The Effects of Antiretroviral Therapy Scale-Up on Tuberculosis and Non-Communicable Diseases Health Service Utilization and Mortality Risk among the General Population in Rural South Africa, 2009-2014

Suzue Saito

Submitted in partial fulfillment of the
requirements for the degree
of Doctor of Philosophy
under the Executive Committee
of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2018

ABSTRACT

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The overall purpose of this dissertation was to examine evidence of spillover effects of HIV care and treatment service scale up in sub-Saharan Africa in the past decade. Particularly the focus was to quantify any effect HIV treatment initiation by a person living with HIV (PLHIV) may confer health benefits to the HIV negative population by increasing utilization of non-HIV services or reduce mortality risk.

This dissertation had three primary aims. The first aim was to conduct a systematic review of the effect of increasing ART uptake in high HIV prevalence communities on use of non-HIV health services, including maternal, child, in/out-patient, non-HIV laboratory, and TB diagnosis and treatment services. Overall positive effects were found on the majority of health service indicators examined for non-HIV laboratory service utilization and Tuberculosis diagnosis and treatment services. We found negative associations on the majority of indicators examined for child health services. The existing evidence did not point to clear tendencies for maternal health services and outpatient and inpatient services. Restricting the sample to studies with stronger study designs for causal inference, the positive effect on non-HIV laboratory services and the negative impact on child health services held but evidence was mixed for TB diagnosis and treatment services, maternal health services and outpatient and inpatient services.

The second aim of this dissertation was to conduct regression discontinuity quasi-experiments to determine whether exposure to health benefits from ART utilization by a person living with HIV (PLHIV) in a household affects uptake of TB, hypertension (HTN) and diabetes mellitus (DM) treatment by other household members with these conditions. The study was conducted in the comprehensive population cohort followed by the Africa Health Research Institute (AHRI) in Kwazulu-Natal (KZN), South Africa. We linked PLHIV engaged in HIV care to their cohabitating household members aged ≥15 years using a unique identifier for homesteads. Household ART utilization significantly increased treatment for diabetes (RR 1.90: 95% CI 1.07-3.40) but not for TB (RR 1.12: 95% CI 0.71-2.03) or hypertension (RR 1.31: 95% CI 0.97-1.77).

The third aim of this dissertation was to use the same regression discontinuity design and KZN cohort data as in aim 2 to determine whether exposure to health benefits from ART utilization by PLHIV in a household reduces all-cause mortality of other household members. Overall, household ART utilization did not decrease all-cause mortality (Hazard Ratio (HR) 0.95: 95% CI 0.65-1.4), however, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold showed reduced all-cause mortality by 67% (HR 0.43: 95% CI 0.22-0.85) among household members of PLHIV on ART; the reduced risk was driven largely by the significant reduction noted among female household members (HR 0.21: 95% 0.08, 0.56).

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Acknowledgements

I would like to thank the members of my dissertation committee who have provided support, guidance and expertise in assisting me to define my research question and complete my dissertation. In particular I am grateful to Dr. Andrea Howard for her many years of mentorship and friendship. I would also like to especially thank Dr. Till Baernighausen for providing invaluable analytic support throughout the process of designing and completing this dissertation. In addition, thanks to Drs. Wafaa El-Sadr, Magda Cerda, and Frank Tanser for their time and insightful and substantive feedback to the dissertation papers. I am also grateful to the Africa Health Research Institute for sharing their data, and in particular to Dr. Jacob Bor for sharing his work on Regression Discontinuity Design using the same cohort data.

I am deeply grateful to Drs. Elaine Abrams, Batya Elul, Tiffany Harris, Matthew Lamb and Yen Pottinger for providing critical feedback on my dissertation defense presentation. Additionally, I would like to thank Drs. Chloe Teasdale and Stephanie Shiau for their friendship, support and technical assistance throughout the doctoral program, and Dr. Stephanie Kujawski who served as the second reviewer for my systematic review. Finally thanks to Dr. Leslie Davidson and Liliane Zaretsky for their encouragement, support and consideration throughout my studies and dissertation writing.

Dedication

This dissertation is dedicated to my children Nadia and Aleksandar Mitic and my husband, Ninoslav Mitic, who supported me with patience and love throughout the doctoral studies and to my father and mother, Norio and Helen Saito, who taught me the value of hard work, persistence, and critical thinking from my early years.

Chapter 1: Introduction

The expansion of antiretroviral therapy (ART) to 14 million people in Sub-Saharan Africa (SSA) is one of the most successful global public health programs ever undertaken (1) with more than 70 billion dollars contributed since 2004 through the United States President's Emergency Plan for AIDS Relief (PEPFAR) alone (2). This massive investment, along with other contributions by the Global Fund to Fight AIDS, Tuberculosis and Malaria and investments from the affected countries, have achieved substantial results for the health of people living with HIV (PLHIV). Antiretroviral therapy (ART) coverage in SSA increased rapidly from single digits in the early 2000s to 53% in 2016 (1). Modeling studies have estimated that scale-up of ART has saved more than nine million life-years in SSA (3). Empirical studies have also linked increasing coverage of ART to decreased HIV-related mortality and all-cause adult mortality among PLHIV (4-10). #

Beyond the well-documented benefits of ART for PLHIV, the potential effect of these investments on the broader health system and on the health and survival of overall populations without HIV infection has been an active area of research and debate. It is widely acknowledged that HIV program funding has contributed to improving several components of the health systems, from renovations of health facilities and laboratories, strengthening processes to coordinate and manage patient care and modernization of health information and supply chain management systems (11-17). At the same time, there is evidence that the HIV epidemic has adversely affected the limited number of health workers in the severely affected countries. The need to provide comprehensive HIV care to large numbers of PLHIV has added additional burden to a persistently overstretched workforce (18-25).

It remains unclear whether the investments in HIV programs have on balance translated to improved overall quality of health services and access to such services− a plausible pathway through which improved health and survival of the general population can be achieved. Some studies have reported a decrease in utilization of non-HIV services, particularly in relation to child health services (26-30) and maternal health services (20, 26, 30) subsequent to the launch of HIV treatment services at health facilities. At the same time, other studies have noted the opposite using different metrics or in different settings (19, 20, 27, 31-37)—with ART availability associated with increased utilization of non-HIV health services. Still other studies noted no significant effect (19, 21, 26-28, 30, 31, 35, 36, 38). The diverse contexts where these studies were conducted and the use of non-experimental study designs have prevented the rigorous synthesis of existing evidence.

The overall goal of this dissertation work is to generate stronger evidence of spillover effect of ART scale up on access to health care and in turn improved health outcomes in the general population. Specifically, we examined the effect of PLHIV initiating treatment on the propensity for HIV negative cohabitating household members to seek care for non-HIV conditions, including TB, HTN and DM. We additionally examined whether there were any survival benefits on cohabitating household members after PLHIV initiated their HIV treatment.

Chapter 2 presents results from a systematic literature review of the existing data on impact of HIV treatment scale up utilization of other non-HIV related services. This chapter

provides an overview and assessment of the available data, synthesizing findings from all existing English-language studies published from January 2000 to July 2017 which studied impact of HIV treatment on utilization of non-HIV related services.

Chapter 3 presents results from analyses examining the effect of HIV treatment initiation by PLHIV on the propensity for cohabitating HIV negative adults to report utilizing non-HIV related health services for conditions including TB, HTN, and DM. The study was conducted in the comprehensive population cohort followed by the Africa Health Research Institute (AHRI) in Kwazulu-Natal, South Africa (KZN). We linked PLHIV engaged in HIV care to their cohabitating household members aged ≥15 years using a unique identifier for homesteads. We implemented regression discontinuity quasi-experiments fitting Weibull and Cox survival models to establish the causal effect of ART utilization on uptake of TB, HTN, and DM treatment among household members. We ran unadjusted models and models adjusting for age and sex, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold.

Chapter 4 presents results from analyses examining the effect of HIV treatment initiation by PLHIV on the risk of all-cause mortality for cohabitating HIV negative adults. The study was conducted in the same comprehensive population cohort followed by AHRI in KZN. We linked PLHIV engaged in HIV care to their cohabitating household members aged ≥15 years using a unique identifier for homesteads. We implemented regression discontinuity quasi-experiments fitting Weibull and Cox survival models to establish the causal effect of ART utilization on all-cause mortality among household members. We ran unadjusted models and models adjusting for

age and sex, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold.

To our knowledge, this dissertation represents the first examination of spillover effects of HIV treatment scale up on non-HIV health service utilization and survival of the general population using a regression discontinuity design—a quasi-experimental study that allows for stronger causal inference. In the research field dominated by non-experimental studies, the work represents a significant contribution. In addition, our study uses the Africa Health Research Institute (AHRI) demographic surveillance cohort data that allows generating population based estimates of causal effects, a significant contribution to the spillover effects research that is dominated by facility-based data.

In summary, this dissertation work aims to contribute to the spillover effects literature by employing a novel quasi-experimental method on a population cohort with follow up during the scale up of ART and specifically examines whether social exposure to PLHIV who initiated ART through cohabitation can impact propensity to utilize health services for non-HIV related services or risk of mortality of HIV negative household members. In the era of plateau in external development resources available for health programs, identifying and capitalizing on synergies to achieve wider impact is critical. Harnessing positive synergy from HIV programming to expand supply and demand for other health services through targeted outreach to household members living and caring for PLHIV should become routine programming

Chapter 2: The Effects of Scale-up of HIV Treatment Programs on Utilization of Non-HIV Health Services: A Systematic Review

Abstract

Background: The global response to the HIV epidemic has achieved remarkable increase in access to antiretroviral therapy (ART) through largely vertical programs. Whether the HIV treatment programs have strengthened the broader health system to achieve better access to non-HIV health services, including maternal, child, in/out-patient, non-HIV laboratory, and TB diagnosis and treatment services is unclear.

Methods: A systematic literature search of English language peer review journal articles published from 2000 to 2017 was conducted to assess whether ART scale up was associated with greater access to the five non-HIV health service domains. All study types were included, except exclusively qualitative studies. Studies were grouped into three tiers based on score obtained from the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool. As there were no standardized measures of associations used across the studies, we summarized the findings by counting the number of health service indicators with positive, negative and no association with ART scale up.

Results: Seventeen papers were included in the final review. Twelve studies examined 40 health services indicators in maternal health services, eleven studies examined 37 indicators in child health services, six studies examined 10 indicators in in/out patient services, five studies examined 13 indicators in non-HIV laboratory services and five studies examined 6 indicators in TB diagnosis and treatment services. Overall positive effects were found on the majority of health service indicators examined for non-HIV laboratory service utilization and TB diagnosis

and treatment services. We found negative associations on the majority of indicators examined for child health services. The existing evidence did not point to clear tendencies for maternal health services and outpatient and inpatient services. Restricting the sample to studies with stronger study designs for causal inference (Tiers 1 and 2), the positive effect on non-HIV laboratory services and the negative impact on child health services held but evidence was mixed for TB diagnosis and treatment services, maternal health services and outpatient and inpatient services.

Conclusion: In the first synthesis of the evidence for potential effects of ART scale-up on utilization of non-HIV related health services, we found a strong suggestion that utilization of non-HIV laboratory services increased while utilization of child health services appears to have declined. Future research should focus on strengthening the evidence base with use of prospective and quasi-experimental studies and to employ standardized exposures and outcome measures to facilitate comparative analysis across studies as well as quantitative synthesis. Findings from such research could be invaluable in shaping the HIV response in a manner to enhance broader health outcomes.

Introduction

The expansion of access to antiretroviral therapy (ART) to more than 14 million people in Sub-Saharan Africa (SSA) is one of the most successful global public health programs ever undertaken (1) with President's Emergency Plan for AIDS Relief (PEPFAR) alone contributing more than 70 billion dollars since 2004 (2). These investments have achieved resulted in remarkable advances in preventing morbidity and mortality among people living with HIV (PLHIV) . ART coverage in SSA increased rapidly from single digits in the early 2000s to 53% in 2016 (1). Modeling studies have estimated that scale-up of ART has saved more than nine million life-years in SSA (3). Empirical studies have also linked increasing coverage of ART to decreased HIV-related mortality and all-cause adult mortality (4-10). #

Beyond the well-documented benefits of ART for PLWH, the potential impact of these investments on the broader health system and non-HIV related health indices has been an active area of debate and research. There is wide recognition that HIV program funding has contributed to strengthening the broader health care system, from renovations of health facilities and laboratories, improving processes to coordinate and manage patient care to modernization of health information and supply chain management systems (11-13, 16, 39). However whether these achievements have contributed to increased utilization of health services beyond HIV prevention, care and treatment or in fact have led to decreased utilization due to a crowding out effect remains unclear.

While there has been much debate and active research on the effects of investment in scale-up of HIV treatment programs on the broader health care system (11-16, 18-23, 25-51), no systematic

review of existing evidence has been done to help inform decision makers of the need for adjustment in HIV programming to enhance its potential synergistic effects or to minimize any unintended negative consequences. In this paper, we provide findings from a systematic review conducted from February 18th to April 6th 2016 and updated in August 6th 2017.

Methods

We conducted a systematic literature review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (52). Studies were eligible for inclusion if they reported data on at least one of the following outcomes: Utilization of non-HIV health services or treatment seeking for non-HIV diseases operationalized as counts of individuals or proportions of population. Studies exclusively representing qualitative measures were excluded. The studies also needed to assess association of the outcomes with one of the following exposures: ART scale-up operationalized as counts of individuals or proportion of population accessing ART over time, across health facilities, or communities. The target population was defined as the general population including HIV positive and HIV negative populations.

Box 1: MeSH terms used

exp Health Services [Economics, Manpower, Standards, Statistics & Numerical Data, Utilization], OR
Delivery of Health Care [Economics, Manpower, Organization & Administration, Standards, Statistics & Numerical Data, Utilization], OR
Primary Health Care [Economics, Manpower, Organization & Administration, Standards, Statistics & Numerical Data, Utilization], AND
Africa, AND
Antiretroviral Therapy, Highly Active/ or Acquired Immunodeficiency Syndrome/ or HIV Infections/ or HIV/ or Anti-HIV Agents.

The author conducted the search on Ovid Medline and Ovid Medline In Process & Other Non-Indexed Citations databases between February 18th and April 6th 2016 and updated on August 6th

2017. The Medical Subject Headings (MeSH) terms were used after consultation with a medical librarian and are listed in Box 1.

The search was augmented with screening of the bibliographies of relevant papers. All human studies including a quantitative assessment of utilization of non-HIV services reported in English language were considered. We restricted the timeframe to studies conducted during the ART scale up period in sub-Saharan Africa from 2000 to July 2017.

Figure 1 summarizes the search strategy and results. A total of 2,964 publications were identified using the search terms in the databases. After deduplication, there were 2,775 records that were screened by the author and one independent reviewer. A total of 2,741 records were excluded because their titles and abstracts did not contain any reference to the general population or HIV uninfected population. Between the independent reviewer and the author, 34 publications were identified for full text and bibliography reviews. The author additionally identified 23 articles during the bibliography review of the original 34 publications. Through the full-text review, 40 publications were excluded because they did not directly address the outcome of interest (n=15), only provided qualitative measures of the outcome (n=16), or were exclusively opinion pieces (n=9). Thus, overall, the systematic review resulted in 17 studies for inclusion in the synthesis.

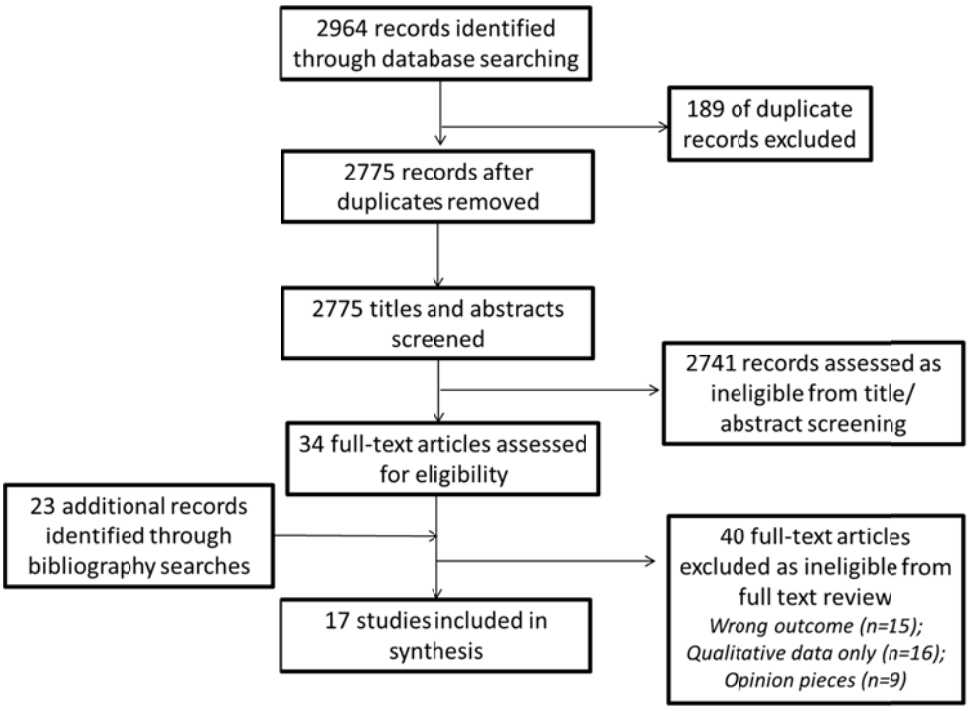


Figure 1: Flow diagram of the search strategy and results

To facilitate the synthesis of the studies, we grouped them into tiers based on the strength of the study design to make causal inferences, using the bias due to confounding domain of the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool (53). Tier 1 consisted of prospective cohort and quasi-experimental designs that were determined to have low risk of confounding bias. Tier 2 consisted of retrospective longitudinal panel designs with moderate risk of confounding bias, and Tier 3 consisted of retrospective pre-post and descriptive designs that had severe risk of confounding bias. There were no randomized control trials among the included studies. As there was no standardization in definitions of exposures and outcomes across the various studies as well as the measures of associations used to summarize their relationship, we were not able to perform a meta-analysis. Instead, we listed all outcomes examined in the studies included in the sample—or health services indicators—and grouped them into five domains of health services: maternal health services, child health services,

outpatient and inpatient services, non-HIV laboratory services and tuberculosis (TB) diagnosis and treatment services. For each health services indicator examined, we summarized the measures of associations used into three categories: positive association ($p<0.05$), negative association ($p<0.05$) and no association ($p\geq0.05$). We computed the proportion out of all health service indicators examined in each of the five health services domains with positive, negative and no associations. We additionally stratified the proportion by study tier based on study design as indicated above.

Results

Characteristics of the studies:

Of the 17 studies included in the systematic review, 12 were single country studies and 5 were multi-country studies. Together the studies included 47 countries in Africa and Haiti spanning the period between 1988 and 2012 (Table 1). All studies were observational studies and the exposure was not randomized at participant or clinic levels. The majority (n= 15 studies) utilized retrospective designs, including longitudinal panel (n=8), pre-post (n=2), and descriptive designs (n=5). There were two studies with a stronger design for causal inference: one employed a prospective cohort design (37) and the second a Difference-in-Difference quasi-experimental design (38). Three studies used aggregate national level estimates from survey and service data reporting on results from 2, 36, and 46 countries (27, 28, 32); 11 studies used aggregate clinic level service data and reporting results from 2,257 clinics (19-21, 30, 31, 33-36, 38, 40) and three used individual level interview data with sample sizes ranging from 11,700 to 217,000 (26, 29, 37).

Focus of the Studies:

The 17 studies included in this systemic review examined the effect of ART scale up on utilization of a wide range of non-HIV health service domains, including maternal health services (n=12) (19-21, 26, 27, 30-36), child health services (n=11) (19, 26-32, 34, 36, 38), outpatient and inpatient clinic services (n=6) (28, 31, 34, 37, 38), TB services (n=5) (28, 31, 32, 34, 36) and non-HIV laboratory tests (n=5) (21, 30, 31, 36, 40) (Table 2). The most common domains of non-HIV health services that have been the focus of study were maternal and child health services. Twelve studies examined the change in utilization of maternal health services using health services indicators including first antenatal care (ANC) visits, any ANC visit, four or more ANC visits, facility deliveries, deliveries by a trained birth attendant and postpartum care visits and the following assessments among pregnant women: urine and blood tests, blood pressure and weight measurements, syphilis screening conducted during ANC visits, family planning services, syphilis screening and Pap smear tests (19-21, 26, 27, 30-36). Eleven studies examined utilization of essential child health services, including uptake of childhood vaccines, such as measles, polio, Bacillus Calmette-Guerin (BCG), diphthria, pertussis, tetanus (DPT-3), and neonatal tetanus, as well as uptake of treatment for acute respiratory infections and fever and growth monitoring and other child-specific outpatient visits (19, 26-32, 34, 36, 38). Six studies examined utilization of overall outpatient and inpatient services using the number of visits to the outpatient department or hospitalizations as key metrics (28, 31, 34, 37, 38). Five studies assessed the volume of non-HIV laboratory tests, including malaria, syphilis, and TB diagnostic tests, chemistry, and hematology tests (21, 30, 31, 36, 40). Finally, five studies used TB detection and treatment success rates as outcome measures (28, 31, 32, 34, 36).

The exposure of interest was operationalized in a variety of ways. Ten studies used time to compare the effects on ART scale up (19, 21, 31-34, 36, 37, 40). The latter studies compared data from before or during the initial years of ART scale up at the national level (27, 28, 32) or before or during introduction of HIV services at the clinic or community levels (19-21, 31, 33, 34, 36, 37, 40) versus data from after or later years of ART scale up at the national level or HIV services start at the clinic or community levels. Six studies used presence or the scale of the ART program at the national (PEPFAR focus countries versus non focus countries) (27, 28) or clinic level (HIV program on site or no HIV program on site) (38); large ART program on site versus small ART program on site) (30, 35), or population level (living in regions with more HIV funding versus less HIV funding) (29). One study used HIV disease burden to compare utilization behavior between those living in high burden subnational regions versus low burden subnational regions (26).

Associations between ART scale-up and non-HIV services:

Table 3 summarizes the associations for each health services indicator examined—positive, negative, or no association—by the domain of non-HIV health services as well as by study design tier. Overall, in all domains, except in child health services, studies found more positive associations than negative or no associations in the 17 studies and 106 health service indicators across the five domains of non-HIV health services. Of the 40 health service indicators examined in the 12 studies that addressed effect on maternal health services, 18 (45%) were positive and utilization increased with increase in ART services, 8 (20%) were negative and utilization decreased with increase in ART services, and in 14 (35%) there was no association between increase in ART services and utilization of maternal health services (19-21, 26, 27, 30-36). Of

the 37 health service indicators examined in the 11 studies that evaluated effect on child health services, 7 (19%) were positive, 17 (46%) were negative, and in 13 (35%) there was no association found (19, 26-32, 34, 36, 38). Of the 10 health service indicators examined across the 6 studies that addressed impact on outpatient and inpatient services, 5 (50%) were positive, 1 (10%) was negative, and in 4 (40%), there were no association found (28, 31, 34, 37, 38). With regards to non-HIV lab tests, 13 health service indicators were examined across the 5 studies (21, 30, 31, 36, 40). Of those, 7 (54%) were positive, 4 (31%) were negative, and in 2 (15%) there were no association found. Finally, with TB diagnosis and treatment services, 6 health service indicators were examined across the 5 studies (28, 31, 32, 34, 36). Of those, 4 (67%) were positive, none showed negative association and in 2 (33%) there were no association found.

Associations by Study Tier:

Overall, tier 1 (n=2) (37, 38) studies found no associations between ART scale up and non-HIV health service utilization, and tier 2 (n=8) (26-30, 35, 36, 40) studies found negative or no associations between ART scale up and non-HIV health service utilization in all domains except in non-HIV lab services. On the other hand, Tier 3 studies (n= 7) found positive associations in all domains (19-21, 31-34).

In the two Tier 1 studies, there were seven health service indicators examined for child health services, all of which yielded no association between increase in ART service and utilization of child health services (37, 38). For outpatient and inpatient services, one study found increase in public sector clinic visits and decrease in hospitalizations while another found no change in curative care visits and hospitalizations. None of the Tier 1 studies examined the association of

ART scale up and maternal health services, non-HIV laboratory services and TB diagnosis and treatment services.

Of the eight Tier 2 studies, there were 22 health service indicators examined for maternal health services across five studies (26-30, 35, 36, 40). Of those 5 (23%) were positive, 7 (32%) were negative and 10 (45%) had no association. There were 23 health service indicators examined for child health services across the six studies. Of those 2 (9%) were positive, 17 (74%) were negative, and 4 (17%) yielded no association. There were nine health service indicators examined for non-HIV laboratory services across three studies. Of those 5 (63%) were positive, 3 (33%) were negative and 1 (11%) had no association. Finally, there were two health service indicators examined for TB diagnosis and treatment services in two studies. Of those 1 (50%) was positive and 1 (50%) yielded no association. None of the Tier 2 studies examined the association of ART scale up and outpatient and inpatient services.

Of the seven Tier 3 studies, there were 18 health service indicators examined for maternal health services across all seven Tier 3 studies (19-21, 31-34). Of those, 13 (72%) health indicators were positive, 1 (6%) were negative and 4 (22%) had no association. There were seven health service indicators examined for child health services across three studies. Of those 5 (71%) health indicators were positive, 0 (0%) were negative, and 2 (29%) yielded no association. There were four health service indicators examined for non-HIV laboratory services across the two studies. Of those 2 (50%) indicators were positive, 1 (25%) were negative and 1 (25%) had no association. Finally, there were four health service indicators examined for TB diagnosis and

treatment services across two studies. Of those 3 (75%) were positive, 0 (0%) were negative and 1 (25%) yielded no association.

Discussion

In our study, which is the first to synthesize the evidence for potential effects of ART scale-up on utilization of non-HIV related health services, we found overall positive effects on the majority of health service indicators examined for non-HIV laboratory service utilization and TB diagnosis and treatment services. We found negative associations on the majority of indicators examined for child health services. The existing evidence did not point to clear tendencies for maternal health services and outpatient and inpatient services. Restricting the sample to studies with stronger study designs for causal inference (Tiers 1 and 2), the positive effect on non-HIV laboratory services and the negative impact on child health services remained but evidence was mixed for the other domains, including TB diagnosis and treatment services, maternal health services and outpatient and inpatient services.

The evidence for reduction in utilization of child health services with ART scale up appears strongest with 16 out of 23 health service indicators examined across 6 Tier 2 studies finding reduction in utilization (26-30) and seven out of seven associations examined in one Tier 1 study finding no change in utilization of child health services (38). The negative associations were found mainly in childhood immunization uptake, including neonatal tetanus, polio, measles, BCG, DPT-3 vaccines for children as well as in one study, outpatient visits for children. The two positive associations were found in a Tier 2 study conducted in Kampala, Uganda at six governmental hospitals (36). The latter study found an increased uptake in childhood

immunizations and malaria diagnostic testing. However, the study did not include information on specific vaccines and did not consider any confounding variables. While the increased utilization of child health services that the study observed may have resulted from influences other than ART scale up, it is possible that the trend was real in the limited context of the 6 sites where the assessments were done. The studies that found negative associations speculated on several possible reasons for the reduction in utilization of child health services, including the epidemic itself having a deleterious effect on availability of health workers (26) and the vertical programming of ART programs garnering more political attention and the assignment of more health workers for HIV in contrast to non-HIV health services (27, 30). It is important to note that the apparent decline in the utilization of child health services in some settings are inconsistent with the broader positive child health outcomes noted such as declines in under five and infant mortality rates noted in all countries in East and Southern Africa between 1990 and 2015 (54).

While the number of studies is limited, the evidence for increased utilization of non-HIV laboratory services with ART scale up is encouraging with the majority (five out of the eight) health service indicators examined across three Tier 2 studies finding positive associations (30, 36, 40). One study found ART expansion was associated with increased syphilis and chemistry tests while finding negative associations with a decrease in TB and hematology tests. The negative associations could indicate reduction in disease conditions requiring these tests. Studies have found substantial reductions in TB among both HIV positive and negative population coinciding with ART scale up (55, 56). The reason for decrease in hematology tests is less clear.

Evidence of effect of ART expansion on maternal health services was mixed with most of the available evidence suggesting neither positive nor negative effects. No Tier 1 study examined the effect of ART expansion on maternal health service indicators, and 45% of health service indicators examined across the five Tier 2 studies found no association while 23% and 32% of health services indicators examined found positive and negative associations, respectively (26, 27, 30, 35, 36). The majority of Tier 3 studies found positive associations, but none of them adjusted for potential confounding variables making the evidence limited at best (19-21, 31-34). Further, within the Tier 2 studies, depending on the study, the same maternal health service indicator had no association, i.e. neither positive or negative associations with ART scale up. For example, ART scale-up was not associated with facility-based deliveries in the study by Case et al (26), had a positive association in the study by Kruk et al (35) and a negative association in the study by Luboga et al (30). The reasons for these contradictory effects are unclear, however, the lack of an effect as noted by the Case et al study may have been due to the fact that it involved a period prior to 2005, when ART program expansion was only beginning. In contrast, both the Kruk et al and Luboga et al studies were conducted almost contemporaneously, although they differed in the contexts which may have influenced the results. The Kruk et al study included a large number of health facilities from Cote d'Ivoire, Ethiopia, Lesotho, Mozambique, Nigeria, Rwanda, South Africa, Tanzania while the Luboga et al study included health facilities from one country, Uganda. Finally we cannot rule out residual confounding contributing to the diverging findings.

Evidence for association between ART scale-up and utilization of TB diagnosis and treatment services varied with no clear trend noted. As with maternal health services, no Tier 1 study

examined the effect of ART expansion on TB diagnosis and treatment service indicators, while the two Tier 2 studies found conflicting results, with Duber et al finding no change in TB detection rates (28) and Matsubayashi et al finding increased TB case detection rates (36). While the Matsubayashi et al study was focused on Kampala, Uganda, the Duber et al study was broader in scope covering 46 African countries, including Uganda. Duber et al did not report country-specific results regarding TB case detection rates, but noted that ART scale up was associated with overall positive association in Uganda in relation to the 13 health service indicators measured. It is therefore likely that the direction of association may have varied by country and that unmeasured country level factors may need further examination to explain this variation. As with maternal health services, the majority of Tier 3 studies found positive associations, but none of them adjusted for potential confounding variables which limits the veracity of these findings.

Finally, evidence for outpatient and inpatient services was mixed. The two Tier 1 studies that assessed the effect of ART on clinic visits and hospitalizations reached different conclusions, with the Hontelez et al study finding an increase in clinic visits and decrease in hospitalizations (37) while Shephard et al (38) noting no such association. This divergence could suggest that the effect of ART scale up may be country-, site-, or time-specific. The study by Hontelez et al was conducted in a rural community of Kwazulu-Natal Province in South Africa between 2009-2012 whereas the study by Shepard et al was conducted at an earlier time in rural Rwanda between 2002-2006. It is plausible that no effect was observed in the latter study as it took place early in the history of the ART scale up. It is also plausible that the positive effect noted by Hontelez et al may reflect certain country- or community-specific enablers that are yet to be defined.

This systematic review has several strengths. It provides the first synthesis of evidence to date regarding potential spillover effects of ART scale up on non-HIV related health services. The review included 17 studies covering 47 African countries and Haiti spanning the period of 1988 and 2012 during which ART coverage grew exponentially. The review was expansive, covering 5 health service domains and 106 health service indicators. We found a strong suggestion that utilization of non-HIV laboratory services increased while utilization of child services appear to have declined. For other services, the effect of ART scale up appears to be time and context dependent.

This review also has several limitations. Due to the heterogeneous study designs, definitions of exposure and outcome variables, we were only able to use broad health service domains to summarize the general direction of the association. We were unable to summarize evidence at the health service indicator level and were not able to quantify the magnitude of the association using standardized measures. The majority of studies included in this review were retrospective analyses prone to confounding biases, which could partly explain the contradictory results described.

Our systematic review demonstrated important trends in increased uptake of non-HIV laboratory services and decreased utilization of child health services, specifically around immunization coverage. These results also suggest that the association between ART scale up and health utilization may be context-specific. It is plausible that there are mediating factors that determine the relationship between ART scale up and increased utilization of non-HIV services. Thus, to

advance our understanding of the effects of scale-up of HIV programs on non-HIV measures, it will be important to strengthen the evidence base with use of prospective and quasi-experimental studies and to employ standardized exposures and outcome measures to facilitate comparative analysis across studies as well as quantitative synthesis. Findings from such research could be invaluable in shaping the HIV response in a manner to enhance broader health outcomes.

Chapter 2: Tables

Table 1: Studies examining spillover effects of ART scale up on non-HIV health service utilization

Author	Title	Country	Years	Design	Data	Sample size	Non-HIV health service	Exposed group	Unexposed group	Measure of association	Effect size	Adjust-ments	Limitations
Tier 1													
Hontelez (37)	The Effect of Antiretroviral Treatment on Health Care Utilization in Rural South Africa	South Africa	2009-2012	Pros-pective cohort design	Inter-view data	13,500 (2009)-14,713 (2012) OBS	Outpatient and inpatient services	2010, 2011, 2012	2009	AOR, AIRR (random effects, logistic and Poisson regression)	(Positive) Public sector primary clinic visits: 2009 vs. 2012: 1.24 (p<0.001) Hospitalization rate: 2009 vs. 2012: 0.52 (p<0.001) (Negative) Private sector primary clinic visits: 2009 vs. 2012: 0.52 (p<0.001)	1. Age 2. Sex 3. Resi-dence 4. Calendar year 5. HIV status 6. Repeated measures	1. Self-reported utilization data 2. Survivor bias
Shepard (38)	A controlled study of funding for human immunodeficiency virus/acquired immunodeficiency syndrome as resource capacity building in the health system in Rwanda.	Rwanda	2002-2006	Differe nce-in-differen ce design	Aggre gate clinic data	50 HFs	1. Child health services 2. Outpatient and inpatient services	HIV services on site	No HIV services on site	Coefficients for DiD interaction term; Difference in growth rate (%) 2002/2003 vs. 2006/2007 between HCs with and without HIV services	(No difference) BCG doses: 0.105 (p=0.06, border line NS) DPT doses: 0.005 Polio doses: 0.036 Measles doses : 0.045 Curative	1. Facility ownership 2. PBF status 3. District income levels	1. Aggregate clinic data susceptible to ecologic fallacy

											care visits ages <5y: -0.009 Curative care visits ages 5-14y: 0.077 Curative care visits ages >14y: 0.118 Hospitalization: -0.278 Growth monitoring: 0.049		
Tier 2													
Case (26)	The Impact of the AIDS Pandemic on Health Services in Africa: Evidence from Demographic and Health Surveys	Burkina Faso Came-roon Cote d'Ivoire Ethiopia Ghana Guinea Mali Niger Senegal Kenya Malawi Tanzania Zambia Zimbabwe	1988-2005	Retrospective longitudinal panel design	Interview data	69,000-217,000 OBS	1. Maternal health services 2. Child health services	High HIV preva-lence regions	Low HIV prevalence regions	Coefficient of multivariable ordinary least squares (OLS) regression with 1% increase in regional prevalence and change in utilization of non-HIV health services	(No difference) Delivered in a public or private clinic: -0.768 (SD: 0.531) If delivered in a clinic, clinic was public: -0.509 (SD: 0.320) (Negative) Accessed ANC: -1.734 (SD 0.331) Urine test in ANC: -2.220 (SD 0.677) Blood test in ANC: -1.214 (0.522) Blood	1. Mother's years of education 2. Mother's age in years at the time of birth 3. Child's age in months 4. Child's sex 5. Resi-dence (urban/ rural) 6. Country fixed effect 7. Region fixed effect	1. Self-reported utilization data 2. Survivor bias

											pressure measurement in ANC: -2.058 (SD: 0.638) Weight taken in ANC: 0.186 (SD: 0.228) Trained birth attendant: -1.353 (SD: 0.283) Polio vaccine at birth: -7.018 (SD: 0.571) Ever received Polio vaccine:-2.708 (SD: 0.535) Ever received Measles vaccine: -2.767 (SD: 0.523) Ever received BCG vaccine: -2.021 (SD: 0.393) Ever received DPT vaccine: -2.657 (SD: 0.623)		
Chima (29)	Spillover effect of HIV-	Nigeria	2003, 2008	Retros pective	Intervi ew	11,700 OBS	Child health services	More per capita HIV	Less per capita HIV	Coefficient of multivariable	(Negative) Ever	Yes, however	1. Self-reported

	specific foreign aid on immunization services in Nigeria			longitudinal panel design	data			funding	funding	OLS regression with $1 increase in HIV funding and change in health care utilization	received Polio-1 vaccine: 8% reduction Ever received Polio-3 vaccine: 9% reduction Ever received DPT-1 vaccine: 11% reduction Ever received DPT-3 vaccine: 19% reduction Ever received Measles vaccine: 31% reduction Ever received Polio and DPT final doses & Measles: 8% reduction	not available to author	utilization data 2. Survivor bias
Grepin (27)	HIV Donor Funding Has Both Boosted And Curbed The Delivery Of Different Non-HIV Health	36 Sub-Saharan African countries	2003-2010	Retrospective longitu-dinal panel design	Aggre-gate national data from surveys	36 COs	1. Maternal health services 2. Child health services	More per capita HIV funding	Less per capita HIV funding	Coefficient of multivariable OLS regression with $1 increase in HIV aid per capita and	(Positive) 4 or more ANC visits (Low HR density): 3.61 ($p<0.01$) Blood test	1. Country 2. Year 3. GDP 4. Urban population 5. Polity II measure (democracy	1. Retro-spective analysis of longitudinal panel data (not cohort) 2. National level data

	Services In Sub-Saharan Africa				and administrative data					change in utilization of non-HIV health services	in ANC (Low HR density): 3.76 ($p<0.05$) Trained birth attendant (Low HR density): 4.13 ($p<0.01$) (No difference) Any ANC visits: 0.07 4 or more ANC care visit: -0.06 Urine test in ANC -0.01 Blood test in ANC: -0.04 Blood pressure measurement in ANC: -0.01 Weight taken during ANC visit: -0.02 Trained attendant at birth: 0.04 DPT-1 vaccine: -0.11 Measles vaccine: -0.10 (Negative)	measure) 6. Health expenditures as % of GDP 7. HIV preva-lence 8. Physicians /1000 population 9. Aid for immunization	susceptible to ecologic fallacy

											DPT-1 vaccine (Low HR density): -2.17 (p<0.01) DPT -3 vaccine: -0.15 (p<0.05) Polio-vaccine: -0.18 (p<0.05) Measles vaccine (Low HR density): -1.55 (p<0.10)		
Kruk (35)	PEPFAR Programs Linked To More Deliveries In Health Facilities By African Women Who Are Not Infected with HIV	Cote d'Ivoire Ethiopia Lesotho Mozambique Nigeria Rwanda South Africa Tanzania	2007-2011	Retrospective longitudinal panel design	Aggregate clinic data	257 HFs	Maternal health services	Larger size of HIV program	Smaller size of HIV program	AIRR (GEE, negative binomial regression)	(Positive) Facility deliveries: Large vs. small (IRR=1.134) (p<0.01) (No difference) Any ANC: Large vs. small (IRR=1.005)	1. Clustering by clinic 2. Facility level characteristics 3. HIV program characteristics	1. Substantial missing data (35% missing 1 or more variables) 2. Aggregate clinic data susceptible to ecologic fallacy 3. Non-random selection of HCs
Luboga (30)	Did PEPFAR investments result in health system strengthening ? A retrospective longitudinal study	Uganda	mid 2005-mid 2011	Retrospective longitudinal panel design	Aggregate clinic data	112 HFs	1. Child health services 2. Non-HIV laboratory tests	Larger size of HIV program	Smaller size of HIV program	AIRR (random effects, negative binomial regression)	(No difference) Malaria blood smears: 1.01 (p=0.835) (Negative) Outpatient	HIV prevalence Sanitation Elementary education	1. Substantial missing data in 2005-2007 years 2. Aggregate clinic data susceptible to ecologic

	measuring non-HIV health service utilization at the district level										visit for age <5y: 0.89 (p<0.001) Facility deliveries: 0.95 (p<0.033) DPT3 vaccine <1: 0.94 (p<0.017) TB diagnostic tests: 0.78 (p<0.0001)		fallacy 3. Non-random selection of HCs
Duber (28)	Is there an association between PEPFAR funding and improvement in national health indicators in Africa? A retrospective study	46 African countries	2000, 2006	Retrospective longitudinal panel design	Aggregate national data from surveys and administrative data	46 COs	1. Child health services 2. TB diagnosis & treatment services	12 PEPFAR focus countries	34 PEPFAR non focus countries	Fractional change (bigger negative change indicates bigger improvement) between 2000 and 2006 PEPFAR-focus vs. non-focus countries (Wilcoxon rank sum test)	(Negative) Neonatal tetanus vaccine: -0.099 vs. -0.328 (p=0.011) (No difference) Measles vaccine: -0.094 vs. -0.157 (p=0.507) DTP vaccine: -0.085 vs. 0.173 (p=0.460) TB case detection: -0.056 vs. 0.000 (p=0.659)	None	1. National data susceptible to ecologic fallacy 2. No adjustment for confounding variables

Matsubayashi (36)	The effects of an HIV project on HIV and non-HIV services at local government clinics in urban Kampala	Uganda	2006-2009	Retrospective longitudinal panel design	Aggregate clinic data	6 HFs	1. Maternal health services 2. Child health services 3. Non-HIV laboratory services 4. TB diagnosis and treatment services	After introduction of HIV services	Before introduction of HIV services	Risk difference (random effects, linear regression)	(Positive) Children immunized: 1.69 vs. 55.12 (p=<0.001) Pregnant women immunized: -0.64, 9.69 (p=0.004) Number of pregnancy tests: 0.23 vs. 2.22 (p=0.003) Malaria lab tests (children): 0.03 vs. 1.23 (p<0.001) Malaria diagnosis (children): 0.12 vs. 7.22 (p=0.029) Number of TB lab tests: 0.70 vs. 1.89 (p=0.013) Number of TB diagnosis:-0.07 vs. 0.28 (p=0.023) (No difference) FP services clients: -0.19 vs. 0.69	Clustering by clinic	1. Aggregate clinic data susceptible to ecologic fallacy 2. Non-random selection of HCs

											(p=0.421) ANC clients: 2.72 vs. 3.63 (p=0.316)		
McNairy (40)	Increased utilization of PEPFAR-supported laboratory services by non-HIV patents in Tanzania	Tanzania	2009, 2011	Retrospective longitudinal panel design	Aggregate clinic data	61 HFs	Non-HIV laboratory services	2011	2009	AOR (random effects, logistic regression)	(Positive) Chemistry 2009vs. 2011: 1.9 (95% CI: 1.7, 2.0) Syphilis 2009 vs. 2011: 13.0 (95% CI: 11.0, 17.0) (Negative) Hematology 2009 vs. 2011: 0.75 (95% CI: 0.7, 0.8) Tuberculosis 2009 vs. 2011: 0.6 (95% CI: 0.5, 0.7)	Clustering by clinic Year, facility location and total volume of tests performed at each facility	1. Aggregate clinic data susceptible to ecologic fallacy 2. Non-random selection of HCs
Tier 3													
Brugha (19)	How HIV/AIDS scale-up has impacted on non- HIV priority services in Zambia	Zambia	2005, 2007	Retrospective descriptive analysis	Aggregate clinic data	9 HFs	1. Maternal health services 2. Child health services	2007	2005	Spearman rank correlations between % change in client loads on ART vs. non-HIV services	(Positive) ART vs. ANC clients: 0.22 ART vs. FP service clients: 0.83	None	1. Aggregate clinic data, susceptible to ecologic fallacy 2. No adjustments made for confounding

										between 2005 and 2007	ART vs. BCG vaccine: 0.27 (No difference) ART vs. DPT3 vaccine: 0		variables 3. Non-random selection of HCs
Price (31)	Psychological and Socio-medical Aspects of AIDS/HIV Integrating HIV clinical services into primary health care in Rwanda: a measure of quantitative effects	Rwanda	2004-2006	Pre-post design	Aggregate clinic data	30 HFs	1. Maternal health services 2. Child health services 3. Outpatient and inpatient services 4. Non-laboratory tests	After introduction of HIV services(Non-HAART vs. HAART clinics)	Before introduction of HIV services(Non-HAART vs. HAART clinics)	Median difference between before and after service introduction on mean number of clients per primary HC per month non-HAART vs. non-HAART (Two-sample Wilcoxon test)	(Positive) New ANC clients (not ART offered vs. ART offered): 5 vs. 15 (p=0.002) FP service clients: 4 vs. 35 (p=0.017) Syphilis screening in ANC: 61 vs. 75 (p<0.001) Growth monitoring: 68 vs. 412 (p=0.002) Facility deliveries: 4 vs. 11 (p=0.002) Outpatient visits: 271 vs. 374 (p=0.003) (No difference) 4 ANC visits completed 5 vs. 2	None	1. Aggregate clinic data susceptible to ecologic fallacy2. No adjustment for confounding variables3. Non-random selection of HCs

											(p=0.298) Vaccinations completed: 4 vs. 16 (p=0.066) Hospitalizations: 15 vs. -15 (p=0.148) (Negative) Non-HIV lab tests: 137 vs. -2 (p=0.027)		
Rasschaert (32)	Positive spill-over effects of ART scale up on wider health systems development: evidence from Ethiopia and Malawi	Malawi Ethiopia	2004-2009	Retrospective descriptive analysis	Aggregate national data from surveys and administrative data	2 COs	1. Maternal health services 2. Child health services 3. Outpatient and inpatient services 4. TB diagnosis and treatment services	After ART scale up (2009)	Pre ART scale up (2004 for Malawi and 2005 for Ethiopia)	Change in % coverage & number of visits per 1000 population per year for OPD visits between 2004 and 2009; No statistical test	Malawi (Positive) ARI/fever treatment: 19.6% vs. 51.8% TB treatment success: 71% vs. 84.7% Facility deliveries: 38% vs. 52% Measles vaccinations coverage: 59% vs. 89% Outpatient visits: 800 vs. 1290 (No difference) TB case detection: 50.3% vs. 49.7%	None	1. National level data susceptible to ecologic fallacy 2. No adjustments for confounding variables 3. No statistical test

											Ethiopia (Positive) ARI/fever treatment: 45% vs. 90% TB case detection: 41.9% vs. 47.5% Facility deliveries: 15% vs. 34% Measles vaccinations coverage: 55% vs. 66% TB treatment success: 79.3% vs. 84% (NO difference) Outpatient visits: 300 vs. 330		
Rensburg-Bonthuyzen (21)	Resources and infrastructure for the delivery of antiretroviral therapy at primary health care facilities in the Free State Province, South Africa	South Africa	2004-2006	Pre-post design	Aggregate clinic data	16 HFs	1. Maternal health services 2. Non-HIV laboratory services	After introduction of HIV services	Before introduction of HIV services	Lab tests offered; TAT	(Positive) Pap smear TAT (Baseline vs. Second follow up): 10 days to 8 days Sputum AFB TAT (Baseline vs. Second follow up: 4 days to 3 days	None	1. Aggregate clinic data susceptible to ecologic fallacy 2. No adjustments for confounding variables 3. Non-random selection of HCs

											(No difference) Urine test in ANC Syphilis test in ANC Pap smear TB lab test		
van den Akker (33)	HIV care need not hamper maternity care: a descriptive analysis of integration of services in rural Malawi	Malawi	2005, 2010	Retrospective descriptive analysis	Aggregate clinic data	25 HFs	Maternal health services	2010	2005	Prevalence ratios (2005 vs. 2010)	(Positive) At least one ANC visit: RR 1.5 (95% CI: 1.48-1.51) At least 4 ANC visits: RR 1.18 (95%CI: 1.14-1.23) Facility deliveries: 2.05 (95% CI: 2.01-2.08) Postnatal care: 4.40 (95% CI: 4.25-4.55)	None	1. Aggregate clinic data susceptible to ecologic fallacy 2. No adjustment for confounding variables 3. No-random selection of HCs
Walsch(20)	Task sharing in Zambia: HIV service scale-up compounds the human resource crisis	Zambia	2005, 2007	Retrospective descriptive analysis	Aggregate clinic data	39 HFs	1. Maternal health services 2. Outpatient and inpatient services	2007	2005	Counts (2005 vs. 2007)	(Positive) ANC clients: 41798 (2005) vs. 46656 (2007) (Negative) FP clients: 37093 (2005) vs. 33653 (2007) Outpatient visits:	None	1. Aggregate clinic data susceptible to ecologic fallacy 2. No adjustment for confounding variables 3. No-random selection of HCs

											397,374 (2005) vs. 342,279 (2007)		
Walton (34)	Integrated HIV Prevention and Care Strengthens Primary Health Care: Lessons from Rural Haiti	Haiti	2002-2003	Retrospective descriptive analysis	Aggregate clinic data	2 HFs	1. Maternal health services 2. Child health services 3. Outpatient and inpatient services 4. TB diagnosis and treatment services	After introduction of HIV services	Before introduction of HIV services	Trend in number of clients (no trend test provided)	(Positive) Patient visits: ~500 to ~6800 TB cases detected: 0 to ~58 down to ~18 ANC visits: ~100 to ~500 Vaccinations: ~1300 to ~2700	None	1. Aggregate clinic data susceptible to ecologic fallacy 2. No adjustments for confounding variables 3. Non-random selection of HCs

*COs=Countries; HFs=health facilities; OBS=observations; TAT=turnaround time

Table 2: Health service indicators examined by domain and study tier

Author	Maternal Health Services	Child Health Services	Outpatient/inpatient services	Non-HIV Laboratory Services	TB Diagnosis and Treatment Services
		Tier 1			
Hontelez			Public sector primary health clinic visits Hospitalization		
Shepard		Number of BCG doses distributed Number of DPT doses distributed Number of Polio doses distributed Number of Measles doses distributed Number of Curative care visits, age <5 Number of Curative care visits, age <5-14 Number of child growth monitoring visits	Curative care visits, age >14 Hospitalizations		
		Tier 2			
Case	Gave birth at facility for last child birth Accessed any ANC for last pregnancy Urine test in ANC for last pregnancy Blood test in ANC for last pregnancy Blood pressure measurement in ANC for last pregnancy Weight taken in ANC for last pregnancy Had trained birth attendant for last child birth	Received Polio vaccine at birth Ever received Polio vaccine Ever received Measles vaccine Ever received BCG vaccine Ever received DPT vaccine			
Chima		Ever received Polio-1 vaccine Ever received Polio-3 vaccine Ever received DPT-1 vaccine Ever received DPT-3 vaccine Ever received Measles vaccine			
Grepin	Accessed any ANC for last pregnancy Had 4 or more ANC visits for last pregnancy (Overall) Had 4 or more ANC visits for last pregnancy (Countries with health professional shortage) Urine test in ANC for last pregnancy Blood test in ANC for last pregnancy Blood pressure measurement in ANC Weight taken in ANC for last pregnancy Had trained birth attendant for last child birth (Overall) Had trained birth attendant for last child birth (Countries with health professional shortage)	Number of DPT-1 vaccine clients (Over all) Number of DPT-1 vaccine clients (Countries with health professional shortage) Number of measles vaccine clients (Overall) Number of measles vaccine clients (Countries with health professional shortage) Number of DPT-3 vaccine clients Number of polio vaccine clients			
Kruk	Number of facility deliveries				

	Number of ANC clients				
Luboga	Number of facility deliveries	Number of outpatient visits for children Number of DPT-3 vaccine clients		Number of Malaria blood smears Number of TB diagnostic tests	
Duber		Number of neonatal tetanus vaccine clients Number of measles vaccine clients DPT vaccine clients			TB case detection
Matsubayashi	Number of pregnant women immunized Number of women accessing family planning (FP) services Number of ANC clients	Number of children immunized Number of children with malaria diagnosis		Number of pregnancy tests Number of malaria lab tests Number of TB lab tests	TB case detection
McNairy				Number of chemistry tests Number of syphilis tests Number of hematology tests Number of TB lab tests	
Tier 3					
Brugha	Number of ANC clients Number of family planning (FP) services clients	BCG vaccine clients DPT-3 vaccine clients			
Price	Number of ANC clients Number of women completing 4 ANC visits Number of FP services clients Number of clients screened for syphilis in ANC Number of facility deliveries	Number of new growth monitoring clients Number of clients with completed vaccinations	Number of outpatient visits Number of hospitalizations	Number of non-HIV lab tests	
Rasschaert	Number of facility deliveries (Mal/Eth)	ARI/fever treatment clients (Malawi/Ethiopia) Measles vaccine clients (Malawi/Ethiopia)	Number of outpatient visits (Malawi) Number of outpatient visits (Ethiopia)		TB treatment success (Malawi/Ethiopia) TB case detection (Ethiopia) TB case detection (Malawi)
van den Akker	Number of women completing at least 1 ANC visit completed Number of women completing at least 4 ANC visits Number of facility deliveries Number of women accessing postpartum care				
Walsch	Number of antenatal care clients Number of FP services clients		Number of outpatient visits		
Rensburg-Bonthuyzen	Urine test in ANC offered Syphilis screening in ANC offered Number of PAP smears offered			Number of sputum acid-fast bacilli (AFB) tests Pap smear turnaround time (TAT) Sputum AFB TAT	
Walton	Number of ANC visits	Number of Vaccinations	Number of outpatient visits		TB case detection

Table 3: Associations of ART scale up and non-HIV health services utilization by health service domain and study design tier

	Maternal Health Services		Child Health Services		Outpatient/inpatient services		Non-HIV Laboratory Services		TB Diagnosis and Treatment Services	
Number of studies	12		11		6		5		5	
OVERALL (17 studies)										
Number of health service indicators	40		37		10		13		6	
Positive association	18	45%	7	19%	5	50%	7	54%	4	67%
Negative association	8	20%	17	46%	1	10%	4	31%	0	0%
No association	14	35%	13	35%	4	40%	2	15%	2	33%
Tier 1 (2 studies)										
Number of health service indicators	NA		7		4		NA		NA	
Positive association	NA	NA	0	0%	2	50%	NA	NA	NA	NA
Negative association	NA	NA	0	0%	0	0%	NA	NA	NA	NA
No association	NA	NA	7	100%	2	50%	NA	NA	NA	NA
Tier 2 (8 studies)										
Number of health service indicators	22		23		NA		9		2	
Positive association	5	23%	2	9%	NA	NA	5	56%	1	50%
Negative association	7	32%	17	74%	NA	NA	3	33%	0	0%
No association	10	45%	4	17%	NA	NA	1	11%	1	50%
Tier 3 (7 studies)										
Number of health service indicators	18		7		6		4		4	
Positive association	13	72%	5	71%	3	50%	2	50%	3	75%
Negative association	1	6%	0	0%	1	17%	1	25%	0	0%
No association	4	22%	2	29%	2	33%	1	25%	1	25%

Chapter 3: The Effects of HIV Treatment on Uptake of Tuberculosis and Non-Communicable Diseases Treatment by Adult Household Members

Abstract

Background: The global response to the HIV epidemic has achieved a remarkable increase in access to antiretroviral therapy (ART) through largely vertical programs. Whether HIV treatment programs have strengthened the broader health system to achieve better outcomes for other conditions such as tuberculosis (TB) and non-communicable diseases (NCDs) is unclear. We conducted a quasi-experimental study in rural Kwazulu-Natal (KZN), South Africa, to determine whether exposure to health benefits from ART utilization by a person living with HIV (PLHIV) in a household affects uptake of TB, hypertension (HTN) and diabetes mellitus (DM) treatment by other household members with these conditions.

Methods: The study was conducted in the comprehensive population cohort followed by the Africa Health Research Institute (AHRI) in KZN. We linked PLHIV engaged in HIV care to their cohabitating household members aged ≥15 years using a unique identifier for homesteads. We implemented regression discontinuity quasi-experiments fitting Weibull and Cox survival models to establish the causal effect of ART utilization on uptake of TB, HTN, and DM treatment among household members. We ran unadjusted models and models adjusting for age and sex, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold.

Results: There were 4867 PLHIV enrolled in care living with 17,253 household members ≥15 years in 4212 unique homesteads between 2008-2014. Most PLHIV in care were women (77%) with mean age of 33 years. Cohabitating household members were 55% female with mean age of

31 years and a median household ART utilization exposure of 1.7 years (IQR: 0.6-3.2). During the study period, 3.0% (95.6% of those with TB), 11.4% (86.0% of those with HTN) and 3.1% (83% of those with DM) of cohabitating household members reported that they were currently being treated for TB, HTN, or DM, respectively. Household ART utilization significantly increased treatment for diabetes (RR 1.90: 95% CI 1.07-3.40) but not for TB (RR 1.12: 95% CI 0.71-2.03) or hypertension (RR 1.31: 95% CI 0.97-1.77) (Table 1).

Conclusion: Household exposure to HIV treatment programs substantially increased uptake of DM treatment but not HTN and TB treatment among household members with the latter conditions. Future research needs to establish the mechanisms leading to these effects and how HIV treatment programs can be even better leveraged to improve access to other needed chronic care in Africa.

Introduction

The expansion of antiretroviral therapy (ART) to more than 14 million people in Sub-Saharan Africa (SSA) is one of the most successful global public health programs ever undertaken (1) with more than 70 billion dollars contributed since 2004 through the United States President's Emergency Plan for AIDS Relief (PEPFAR) alone (2). This massive investment, along with other contributions by the Global Fund to Fight AIDS, Tuberculosis and Malaria, and investments from the affected countries, has achieved substantive results for the health of people living with HIV (PLHIV). Antiretroviral therapy coverage in SSA increased rapidly from single digits in the early 2000s to 53% in 2016 (1). Modeling studies have estimated that scale-up of ART has saved more than nine million life-years in SSA (3). Empirical studies have also linked increasing coverage of ART to decreased HIV-related mortality and all-cause adult mortality (4-10). #

Beyond the well-documented benefits of ART for PLHIV, the potential impact of these investments on the broader health system and on the health of overall populations without HIV infection has been an active area of research and debate. It is widely acknowledged that HIV program funding has contributed to improving many components of health systems, from renovations of health facilities and laboratories, strengthening processes to coordinate and manage patient care and modernization of health information and supply chain management systems (11-17). At the same time, there is evidence that the HIV epidemic has adversely affected the limited number of health workers in the severely affected countries. The need to provide comprehensive HIV care to large numbers of PLHIV has added additional burden to persistently overstretched workforce (18-25).

Whether the investments in HIV programs have on balance successfully translated to improved access and higher quality of care beyond HIV-related care and treatment remains unclear. Some studies have reported a decrease in utilization of non-HIV services, particularly in the areas of child health (26-30) and maternal health services (20, 26, 30) after facilities began offering HIV treatment. At the same time, other studies have noted the opposite using different metrics or in different settings (19, 20, 27, 31-37)—with ART availability associated with increased utilization of non-HIV health services. Still others have found no significant change (19, 21, 26-28, 30, 31, 35, 36, 38). No synthesis of existing evidence on spillover effects has been conducted to date.

Existing evidence on spillover effects of HIV programming summarized above has been exclusively based on non-experimental studies with weak bases for causal inference. There has only been one prospective cohort study and one quasi-experimental study to date (37, 38). Associations between start of HIV treatment at health facilities and utilization of non-HIV health services could be confounded by a variety of factors, including population growth, the number of PLHIV living in the community, other secular trends, such as change in prevalence of other conditions or general economic growth or decline. At the individual level, associations between ART uptake and non-HIV health service utilization are likely substantially confounded by similar factors, such as sex, age, socio-economic status, alcohol use, long wait times, and distance to health facility, all of which have been shown to lower ART uptake as well as more broadly general health service use (57-60).

The current literature has largely focused on the effect of ART expansion on maternal and child health services with limited research on tuberculosis (TB) care utilization (28, 32, 34). In addition, no studies have assessed the effect of HIV programs on treatment uptake for non-communicable diseases (NCDs), a growing health threat which currently accounts for approximately a third of all deaths in SSA (61, 62). It is well documented that despite this substantial burden, awareness and treatment uptake for NCDs are very low overall (63-68).

We conducted a quasi-experimental study using longitudinal demographic surveillance data from rural Kwazulu-Natal, South Africa, to determine whether exposure to ART utilization by a person living with HIV (PLHIV) in a household could promote uptake of TB, hypertension (HTN) and diabetes mellitus (DM) treatment by other household members with these conditions.

Methods

Study setting and population

The data used in this study were derived from demographic surveillance data, including annual health questionnaire data from the Africa Center Demographic Information System (ACDIS) run by the Africa Health Research Institute, in the Hlabisa sub-district of Kwazulu-Natal, South Africa (69). Clinic data from PLHIV in care at six primary health clinics located within the surveillance area and the annual health questionnaire data for cohabitating household members were linked by the unique identifiers for their shared homesteads. While individuals could only be associated with one homestead per annual assessment they could be associated with multiple homesteads across assessments. The analysis included resident adults aged 15 and older who were enrolled in HIV care between 2008 and 2013 and their cohabitating household members 15

and older who were captured at least once in the annual General Health Questionnaire Surveys between 2009-2014. Data for 2008 were not available for cohabitating members. We allowed for an extra year of follow up for the cohabitating members to capture the effect of PLHIV enrolled in 2013. Non-residents, children <15 and those with history of TB or NCD at baseline were also excluded. Figure 1 summarizes the study sample. Ethical approval for all data collected within the cohorts was obtained from the University of KwaZulu-Natal's Ethics Committee.

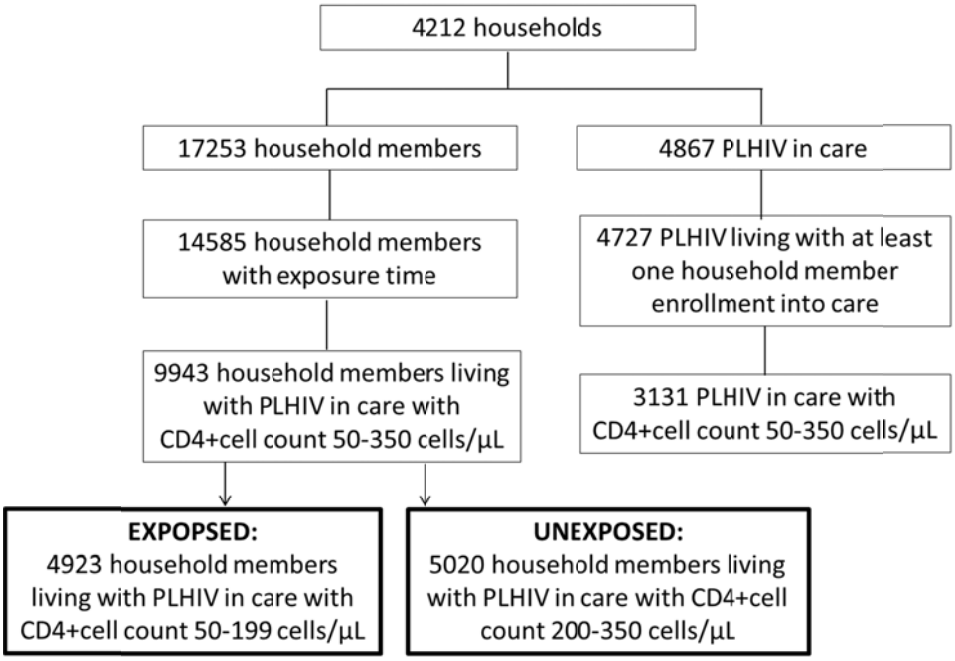


Figure 1: Participant flow diagram

Study Design

To evaluate the causal effect of exposure to PLHIV's uptake of ART on a cohabitating household member's propensity to seek care for TB, HTN and DM treatment, we conducted regression discontinuity quasi-experiments, utilizing the CD4+ cell count threshold rule for ART eligibility in South Africa (34, 35). CD4+ cell count measurements are known to fluctuate naturally and due to random measurement errors. In this study cohort, Bor, et al, found

substantial within-person variation of CD4+ cell counts among 146 participants who had two or more measurements done on the same day or one day apart (70). In the latter study, the authors found that a participant with a "true, underlying" CD4+ cell count of 200 cells/μL tested within 95% CI: 120 cells, 300 cells (70). There is substantial overlap in the "true" CD4+ counts among eligible and ineligible participants close to the treatment eligibility threshold, so groups slightly below and above the threshold are interchangeable in terms of their immunological status. In this study we exploited the random variation that occurs with enrollment CD4+ cell counts as our treatment assignment variable to construct the ART group (exposed) whose CD4+ cell count was just below the prevailing clinical threshold for ART initiation and non-ART group (unexposed) whose enrollment CD4+ cell count was just above the threshold.

Treatment assignment can be either deterministic or probabilistic. If the assignment is deterministic, every participant on the one side of the threshold value receives the treatment and every participant on the other side does not. If the assignment is probabilistic the probability of receiving the treatment is higher on the one side of the threshold value than on the other side. The first case is referred to as ''sharp'' regression discontinuity (RD) and the second ''fuzzy'' RD design. In this study, the "fuzzy" RD design (FRD) was implemented, as ART eligibility is often assigned with the CD4+ cell count threshold rule in combination with WHO clinical staging and behavioral factors that may impact adherence, the latter likely influencing provider's willingness to prescribe ART. As there are individuals who start ART even when their enrollment CD4+ cell counts are above the clinical threshold and others who do not start ART even when their CD4+ cell counts are below the threshold, this results in a situation resembling randomization in a clinical trial where some would always take up the treatment, regardless of

treatment assignment while others would never take up the treatment even if assigned. The hallmark of analytic approach in a randomized clinical trial (RCT) is the intent-to-treat (ITT) effect, which is the effect of treatment assignment. FRD design therefore also estimates ITT_{FRD}. In a FRD design, ITT (ITT_{FRD}) measures the effect of treatment eligibility, as determined by the threshold rule, and is often of interest in its own right. If randomization worked, ITT_{FRD} is not confounded. ITT_{FRD} often is considered a causal effect that is more reflective of reality because it would include those who adhere with assigned treatment and those who do not. In particular, ITT_{FRD} can also be interpreted as the effect of raising the threshold on outcomes for the full population of participants close to the threshold. The ITT_{FRD} can be summarized in Equation 1:

$$ITT_{FRD}=lim_{(z\uparrow c)}E[Y_i|Z_i=z]-lim_{(z\downarrow c)}E[Y_i|Z_i=z] \quad (1)$$

where c is the threshold value, of a continuous assignment variable, Zi.

Study Measures

Exposure measures:

The exposure status, cohabitation with PLHIV whose enrollment CD4+ cell count is under 200 cells/μL (ART eligible) versus above 200 cells/μL (ART ineligible) was operationalized as a binary variable. The true exposure of interest is cohabitation with PLHIV initiating ART. As ART initiation and uptake of treatments for other conditions are likely heavily confounded, we made use of an assignment variable—CD4+ cell count at enrollment—that is tightly correlated with the exposure of interest, ART initiation by PLHIV in the household, but is not independently associated with the outcome of interest, cohabitating household member's propensity to uptake other treatments, when limiting the analysis within a small range around the

ART eligibility threshold. Various sizes of margins around the ART eligibility threshold used were examined, including ±50, 100, 150 cells/μL around the threshold. The analysis time for the study was defined as the time period between the date of enrollment CD4+ cell count of PLHIV or start date for cohabitation whichever came later and last recorded clinic visit by PLHIV or last recorded date for cohabitation whichever came sooner. Figure 2 shows the different exposure time scenarios that were available in the study population. The black line indicates total follow up time of the household member and the blue represents the time the member cohabitated with PLHIV in care. Scenarios 1-4 have exposure time while scenarios 5 and 6 do not and were excluded from our analysis.

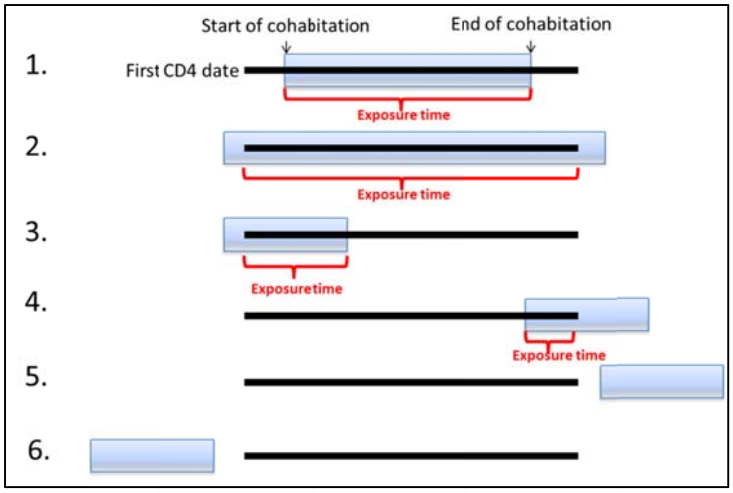


Figure 2: Schematic describing variation of potential exposure time based on common residence in homestead

Outcome measures:

The outcome variables included in this study are self-reported uptake of TB, HTN and DM treatment by cohabitating household members while PLHIV sharing the same homestead were in HIV care. We operationalized the outcomes of interest in two ways. First, as time to first treatment uptake event and conducted survival analyses to estimate the causal effect of living

with a PLHIV eligible for ART versus living with a PLHIV ineligible for ART. Second, as counts of treatment episodes as cohabitating household members could have sought care for these conditions multiple times during the study period.

Statistical analysis:

Descriptive statistics were used to summarize characteristics of the PLHIV in care and their cohabitating household members. Chi-square tests and two sample t tests were used to compare characteristics by exposure status. We assessed whether the underlying assumptions for FRD design were met in the study dataset. The three FRD assumptions are: 1) distribution of the assignment variable, in this case enrollment CD4+ cell count, must not show any signs of manipulation, such as bunching at the threshold that could happen if clinicians or participants manipulate the CD4+ cell counts to qualify for ART eligibility, an impossible scenario unless documentation of CD4+ cell counts were manipulated; 2) continuity in baseline variables, such as age, sex, date of CD4+ cell count measurement across the exposure groups; 3) the cumulative probability of the exposure, in this case initiating ART following a participant's first CD4+ cell count, should show a large discontinuity at the threshold. We examined the discontinuity at the threshold within 6, 12, and 24 months after enrollment to assess whether discontinuity persisted over the study period.

ART initiation was estimated on the risk difference scale, using linear probability (OLS) models to estimate the Equation 1, which models the conditional expectation function (CEF) as a continuous function of the enrollment CD4+ cell count, except for an intercept shift at the

threshold. We allowed for different slopes on either side of the threshold, which would arise in the case of effect heterogeneity.

Equation 1: $E[Y_i|CD4_i] = \beta_0 + \beta_1(CD4_i\text{-}200) + \beta_2 1[CD4_i<200] + \beta_3(CD4_i\text{-}200)*1[CD4_i<200]$

where β_1 is the slope of the line below the threshold, $\beta_{1+}\ \beta_3$ is the slope of the line above the threshold, and β_2, is the effect of eligible on the probability of ART initiation for individuals presenting with CD4+ cell count close to the threshold. We can interpret the difference in outcomes between those just above versus just below the cutoff as the effect of eligible CD4+ cell counts at enrollment on ART initiation.

Next, we implemented FRD in parametric and semi-parametric survival models to compare time to first treatment uptake event for TB, hypertension and diabetes at the threshold point for ART with a binary exposure variable for enrollment CD4+ cell count above and below 200 cells/μL. We fitted exponential and Weibull survival models as well as cox proportional hazard model to examine the robustness of findings. Additionally, we examined all episodes of treatments and fitted a Poisson model. The treatment episodes events were aggregated to one count per person and analysis time in years was used as an offset term. Correlation within those living in the same homesteads was accounted for using generalized estimating equations with exchangeable correlation structure specified. We ran models that included and excluded cohabitating household members that were HIV-infected but are not documented to be in HIV care to assess whether heterogeneous effects can be observed by HIV status of the cohabitating household member. All statistical tests were two-sided and $p<0.05$ was considered significant.

In the FRD design, the groups right above and below the threshold are assumed to be comparable in all other causes of the outcome. We examined the balance in key covariates, including age, sex, and exposure time across the exposure groups. We ran both unadjusted and adjusted models with sex, age, and enrollment CD4+cell count. To allow for effect heterogeneity across the threshold we included interaction terms with the exposure variable and CD4+cell count. We additionally examined the effect of the number of PLHIV eligible for ART in the shared homestead.

As part of sensitivity analyses, pre-treatment assignment characteristics of the analytic sample that restricts to the first associated homestead vs. all associated homesteads allowing for change in associated homestead over time were compared. We additionally compared pre-treatment assignment characteristics of cohabitating household members included in the analysis vs. those who dropped out because their cohabitation with the PLHIV did not coincide with when the PLHIV were in care to assess whether any systematic differences exist that may suggest potential selection bias. Data set preparations were done in SAS 9.3 (SAS, Cary, NC). Statistical analyses were conducted by using STATA12.0 (StataCorp, College Station, Texas).

Results

Characteristics of the study population

Table 1.1 and 1.2 summarize characteristics by exposure status of the index PLHIV in HIV care and their cohabitating household members. There were 4867 PLHIV receiving HIV care living with 17,253 household members >15 years who participated in at least one general health survey

during the study period. A median of 5 (IQR: 3-7) PLHIV in care and household members >15 years lived in 4212 unique homesteads; 12% of PLHIV in care were associated with >1 homesteads. The large majority of PLHIV in care were women (77%) and their average age was 33 years. More than half were enrolled between 2007 and 2009 (55%) and the median follow up time was 2.0 years (IQR: 0.9-4.4). During the study period, 10.0%, 12.6% and 2.4% of PLHIV reported that they had TB, hypertension and diabetes, respectively, in the preceding 12 months. Of those who had these conditions, 98.3%, 79.0%, and 79.2% were on treatment for TB, hypertension and diabetes, respectively.

Cohabitating household members were 55% female with a mean age of 31 years. Median follow up time was 2.0 years (IQR: 0.9-4.4) and median analysis time or time at risk was 1.7 years (IQR: 0.6-3.2). More than a quarter (27%) of household members lived with more than one PLHIV in HIV care. About 6% of the cohabitating household members had a documented HIV positive diagnosis but were not in care. During the study period, 3.8%, 11.4% and 3.1% of cohabitating household members reported that they had TB, hypertension and diabetes, respectively, in the preceding 12 months. Of those who had these conditions, 95.6%, 86.0% and 83.2% were on treatment for TB, hypertension and diabetes, respectively. Baseline characteristics did not differ significantly by exposure status.

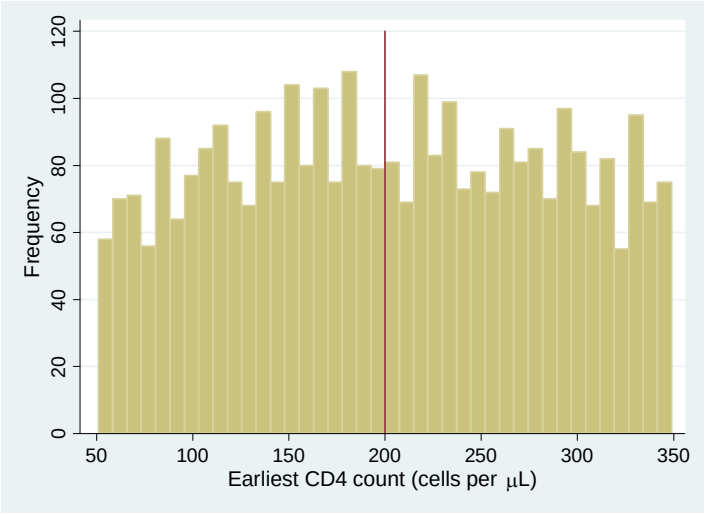


Figure 3: Distribution of enrollment CD4+ cell counts among participants enrolled in HIV care between 2008-2013

Assessment of RD assumptions

Figure 3 shows the distribution of CD4+ cell count at enrollment of the cohabitating PLHIV in HIV care. There was no discernable bunching at the clinical threshold of 200 cells/μL, suggesting that the assumption of non-manipulation of the treatment assignment variable (CD4+ cell count) held true in the study sample. Figures 4.1, 4.2, 4.3 show the association between age, sex, and enrollment CD4+ cell count and predicted hazard for TB, hypertension and diabetes treatments, fitting separate regression lines below and above the threshold. The dots represent individuals in 10-cell CD4+count bins. There was little to no discontinuity in the distribution of age, sex, and date of first CD4+ cell counts at the threshold vis-à-vis the predicted hazard for first episode of treatment outcomes of interest, indicating balance in these characteristics between the exposed and unexposed groups.

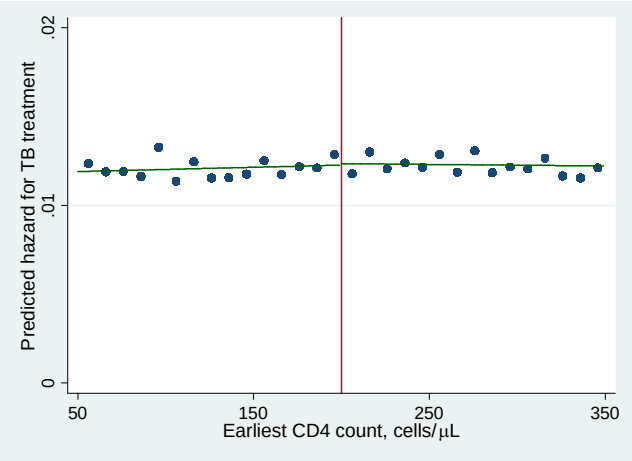


Figure 4.1: Predicted hazards by 10 CD4+ cell count bins adjusting for baseline age, sex and date of first CD4+ cell count (Treatment for TB)

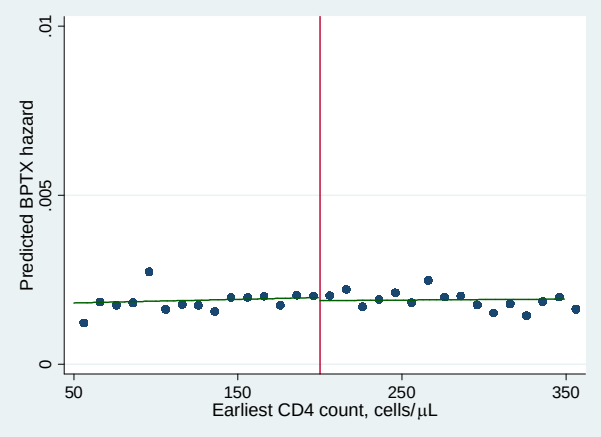


Figure 4.2: Predicted hazards by 10 CD4+ cell count bins adjusting for baseline age, sex and date of first CD4+ cell count (Treatment for hypertension)

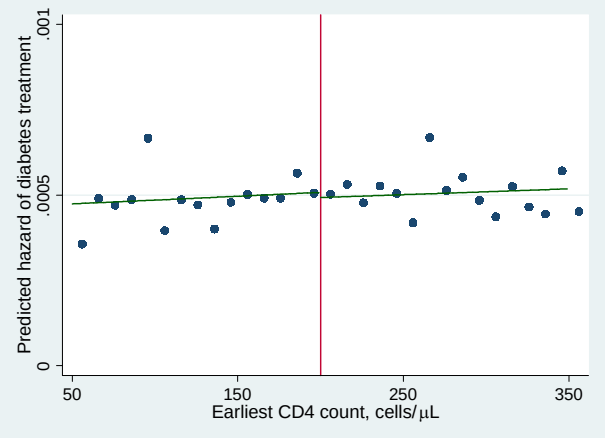


Figure 4.3 Predicted hazards by 10 CD4+ cell count bins adjusting for baseline age, sex and date of first CD4+ cell count (Treatment for diabetes)

Finally, we found a substantial discontinuity in the probability of HIV treatment initiation between PLHIV with CD4+ cell count of below and above the 200 cell/μL threshold (Figure 5.1). The discontinuity was observed in 6, 12 and 24 month time frames since enrollment, suggesting that enrollment CD4+ cell count remains a strong assignment variable over the study period (Figure 5.2).

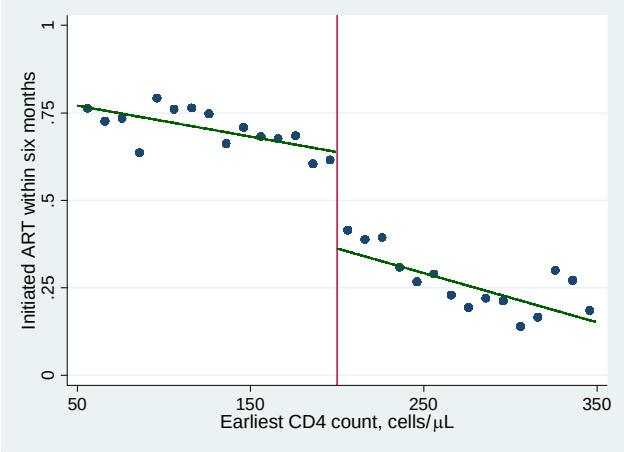


Figure 5.1: Cumulative probabilities of ART initiation within 6 months by 10 cell CD4+ count bins using the Kaplan-Meier estimator

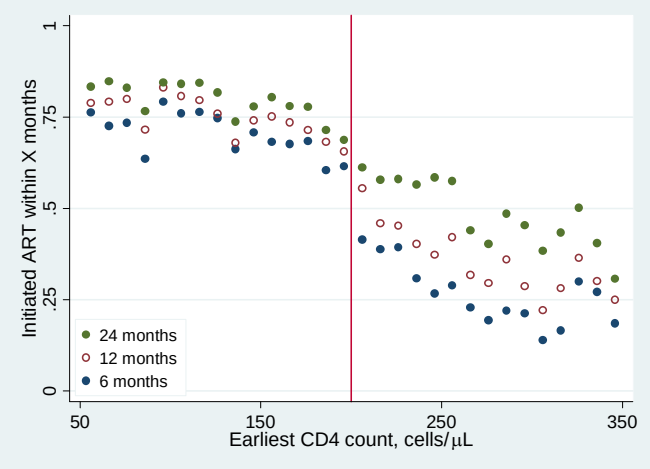


Figure 5.2: Cumulative probabilities of ART initiation within 6, 12, and 24 months by 10 cell CD4+ count bins using the Kaplan-Meier estimator

In addition to visual inspection, we ran linear probability models to quantify the discontinuity in the probability of ART initiation at the clinical threshold (Table 2.1-2.2). Having a baseline CD4+ cell count less than 200 cells/μL increased the probability of initiation within six months

by 26 absolute percentage points (95% CI: 19%, 32%) restricting the analysis range between 50 and 350 cells/μL. As we increased the observation time from initiation within 6 months to 24 months, the difference persisted but with a smaller magnitude. Probability of initiation within a year and within two years, restricting the analysis range to between 50 and 350 cells/μL, continued to show a large discontinuity with a difference of 19 percentage points (95% CI 13%, 26%) and 11 percentage points (95% CI:5%, 17%) .

FRD modeling results

Cumulative hazard functions at year 6 for first treatment episodes by exposure status without adjustment using the largest CD4+cell count bandwidth of 50 and 350 cell/μL are summarized in Table 3.1. Cumulative hazard functions for treatment uptake were higher in the exposed group for all three conditions, TB, hypertension and diabetes. Treatment uptake for hypertension was statistically significantly different (0.153 vs. 0.141, Logrank test p=0.011) while a trend for treatment for diabetes approached statistical significance (0.045 vs. 0.035, Logrank test p=0.070). The differences were not statistically significant for TB treatment.

Overall average rates per 100 person-years of treatment uptake over the study period are shown in Table 3.2. Average rates of treatment uptake were higher for the exposed group for all three diseases. Treatment uptake for diabetes was statistically significantly different (2.7 vs. 1.6 per 100 person years, Wald test p=0.049). The differences were not statistically significant for TB and hypertension treatment uptake.

Adjusted FRD results with exponential survival models using different CD4+ cell count bandwidths are shown in table 4.1−4.3. Results from Weibull and Cox models are included in tables 4.1a−4.3a and 4.1b−4.3b in the supplementary materials. Those cohabitating with PLHIV with CD4+ cell count just below the treatment threshold had an increased likelihood of treatment uptake for diabetes compared to those cohabitating with PLHIV with CD4+ cell count just above the treatment threshold. The effect was observed in all analysis bandwidth but only reached statistical significance in the largest bandwidth. The effects strengthened in models adjusting for sex and age. The increased likelihood for treatment uptake for diabetes was also found in models restricting the sample to HIV uninfected cohabitating household members while the association did not meet the statistical significance threshold. We did not find any strengthening effect in models restricting the sample to those living with more than one PLHIV. Sex specific models were also run and did not show any effect heterogeneity by sex (data not shown). For TB treatment uptake, while the exposed group showed increased tendency for treatment uptake, none of the models reached statistical significance. For hypertension treatment, no positive or negative tendencies were observed. Results were robust to specification changes as shown in Weibull and Cox model results included in the supplementary materials. Figures 6.1−6.3 show the predicted hazards from the exponential survival models for TB, hypertension and diabetes treatment with separate slopes fitted for exposed and unexposed groups. The dashed lines represent extrapolated prediction if all participants were treatment eligible at time of enrollment.

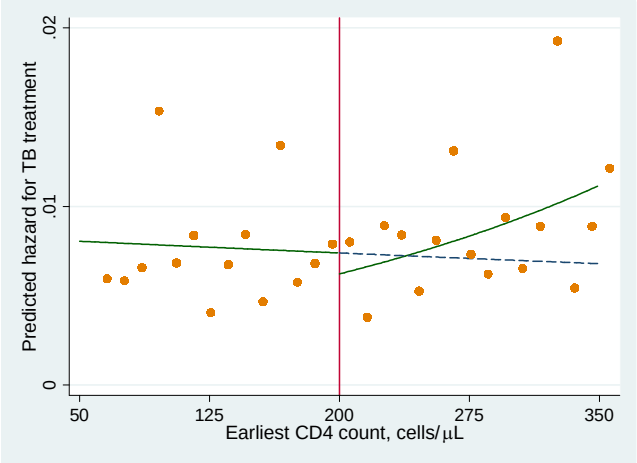


Figure 6.1: First CD4+ cell count in 10 CD4+ cell count bins and predicted hazard rates for first episode of TB treatment

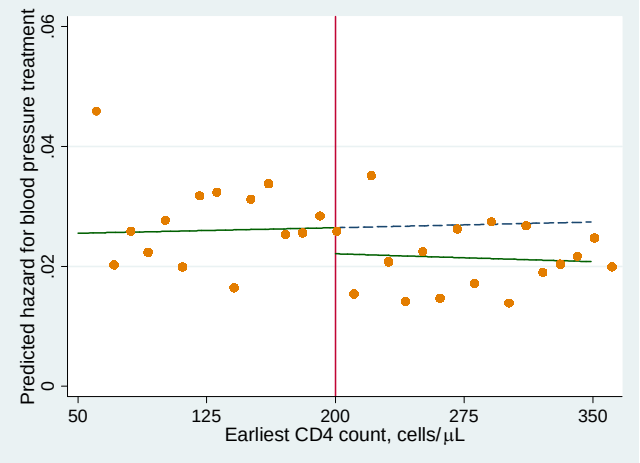


Figure 6.2: First CD4+ cell count in 10 CD4+ cell count bins and predicted hazard rates for first episode of hypertension treatment

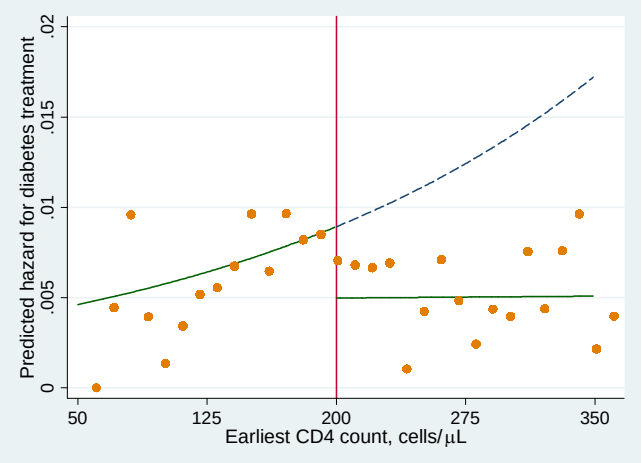


Figure 6.3: First CD4+ cell count in 10 CD4+ cell count bins and predicted hazard rates for first episode of diabetes treatment.

Adjusted FRD results with Poisson regression models with GEE using different CD4+ cell count bandwidths are shown in tables S3.1−3.3. Consistent with the survival models, the exposed group had an increased likelihood of initiating diabetes treatment compared to the unexposed group while no significant differences were observed between the groups for TB and hypertension treatment. Figures S1.1−1.3 included in the supplementary materials show predicted rates of treatment by first CD4+ cell count.

Sensitivity analyses

Pre-treatment assignment characteristics in a sample allowing for change in homesteads over time did not show any significant difference with the analytic sample restricting to first associated homestead (Supplementary materials tables S2). In addition, we examined pre-treatment assignment characteristics in the overall study sample vs. those who were included in the analysis. No significant differences were found (Supplementary materials tables S1).

Discussion

In this rural community in SSA with substantial burden of HIV and TB and NCDs that has seen rapid ART expansion in the past decade (4), we identified a significant causal link between ART uptake by PLHIV on cohabitating household member's treatment uptake for diabetes treatment. We found positive trend, but not statistically significant, causal effects between ART uptake and TB and hypertension treatment uptake. Our study strengthens the evidence base for the association between investments in HIV treatment with positive spillover effects in increasing utilization of non-HIV related services (11, 19, 20, 27, 31-37, 40, 41).

Non-communicable diseases are an emerging health threat in SSA (71). In this study population, approximately 38% and 11% of adults 40 years and older reported having hypertension and diabetes mellitus in the preceding 12 months. Timely diagnosis and consistent care provided by the formal health sector are critical for the effective clinical management of NCDs. Medical pluralism, a practice of obtaining health care from the informal sector in addition to or instead of the formal sector, has been shown to delay or prevent diagnosis and treatment uptake for many conditions in SSA (72-76). Studies have shown that treatment for NCDs are often delayed due to misperceptions about the causes of disease and reliance on self-care and traditional healers (77, 78). In this context, it is encouraging to observe that treatment uptake for diabetes disease among cohabitating household members increase with the social exposure of HIV treatment.

The lack of significant effect on TB treatment uptake is consistent with past studies. In the most comprehensive study, Duber found that there was no difference in TB detection rates between 2000 and 2006 comparing data from 12 PEPFAR focused countries (receiving more funding for HIV) versus 34 PEPFAR non-focused countries (receiving less funding for HIV) (28). However, this finding may be due to the fact that the study period included only early years of efforts to scale-up access to ART. Other smaller studies have found positive associations, although these studies had designs that limited causal inference (32, 34, 36). The lack of effect in this study population is likely due to the high rates of TB treatment (about 95%) at baseline in this population among cohabitating household members reporting having TB in the preceding 12 months irrespective of exposure to PLHIV on ART in their households.

It is also important to note that we did not find evidence of deleterious effects as some past studies have found in other domains of non-HIV health services, including maternal and child health services (26, 27, 29, 30). The authors of the latter studies speculated that resource reallocation within national budgets and human resources for health to prioritize HIV and deprioritize non-HIV health services as well as the impact of HIV on household budgets could explain the decline in accessing non-HIV health services.

The mechanisms that could have led to increasing treatment uptake by cohabitating household members was not explored in this study. There is some evidence that PLHIV on ART may be improving their own treatment seeking behaviors for non-HIV health services, including antenatal care, hypertension, and diabetes, and experiencing better health outcomes (68, 79-82). In a cohort of ~5000 older individuals in rural South Africa, Manne-Gohler et al found that those with HIV infection and on treatment had 63% higher odds of being treated for diabetes compared to HIV-uninfected individuals with similar baseline characteristics (68). Could exposure to PLHIV initiating HIV and other health care and having positive health outcomes influence treatment seeking behavior by the HIV uninfected individuals in their households and communities? With high HIV prevalence in many SSA countries, the impact of HIV and the benefits of its treatment are relevant to a large segment of the population. Bor et al found that 40% of the population in the same district where our study was conducted shared household or living arrangements with people who had either initiated ART or were enrolled in HIV care (83). Such social exposure to HIV treatment has been found to change risk perceptions among HIV-uninfected individuals (84), to improve attitudes toward PLHIV at a population level (85), and increase testing among male household members (86). In light of these findings, it is plausible

that that favorable health care experiences and improved treatment outcomes by PLHIV visiting health facilities can be an important mechanism, as others have speculated (35, 37).

It is important to note that we found relatively modest effect sizes, and statistically significant findings were limited to models with the largest CD4+ cell count bandwidth. Employment of FRD design means that we allow for crossovers between exposure groups which as in RCTs dilute the treatment effect. In our sample we had 26% of those who were in the unexposed group initiating treatment and 30% in the exposed group not initiating treatment during the entire follow up period. The modest effect sizes are likely due to the crossovers. However, as many RD researchers have noted in the past, the causal effects estimated in FRD studies are considered to reflect real world conditions where lost to follow up, adherence issues, and non-compliance to treatment assignment are common (87-89). The small effect sizes can also be explained by presence of other causes of treatment uptake. Treatment uptake has been shown to be influenced by multiple factors (90-96). Any incremental increase in treatment uptake due to social exposure of ART through cohabitating with PLHIV is likely not large. Improving quality of health services have been shown to influence treatment seeking behavior of individuals in past studies. If ART scale up brought general improvements in the health clinics, the marginal effect of sharing dwelling with someone on ART vs. community perception of the improvements in the quality of services may be important but small.

The main strength of our study is that it utilized the ACDIS demographic surveillance cohort data that allows generating population based estimates of causal effects, a significant contribution the spillover effects research that is dominated by facility-based data. The ACDIS

cohort data also uniquely allows linking of data collected from PLHIV in their attending clinics with data collected about their cohabitating household members captured as part of the community health surveys. The ability to link these two sources of data allowed implementing the FRD design that requires CD4+ cell count data from the clinic and measure the potential effects of ART uptake by PLHIV on their cohabitating household members

Another strength is the FRD design that provides strong basis for causal inference in an area where implementing an RCT—a gold standard for causal inference—is not feasible. The FRD design is widely used to estimate unbiased causal effects of economic, social and medical interventions that uses a threshold value of a continuous measure to determine eligibility, such as income, age, or birthweight (88, 89, 97). We successfully employed FRD designs to obtain unbiased causal estimates removing the potential confounding effects of individual and household characteristics, such as education, income, employment status, smoking or alcohol use, on the relationship between PLHIV's ART uptake and their cohabitating household member's treatment uptake behaviors. The study is a significant contribution to the spillover research of HIV programs that has thus far been dominated by association studies using aggregate clinic level data. To our knowledge, there has only been one prospective cohort study (37) and one quasi-experimental study (38) in the research area of spillover effects.

Our study had limitations. Regression Discontinuity requires large sample sizes to allow for sufficient analytic sample within the narrow range across a clinical threshold used to maintain comparability between the exposure groups (88). While our total sample size was sufficiently large, we had relatively few treatment events, especially for the narrower bandwidths, making it

challenging to detect statistically significant results. In addition, external validity of our study is arguably limited as analysis was limited to a narrow range across the clinical threshold for ART eligibility. Another limitation is that we used self-reported treatment uptake data for our outcomes. To the extent that there is stigma for seeking care for these conditions, there is likely a downward bias. However, the FRD design ensures that any bias is present equally between exposure groups.

In summary, in this study we demonstrated that social exposure to PLHIV who initiated ART through cohabitation increased the likelihood of accessing a non-HIV health service. Although prior studies have found correlation between expanded access to HIV treatment in communities and utilization of non-HIV related services, this study is one of the first to demonstrate a stronger causal link. However, future research is needed to identify the mechanisms leading to these observed effects. Furthermore, in the era of plateau in external development resources available for health programs, identifying and capitalizing on synergies to achieve wider impact is critical. Harnessing positive synergy from HIV programming to expand supply and demand for services for NCDs should become routine programming (98). Finally, lessons learned from the management of HIV, a chronic communicable disease, can also inform the development of appropriate programs to successfully manage NCDs.

Chapter 3: Tables

Table 1: Characteristics of study population, restricted to first associated dwelling structure

1.1: PLHIV in HIV care	Exposure (below threshold)	Control (above threshold)	Total
	n (%)	n (%)	n (%)
Total	1981 (40.7)	2886 (59.3)	4867 (100)
Proportion female	1395 (70.4)	2328 (80.7)	3723 (76.5)
Mean age at first visit , min-max	34.8 (15-90)	32.3 (15-90)	33.3 (15-90)
Median enrollment CD4 count, IQR	114 (64-158)	333 (265-405)	239 (135-354)
Year of enrollment			
2007	332 (16.7)	534 (18.5)	866 (17.8)
2008	419 (21.2)	584 (20.2)	1003 (20.6)
2009	305 (15.4)	513 (17.8)	818 (16.8)
2010	392 (19.8)	422 (14.6)	814 (16.7)
2011	276 (13.9)	379 (13.1)	655 (13.5)
2012	166 (8.4)	289 (10.0)	455 (9.4)
2013	91 (4.6)	165 (5.7)	256 (5.3)
Median follow time in care (years)	3.3 (1.7, 5.1)	3.6 (2.0, 5.2)	3.5 (1.9, 5.2)
Associated bounded structures	1711 (40.6)	2501 (59.4)	4212 (100.0)
Median number of household members, IQR	5 (3, 7)	5 (3, 7)	5 (3, 7)
Associated with 1 bounded structure	1754 (88.5)	2530 (87.7)	4284 (88.0)
Associated with >1 bounded structure	227 (11.5)	356 (12.3)	583 (12.0)
TB disease in the last 12 months	192 (11.8)	216 (8.8)	408 (10.0)
Hypertension in the past 12 months	199 (12.3)	311 (12.7)	510 (12.6)
Diabetes in the last 12 months	44 (2.7)	52 (2.1)	96 (2.4)
Of those with TB disease, in treatment	188 (97.9)	213 (98.6)	401 (98.3)
Of those with hypertension, in treatment	155 (77.9)	248 (79.7)	403 (79.0)
Of those with diabetes, in treatment	36 (81.8)	40 (76.9)	76 (79.2)

1.2: Cohabitating household members		Exposure (below threshold)	Control (above threshold)	Total
		n (%)	n (%)	n (%)
Total		7066 (41.0)	10187 (59.0)	17253
Proportion female		3872 (54.8)	5583 (54.8)	9455 (54.8)
Mean age , min-max		32.9 (15-116)	33.2 (15-103)	33.1 (15-116)
Proportion living with >1 PLHIV in care		2001 (28.3)	2681(26.3)	4682 (27.1)
Median (IQR) time associated with bounded structure (years)		9.0 (4.0-13.3)	8.6 (3.9-13.1)	8.8 (3.9-13.2)
Median (IQR) time since enrollment of PLHIV member (years)		2.5 (1.0-4.1)	2.6 (1.3-4.2)	2.6 (1.2-4.2)
% HIV positive not in care		609 (6.0)	377 (5.3)	986 (5.7)
Associated bounded structures		1711 (40.6)	2501 (59.4)	4212 (100)
TB disease in the last 12 months				
	1	187 (2.7)	314 (3.1)	501 (2.9)
	>1	58 (0.8)	97 (1.0)	155 (0.9)
Hypertension in the past 12 months				
	1	370 (5.2)	514 (5.1)	884 (5.1)
	>1	449 (6.4)	643(6.3)	1092 (6.3)
Diabetes in the last 12 months				
	1	126 (1.8)	193 (1.9)	319 (1.9)
	>1	100 (1.4)	112 (1.1)	212 (1.2)
Of those with TB disease, in treatment		233 (95.1)	394 (95.9)	627 (95.6)
Of those with hypertension, in treatment		698 (85.2)	1001 (86.5)	1699 (86.0)
Of those with diabetes, in treatment		191 (84.5)	251 (82.3)	442 (83.2)

Table 2: Treatment eligibility and ART initiation within 6,12, and 24 months*

2.1 Probability of ART initiation within six months

	Earliest CD4+ cell count	Probability of initiation ART within six months				Sample
	Specification, Range	E[Y|Z ≥200]	E[Y|Z<200]	Difference	95% CI	N
1)	Linear; 0-350	0.389	0.644	0.255	0.194, 0.316	3438
2)	Linear; 50-350	0.389	0.645	0.256	0.191, 0.321	3120
3)	Linear; 100-350	0.441	0.614	0.173	0.094, 0.253	2214
4)	Linear; 150-250	0.489	0.602	0.113	-0.002, 0.239	1126
5)	Linear; 175-225	0.47	0.601	0.131	-0.037, 0.299	559

2.2 Probability of ART initiation within 12 months

	Earliest CD4+ cell count	Probability of initiation ART within 1 year				Sample
	Specification, Range	E[Y|Z ≥200]	E[Y|Z<200]	Difference	95% CI	N
1)	Linear; 0-350	0.510	0.701	0.191	0.130, 0.253	3369
2)	Linear; 50-350	0.51	0.697	0.187	0.122, 0.253	3055
3)	Linear; 100-350	0.550	0.676	0.126	0.047, 0.205	2168
4)	Linear; 150-250	0.591	0.659	0.068	-0.046, 0.184	1104
5)	Linear; 175-225	0.607	0.650	0.043	-0.122, 0.208	549

2.3 Probability of ART initiation within 24 months

	Earliest CD4+ cell count	Probability of initiation ART within 2 year				Sample
	Specification, Range	E[Y|Z ≥200]	E[Y|Z<200]	Difference	95% CI	N
1)	Linear; 0-350	0.659	0.771	0.112	0.051, 0.172	3237
2)	Linear; 50-350	0.659	0.760	0.101	0.037, 0.165	2928
3)	Linear; 100-350	0.675	0.737	0.062	-0.016, 0.139	2082
4)	Linear; 150-250	0.653	0.71	0.057	-0.056, 0.169	1067
5)	Linear; 175-225	0.641	0.696	0.055	-0.106, 0.217	527

* Ordinary least squares linear probability model

Table 3: Treatment eligibility and treatment seeking

3.1 Cumulative hazard functions for first treatment seeking episode by disease at year 6

Range 50-350 cells					Sample	Events
Treatment seeking	E[Y|Z ≥200]	E[Y|Z<200]	Difference	Log rank test	N	n
TB	0.045	0.052	0.007	0.543	9780	221
Hypertension	0.141	0.153	0.012	0.017	9813	614
Diabetes	0.035	0.045	0.010	0.070	9479	162

* Nelson Aalen cumulative hazard functions

3.2 Mean rates per 100 person years for treatment seeking by disease

Range 50-350 cells					Sample	Events
Treatment seeking	E[Y|Z ≥200]	E[Y|Z<200]	Rate ratio	Wald test	N	n
TB	2.3	2.8	1.216	0.436	9943	287
Hypertension	13.5	14.3	1.064	0.527	9943	1452
Diabetes	1.6	2.7	1.705	0.049	9943	222

* GEE Poisson models

Table 4: Effect of treatment assignment on treatment seeking, parametric and semi-parametric survival models

4.1: Time to first TB treatment seeking	(EXP) ITT_{FRD}	95% CI	P	(WEI) ITT_{FRD}	95% CI	P	(COX) ITT_{FRD}	95% CI	P	Sample	Events
Overall, adjusting for CD4											
50-350	1.188	0.701, 2.013	0.522	1.184	0.699, 2.016	0.530	1.187	0.700, 2.011	0.525	9780	221
100-300	1.238	0.650, 2.357	0.516	1.219	0.640, 2.321	0.547	1.218	0.639, 2.322	0.548	7000	147
150-250	1.400	0.542, 3.616	0.487	1.329	0.521, 3.493	0.537	1.349	0.522, 3.489	0.536	3648	78
Overall, adjusting for CD4, age											
50-350	1.199	0.708, 2.030	0.499	1.195	0.706, 2.022	0.507	1.198	0.708, 2.029	0.501	9780	221
100-300	1.259	0.661, 2.401	0.483	1.239	0.650, 2.363	0.515	1.242	0.651, 2.371	0.510	7000	147
150-250	1.426	0.549, 3.705	0.466	1.369	0.525, 3.566	0.520	1.375	0.529, 3.576	0.650	3648	78
Overall, adjusting for CD4, age, sex											
50-350	1.202	0.710, 2.035	0.493	1.197	0.707, 2.026	0.502	1.201	0.709, 2.034	0.495	9780	221
100-300	1.266	0.664, 2.415	0.473	1.245	0.653, 2.375	0.506	1.250	0.655, 2.386	0.499	7000	147
150-250	1.445	0.557, 3.748	0.449	1.389	0.534, 3.613	0.500	1.396	0.537, 3.625	0.493	3648	78
Overall, adjusting for CD4, age, sex, restricting to HIV uninfected household members											
50-350	1.001	0.559, 1.809	0.986	1.003	0.558, 1.804	0.992	1.001	0.560, 1.815	0.978	9266	171
100-300	1.270	0.623, 2.592	0.511	1.254	0.614, 2.559	0.534	1.262	0.523, 0.618	0.523	6630	117
150-250	1.257	0.449, 3.522	0.663	1.203	0.428, 3.380	0.726	1.229	0.438, 3.445	0.695	3462	65
Overall, adjusting for CD4, age, sex, restricting to HH with more than 1 PLHIV in care											
50-350	2.137	0.845, 5.399	0.108	2.053	0.814, 5.177	0.127	2.116	0.837, 5.774	0.113	2734	64
100-300	2.193	0.672, 7.159	0.193	2.102	0.642, 6.883	0.220	2.168	0.663, 7.094	0.201	2000	50
150-250	2.814	0.572, 13.85	0.203	2.754	0.559, 13.58	0.213	2.845	0.580, 13.94	0.197	1068	26

4.2: Time to first hypertension treatment seeking	ITT_{FRD}	95% CI	P	(WEI) ITT_{FRD}	95% CI	P	(COX) ITT_{FRD}	95% CI	P	Sample	Events
Overall, adjusting for CD4											
50-350	1.197	0.884, 1.619	0.245	1.192	0.881, 1.613	0.256	1.193	0.881, 1.614	0.254	9479	614
100-300	1.047	0.725, 1.512	0.805	1.038	0.719, 1.499	0.843	1.037	0.718, 1.497	0.848	6807	454
150-250	0.757	0.454, 1.259	0.283	0.747	0.449, 1.245	0.263	0.753	0.452, 1.254	0.275	3561	230
Overall, adjusting for CD4, age											
50-350	1.251	0.927, 1.687	0.143	1.187	0.878, 1.605	0.264	1.309	0.970, 1.766	0.079	9479	614
100-300	1.086	0.748, 1.576	0.666	1.019	0.705, 1.473	0.920	1.129	0.776, 1.642	0.526	6807	454
150-250	0.743	0.444, 1.241	0.256	0.695	0.419, 1.153	0.159	0.861	0.517, 1.433	0.564	3561	230
Overall, adjusting for CD4, age, sex											
50-350	1.309	0.970, 1.767	0.079	1.307	0.968, 1.763	0.080	1.309	0.970, 1.766	0.079	9479	614
100-300	1.144	0.787, 1.662	0.481	1.125	0.774, 1.635	0.537	1.129	0.776, 1.642	0.526	6907	454
150-250	0.868	0.521, 1.445	0.587	0.844	0.507, 1.406	0.514	0.861	0.517, 1.433	0.564	3561	230
Overall, adjusting for CD4, age, sex, restricting to HIV uninfected household members											
50-350	1.308	0.959, 1.783	0.090	1.306	0.958, 1.780	0.091	1.307	0.959, 1.783	0.090	8949	573
100-300	1.161	0.789, 1.708	0.448	1.437	0.777, 1.683	0.495	1.147	0.780, 1.689	0.485	6423	422
150-250	0.884	0.522, 1.498	0.647	0.862	0.508, 1.461	0.581	0.882	0.520, 1.495	0.641	3361	215
Overall, adjusting for CD4, age, sex, restricting to HH with more than 1 PLHIV in care											
50-350	1.403	0.785, 2.509	0.253	1.363	0.762, 2.437	0.296	1.353	0.756, 2.422	0.308	2675	165
100-300	1.616	0.786, 3.323	0.192	1.584	0.769, 3.264	0.212	1.591	0.771, 3.280	0.209	1966	123
150-250	1.201	0.482, 2.992	0.693	1.207	0.484, 3.013	0.687	1.262	0.503, 3.165	0.619	1053	70

4.3: Time to first diabetes treatment seeking	(EXP) ITT_{FRD}	95% CI	P	(WEI) ITT_{FRD}	95% CI	P	(COX) ITT_{FRD}	95% CI	P	Sample	Events
Overall, adjusting for CD4											
50-350	1.792	1.001, 3.212	0.050	1.786	0.995, 1.001	0.051	1.790	0.999, 3.205	0.050	9813	162
100-300	1.678	0.835, 3.372	0.146	1.666	0.829, 3.349	0.152	1.657	0.824, 3.332	0.157	7033	122
150-250	1.247	0.473, 3.289	0.656	1.234	0.467, 3.256	0.672	1.201	0.454, 3.177	0.712	3673	70
Overall, adjusting for CD4, age											
50-350	1.829	1.025, 3.265	0.041	1.829	1.025, 3.264	0.041	1.829	1.025, 3.264	0.041	9813	162
100-300	1.750	0.865, 3.539	0.119	1.744	0.862, 3.527	0.122	1.734	0.857, 3.509	0.126	7033	122
150-250	1.288	0.481, 3.445	0.614	1.275	0.476, 3.415	0.628	1.233	0.460, 3.306	0.677	3673	70
Overall, adjusting for CD4, age, sex											
50-350	1.907	1.068, 3.407	0.029	1.904	1.066, 3.401	0.029	1.902	1.065, 3.396	0.030	9813	162
100-300	1.853	0.916, 3.749	0.086	1.845	0.912, 3.732	0.088	1.836	0.907, 3.719	0.091	7033	122
150-250	1.406	0.527, 3.748	0.496	1.393	0.522, 3.716	0.509	1.351	0.505, 3.614	0.549	3673	70
Overall, adjusting for CD4, age, sex, restricting to HIV uninfected household members											
50-350	1.702	0.938, 3.088	0.080	1.670	0.937, 3.082	0.081	1.699	0.937, 3.080	0.081	9267	150
100-300	1.789	0.870, 3.682	0.114	1.781	0.865, 3.664	0.117	1.770	0.860, 3.646	0.121	6639	112
150-250	1.344	0.494, 3.657	0.563	1.334	0.490, 3.632	0.573	1.296	0.475, 3.534	0.613	3469	65
Overall, adjusting for CD4, age, sex, restricting to HH with more than 1 PLHIV in care											
50-350	1.475	0.462, 4.706	0.512	1.483	0.464, 4.738	0.506	1.433	0.448, 4.580	0.544	2754	33
100-300	1.683	0.443, 6.397	0.445	1.697	0.446, 6.449	0.438	1.640	0.429, 6.264	0.470	2021	30
150-250	1.026	0.179, 5.878	0.977	1.051	0.183, 6.002	0.956	1.014	0.176, 5.831	0.988	1078	19

Chapter 4: The Effects of HIV Treatment on Risk of All-Cause Mortality of Adult Household Members

Abstract

Background: The global response to the HIV epidemic has achieved a remarkable decrease in mortality and morbidity among people living with HIV (PLHIV). Whether the investments in HIV treatment programs have had spillover effects on health outcomes for the general population is unclear. We conducted a quasi-experimental study in rural Kwazulu-Natal (KZN), South Africa, to determine whether exposure to health benefits from ART utilization by a person living with HIV (PLHIV) in a household reduces all-cause mortality of other household members.

Methods: The study was conducted in the comprehensive population cohort followed by the Africa Health Research Institute (AHRI) in KZN. We linked PLHIV engaged in HIV care to their cohabitating household members aged ≥15 years using a unique identifier for homesteads. We implemented regression discontinuity quasi-experiments fitting Weibull and Cox survival models to establish the causal effect of ART utilization on all-cause mortality among household members. We ran unadjusted models and models adjusting for age and sex, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold.

Results: There were 5085 PLHIV enrolled in care living with 22,062 household members ≥15 years in 4612 unique homesteads between 2008-2014. Most PLHIV in care were women (76%) with mean age of 37 years. Cohabitating household members were 54% female with mean age of 33 years and a median household ART utilization exposure of 2.2 years (IQR: 1.0-3.8). During the study period, there were 1023 deaths (4.6%) among cohabitating household members, 574 of which took place after PLHIV engaged in HIV care (12.5 deaths per 1000 person years).

Overall, household ART utilization did not decrease all-cause mortality (Hazard Ratio (HR) 0.95: 95% CI 0.65-1.4), however, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold, showed reduced all-cause mortality by 67% (HR 0.43: 95% CI 0.22-0.85) among household members of PLHIV on ART; the reduced risk was driven largely by the significant reduction noted among female household members (HR 0.21: 95% 0.08, 0.56).

Conclusion: Exposure by household members to HIV treatment programs through treatment of PLHIV in their household may be linked to decreased all-cause mortality among female household members. Future research is needed to further define reasons for this effect and to explore how HIV treatment programs can be even better leveraged to improve access to other needed health needs in sub Saharan Africa.

Introduction

The expansion of antiretroviral therapy (ART) to 14 million people in Sub-Saharan Africa (SSA) is one of the most successful global public health programs ever undertaken (1) with more than 70 billion dollars contributed since 2004 through the United States President's Emergency Plan for AIDS Relief (PEPFAR) alone (2). This massive investment, along with other contributions by the Global Fund to Fight AIDS, Tuberculosis and Malaria and investments from the affected countries, have achieved substantial results for the health of people living with HIV (PLHIV). Antiretroviral therapy (ART) coverage in SSA increased rapidly from single digits in the early 2000s to 53% in 2016 (1). Modeling studies have estimated that scale-up of ART has saved more than nine million life-years in SSA (3). Empirical studies have also linked increasing coverage of ART to decreased HIV-related mortality and all-cause adult mortality among PLHIV (4-10). #

Beyond the well-documented benefits of ART for PLHIV, the potential effect of these investments on the broader health system and on the health and survival of overall populations without HIV infection has been an active area of research and debate. It is widely acknowledged that HIV program funding has contributed to improving several components of the health systems, from renovations of health facilities and laboratories, strengthening processes to coordinate and manage patient care and modernization of health information and supply chain management systems (11-17). At the same time, there is evidence that the HIV epidemic has adversely affected the limited number of health workers in the severely affected countries. The need to provide comprehensive HIV care to large numbers of PLHIV has added additional burden to persistently overstretched workforce (18-25).

It remains unclear whether the investments in HIV programs have on balance translated to improved overall quality of health services and access to such services− a plausible pathway through which improved health and survival of the general population can be achieved. Some studies have reported a decrease in utilization of non-HIV services, particularly in relation to child health services (26-30) and maternal health services (20, 26, 30) subsequent to the launch of HIV treatment services at health facilities. At the same time, other studies have noted the opposite using different metrics or in different settings (19, 20, 27, 31-37)—with ART availability associated with increased utilization of non-HIV health services. Still other studies noted no significant effect (19, 21, 26-28, 30, 31, 35, 36, 38). The diverse contexts where these studies were conducted and the use of non-experimental study designs have prevented the rigorous synthesis of existing evidence.

In absence of consistent evidence on the relationship between ART expansion and non-HIV health care utilization, some studies have directly examined the relationship between ART expansion and health outcomes among the general population, including all-cause mortality. In a prospective cohort study in three districts in Uganda, Mermin et al found that HIV-negative children under 10 years of age had a 81% reduction in mortality after a cohabitating HIV-infected adult started taking co-trimoxazole and ART compared to co-trimoxazole alone (99). In a health and demographic surveillance system (HDSS) in Kenya, Gargano et al observed declines in all-cause mortality, AIDS/Tuberculosis (TB)-related mortality, other infectious disease related mortality, and unknown/ unclassifiable mortality (100). The authors of the latter study speculated that as PLHIV engaged in care had greater access to co-trimoxazole, TB screening, bed nets and chlorine water treatment compared to the rest of the residents living in

HDSS, their household members may also have experienced fewer infectious diseases and hence experienced lower mortality (100). Bendavid et al. found that in 9 PEPFAR-focus countries receiving substantial funding for HIV care and treatment, there was a 16% lower odds of adjusted all-cause adult deaths compared to 18 PEPFAR non-focus countries between 2004 and 2008 (5). The authors, however, could not confirm whether the reduction included a spillover effect in terms of survival benefits among the HIV-negative population within those countries (5). #

The major limitation faced in efforts to better define the spillover effects of HIV treatment on mortality is due to the fact that all studies that evaluated this association utilized non-experimental designs with weak bases for causal inference. Associations between start of HIV treatment scale up and mortality in the general population could be confounded by a variety of factors, including population growth, the number of PLHIV in the community, and other secular trends, such as change in prevalence of other conditions or general economic growth or decline.

To address these limitations, we conducted a quasi-experimental study using longitudinal population-based demographic surveillance data from rural Kwazulu-Natal, South Africa, to determine whether exposure to ART utilization by a PLHIV in a household was associated with change in all-cause mortality among their adult household members.

Methods

Study setting and population

The data used in this study were derived from demographic surveillance data, including annual health questionnaire data from the Africa Center Demographic Information System (ACDIS) led by the Africa Health Research Institute, in the Hlabisa sub-district of Kwazulu-Natal, South Africa (69). Clinic data from PLHIV in care at six primary health clinics located within the surveillance area and vital status of cohabitating household members ascertained through the annual household visits were linked by the unique identifiers for their shared homesteads. While individuals could only be associated with one homestead per annual assessment they could be associated with multiple homesteads across assessments. The analysis included resident adults aged 15 years and older who were enrolled in HIV care between 2008 and 2013 and their cohabitating household members aged 15 years and older who were captured at least once by household surveys during the same period. Non-residents, children <15 years were excluded. Ethical approval for all data collected within the cohorts was obtained from the University of KwaZulu-Natal's Ethics Committee.

Study Design

To evaluate the effect of exposure to PLHIV's uptake of ART on a cohabitating household member's risk of all-cause mortality, we conducted regression discontinuity quasi-experiments, utilizing the CD4+ cell count threshold rule for ART eligibility in South Africa (34, 35). CD4+ cell count measurements are known to fluctuate naturally and due to random measurement errors. In this study cohort, Bor, et al, found substantial within-person variation of CD4+ cell counts among 146 participants who had two or more measurements done on the same day or one day apart (70). In the latter study, the authors found that a participant with a "true, underlying" CD4+ cell count of 200 cells/μL tested within 95% CI: 120 cells, 300 cells (70). There is substantial overlap in the "true" CD4+ counts among eligible and ineligible participants close to

the HIV treatment eligibility threshold, so groups slightly below and above the threshold are interchangeable in terms of their immunological status. In our study, we exploited the random variation that occurs with enrollment CD4+ cell counts as our treatment assignment variable to construct the ART group (exposed) whose CD4+ cell count was just below the prevailing threshold for ART initiation and non-ART group (unexposed) whose enrollment CD4+ cell count was just above the threshold.

Treatment assignment can be either deterministic or probabilistic. (every participant on the one side of the cutoff value receives the treatment and every participant on the other side does not) or probabilistic (the probability of receiving the treatment is higher on the one side of the cutoff value than on the other side). The first case is referred to as ‘‘sharp’’ regression discontinuity (RD) and the second ‘‘fuzzy’’ RD design. In this study, the “fuzzy” RD design (FRD) was implemented, as ART eligibility is often assigned with the CD4+ cell count threshold rule in combination with WHO clinical staging and behavioral factors that may impact adherence, the latter likely influencing provider’s willingness to prescribe ART. As there are individuals who start ART even when their enrollment CD4+ cell counts are above the threshold and others who do not start ART even when their CD4+ cell counts are below the threshold, this results in a situation resembling randomization in a clinical trial where some would always take up the treatment, regardless of treatment assignment while others would never take up the treatment even if assigned. The hallmark of analytic approach in a randomized clinical trial (RCT) is the intent-to-treat (ITT) effect, which is the effect of treatment assignment. FRD design therefore also estimates ITT_{FRD}. In a FRD design, ITT (ITT_{FRD}) measures the effect of treatment eligibility, as determined by the threshold rule, and is often of interest in its own right. If

randomization worked, ITT_{FRD} is not confounded. ITT_{FRD} often is considered a causal effect that is more reflective of reality because it would include those who adhere with assigned treatment and those who do not. In particular, ITT_{FRD} can also be interpreted as the effect of raising the threshold on outcomes for the full population of participants close to the threshold. The ITT_{FRD} can be summarized in Equation 1:

$$ITT_{FRD}=lim_{(z\uparrow c)}E[Y_i|Z_i=z]-lim_{(z\downarrow c)}E[Y_i|Z_i=z]$$

#

where c is the threshold value, of a continuous assignment variable, Zi.

Study Measures

Exposure measures

The exposure status, cohabitation with PLHIV whose enrollment CD4+ cell count is under 200 cells/μL (ART eligible) versus above 200 cells/μL (ART ineligible) was operationalized as a binary variable. The true exposure of interest is cohabitation with PLHIV initiating ART. As the relationship between ART initiation by PLHIV and survival of household members is likely heavily confounded, we made use of an assignment variable— CD4+ cell count at enrollment— that is tightly correlated with the exposure of interest, but is not independently associated with the outcome of interest.. Various sizes of margins around the ART eligibility threshold were examined, including $\pm$50, 100, 150, 175 cells/μL around the threshold. The smaller the margins, the more comparable are the comparison groups and less biased are the estimates; however due to smaller number of observations estimates become less imprecise (87). The analysis time for the study was defined as the time period between the date of enrollment CD4+ cell count of PLHIV or start date for cohabitation whichever came later and last recorded clinic visit by

PLHIV or last recorded date for cohabitation whichever came sooner. Figure 1 shows the different exposure time scenarios that were available in the study population. The black line indicates total follow up time of the household member and the blue represents the time the member cohabitated with PLHIV in care. Scenarios 1-4 have exposure time while scenarios 5 and 6 do not and were excluded from our analysis.

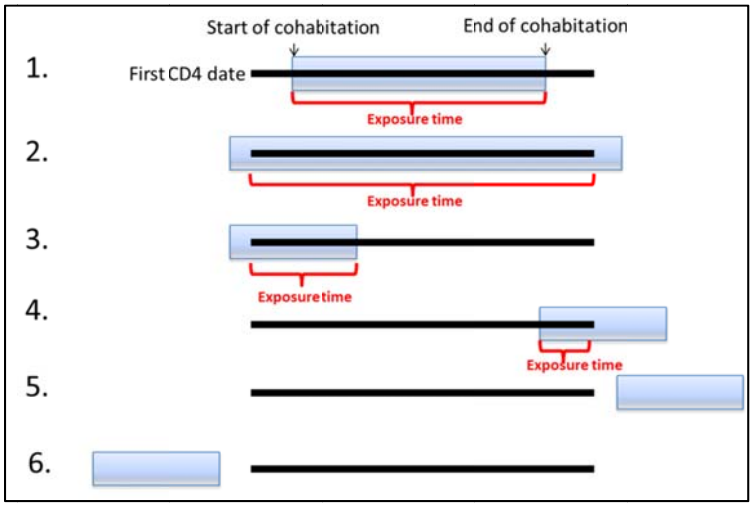


Figure 1: Schematic describing variation of potential exposure time based on common residence in homestead.

Outcome measures:

The outcome variable is all-cause deaths of cohabitating household members ascertained during annual household visits while PLHIV sharing the same homestead were in HIV care. We operationalized the outcome of interest as time to death or last date of known exposure—cohabitation with PLHIV engaged in HIV care.

Statistical analysis:

Descriptive statistics were used to summarize characteristics of the PLHIV in care and their cohabitating household members. Chi-square tests and two sample t tests were used to compare

characteristics by exposure status. We assessed whether the underlying assumptions for FRD design were met in the study dataset. The three FRD assumptions are: 1) distribution of the assignment variable, in this case enrollment CD4+ cell count, must not show any signs of manipulation, such as bunching at the threshold that could happen if clinicians or participants manipulate the CD4+ cell counts to qualify for ART eligibility, an impossible scenario unless documentation of CD4+ cell counts were manipulated; 2) continuity in baseline variables, such as age, sex, date of CD4+ cell count measurement across the exposure groups to examine comparability of the groups right above and below the threshold on all other causes of the outcome; 3) the cumulative probability of the exposure, in this case initiating ART following a participant's first CD4+ cell count, should show a large discontinuity at the threshold. To assess the first assumption, we generated histograms to visually inspect the distribution of the assignment variable to rule out manipulation. To assess the second assumption, we examined the balance in key covariates, including age, sex, and exposure time of the cohabitating household members across the exposure groups plotting the log hazards of death predicted from exponential regression models. Finally, to assess the third assumption, we examined the discontinuity at the threshold within 6, 12, and 24 months after enrollment in HIV care to assess whether discontinuity persisted over the study period.

ART initiation was estimated on the risk difference scale, using linear probability (OLS) models to estimate the Equation 1, which models the conditional expectation function (CEF) as a continuous function of the enrollment CD4+ cell count, except for an intercept shift at the threshold. We allowed for different slopes on either side of the threshold, which would arise in the case of effect heterogeneity.

Equation 1: $E[Y_i|CD4_i] = \beta_0 + \beta_1(CD4_i\text{-}200) + \beta_2 1[CD4_i<200] + \beta_3(CD4_i\text{-}200)*1[CD4_i<200]$

where β_1 is the slope of the line below the threshold, $\beta_1 + \beta_3$ is the slope of the line above the threshold, and β_2, is the effect of eligible on the probability of ART initiation for individuals presenting with CD4+ cell count close to the threshold. We can interpret the difference in outcomes between those just above versus just below the cutoff as the effect of eligible CD4+ cell counts at enrollment on ART initiation.

Next, we implemented FRD in parametric and semi-parametric survival models to compare hazard ratios at the threshold point for ART eligibility to estimate the causal effect of living with a PLHIV eligible for ART versus living with a PLHIV ineligible for ART. If FRD assumptions hold, because ART eligibility is tightly correlated with the exposure of interest, ART initiation, but not associated with the survival status of household members, the effect observed is attributable to ART initiation. We fitted exponential and Weibull survival models as well as cox proportional hazard model to examine the robustness of findings. We ran models that included and excluded cohabitating household members that were HIV-infected but are not documented to be in HIV care to assess whether heterogeneous effects can be observed by HIV status of the cohabitating household member. All statistical tests were two-sided and $p<0.05$ was considered significant.

We ran both unadjusted and adjusted models with sex, age, and enrollment CD4+cell count. To allow for effect heterogeneity across the threshold we included interaction terms with the

exposure variable and CD4+cell count. We additionally examined the effect of the number of PLHIV eligible for ART in the shared homestead. Data set preparations were done in SAS 9.3 (SAS, Cary, NC). Statistical analyses were conducted by using STATA12.0 (StataCorp, College Station, Texas).

Results

Characteristics of the study population

Figure 2 summarizes the study sample obtained from the larger AHRI cohort. Table 1.1 and 1.2 summarize characteristics by exposure status of the index PLHIV in HIV care and their cohabitating household members. There were 5085 PLHIV receiving HIV care living with 22,062 household members >15 years who participated in at least one household survey during the study period. A median of 6 (IQR: 4-8) PLHIV in care and household members >15 years lived in 4612 unique homesteads; 16% of PLHIV in care were associated with >1 homesteads. The large majority of PLHIV in care were women (76%) and their average age was 37 years. More than half were enrolled between 2007 and 2009 (57%) and the median follow up time was 3.6 years (IQR: 1.9-5.2). During the study period, there were 545 deaths (10.7%) among PLHIV.

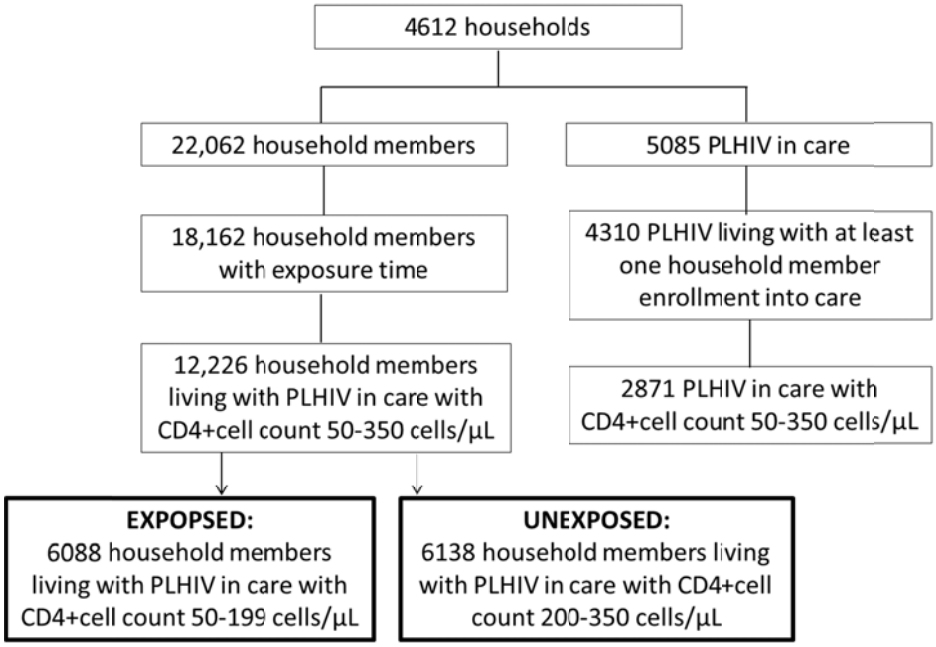


Figure 2: Participant flow diagram

Cohabitating household members were 54% female with a mean age of 33 years. Median follow up time was 6.9 years (IQR: 2.5-12.0) and median analysis time or time at risk was 2.2 years (IQR: 1.0-3.8). More than a quarter (27%) of household members lived with more than one PLHIV in HIV care. About 4% of the cohabitating household members had a documented HIV positive diagnosis but were not in care. During the study period, there were 1023 deaths (4.6%) among cohabitating household members, 574 of which took place after PLHIV engaged in HIV care. With a total exposure time of 45,763 person years, the rate of all-cause death was 12.5/1000 person years. Baseline characteristics did not differ significantly by exposure status.

Assessment of RD assumptions

Figure 3 shows the distribution of CD4+ cell count at enrollment of the cohabitating PLHIV in HIV care. There was no discernable bunching at the threshold of 200 cells/µL, suggesting that the assumption of non-manipulation of the treatment assignment variable (CD4+ cell count) held

true in the study sample. Figures 4 shows the association between age, sex, and enrollment CD4+ cell count and predicted hazard for death, fitting separate regression lines below and above the threshold. The dots represent individuals in 10-cell CD4+count bins. There was little to no discontinuity in the distribution of age, sex, and date of first CD4+ cell counts at the threshold vis-à-vis the predicted hazard for deaths, indicating balance in these characteristics between the exposed and unexposed groups.

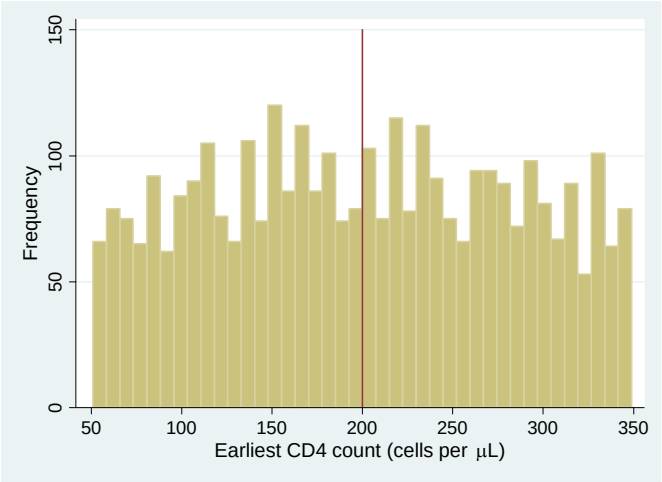


Figure 3: Distribution of enrollment CD4+ cell counts among participants enrolled in HIV care between 2008-2013

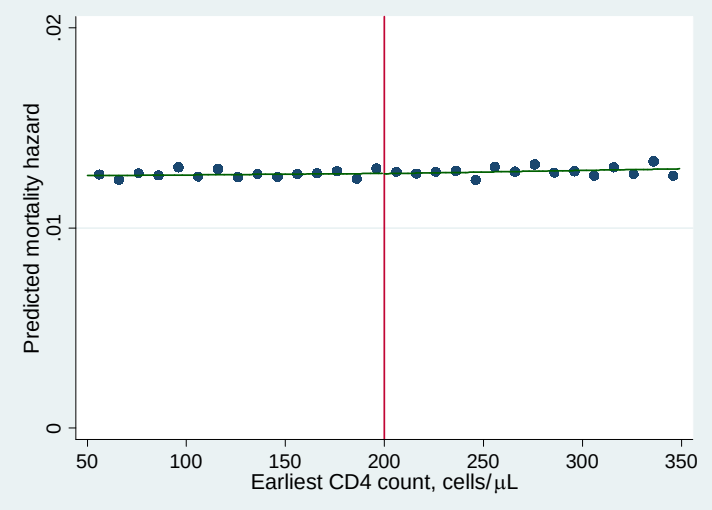


Figure 4: Predicted hazards of death by 10 CD4+ cell count bins adjusting for baseline age, sex and date of first CD4+ cell count

Finally, we found a substantial discontinuity in the probability of HIV treatment initiation between PLHIV with CD4+ cell count of below and above the 200cell/μL threshold (Figure 5.1). The discontinuity was observed in 6, 12 and 24 month time frames since enrollment, suggesting that enrollment CD4+ cell count remains tightly correlated with ART initiation and is a strong assignment variable over the study period (Figure 5.2).

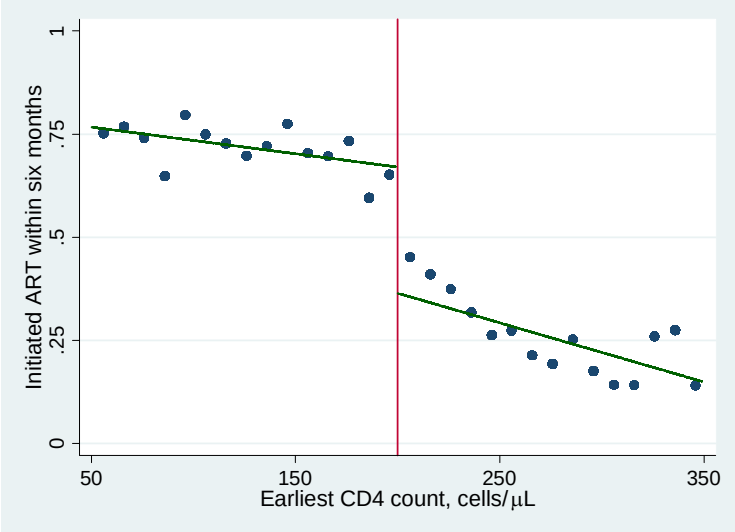


Figure 5.1: Cumulative probabilities of ART initiation within 6 months by 10 CD4+ cell count bins using the Kaplan-Meier estimator

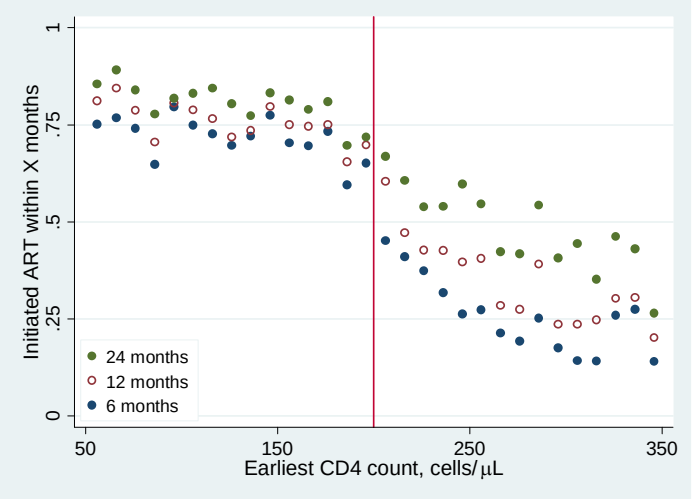


Figure 5.2: Cumulative probabilities of ART initiation within 6, 12, and 24 months by 10 CD4+ cell count bins using the Kaplan-Meier estimator

In addition to visual inspection, we ran linear probability models to quantify the discontinuity in the probability of ART initiation at the threshold (Table 2.1-2.3). Having a baseline CD4+ cell count less than 200 cells/μL increased the probability of initiation within six months by 26 absolute percentage points (95% CI: 21%, 32%) restricting the analysis range between 50 and 350 cells/μL. As we increased the observation time from initiation within 6 months to 24 months, the difference persisted but with a smaller magnitude. Probability of initiation within a year and within two years, restricting the analysis range to between 50 and 350 cells/μL, continued to show a large discontinuity with a difference of 19 percentage points (95% CI 13%, 25%) and 12 percentage points (95% CI:6%, 17%) .

FRD modeling results

Cumulative hazard functions at year 6 for mortality by exposure status without adjustment by varying CD4+cell count bandwidths are summarized in Table 3. Cumulative hazard functions for mortality were similar between the exposure groups across all bandwidth analyses.

Adjusted FRD results with exponential survival models using different CD4+ cell count bandwidths are shown in table 4.1. Those cohabitating with PLHIV with CD4+ cell count just below the treatment threshold did not have a decreased risk of death compared to those cohabitating with PLHIV with CD4+ cell count just above the treatment threshold in the main model with the largest bandwidth of CD4+ cell counts (HR: 0.95; 95% CI: 0.65, 1.39). Age and sex adjusted models and sex specific models also did not show any effect of household ART utilization. However, restricted analyses limiting the analyses to the two narrowest bandwidths from the discontinuity threshold showed a significantly decreased risk of death among those

cohabiting with PLHIV with CD4+ cell count just below the treatment threshold (HR: 0.46; 95% CI: 0.24, 0.89). The effects were additionally strengthened in models adjusting for sex and age (HR: 0.43; 95%CI: 0.23, 0.85). Sex specific models were also run within the restricted sample, which showed the decreased risk of death reached statistical significance in models that included only females (HR: 0.21; 95% CI: 0.08, 0.56) but not in those that included only males (HR: 0.92; 95% CI: 0.32, 2.63). A significantly decreased risk of death was also found in models restricting the sample to HIV-uninfected cohabitating household members in the narrowest bandwidths (HR: 0.33; 95% CI: 0.12, 0.89). We did not find any larger effect in models restricting the sample to those living with more than one PLHIV. Results were robust to specification changes as shown in Weibull and Cox model results included in the supplementary materials (Tables 4.2-4.2). Figures 6 show the predicted hazards from the exponential survival model with separate slopes fitted for exposed and unexposed groups. The dashed lines represent extrapolated prediction if all patients were treatment eligible at time of enrollment.

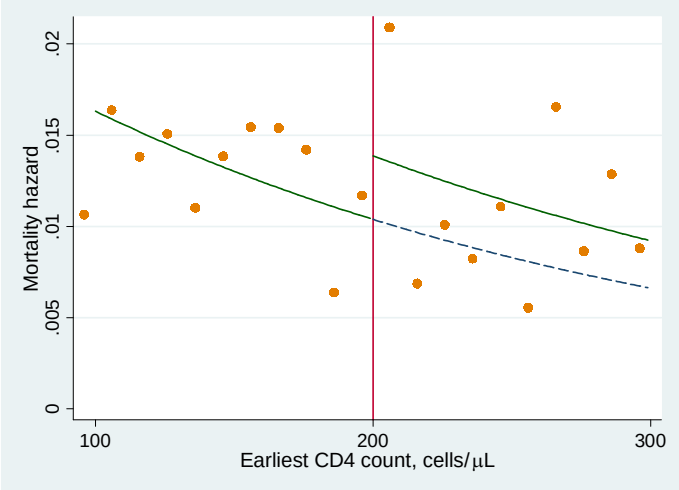


Figure 6: First CD4+ cell count and predicted mortality hazard rates

Discussion

In this rural community in South Africa with substantial burden of HIV disease which has seen rapid ART expansion in the past decade (4), we identified a significant effect of ART uptake by PLHIV in reducing the risk of all-cause death on cohabitating female household members. We did not observe any effect on male household members. Our study strengthens the evidence base for the association between HIV treatment with positive spillover effects in health and survival of the general population (5, 99-101).

There are several potential explanations for our findings. First, in several studies, PLHIV engaged in HIV care have been found to have greater access to general heath and safe water and sanitation compared to their HIV-negative counterparts (68, 100). These patients may confer benefits to those living with them. Second, there is growing evidence suggesting ART scale up has resulted in increased utilization of other non-HIV health services (19-21, 27, 31-37, 40). Increased investments in human resources, infrastructure and equipment in health facilities that deliver not only HIV services but other health services as well could have synergetic effects to increase utilization of other health services, particularly maternal and child health, TB, and laboratory services, as these are closely integrated with HIV services in many settings. Third, several studies indicate that caregivers of the PLHIV are predominantly female household members (102, 103). They not only care for the PLHIV but also accompany them to the clinics and serve as treatment supporters. This may create opportunities for such caregivers to seek care for their own health. Fourth, as use of ART with associated virological suppression has been shown to reduce the risk of HIV transmission to uninfected partners (104), the survival benefit

could also be a result of decreased transmission occurring within the households, although with the relatively short period of observation period, this is unlikely to be the case.

It is important to note that in our main model with a larger CD4+ cell count bandwidth including both female and male household members, we did not observe reduction in mortality risk. This is consistent with findings from Bor, et al. who used the same ACDIS cohort to examine trends in adult life expectancy between 2000 and 2011. The authors found substantial increase in overall adult life expectancy but did not find a similar trend in adult life expectancy removing the effects of HIV-specific deaths after the expansion of ART in this community in 2004 (4). The authors therefore concluded that the increase in overall adult life expectancy was largely driven by increased life expectancy of PLHIV and not by spillover effects. The reduced risk of death found among female household members we found within the narrow CD4+ count bandwidth analysis was not likely generalizable to the target population at large. While the effect is less biased in that the comparison groups are more comparable due to the narrow bandwidth, the results are only interpretable for the small group of household members cohabitating with PLHIV with enrollment CD4 counts within 50cells/μL of the treatment threshold of 200 cells/μL.

The main strength of our study is that it utilized the ACDIS demographic surveillance cohort data that allows generating population based estimates of causal effects, a significant contribution to the spillover effects research that has largely relied on facility-based data. The ACDIS cohort data also uniquely allows linking of data collected from PLHIV in their attending clinics with data collected about their cohabitating household members captured as part of the community health surveys. The ability to link these two sources of data allowed implementing

the FRD design that requires CD4+ cell count data from the clinic to measure the potential effects of ART uptake by PLHIV on their cohabitating household members.

Another strength is the FRD design that provides strong basis for causal inference in an area where implementing an RCT—a gold standard for causal inference—is not feasible. The FRD design is widely used to estimate unbiased causal effects of economic, social and medical interventions that uses a threshold value of a continuous measure to determine eligibility, such as income, age, or birthweight (88, 89, 97). We successfully employed FRD designs to obtain unbiased causal estimates removing the potential confounding effects of individual and household characteristics, such as education, income, employment status, smoking or alcohol use, on the relationship between PLHIV's ART uptake and their cohabitating household member's risk of death. The study is a significant contribution to the spillover research of HIV programs that has thus far been dominated by studies using non-experimental designs. To our knowledge, there have only been two prospective cohort studies (99, 100) that have examined spillover survival benefits to the general population and they are limited in the ability to adjust out effects of confounding and selection bias in comparison to this quasi-experimental study.

Our study had limitations. Regression Discontinuity requires large sample sizes to allow for sufficient analytic sample within the narrow range across a threshold used to maintain comparability between the exposure groups (88). While our total sample size was sufficiently large, we had relatively few deaths, making it challenging to detect statistically significant results. In addition, external validity of our study is arguably limited as analysis was limited to a narrow range across the threshold for ART eligibility. Another limitation is that we were unable

to examine cause-specific death data due to limited sample size. Cause-specific death data would have allowed more nuanced examination of the potential mechanisms at play that resulted in the reduction in the risk of death observed among female household members. However, it is also widely acknowledged that attribution of cause of deaths is rarely available with accuracy in developing countries where coverage of vital registration systems is low (105).

In summary, in this study we demonstrated that social exposure to PLHIV who initiated ART through cohabitation decreased the risk of death among female household members. Although prior studies have found beneficial effects in cohabiting children of PLHIV on ART, this study is one of the first to demonstrate a potential survival benefit among female adult household members. Future research is needed to identify the mechanisms leading to these observed effects. In the era of plateau in external development resources available for health programs, identifying and capitalizing on synergies to achieve wider impact is critical. Harnessing positive synergy from HIV programming to expand supply and demand for services for other health services through targeted outreach to household members living and caring for PLHIV should become routine programming (98).

Chapter 4: Tables

Table 1: Characteristics of study population, restricted to first associated dwelling structure

1.1: PLWH in HIV care	Exposure (below threshold)	Control (above threshold)	Total
	n (%)	n (%)	n (%)
Total	2090 (41.1)	2995 (58.9)	5085 (100.0)
Proportion female	1497 (71.6)	2365 (79.0)	3862 (76.0)
Mean age at last visit, min-max	37.9 (16-95)	36.1 (16-94)	36.9 (16-95)
Median enrollment CD4 count, IQR	114 (64-157)	330 (263-405)	235 (134-352)
Year of enrollment			
2007	372 (17.8)	586 (19.6)	958 (18.8)
2008	433 (20.7)	618 (20.6)	1051 (20.7)
2009	338 (16.2)	565 (18.9)	903 (17.8)
2010	416 (19.9)	430 (14.4)	846 (16.6)
2011	276 (13.2)	365 (12.2)	641 (12.6)
2012	155 (7.4)	265 (8.9)	420 (8.3)
2013	100 (4.8)	166 (5.5)	266 (5.2)
Median follow time in care (years)	3.4 (1.7-5.2)	3.7 (2.0-5.3)	3.6 (1.9-5.2)
Associated bounded structures	1864 (40.4)	2748 (59.6)	4612 (100)
Median number of household members, IQR	6 (4-8)	6 (4-8)	6 (4-8)
Associated with 1 residence	1763 (84.3)	2488 (83.5)	4251 (83.6)
Associated with >1 residence	329 (15.7)	505 (16.9)	834 (16.4)
All cause mortality	304 (14.6)	241 (8.1)	545 (10.7)
TB deaths	154 (7.4)	127 (4.2)	281 (5.5)
NCD deaths	4 (0.2)	3 (0.1)	7 (0.1)

1.2: Cohabitating household members	Exposure (below threshold)	Control (above threshold)	Total
	n (%)	n (%)	n (%)
Total	9055 (41.0)	13007 (59.0)	22062 (100.0)
Proportion female	4881 (53.9)	6964 (53.5)	11845 (53.7)
Mean age at last visit , min-max	32.4 (15-118)	32.7 (15-105)	32.6 (15-118)
Proportion living with >1 PLWH in care	2561 (28.3)	3438 (26.4)	5999 (27.2)
Median (IQR) time associated with bounded structure (years)	7.0 (2.5-12.1)	6.8 (2.5-12.0)	6.9 (2.5-12.0)
Median (IQR) time since enrollment of PLWH member (years)	2.1 (0.8-3.8)	2.2 (1.0-3.9)	2.2 (1.0-3.8)
% HIV positive not in care	419 (4.6)	663 (5.1)	1082 (4.9)
Associated bounded structures	1864 (40.4)	2748 (59.6)	4612 (100)
All cause mortality	435 (4.8)	588 (4.5)	1023 (4.6)
TB deaths	133 (1.5)	174 (1.3)	307 (1.4)
NCD deaths	27 (0.3)	25 (0.2)	52 (0.2)
All cause mortality during exposure	243 (2.7)	331 (2.5)	574 (2.6)
Total exposure time	18830	27432	45763
Rate per 1000 person years	13.3	12.1	12.5
TB deaths during exposure	66 (0.7)	91 (0.7)	157 (0.7)
NCD deaths during exposure	18 (0.2)	13 (0.1)	31 (0.1)

Table 2: Treatment eligibility and ART initiation within 6, 12, and 24 months*

2.1 Probability of ART initiation within six months

	Earliest CD4+ cell count	Probability of initiation ART within six months				Sample
	Specification, Range	E[Y|Z ≥200]	E[Y|Z<200]	Difference	95% CI	N
1)	Linear; 0-350	0.406	0.669	0.263	0.205, 0.321	3645
2)	Linear; 50-350	0.406	0.679	0.273	0.210, 0.335	3297
3)	Linear; 100-350	0.460	0.654	0.194	0.118, 0.270	2338
4)	Linear; 150-250	0.512	0.633	0.121	0.01, 0.231	1219
5)	Linear; 175-225	0.502	0.622	0.120	-0.037, 0.277	595

2.2 Probability of ART initiation within 12 months

	Earliest CD4+ cell count	Probability of initiation ART within 1 year				Sample
	Specification, Range	E[Y|Z ≥200]	E[Y|Z<200]	Difference	95% CI	N
1)	Linear; 0-350	0.530	0.720	0.190	0.131, 0.248	3545
2)	Linear; 50-350	0.530	0.721	0.191	0.128, 0.253	3221
3)	Linear; 100-350	0.576	0.710	0.134	0.059, 0.211	2287
4)	Linear; 150-250	0.608	0.685	0.077	-0.032, 0.186	1189
5)	Linear; 175-225	0.67	0.644	-0.026	-0.126, 0.179	582

2.3 Probability of ART initiation within 24 months

	Earliest CD4+ cell count	Probability of initiation ART within 2 yearr				Sample
	Specification, Range	E[Y|Z ≥200]	E[Y|Z<200]	Difference	95% CI	N
1)	Linear; 0-350	0.672	0.789	0.117	0.060, 0.174	3419
2)	Linear; 50-350	0.672	0.777	0.105	0.04, 0.165	3099
3)	Linear; 100-350	0.683	0.761	0.078	0.00, 0.152	2204
4)	Linear; 150-250	0.680	0.722	0.042	-0.063, 0.147	1156
5)	Linear; 175-225	0.679	0.698	0.019	-0.129, 0.168	561

* Ordinary least squares linear probability model

Table 3: Table 3: Cumulative hazard functions* for death at year 6 by CD4+ count range

CD4+ count range	E[Y|Z ≥200]	E[Y|Z<200]	Difference	Logrank test	N	n
50-350	0.077	0.078	0.001	0.168	12129	379
100-300	0.080	0.075	-0.005	0.281	8662	277
150-250	0.077	0.064	-0.013	0.856	4554	145
175-225	0.088	0.052	-0.036	0.388	3514	102

* Nelson Aalen cumulative hazard functions

Table 4: Effect of treatment assignment on all-cause deaths, parametric and semi-parametric survival models

	(EXP) ITT_{FRD}	95% CI	P	(WEI) ITT_{FRD}	95% CI	P	(COX) ITT_{FRD}	95% CI	P	Sample	Events
Overall, adjusting for CD4											
50-350	0.952	0.650, 1.394	0.801	0.949	0.649, 1.389	0.789	0.952	0.651, 1.393	0.800	12129	379
100-300	0.749	0.471, 1.191	0.222	0.741	0.466, 1.180	0.206	0.744	0.467, 1.183	0.211	8662	277
150-250	0.458	0.235, 0.893	0.022	0.451	0.231, 0.880	0.020	0.454	0.233,0.886	0.021	4554	145
175-225	0.279	0.106, 0.736	0.010	0.276	0.104, 0.731	0.010	0.277	0.105, 0.734	0.010	2230	67
Overall, adjusting for CD4, age											
50-350	0.952	0.651, 1.393	0.801	0.970	0.663, 1.417	0.875	0.973	0.666, 1.422	0.888	12129	379
100-300	0.749	0.471, 1.191	0.222	0.756	0.475, 1.204	0.239	0.761	0.478, 1.211	0.249	8662	277
150-250	0.458	0.235, 0.893	0.022	0.450	0.228, 0.887	0.021	0.457	0.232, 0.901	0.024	4554	145
175-225	0.279	0.106, 0.737	0.010	0.271	0.102, 0.722	0.009	0.285	0.107, 0.759	0.012	2230	67
Overall, adjusting for CD4, age, sex											
50-350	0.953	0.652, 1.392	0.802	0.952	0.651, 1.391	0.799	0.955	0.653, 1.395	0.811	12128	379
100-300	0.744	0.467, 1.185	0.213	0.740	0.465, 1.178	0.204	0.744	0.467, 1.185	0.213	8661	277
150-250	0.429	0.217, 0.849	0.015	0.424	0.214, 0.838	0.014	0.431	0.218, 0.852	0.016	4554	145
175-225	0.250	0.093, 0.671	0.006	0.244	0.090, 0.657	0.005	0.256	0.095, 0.691	0.007	2230	67
Overall, adjusting for CD4, age, female only											
50-350	0.834	0.501, 1.391	0.487	0.828	0.497, 1.381	0.470	0.833	0.299, 1.388	0.482	6567	210
100-300	0.651	0.349, 1.215	0.177	0.643	0.344, 1.200	0.165	0.649	0.347, 1.212	0.175	4675	151
150-250	0.214	0.082, 0.562	0.002	0.209	0.080, 0.550	0.002	0.211	0.080, 0.554	0.002	2503	83
175-225	0.044	0.007, 0.290	0.001	0.040	0.006, 0.270	0.001	0.043	0.006, 0.283	0.001	1229	37
Overall, adjusting for CD4, age, male only											
50-350	1.098	0.619, 1.948	0.748	1.100	0.620, 1.950	0.745	1.088	0.613, 1.930	0.773	5561	169
100-300	0.877	0.432, 1.782	0.718	0.877	0.432, 1.781	0.716	0.870	0.428, 1.768	0.700	3986	126
150-250	0.922	0.323, 2.631	0.879	0.917	0.321, 2.616	0.871	0.944	0.3301, 2.698	0.914	2051	62
175-225	0.812	0.195, 3.372	0.774	0.809	0.195, 3.364	0.771	0.861	0.206, 3.593	0.837	1001	30
Overall, adjusting for CD4, age, sex, restricting to HIV negative family members											
50-350	1.059	0.709, 1.581	0.779	1.058	0.709, 1.580	0.782	1.037	0.694, 1.548	0.860	11543	343
100-300	0.796	0.488, 1.299	0.362	0.792	0.485, 1.292	0.350	0.773	0.473, 1.260	0.302	8241	248
150-250	0.516	0.255, 1.042	0.065	0.509	0.252, 1.030	0.061	0.481	0.237, 0.977	0.043	4337	131
175-225	0.332	0.124, 0.887	0.028	0.323	0.121, 0.866	0.025	0.302	0.111, 0.822	0.019	2122	62
Overall, adjusting for CD4, age, sex, restricting to HH with more than 1 PLWH in care											
50-350	0.840	0.429, 1.644	0.610	0.843	0.430, 1.650	0.617	0.860	0.440, 1.681	0.660	3373	105
100-300	0.704	0.312, 1.589	0.389	0.703	0.311, 1.586	0.396	0.718	0.320, 1.612	0.422	2469	86
150-250	0.706	0.233, 2.139	0.538	0.702	0.232, 2.129	0.532	0.707	0.232, 2.154	0.542	1324	47
175-225	0.608	0.128, 2.886	0.531	0.609	0.128, 2.895	0.533	0.597	0.127, 2.810	0.514	612	24

Chapter 5: Conclusion

The overall purpose of this dissertation was to examine evidence of spillover effects of HIV care and treatment service scale up in sub-Saharan Africa in the past decade. Particularly the focus was to quantify any effect HIV treatment initiation by a person living with HIV (PLHIV) may have had on increasing utilization of non-HIV services among or reduced risk of mortality of the HIV negative population.

In chapter 2, we presented results from a systematic review of the effect of increasing ART uptake in high HIV prevalence communities on use of non-HIV health services, including maternal, child, in/out-patient, non-HIV laboratory, and TB diagnosis and treatment services. Overall positive effects on the majority of health service indicators examined for non-HIV laboratory service utilization and TB diagnosis and treatment services. We found negative associations on the majority of indicators examined for child health services. The existing evidence did not point to clear tendencies for maternal health services and outpatient and inpatient services. Restricting the sample to studies with stronger study designs for causal inference, the positive effect on non-HIV laboratory services and the negative impact on child health services held but evidence was mixed for TB diagnosis and treatment services, maternal health services and outpatient and inpatient services.

The systematic review, to the authors' knowledge is the first synthesis of evidence to date on potential spillover effects of ART scale up on non-HIV related health services. The review included 17 studies covering 47 African countries and Haiti spanning the period of 1988 and 2012 during which ART coverage grew exponentially. The review was expansive, covering 5 health service domains and 106 health service indicators.

In chapter 3, we presented results from regression discontinuity quasi-experiments to determine whether exposure to health benefits from ART utilization by a person living with HIV (PLHIV) in a household affects uptake of TB, hypertension (HTN) and diabetes mellitus (DM) treatment by other household members with these conditions. The study was conducted in the

comprehensive population cohort followed by the Africa Health Research Institute (AHRI) in Kwazulu-Natal (KZN), South Africa. We linked PLHIV engaged in HIV care to their cohabitating household members aged ≥15 years using a unique identifier for homesteads. Household ART utilization significantly increased treatment for diabetes (RR 1.90: 95% CI 1.07-3.40) but not for TB (RR 1.12: 95% CI 0.71-2.03) or hypertension (RR 1.31: 95% CI 0.97-1.77).

The analysis to the authors' knowledge is the first to implement regression discontinuity quasi-experiment to examine the question of spillover effects of HIV treatment initiation and utilization of non-HIV services. It is to our knowledge the first to find evidence of increased diabetes treatment utilization among HIV negative individuals.

In chapter 4, we presented results from another set of regression discontinuity quasi-experiments in the same KZN cohort as in chapter 4 to determine whether exposure to health benefits from ART utilization by PLHIV in a household reduces all-cause mortality of other household members. Overall, household ART utilization did not decrease all-cause mortality (Hazard Ratio (HR) 0.95: 95% CI 0.65-1.4), however, restricting the analysis to a narrow CD4+ cell count range around the regression discontinuity threshold, showed reduced all-cause mortality by 67% (HR 0.43: 95% CI 0.22-0.85) among household members of PLHIV on ART; the reduced risk was driven largely by the significant reduction noted among female household members (HR 0.21: 95% 0.08, 0.56).

The analysis to the authors' to find evidence of decreased risk of mortality associated with HIV treatment initiation among female household members.

In conclusion, the dissertation work has contributed to the spillover research field on HIV treatment scale up and utilization of non-HIV health services the first systematic review to summarize the current evidence, implemented the first quasi-experimental study to provide robust evidence of spill over for diabetes treatment and positive but non-significant trend for TB and hypertension treatment. The dissertation work further found evidence of potential spillover effect in reducing risk of mortality among female household members.

Supplementary Tables and Figures

Table S1: Characteristics of study population, restricting to first associated bounded structure with exposure time and with CD4 range restriction

S1.1a: PLHIV in HIV care living with cohabitating household members with exposure time	Exposure (below threshold)	Control (above threshold)	Total
	n (%)	n (%)	n (%)
Total	1923 (40.7)	2804 (59.3)	4727 (100)
Proportion female	1360 (70.7)	2267 (80.9)	3627 (76.7)
Mean age at first visit , min-max	34.7 (15, 90)	32.2 (15, 90)	33.2 (15, 90)
Median enrollment CD4 count, IQR	115 (64-158)	332 (264, 405)	239 (136, 354)
Year of enrollment			
2007	326 (17.0)	526 (18.8)	852 (18.0)
2008	412 (21.4)	571 (20.4)	983 (30.8)
2009	293 (15.2)	506 (18.1)	799 (16.9)
2010	383 (19.9)	415 (14.8)	798 (16.9)
2011	263 (13.7)	359 (12.8)	622 (13.2)
2012	157 (8.2)	274 (9.8)	431 (9.1)
2013	89 (4.6)	153 (5.5)	242 (5.1)
Median follow time in care (years)	3.4 (1.8, 5.2)	3.7 (2.1, 5.2)	3.6 (2.0, 5.2)
Associated first bounded structures	1638 (40.6)	2397 (59.4)	4035 (100)
Median number of household members, IQR	4 (3, 6)	4 (3, 6)	4 (3, 6)
Associated with 1 residence	1730 (90.0)	2496 (89.0)	4226 (89.4)
Associated with >1 residence	193 (10.0)	308 (11.0)	501 (10.6)
TB disease in the last 12 months	189 (11.9)	208 (8.7)	397 (10.0)
Hypertension in the past 12 months	197 (12.4)	303 (12.7)	500 (12.6)
Diabetes in the last 12 months	43 (2.7)	52 (2.2)	95 (2.4)
Of those with TB disease, in treatment	185 (97.9)	205 (98.6)	390 (98.2)
Of those with hypertension, in treatment	153 (77.7)	241 (79.5)	394 (78.8
Of those with diabetes, in treatment	35 (81.4)	40 (76.9)	75 (79.0)

S1.2a: Cohabitating household members with exposure time		Exposure (below threshold)	Control (above threshold)	Total
		n (%)	n (%)	n (%)
Total		6070 (40.9)	8788 (59.2)	14858 (100)
Proportion female		3330 (54.9)	4848 (55.2)	8178 (55.0)
Mean age , min-max		33.5 (15-116)	33.8 (15-103)	33.7 (15-116)
Proportion living with >1 PLHIV in care		1721 (28.4)	2352 (26.8)	4073 (27.4)
Median (IQR) time associated with bounded structure (years)		9.8 (4.7-14.3)	9.2 (4.6-14.1)	9.4 (4.7-14.2)
Median (IQR) time since enrollment of PLHIV member (years)		2.5 (1.0-4.1)	2.6 (1.3-4.2)	2.6 (1.2-4.2)
% HIV positive not in care		317 (5.2)	524 (6.0)	841 (5.7)
Associated bounded structures		1638 (40.6)	2397 (59.4)	4035 (100)
TB disease in the last 12 months				
	1	165 (2.7)	285 (3.2)	450 (3.0)
	>1	54 (0.9)	94 (1.1)	148 (1.0)
Hypertension in the past 12 months				
	1	340 (5.6)	472 (5.4)	812 (5.5)
	>1	432 (7.1)	618 (7.0)	1050 (7.1)
Diabetes in the last 12 months				
	1	118 (1.9)	184 (2.1)	302 (2.0)
	>1	97 (1.6)	108 (1.2)	205 (1.4)
Of those with TB disease, in treatment		207 (94.5)	365 (96.3)	572 (95.7)
Of those with hypertension, in treatment		662 (85.8)	944 (86.6)	1606 (86.3)
Of those with diabetes, in treatment		184 (85.6)	238 (81.5)	422 (83.2)

S1.1b: PLHIV in HIV care living with cohabitating household members with exposure time (CD4 range restriction)	Exposure (below threshold)	Control (above threshold)	Total
	n (%)	n (%)	n (%)
Total	1562 (49.9)	1569 (50.1)	3131 (100)
Proportion female	1144 (73.2)	1254 (79.9)	2398 (76.6)
Mean age at first visit , min-max	34.5 (15, 90)	32.7 (15, 69)	33.6 (15, 90)
Median enrollment CD4 count, IQR	132 (94, 166)	272 (234, 308)	200 (132, 272)
Year of enrollment			
2007	284 (18.2)	283 (18.0)	567 (18.1)
2008	355 (22.7)	330 (21.0)	685 (21.9)
2009	235 (15.0)	291 (18.6)	526 (16.8)
2010	296 (19.0)	256 (16.3)	552 (17.6)
2011	206 (13.2)	201 (12.8)	407 (13.0)
2012	118 (7.6)	135 (8.6)	253 (8.1)
2013	68 (4.4)	73 (4.7)	141 (4.5)
Median follow time in care (years)	3.5 (2.0, 5.3)	3.7 (2.2, 5.2)	3.6 (2.1, 5.2)
Associated first bounded structures	1340 (49.9)	1348 (50.2)	2688 (100)
Median number of household members, IQR	4 (3,6)	4 (3,6)	4 (3,6)
Associated with 1 residence	1396 (89.4)	1422 (90.6)	2818 (90.0)
Associated with >1 residence	166 (10.6)	147 (9.4)	313 (10.0)
TB disease in the last 12 months	154 (11.8)	128 (9.6)	282 (10.7)
Hypertension in the past 12 months	175 (13.4)	175 (13.1)	350 (13.3)
Diabetes in the last 12 months	38 (2.9)	34 (2.5)	72 (2.7)
Of those with TB disease, in treatment	150 (97.4)	126 (98.4)	276 (97.9)
Of those with hypertension, in treatment	136 (77.6)	146 (83.4)	282 (80.6)
Of those with diabetes, in treatment	31 (81.6)	27 (79.4)	58 (80.6)

S1.2b: Cohabitating household members with exposure time (CD4 range restriction)		Exposure (below threshold)	Control (above threshold)	Total
		n (%)	n (%)	n (%)
Total		4923 (49.5)	5020 (50.5)	9943 (100%)
Proportion female		2704 (54.9)	2759 (55.0)	5463 (54.9)
Mean age , min-max		33.7 (15-116)	33.7 (15-100)	33.7 (15-116)
Proportion living with >1 PLHIV in care		1410 (28.6)	1369 (27.3)	2779 (28.0)
Median (IQR) time associated with bounded structure (years)		9.7 (4.7-14.2)	9.2 (4.5-14.0)	9.4 (4.6-14.1)
Median (IQR) time since enrollment of PLHIV member (years)		2.6 (1.2-4.3)	2.6 (1.4-4.3)	2.6 (1.3-4.3)
% HIV positive not in care		263 (5.3)	290 (5.8)	553 (5.6)
Associated bounded structures		1340 (49.9)	1348 (50.2)	2688 (100)
TB disease in the last 12 months				
	1	139 (2.8)	147 (2.9)	284 (2.9)
	>1	44 (0.9)	51 (1.0)	95 (1.0)
Hypertension in the past 12 months				
	1	279 (5.7)	283 (5.6)	562 (5.7)
	>1	349 (7.1)	339 (6.8)	688 (6.9)
Diabetes in the last 12 months				
	1	99 (2.0)	118 (2.4)	217 (2.2)
	>1	77 (1.6)	47 (0.9)	124 (1.3)
Of those with TB disease, in treatment		174 (95.1)	189 (95.5)	363 (95.3)
Of those with hypertension, in treatment		539 (85.8)	532 (85.5)	1071 (85.7)
Of those with diabetes, in treatment		152 (86.4)	130 (78.8)	282 (82.7)

**Restricted to first associated bounded structure*

Table S2: Characteristics of study population, allowing for multiple associated bounded structures for household members

S2.1: PLHIV in HIV care	Exposure (below threshold)	Control (above threshold)	Total
	n (%)	n (%)	n (%)
Total	2008 (40.6)	2944 (59.5)	4952
Proportion female	1407 (70.1)	2365 (80.3)	3772 (76.2)
Mean age at first visit , min-max	34.9 (15, 90)	32.4 (15, 90)	33.4 (15, 90)
Median enrollment CD4 count, IQR	114 (64, 158)	333 (265, 406)	240 (136, 355)
Year of enrollment			
2007	334 (16.6)	546 (18.6)	880 (17.8)
2008	426 (21.2)	598 (20.3)	1024 (20.7)
2009	310 (15.4)	524 (17.8)	834 (16.8)
2010	397 (19.8)	426 (14.5)	823 (16.6)
2011	280 (13.9)	384 (13.0)	664 (13.4)
2012	169 (8.4)	297 (10.1)	466 (9.4)
2013	92 (4.6)	169 (5.7)	261 (5.3)
Median follow time in care (years)	3.3 (1.7, 5.1)	3.6 (2.0, 5.2)	3.5 (1.9, 5.2)
Associated bounded structures	1789 (40.3)	2650 (59.7)	4439 (100.0)
Median number of household members, IQR	5 (3, 7)	5 (3, 7)	5 (3, 7)
Associated with 1 bounded structure	1720 (85.7)	2478 (84.2)	4198 (84.8)
Associated with >1 bounded structure	288 (14.3)	466 (15.8)	754 (15.2)
TB disease in the last 12 months	194 (11.8)	221 (8.9)	415 (10.1)
Hypertension in the past 12 months	199 (12.1)	318 (12.8)	517 (12.6)
Diabetes in the last 12 months	44 (2.7)	52 (2.1)	96 (2.3)
Of those with TB disease, in treatment	190 (97.9)	218 (98.6)	408 (98.3)
Of those with hypertension, in treatment	155 (77.9)	254 (79.9)	409 (79.1)
Of those with diabetes, in treatment	36 (81.8)	40 (76.9)	76 (79.2)

S2.2: Cohabitating household members		Exposure (below threshold)	Control (above threshold)	Total
		n (%)	n (%)	n (%)
Total		7599 (41.0)	10926 (59.0)	18525 (100)
Proportion female		4161 (54.8)	6025 (55.1)	10186 (55.0)
Mean age , min-max		32.6 (15, 116)	32.9 (15, 103)	32.7 (15, 116)
Proportion living with >1 PLHIV in care		2163 (28.5)	2907 (26.6)	5070 (27.4)
Median (IQR) time associated with bounded structure (years)		8.2 (3.6-13.0)	7.8 (3.4-12.8)	7.9 (3.5-12.9)
Median (IQR) time since enrollment of PLHIV member (years)		2.4 (1.0-4.0)	2.5 (1.2-4.1)	2.5 (1.1-4.0)
% HIV positive not in care		657 (6.0)	415 (5.5)	1072 (5.8)
Associated bounded structures		1789 (40.3)	2650 (59.7)	4439(100)
Associated with 1 residence		6594 (93.0)	9477 (93.3)	16071 (93.2)
Associated with >1 residence		498 (7.0)	684 (6.7)	1182 (6.9)
TB disease in the last 12 months				
	1	206 (2.7)	340 (3.1)	546 (3.0)
	>1	60 (0.8)	99 (0.9)	159 (0.9)
Hypertension in the past 12 months				
	1	387 (5.1)	538 (4.9)	925 (5.0)
	>1	463 (6.1)	662(6.1)	1125 (6.1)
Diabetes in the last 12 months				
	1	127 (1.7)	202 (1.9)	329 (1.8)
	>1	104 (1.4)	115 (1.1)	219 (1.2)
Of those with TB disease, in treatment		253 (95.1)	420 (95.7)	673 (95.5)
Of those with hypertension, in treatment		722 (84.9)	10033 (86.1)	1755 (85.6)
Of those with diabetes, in treatment		196 (85.9)	259 (81.7)	455 (83.0)

Table S3: Effect of treatment assignment on treatment seeking, Poisson model

S3.1: TB treatment seeking	ITT_{FRD}	95% CI	P	Sample	Events
Overall, adjusting for CD4					
50-350	1.216	0.744, 1.988	0.436	9943	287
100-300	1.319	0.724, 2.040	0.366	7126	193
150-250	1.793	0.736, 4.368	0.199	3722	103
Overall, adjusting for CD4, age					
50-350	1.219	0.748, 1.989	0.427	9943	287
100-300	1.320	0.725, 2.405	0.364	7126	193
150-250	1.779	0.725, 4.367	0.209	3722	103
Overall, adjusting for CD4, age, sex					
50-350	1.228	0.753, 2.001	0.411	9943	287
100-300	1.340	0.737, 2.434	0.337	7126	193
150-250	1.815	0.742, 4.440	0.192	3722	103
Overall, adjusting for CD4, age, sex, restricting to HIV uninfected household members					
50-350	0.996	0.572, 1.736	0.990	9390	219
100-300	1.334	0.678, 2.627	0.404	6728	152
150-250	1.635	0.607, 4.407	0.331	3517	82
Overall, adjusting for CD4, age, sex, restricting to HH with more than 1 PLWH in care					
50-350	1.859	0.715, 4.838	0.204	2779	80
100-300	2.329	0.670, 8.098	0.184	2037	63
150-250	3.595	0.603, 21.44	0.160	1085	30

S3.2: High blood pressure treatment seeking	ITT_{FRD}	95% CI	P	Sample	Events
Overall, adjusting for CD4					
50-350	1.064	0.878, 1.288	0.527	9943	1452
100-300	0.913	0.722, 1.153	0.443	7126	1059
150-250	0.743	0.532, 1.039	0.082	3722	515
Overall, adjusting for CD4, age					
50-350	1.094	0.897, 1.335	0.374	9943	1452
100-300	0.942	0.737, 1.206	0.637	7126	1059
150-250	0.751	0.531, 1.0627	0.106	3722	515
Overall, adjusting for CD4, age, sex					
50-350	1.123	0.962, 1.312	0.142	8929	1452
100-300	0.967	0.799, 1.172	0.734	6416	1059
150-250	0.808	0.618, 1.057	0.120	3363	515
Overall, adjusting for CD4, age, sex, restricting to HIV uninfected household members					
50-350	1.147	0.934, 1.409	0.19	9390	1368
100-300	0.998	0.774, 1.287	0.989	6728	994
150-250	0.881	0.616, 0.1259	0.486	3517	487
Overall, adjusting for CD4, age, sex, restricting to HH with more than 1 PLWH in care					
50-350	1.195	0.801, 1.782	0.383	2779	372
100-300	1.041	0.640, 1.694	0.872	2037	270
150-250	0.652	0.489, 1.851	0.884	1085	142

S3.3: Diabetes treatment seeking	ITT_{FRD}	95% CI	P	Sample	Events
Overall, adjusting for CD4					
50-350	1.705	1.002, 2.903	0.049	9943	222
100-300	1.572	0.817, 3.025	0.176	7126	165
150-250	1.636	0.602, 4.444	0.334	3722	79
Overall, adjusting for CD4, age					
50-350	1.771	1.0366, 3.026	0.036	9943	222
100-300	1.646	0.848, 3.194	0.141	7126	165
150-250	1.724	0.627, 4.740	0.291	3722	79
Overall, adjusting for CD4, age, sex					
50-350	1.855	1.081, 3.182	0.025	9943	222
100-300	1.727	0.899, 3.353	0.106	7126	165
150-250	1.896	0.690, 5.207	0.215	3722	79
Overall, adjusting for CD4, age, sex, restricting to HIV uninfected household members					
50-350	1.704	0.978, 2.69	0.060	9390	207
100-300	1.619	0.823, 3.185	0.163	6728	152
150-250	1.813	0.647, 5.078	0.258	3517	74
Overall, adjusting for CD4, age, sex, restricting to HH with more than 1 PLWH in care					
50-350	2.207	0.722, 6.746	0.165	2779	45
100-300	1.701	0.426, 6.797	0.452	2037	42
150-250	1.348	0.120, 9.101	0.759	1085	18

Figure S1.1: TB treatment seeking by household members of PLHIV enrolled in care, adjusting for CD4+ cell count and age

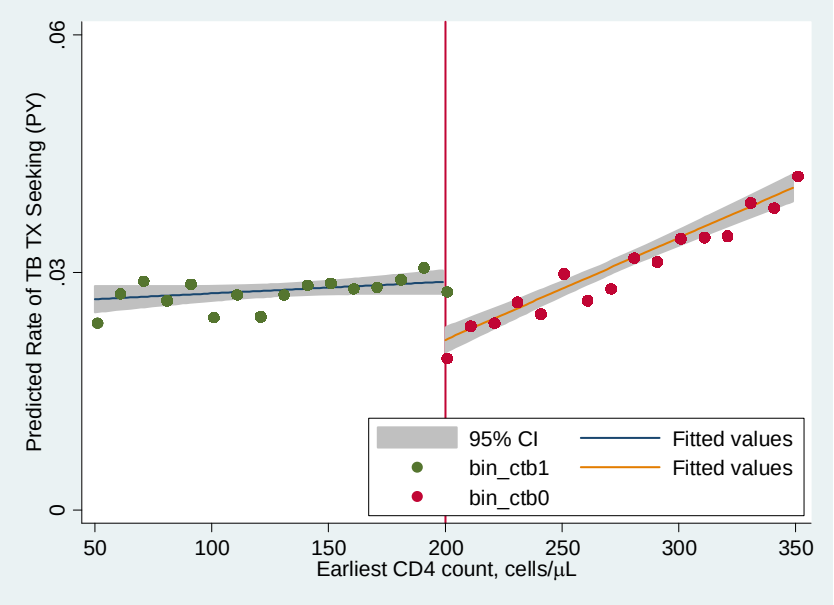


Figure S1.2: High blood pressure treatment seeking by household members of PLHIV enrolled in care, adjusting for CD4+ cell count and age

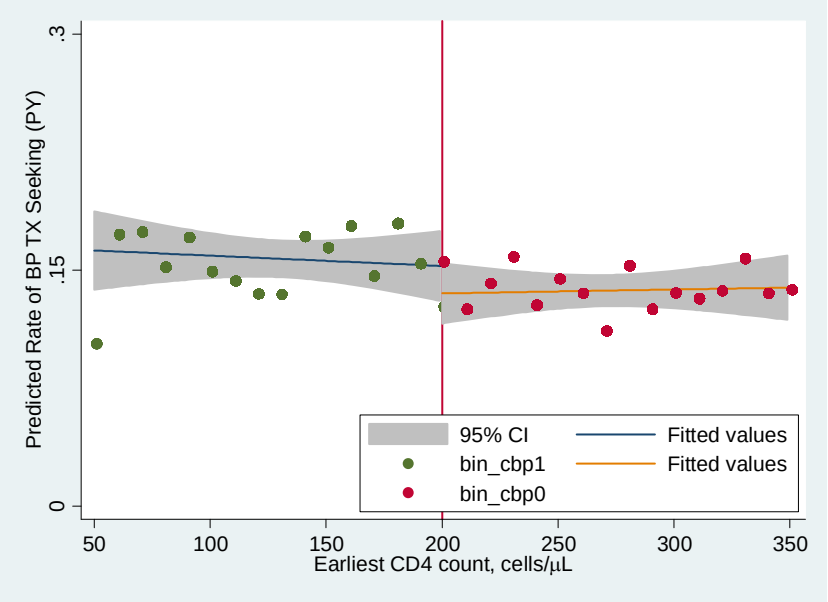
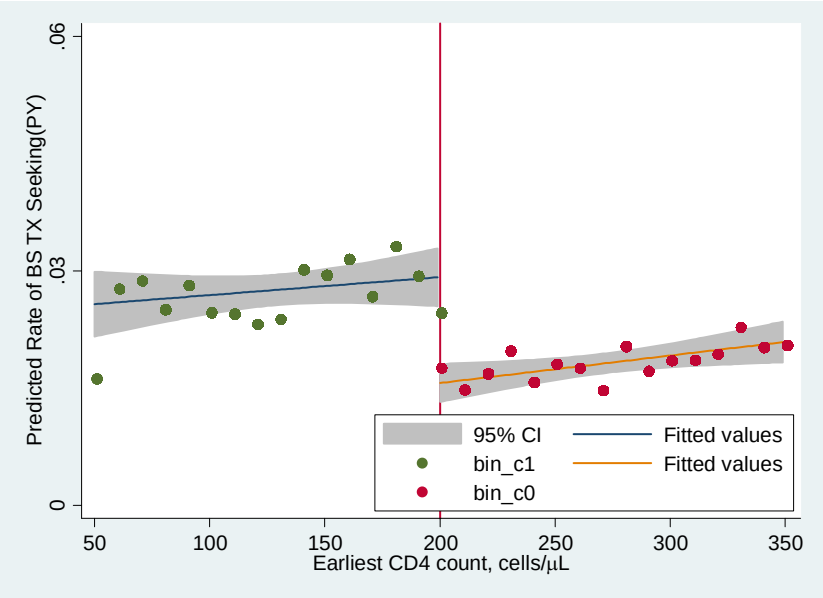


Figure S1.3: Diabetes treatment seeking by household members of PLHIV enrolled in care, adjusting for CD4+ cell count and age



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