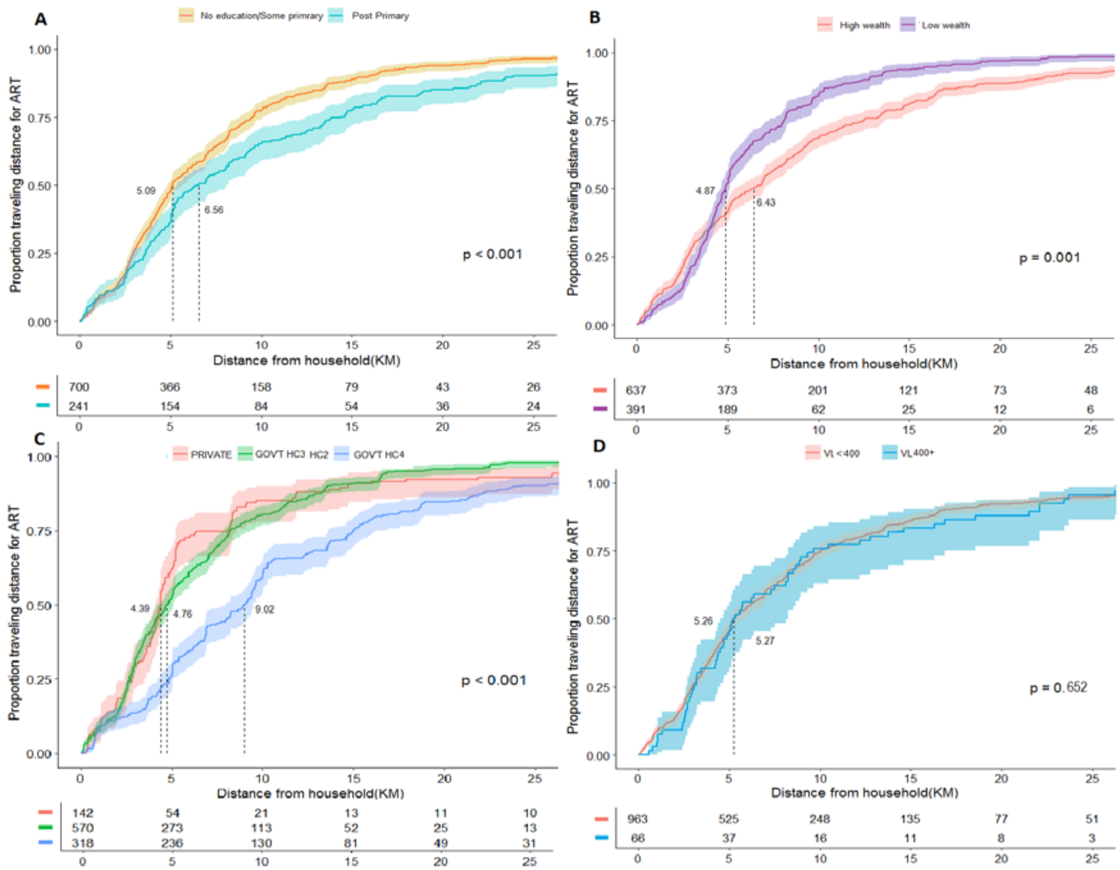

Figure 6.6 Distance traveled for HIV treatment, in the Rakai Community Cohort Study. Figure shows the cumulative proportion who traveled particular distances for ART treatment with 95% CI intervals shown as shaded areas. Distances are from their household to their treatment facility in kilometers. (A) Distance to treatment facility by traveled by education level; (B) Distance to treatment facility by traveled by wealth level; (C) Distance to treatment facility by traveled by health facility type; (D) Distance to treatment facility by traveled by viral load.

Table 6.3 Proportions and Prevalence risk ratios (PRR) of attending nearest ART facility

			Univariate			Adjusted		
	n/N	%	PRR	95% CI	P-value	adjPRR§	95% CI	P-value
Female	438/742	59.0	1.00			1.00		
Male	151/288	52.4	0.89	(0.74-1.07)	0.209	0.88	(0.73-1.06)	0.195
Age, Yrs.								
15-24	48/96	50.0	0.85	(0.62-1.14)	0.297	0.83	(0.60-1.12)	0.236
25-29	88/148	59.5	1.01	(0.79-1.28)	0.945	0.99	(0.77-1.26)	0.962
30-39	247/419	58.9	1.00			1.00		
40+	206/367	56.1	0.95	(0.79-1.15)	0.604	0.96	(0.80-1.15)	0.659
Marital status								
Married	305/573	53.2	1.00			1.00		
Previously Married	224/364	61.5	1.16	(0.97-1.37)	0.099	1.13	(0.95-1.35)	0.175
Never Married	60/93	64.5	1.21	(0.91-1.59)	0.173	1.20	(0.90-1.59)	0.199
Occupation								
Non-high risk occupation	539/935	57.6	1.00			1.00		
Bar/waitress/sex worker/Truck or motorcycle driver/Fisherfolk	46/86	53.5	0.93	(0.68-1.24)	0.626	0.92	(0.67-1.23)	0.594
Distance from household to nearest ART facility (km)	46/83	55.4	1.00			1.00		
<0.5	139/215	64.7	1.17	(0.84-1.64)	0.365	1.18	(0.85-1.66)	0.339
0.5-2	254/457	55.6	1.00	(0.74-1.39)	0.986	1.02	(0.75-1.41)	0.925
2-5	150/275	54.5	0.98	(0.71-1.38)	0.925	0.99	(0.72-1.39)	0.958
Wealth Index								
High wealth	390/637	61.2	1.00			1.00		
Low wealth	198/391	50.6	0.83	(0.70-0.98)	**0.030**	0.83	(0.7-0.99)	**0.038**
Vehicle ownership								
None	477/825	57.8	1.00			1.00		
Car or Motorcycle	112/205	54.6	0.94	(0.77-1.16)	0.590	0.96	(0.78-1.18)	0.720
Viral Load								
<400 copies/mL	551/963	57.2	1.00			1.00		
400+ copies/mL	37/66	56.1	0.98	(0.69-1.35)	0.904	0.99	(0.70-1.37)	0.955
Weight loss	30/52	57.7	0.99	(0.67-1.41)	0.968	0.98	(0.66-1.39)	0.905
Prolonged diarrhea	7/10	70.0	1.21	(0.52-2.35)	0.620	1.25	(0.53-2.43)	0.563
Prolonged fever	21/28	75.0	1.30	(0.82-1.96)	0.235	1.28	(0.80-1.94)	0.263
Hypertension	28/54	51.9	0.89	(0.59-1.27)	0.534	0.86	(0.57-1.24)	0.433
Any symptoms of opportunistic infection	115/200	57.5	1.01	(0.82-1.23)	0.948	0.99	(0.80-1.21)	0.930

§Adjusted for variables identified as potential confounders (age & sex)

Table 6.4 Unadjusted and adjusted prevalence risk ratios (PRR) of traveling to access a tertiary treatment facility (HC4), by demographic and health characteristics

			Univariate			Adjusted§		
	n/N	%	PRR	95% CI	P-Value	PRR§	95% CI	P-Value
Female	170/438	38.8	1.00			1.00		
Male	52/151	34.4	0.89	(0.64-1.20)	0.450	0.94	(0.68-1.28)	0.716
Age, Yrs.								
15-24	29/48	60.4	1.62	(1.05-2.43)	**0.023**	1.61	(1.04-2.41)	**0.028**
25-29	35/88	39.8	1.07	(0.71-1.56)	0.741	1.06	(0.71-1.55)	0.763
30-39	92/247	37.2	1.00			1.00		
40+	66/206	32.0	0.86	(0.62-1.18)	0.350	0.86	(0.63-1.18)	0.359
Marital status								
Married	106/305	34.8	1.00			1.00		
Previously Married	89/224	39.7	1.14	(0.86-1.51)	0.352	1.19	(0.89-1.59)	0.247
Never Married	27/60	45.0	1.29	(0.83-1.94)	0.231	1.16	(0.74-1.77)	0.506
Occupation								
Non-high risk occupation	204/539	37.8	1.00			1.00		
Bar/waitress/sex worker/Truck or motorcycle driver/Fisherfolk	15/46	32.6	0.86	(0.49-1.40)	0.578	0.85	(0.48-1.39)	0.556
Distance from household to nearest ART facility (km)	14/46	30.4	1.00			1.00		
<0.5	45/139	32.4	1.06	(0.60-2.01)	0.840	1.07	(0.60-2.02)	0.827
0.5-2	107/254	42.1	1.38	(0.82-2.53)	0.253	1.37	(0.81-2.51)	0.265
2-5	56/150	37.3	1.23	(0.70-2.29)	0.494	1.21	(0.69-2.25)	0.530
Wealth Index								
High wealth	153/390	39.2	1.00			1.00		
Low wealth	68/198	34.3	0.88	(0.65-1.16)	0.361	0.90	(0.67-1.20)	0.474
Vehicle ownership								
None	186/477	39.0	1.00			1.00		
Car or Motorcycle	36/112	32.1	0.82	(0.57-1.16)	0.289	0.83	(0.57-1.17)	0.305
Viral Load								
<400 copies/mL	203/551	36.8	1.00			1.00		
400+ copies/mL	18/37	48.6	1.32	(0.79-2.08)	0.258	1.25	(0.74-1.97)	0.377
Weight loss	13/30	43.3	1.24	(0.67-2.09)	0.457	1.23	(0.66-2.08)	0.476
Prolonged diarrhea	5/7	71.4	2.04	(0.73-4.46)	0.115	2.01	(0.71-4.41)	0.124
Prolonged fever	14/21	66.7	1.95	(1.08-3.24)	**0.016**	1.87	(1.04-3.12)	**0.024**
Hypertension	15/28	53.6	1.56	(0.88-2.55)	0.101	1.76	(0.98-2.92)	**0.042**
Any symptoms of opportunistic infection	51/115	44.3	1.23	(0.89-1.67)	0.196	1.28	(0.92-1.75)	0.127

§Adjusted for variables identified as potential confounders (age & sex)

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Chapter 7 Conclusions

7.1 Summary of Results

This dissertation focused on the HIV care cascade and factors associated with engagement in HIV care in rural Uganda. Using unique data from a large population-based cohort, we sought to determine what individual and structural factors are associated with engagement in care within rural Ugandan communities. We examined the care cascade and whether engagement in HIV care differed (1) among key demographics and sub-populations, (2) among individuals at higher risk for transmission of HIV, and (3) by geographic access to antiretroviral therapy (ART) treatment facilities. Our studies were conducted using data from the Rakai Community Cohort Study, a well-characterized population-based study in Rakai, Uganda.

Chapter 3 of this dissertation presents the first study characterizing the HIV care cascade in the Rakai Community Cohort. Our main findings were high levels of acceptance of HIV counseling and diagnoses, high levels of ART initiation among those enrolled in care and high rates of viral suppression among those retained on ART. However, low linkage to care was the most significant barrier within the HIV care continuum, impeding access to other critical components of care and resulting in suboptimal viral suppression among all HIV-positive persons. Our results suggest the need to promote enrollment into HIV care and target interventions towards HIV-positive males, younger individuals, and in-migrants.

In Chapter 4, we assessed the association between being on ART and sexual risk behavior among those living with HIV. Our main finding in Chapter 4 was modest, but significantly lower levels of enrollment in HIV care and ART initiation among persons with risky sexual behaviors, particularly among non-monogamous youth. Our results suggest that there were lower levels of enrollment in HIV care and ART initiation among fishermen. The results from Chapter 4 also suggest a need to target interventions and promote ART use among those whose sexual behaviors made them most at risk for onward HIV transmission.

In a setting where HIV care is provided free of charge, the group of individuals who do not utilize services includes those who refuse care and potentially those who have limited physical access to care, e.g., people living in remote areas. Chapter 5 presents our final study in which we examine the geographic distribution of treatment facilities in the region and characterize geospatial patterns of treatment facility utilization and viral suppression. Our primary hypothesis was that ART utilization would be lower in communities located further from an ART treatment facility. In south-central Uganda, we found substantial heterogeneity in the distance to the nearest treatment facility; however, our main finding was that distance to the nearest treatment tactility was not predictive of community ART coverage. Chapter 5 also demonstrated that virologic outcomes among those on ART did not vary by distance traveled for treatment. In addition, we found that 57% of people in care did not utilize the nearest clinic facility, and that distance traveled, and type of HIV services used was associated with socioeconomic status, suggesting that relatively wealthier individuals exercise greater choice of where they receive their HIV treatment.

7.2 Implications for Research, Policy, and Programming

More than thirty years into the global HIV epidemic, there is still no cure; however, there have been major advances in treating HIV[21]. The availability and rapid scale-up of ART has transformed what was an inevitably fatal disease into a manageable chronic condition[139,216]. This has led to notable declines in the worldwide rates of new infections[11,217]and AIDS-related deaths[4,218]. Given these benefits of ART, the Joint United Nations Programme on HIV/AIDS (UNAIDS) has set a '90-90-90' target by 2020 to diagnose and counsel 90% of all HIV-positive individuals, provide ART for 90% of those diagnosed as HIV-positive, and achieve sustained viral suppression for 90% of those treated[14]. This translates to 73% of all HIV-positive individuals achieving viral suppression.

In this dissertation, we found the rate of diagnosis amongst HIV-positive persons was 98%, meeting the 2020 goal of the UNAIDS 90-90-90 initiative. The high rates of HIV diagnosis in this population occurred within a context of a community-based HIV testing strategy, ongoing health education which strongly recommends receipt of results, and psychosocial support services which maintaining contact with people who received positive results. The details of the RHSP counseling program have been described previously[219,220], but in brief, HIV diagnosis during the RCCS surveys is based on a three rapid test algorithm, and same day linkage to HIV counseling and testing. Participants also receive pre-test counseling on HIV prevention and eduaction of the benefits and importance of learning their serostatus. However, participants are given the option of declining their result even if they provide a blood sample. HIV post-test counseling is provided free of charge by trained Rakai Program counselors at the time of the RCCS survey, in participant's homes, satellite counseling offices, or other community venues of the participant's choice. In addition, participants have the option to receive their HIV results individually or together with their partner. While this community-based HIV testing strategy is unique to Rakai, the successes of this community-based approach is likely to be relevant to other African clinical settings.

Amongst those diagnosed with HIV, we found the rate of ART initiation was 65%, and this dissertation highlighted a critical need to improve enrollment in HIV care among males, younger individuals, and in-migrants in order to reach UNAIDS 90-90-90 treatment targets. In order to reach this goal, the Rakai Health Sciences Program has recently expanded a novel demand generation intervention called the "Stylish Man – Stylish Living" campaign. The campaign aims to increase HIV service uptake by demedicalizing HIV care messaging through a combination of community mobilization, edutainment and mass media. Preliminary data show that exposure to this campaign is high among HIV-positive males and younger individuals (Personal Communication Maria Wawer, 7.Dec.2016).

This dissertation adds to the growing body of evidence on the barriers to engagement in HIV care faced by HIV-positive persons. Suboptimal utilization of HIV care and treatment in other contexts has been associated with low awareness and demand for services, as well as poor accessibility or quality of care[84,221,222]. In addition, a systematic review of factors associated with HIV testing, ART initiation, and ART adherence in low-income countries highlighted socioeconomic and health system barriers to HIV care[223]. Other important barriers include (1) interpersonal factors leading to low rates of HIV status disclosure and insufficient social support[91]; (2) environmental barriers including inconvenient clinic hours and location, long waiting times at clinics, lack of available appointments, perceived low quality of HIV services, and disrespectful treatment from HIV care providers or staff [90,92,93,224]; and (3) structural barriers including poverty, gender inequity, and HIV-related stigma and discrimination[90,224]. Qualitative studies may provide some insight into why males, younger individuals, and in-migrants under-utilized HIV services. Since this study was conducted, we have expanded the HIV care questions in the RCCS survey to include more detailed information about the use of HIV services. We anticipate these new data will enable us to target resources for HIV treatment programs appropriately and efficiently within Rakai with the ultimate goal of providing ART for 90% of those diagnosed as HIV-positive.

Lastly, in this dissertation we found the rate of sustained viral suppression for individuals on ART was 98%, meeting the 2020 goal of the UNAIDS 90-90-90 initiative. The high rates of viral suppression in this population occurred within a context of a targeted adherence intervention reported in detail elsewhere[225], in which, people living with HIV are trained as peer health workers to provide adherence monitoring and psychosocial support to fellow patients, both in clinic and during monthly home visits. The impact of these interventions on sustained viral suppression should be generalizable to other HIV treatment programs, and our findings are in line with a growing body of evidence that people living with HIV in sub-Saharan Africa have high levels of adherence[226–229].

7.3 Strengths and limitations

This dissertation represents a novel contribution to the scientific evidence on engagement along the HIV care continuum and has several notable strengths and limitations. Amongst the strengths of this study is the population-based data and large sample size, which facilitated exploration of individual and structural factors associated with engagement in care. Additionally, the highly skilled RHSP implementation team and the strong relationships between the study team and the study population facilitated a rigorous examination of factors associated with engagement in care. Our study was strengthened by the use of laboratory, clinical, geospatial, and survey data linked at an individual level.

This dissertation does, however, have some important limitations. The first limitation to the study is in the selection of participants. After years of follow-up, RCCS communities may be atypical. However, the RCCS is an open cohort, with an annual in-migration of approximately 25-30% (balanced by out-migration), resulting in approximately 2,000 new participants per year with no prior RCCS exposure. We analyzed data from old and new cohort participants and have determined that only a limited number of factors (primarily prior receipt of HCT) are higher among the former group. Sociodemographic characteristics, the age of sexual debut, and number and types of partnerships are similar to those reported in the Uganda National HIV Serosurvey of 2004-05[147], the Uganda UNGASS Progress Reports 2008-09[148], and the 2011 Uganda Demographic and Health Survey[149]. The correlates identified are likely to be generalizable other rural African clinical settings.

A second limitation is that engagement with health services and sexual behavior were assessed through self-report and, therefore, may have been affected by recall or social desirability bias. Efforts were made to minimize this bias through the comfortable, confidential interview environments and through the use of clear time references within questions. Additionally, self-reported ART use has been validated by assays of antiretroviral drugs which showed 76% sensitivity and a specificity of 99%[158]. Thus, self-reports may underestimate true ART use, and our estimates are likely to be conservative. As a retrospective data analysis, some potentially important mediators of engagement in care were unavailable or not ideally measured, such as knowledge of and attitudes towards HIV treatment, fear of stigma or discrimination, and social support.

Additionally, the proportion of the community-based samples used in these studies that comes from the same household as another survey participant in the sample violates the assumption of independently distributed outcomes for the generalized linear model. Acceptance of HIV care by one member of a household is likely associated with the engagement in care of other household members, and by ignoring this potential correlation, the effect size would be consistent, but the confidence intervals would be wider if the within-household correlation was not accounted for in regression models.

A final limitation is that our analysis was cross-sectional limiting the understanding of how participants' engagement changed over time at an individual-level. However, our findings are consistent with other studies which used longitudinal data for cascade analysis[27,230,231]. Similarly, these studies find linkage is the most important bottleneck to engagement in HIV care.

We attempted to follow patients longitudinally, but a major challenge in generating longitudinal patient records in Uganda is the absence of a unique patient identifier. In such instances, probabilistic matching methods, where several personal attribute values (name, age, date of birth, and address) are compared between two records and each personal attributes is assigned a weight that indicates how closely the two values match, have been successfully used in other settings[131]. We attempted to match patients based on names and date of birth, however, this proved challenging since in Uganda names often change (e.g., name changes if they become the parent of twins) and dates of birth are often not known. Moreover, our matching was dependent on the quality of the electronic patient record. We found that in government-run clinics the electronic records were not updated regularly and had missing information compared to paper records. Based on our matching of clinic records only 54% (834/1543) of HIV-positive RCCS participants in 30 continuously followed communities were enrolled in HIV care. However, when we used self-reported information from RCCS surveys, 70% (1079/1543) were enrolled in care. Figure 7.1 shows preliminary findings from our longitudinal examination in RCCS survey communities.

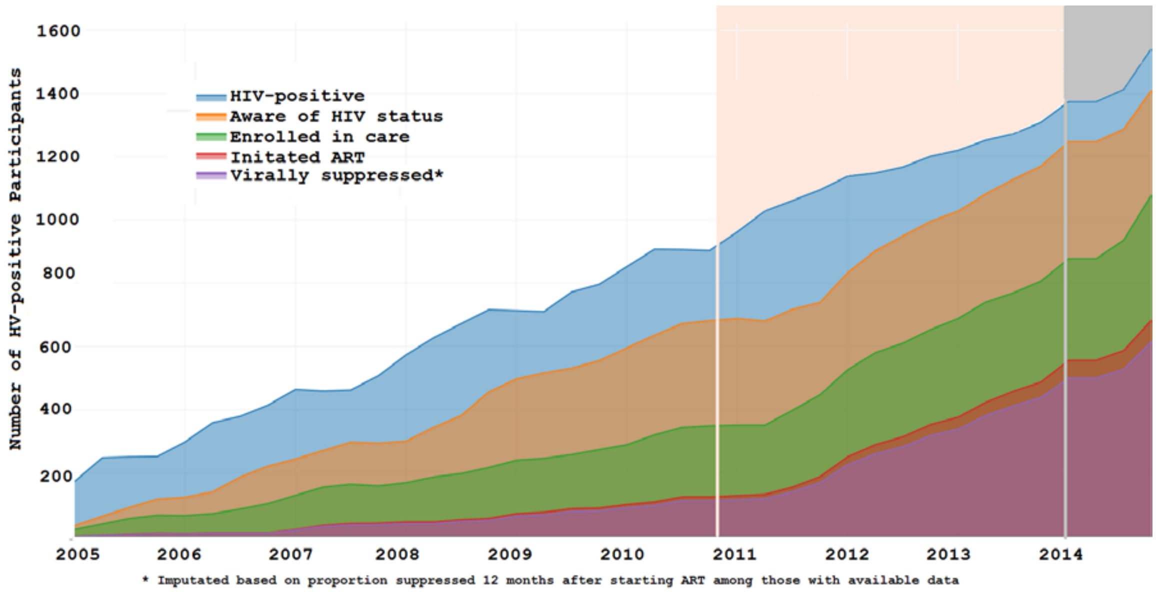

Figure 7.1 Longitudinal HIV care cascade from 30 Rakai Community Cohort Study (RCCS) continuously followed communities. ART was initiated for symptomatic individuals and using a threshold <250 cells/mL through 2010. Starting in 2011 ART initiation used a threshold <350cells/mL and the threshold was raised to <500 cells/mL in 2014.

7.4 Conclusions

Findings from this dissertation have important implications for future research, policy, and programming. This dissertation aimed to answer the question: "If you build a system and provide free HIV-care services, will they come?" The answer, as it frequently is in epidemiologic research, is: "it depends." Relevant to public health policy, this dissertation documented that utilization of HIV care is complex, clinic data are often unsatisfactory, and under-utilization cannot be explained solely by the distance to services. We documented important successes in the areas of HIV diagnoses, ART initiation, and viral suppression. However, interventions are needed to promote enrollment of hard to reach and high-risk groups like HIV-positive males, younger individuals, and in-migrants into HIV care. Engaging these priority populations will require new resources and strategies in order to meet global targets for ART initiation, retention, and viral suppression. Our finding that persons with high-risk profiles were less likely to initiate ART suggests one reason why HIV epidemics in some regions may not have been substantially mitigated despite scale-up of HIV treatment, and that effective treatment as prevention will depend on enrolling and retaining these high-risk individuals on ART.

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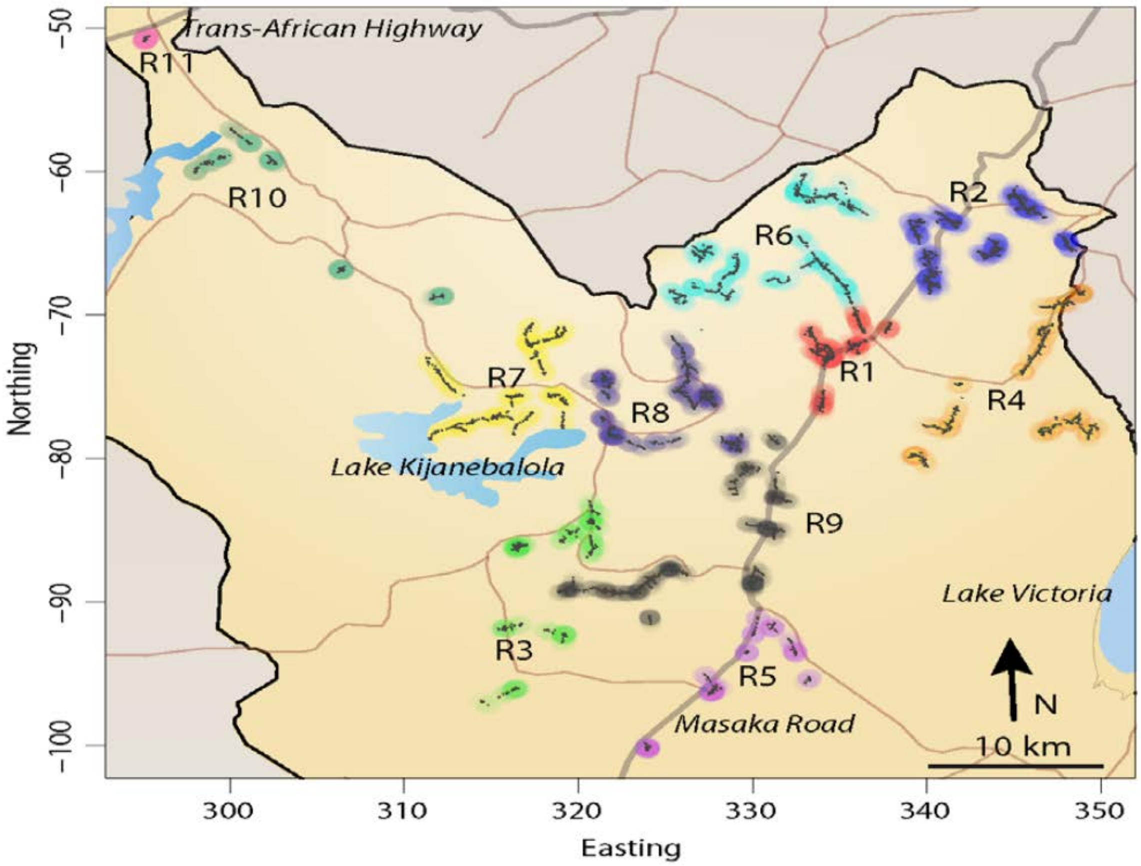
Appendix



Appendix Figure 1. Rakai District, in rural south-central Uganda. There are two primary highways (Masaka Road: part of Kampala-Tanzania Highway and the Trans-African Highway to Rwanda/Congo, with numerous secondary roads. The RCCS study communities are divided between 11 regions (indicated in color).

Appendix Figure 2. Ministry of Health HIV care/ART card (Blue Card).

HIV CARE/ART CARD ____

Unique # ______________

District ______________ Health unit______________ Clinical team leader

Name:__________ Surname __________ __________ Given name __________ Pt clinic #______________

Sex: M ☐ F ☐ DOB (dd/mm/yyyy) Age_____ Marital status______________

Address District______________________ Sub-County ______________

Parish______________________ LC1______________

Telephone (whose):______________________________

Care entry point: ☐ PMTCT ☐ TB ☐ Under 5 ☐ Outreach ☐ Other: Specify
☐ Medical out patient ☐ STI ☐ Inpatient ☐ Exposed infant__________

Treatment supporter/med pick-up if ill: ______________________________

Address District______________________ Sub-County ______________

Parish______________________ LC1______________

Telephone (whose): ______________________________

Home-based care provided by:______________________________

Names of family members and partners	Age	HIV P/N/U	HIV care Y/N	Unique no.

Exposed infant follow-up

Exposed infant (Name/#)	DOB	Infant feeding practice at 3 mos	CTX started by 2 mos	HIV test Type/ Result	Final status	(If confirm +) Unique ID

Prior ART	Yes ☐	None ☐	
Y(√)	Prior ART	Date	
	PEP	(dd/mm/yyyy)	Where__________ ARVs__________
	PMTCT only	(dd/mm/yyyy)	Where__________ ARVs__________
	Earlier ARV not transfer	(dd/mm/yyyy)	Where__________ ARVs__________

HIV care	Date	
Confirmed HIV+ test	(dd/mm/yyyy)	☐ Ab ☐ PCR Where__________
HIV enrolled	(dd/mm/yyyy)	☐ HIV care transfer in from __________
Eligible for ART	(dd/mm/yyyy)	Clinical stage__________ CD4__________ ______
Eligible and ready	(dd/mm/yyyy)	☐ Presumptive clinical HIV diagnosis of severe HIV infection in infant ☐ PCR-infant

Drug allergies	Relevant medical conditions

ART Care COHORT: MM YYYY

Date

(dd/mm/yyyy) ART transfer in from__________ ARVs__________

(dd/mm/yyyy) Start ART 1st-line initial regimen______----__________

1st-line

At start ART: Wt______ Cl. Stage______ CD4______ Preg______

Substitute within 1st-line

(dd/mm/yyyy) New regimen______________________ Why______

(dd/mm/yyyy) New regimen______________________ Why______

2nd-line

Switch to 2nd-line (or substitute within 2nd-line)

(dd/mm/yyyy) New regimen______________________ Why______

(dd/mm/yyyy) New regimen______________________ Why______

ART treatment interruptions -- STOP or missed drug pick-up

Stop or Lost (circle)	Stop Lost	Stop Lost	Stop Lost	Stop Lost	Stop Lost	Stop Lost	Stop Lost
Date	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)
Why							
Date if restart / re-activated	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)	(dd/mm/yyyy)

Status	Date	
Transfer out	(dd/mm/yyyy)	Where__________
Lost to follow-up (drop)	(dd/mm/yyyy)	
Dead	(dd/mm/yyyy)	

Infant Feeding Practice on infant cards:
Exclusive Breast Feeding;
Replacement Feeding;
Mixed Feeding

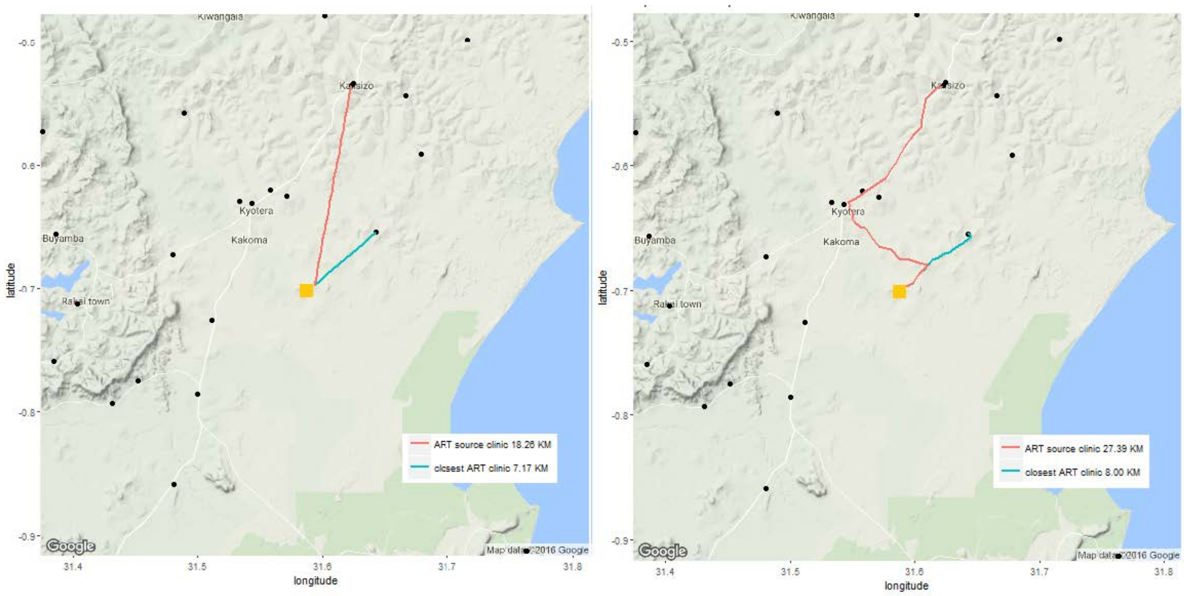
HIV-exposed infant final status at 18 months:
DEAD if dead (write in date of death if known)
P if positive N if negative and no longer breast feeding
N/BF if negative and still breast feeding
U if status unknown

Why SUBSTITUTE or SWITCH codes:
1 Toxicity/side effects
2 Pregnancy
3 Risk of pregnancy
4 Due to new TB
5 New drug available
6 Drug out of stock
7 Other reason (specify)
Reasons for SWITCH to 2nd-line regimen only:
8 Clinical failure
9 Immunologic failure

Why STOP codes:
1 Toxicity/side effects
2 Pregnancy
3 Treatment failure
4 Poor adherence
5 Illness, hospitalization
6 Drugs out of stock
7 Patient lacks finances
8 Other patient decision
9 Planned Rx interruption
10 Other (specify)
11 Excluded HIV infection in infant

Follow-up education, support and preparation for ARV therapy

		Date/comments	Date/comments	Date/comments
Educate on basics, prevention, disclosure	Basic HIV education, transmission			
	Prevention: abstinence, safer sex, condoms			
	Prevention: household precautions, what is safe			
	Post-test counselling: implications of results			
	Positive living			
	Testing partners			
	Disclosure, to whom disclosed (list)			
	Family/living situation			
	Shared confidentiality			
	Reproductive choices, prevention MTCT			
	Child's blood test			
	Progression of disease			
	Malaria prevention, IPT, ITN			
Pro-gression, Rx	Available treatment/prophylaxis (CTX, INH)			
	Follow-up appointments, clinical team			
ART preparation, initiation, support, monitor, Rx	ART -- educate on essentials (locally adapted)			
	Why complete adherence needed			
	Adherence preparation, indicate visits			
	Indicate when READY for ART: DATE/result Clinical team discussion			
	Explain dose, when to take			
	What can occur, how to manage side effects			
	What to do if one forgets dose			
	What to do when traveling			
	Adherence plan (schedule, aids, explain diary)			
	Treatment supporter preparation			
	Which doses, why missed			
	ARV support group			
Home-based care, support	How to contact clinic			
	Symptom management/palliative care at home			
	Caregiver booklet			
	Home-based care – specify			
	Support groups including community support group			



Appendix Figure 3. Nearest ART clinic analysis. The distance from the participant's home to all facilities offering HIV care in the region (black dots) was calculated by taking the travel distance along the open street map road network from households (yellow square) to the facilities. The left panel shows the Euclidian (straight line) distance calculations, and the right panel shows the Open Street map (OSRM) distance calculations.

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Applied epidemiologist with **domestic and international** health system experience coupled with **broad medical research** background, dedicated to improving health by focusing on **vulnerable populations** through addressing social determinants, and **implementation science**.

Work extremely well in teams and individual settings
Ability to coordinate multiple tasks and meet deadlines under pressure
Excellent problem-solving capabilities
Skilled in gathering, analyzing, and managing data
Proficient in R, SAS, SUDAAN, STATA, Mplus, EpiInfo, Word, Excel and Access

EDUCATION

Expected May 2017	**Doctorate of Public Health,** Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD **Dissertation topic:** Trends and Determinants of the HIV Treatment Cascade and ART effectiveness in Rakai, Uganda
2008	**Master of Science,** Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD **Concentration:** Infectious Disease **Thesis project:** Impact of religiosity on risk behaviors and access to care in injection drug users in Baltimore, Maryland
2005	**Bachelor of Arts,** Public Health with Life Science Focus, Case Western Reserve University, Cleveland, OH **Concentration:** Biology Capstone project: Performed a needs assessment of health services in Cleveland for commercial sex workers

PROFESSIONAL EXPERIENCE

2013 – Present **Research Assistant,** Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health.
Rakai Community Cohort Study, a community-based open cohort in rural Uganda.

- Leading process evaluation for the implementation of the "Stylish Ugandan Man" Community Mobilization and HIV education campaign
- Lead biostatistician for the evaluation of the Peer Support and Engagement in HIV Care randomized control trial

-Poster presentation ***Conference on Retroviruses and Opportunistic Infections annual meeting*** 2017

2013 – 2014 **Research Assistant,** Department of Medicine, Johns Hopkins Hospital. Center for Child and Community Health Research

- Conducted a cost-effectiveness evaluation of viral load testing and targeted outreach in Baltimore City HIV surveillance system
- Provided biostatistical support and analysis for center community health projects

2010 – 2012 **Epidemiologist** GS-12, National Center for Health Statistics, Centers for Disease Control and Prevention.

- Analyzed complex survey data to generate national estimates and trend analysis using the National survey of family growth (NSFG).
- Conducted data quality checks to facilitate the timely release of the NSFG public use 2009-2010 data files and associated documentation.
- Developed, evaluated and implemented questionnaire changes for the 2011-2015 continuous NSFG.

2008 – 2010 **Fellow, Emerging Leaders Program** GS-09**,** Department of Health and Human Services

- Conducted a complex analysis of National Health and Nutrition Examination Survey (NHANES) data to generate regional disease estimates for Los Angeles County
  -Oral presentation at the American Public Health Association meeting 2010
- Engaged source organizations to identify and share national and sub-national data on diarrheal disease mortality and malnutrition statistics for the longitudinal cohort study, National Institutes of Health, Fogarty International Center
- Developed objectives for Healthy People 2020 social determinants of health topic area.
- Conducted an outbreak investigation with local health department to identify active tuberculosis cases and break the chain of transmission.
- Conducted an evaluation of recommendations from external consultation meeting to address social determinants of HIV, Viral Hepatitis, STD, and TB.

2007 – 2008 **Research Assistant,** Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health. Community Access to Cervical Health Study, a population-based cross-sectional cervical cancer screening program in rural India.

- Served as the lead in examining barriers to participation in cervical cancer screening and treatment, using qualitative research methods
- Conducted an analysis of predictors of participation in cervical cancer screening program, using statistical methods

2007 – 2008 **Field Supervisor**, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

The National HIV Behavioral Surveillance System, a community-based cross-sectional survey designed to examine risk behaviors and their prevalence over time among persons at highest risk for HIV infection in the United States.

- Supervised field staff in survey administration, HIV testing procedures , and data management
- Interviewed individuals from high-risk populations on neighborhood factors and HIV risk behaviors and counseled for HIV pre- and post-testing

2007 **Office Assistant,** Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
The Multicenter AIDS Cohort Study is an ongoing prospective study of the natural and treated histories of HIV-1 infection in homosexual and bisexual men in Baltimore, Chicago, Pittsburgh and Los Angeles.

- Developed lay language summaries of published research articles for the focused audience of the study participants
- Assisted with the administrative aspects of managing a large cohort study

2000 – 2005 **Research Assistant,** Department of Neurology, Autonomic laboratory University Hospitals, Cleveland, Ohio

- Analyzed and compiled results from autonomic testing on clinical patients

-Poster presentation at the American Autonomic Society International Symposium 2003

2004 **Experiential Learning Fellow,** Case Western Reserve University

Andhra Pradesh, Commissioner of Family Welfare Department Hyderabad, India

- Served as the lead in an ethnographic study of HIV/AIDS policy makers in an Indian urban setting
- Interviewed local experts working on the HIV epidemic and Compiled a report based on ethnographic fieldwork

2003 – 2005 **Research Assistant,** Department of Molecular Biology, Case Western Reserve University

- Conducted laboratory assays on group one intron splicing in Campylobacter

TEACHING EXPERIENCE

2007 - 2008 **Teaching Assistant**, Department of Epidemiology, Johns Hopkins UniversityEpidemiology and Public Health Impact of HIV and AIDS; Advanced Topics On Control and Prevention Of HIV/AIDS; Epidemiology And Natural History Of Human Viral Infections

- Developed exam questions with teaching team and evaluated exams and papers
- Advised students on HIV research question topics and paper writing

2007 **Journal club coordinator,** Department of Epidemiology, Johns University

2005 **Teaching Assistant**, Department of Biology, Case Western Reserve University

- Prepared bacterial cell cultures for microbiology laboratory sessions
- Assisted with laboratory exercises.

OTHER EXPERIENCE

2003 **Americorps service volunteer**, Corporation for National and Community Service
- Completed 450-hour term of health education service
- Provided HIV prevention education through the American Red Cross
- Assisted the American Lung Association in compiling an asthma resource guide
- Assisted the Environmental Health Watch with community education on asthma and household lead exposure

PUBLICATIONS

1. Chang LW, Nakigozi G, **Billioux VG**, Gray RH, Serwadda D, Quinn TC, Wawer MJ, Bollinger RC, Reynolds SJ. Effectiveness of peer support on care engagement and preventive care intervention utilization among pre-antiretroviral therapy, HIV-infected adults in Rakai, Uganda: a randomized trial. AIDS and Behavior. 2015 Oct 1;19(10):1742-51.
2. **Billioux VG,** Sherman SG, Latkin C. Religiosity and HIV-Related Drug Risk Behavior: A Multidimensional Assessment of Individuals from Communities with High Rates of Drug Use. J Relig Health. 2014 Feb;53(1):37-45.
3. Kruszon-Moran D, Porter KS, McQuillan G, **Billioux VG**, Kim-Farley R, Hirsch R. Infectious disease prevalence in Los Angeles county-a comparison to national estimates, 1999-2004. Data from the National Health and Nutrition Examination Survey. National Center for Health Statistics Data Brief. 2012 Apr;(90):1-8.
4. Chandra A, **Billioux VG**, Copen CE, Sionean C. HIV Risk-Related Behaviors in the United States Household Population Aged 15–44: Data from the National Survey of Family Growth, 2002 and 2006–2010. National health statistics reports; no 46. 2012.
5. Chandra A, **Billioux VG**, Copen CE, Balaji A, DiNenno, E. HIV Testing in the U.S. Household Population Aged 15–44: Data From the National Survey of Family Growth, 2006–2010. National health statistics reports; no 58. 2012.

HONORS AND AWARDS

2015 **Alexander Langmuir Graduate Teaching Fellowship in Professional Epidemiology,** Johns Hopkins Universty

2010 **Excellence in Epidemiology award: Four Large TB Outbreaks Investigations – Fulton EpiAid,** National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

2010 **Excellence in Emergency Response: 2009 H1N1 Flu Group - Region 1 Epidemiology desk liaison,** National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention