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Evaluating The Impact Of Early Initiation Of Antiretroviral Therapy (Art) On Patient Outcomes Among Hiv-Infected Adolescents And Young Adults In Uganda

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EVALUATING THE IMPACT OF EARLY INITIATION OF ANTIRETROVIRAL THERAPY (ART) ON PATIENT OUTCOMES AMONG HIV-INFECTED ADOLESCENTS AND YOUNG ADULTS IN UGANDA

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DEDICATION

To My Parents, James (1931-1997) and Robinah Sekabira

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EVALUATING THE IMPACT OF EARLY INITIATION OF ANTIRETROVIRAL THERAPY (ART) ON PATIENT OUTCOMES AMONG HIV-INFECTED ADOLESCENTS AND YOUNG ADULTS IN UGANDA

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Introduction: Since the introduction of anti-retroviral therapy (ART), treatment initiation criteria have continually been revised to start these lifesaving drugs before onset of advanced disease and optimize ART benefits for people living with HIV. However, little is known about the effect of these changes on treatment outcomes among young people. We evaluated the effect of such a policy change on long term adherence and treatment outcomes among young people, aged 15-24 years.

Methods: We conducted a retrospective cohort analysis of young people, 15-24years old, who started ART from January 2012 – December 2016. We used administrative data from the District Health Information System (DHIS2) and the national referral hospital's EMR. We compared young people who started ART in the period July 1st, 2014 to December 31st, 2016 to a historical cohort that was treated in January 1st, 2012 to 30th June 2014 before the policy change. Multivariable logistic regression was used to assess the effect of the 2014 policy

change on ART adherence and opportunistic infections among those who started treatment before and after the guidelines changed. We also run a Cox Proportional Hazards regression to examine the effect of the policy change on survival.

Results: On average, the health facility providing ART and having an opportunistic infection at the start of ART, had an effect on ART adherence. The policy change did not have an effect on ART adherence. Young people who started ART after the policy change had lesser odds of having an OI compared to those who started ART before the policy at 3, 6 and 12 months on ART. Age, the health facility, weight, and WHO disease stage were also associated with having OIs, as well as duration in pre-ART care, ARV regimen and number of pills per day. There was no significant difference in the survival probabilities and the hazard ratios of young people who started ART before and those who started ART after the policy changed. Also, WHO disease stage, weight at ART start and ART adherence at the time of death had an effect on survival.

Conclusion: This study found that ART adherence among young people was mainly driven by differences between health facilities providing ART in Uganda and whether an individual had an OI at ART start and not by policy change. Furthermore, early ART initiation reduced the risk of OIs among this population. Young people who initiated ART after the policy change were less likely to have an OI after starting treatment. Young people were also more likely to survive longer after ART initiation regardless of whether they started ART before or after the policy change.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

INTRODUCTION

Although the current decade has seen an increase in the number of people on life saving antiretroviral medication, the Human Immunodeficiency Virus (HIV) continues to be a public health threat. Antiretroviral therapy (ART) has reduced morbidity and mortality among people living with virus with more than 11 million lives saved globally in the last decade. Efforts have therefore been made to maximize the benefits of antiretroviral therapy (ART) initiation by starting treatment as soon as one is diagnosed with the virus, at higher CD4 thresholds and using once-a-day fixed-dose combination regimen. However, the success of ART depends on sustaining high levels of ART adherence for viral suppression to stall disease progression.

In Uganda, a high prevalence rate, an increase in number of children who were perinatally infected with HIV becoming adolescents and adults, and an increase in new infections among young people, is a growing concern for health professionals and policy makers. Despite increased ART coverage, the threat posed by a higher treatment burden, documented poor adherence, increasing infections and mortality rates that are not decreasing as in other age groups in this population, cannot be overlooked. In addition, little is known about the impact of the changes in ART guidelines on ART adherence and treatment outcomes in this population. We therefore sought to evaluate the effect of the 2014 ART policy on ART adherence, opportunistic infections, and survival among young people, aged 15-24 years and provide information that can be used to improve HIV interventions.

BACKGROUND

Uganda has a population of close to 35 million people, 23% of whom are between 18-30 years and more than 55% are children below 18 years[1] . Despite a decline from 18% in the early 1990s to 7.3% in 2010, Uganda still has a high HIV-related disease burden with a prevalence rate of 6.0% for the general population and nearly 4% among adolescents and young adults 15-24 years[1,2] . Findings from the 2016 Uganda Population HIV Impact Assessment reported a gender disparity in the HIV prevalence among young people aged 15-24 year with females disproportionately affected at 3.3% compared to 0.8% among males[2,3]. Of the estimated 1.4 million people living with HIV, only about 30% of eligible adults and 47% of eligible children received antiretroviral (ARV) drugs. In 2016, only 27% of adolescents and young adults who were eligible for ART were started on treatment[3]. A recent worrying trend is the rise in new infections among this age group, with young women being disproportionately affected. An average of 22,000 new HIV infections among 15-24-year olds, were reported in 2016 [4] of which 68% were young women 15-24 years. AIDS-related mortality is still high and opportunistic infections (OI) are still a major cause of death among those whose treatment is not keeping their HIV levels low enough for their immune system to fight off infections. All these problems can be linked to suboptimal ART adherence as has been widely reported in the literature which increases the risk of poor treatment outcomes.

HIV is an infection that compromises the immune system leaving the infected person susceptible to opportunistic infections, leading to high morbidity and mortality. There is no cure

for HIV. However, the use of a combination of three or more antiretroviral (ARV) drugs, herein referred to as antiretroviral therapy (ART) suppresses the virus from replicating. This suppresses disease progression and prolongs the life of the person living with HIV (PLWH). Viral suppression is still a challenge given that poor ART adherence still persists among PLWH.

Antiretroviral Treatment Guidelines

In Uganda ART is implemented under the WHO guidelines that have been disseminated since 2002. Revisions have been made over the years as new advances in treatment and new data become available. In 2013, WHO provided updated and consolidated guidelines recommending earlier ART initiation at a higher CD4 cell count threshold, after findings from 3 randomized clinical trials and 21 observational studies demonstrated better clinical outcomes for patients who started ART earlier compared to those for whom ART was delayed[5]. Therefore, all adults and adolescents started ART at CD4 cell count ≤ 500cells/mm^3, using a more efficacious first line regimen with less life-threatening side effects. Priority was given to those with advanced disease or with CD4 cell count ≤ 350cells/mm^3. A 2^{nd} edition of the consolidated guidelines was disseminated in 2016 but for this study the focus is on the 2013 ART guidelines (implemented in Uganda in July 2014) because we believe that information has implications for the latest guidelines.

Healthcare System and HIV service provision

In Uganda, the majority of healthcare is provided by the government through a tiered system comprising of the National Referral Hospitals (NRH), Regional referral hospitals (RRH), General hospitals, lower-level health centers (Level IV- Level II) and village health teams (VHT). The RRHs are located in each of the 14 health zones that cover the four geographical regions of the country, within 5 kilometers of the majority of the population. These provide the bulk of HIV treatment services in the country. HIV care and treatment though provided at all levels of the healthcare delivery system, most of the financial support is from international donors like the Centers for Diseases Control and Prevention (CDC), The Joint United Nations Programme on HIV and AIDS (UNAIDS), and The United States Agency for International Development (USAID). These work in collaboration with the Ministry of Health, national implementing partners like Baylor-Uganda and the existing health facilities.

HIV Treatment and Follow-up

Patients who are diagnosed with HIV are referred to the HIV clinic for care and treatment. Those who are eligible for ART receive at least 3 counselling sessions, in accordance with the national treatment guidelines to prepare them to start ART which is a lifelong commitment. The first follow-up visit is scheduled 2 weeks after ART initiation to monitor response to the prescribed regimen including drug toxicity and side-effects. Thereafter monthly visits are scheduled. Patients that are stable are given longer (usually 2 months) appointment times, which

is unusual for adolescents and young adults because of their challenges with adherence. The clinic visits are scheduled to coincide with the ARV drugs refills. During each visit, patients undergo a comprehensive clinical assessment that includes a physical examination and virological testing as described in the national guidelines. The parameters assessed included ARV drug regimen and adherence to medication; potential side effects; weight and height; TB status and presence of other OIs; loss of function; clinical disease stage; laboratory investigations and whether the patient had been hospitalized since the last clinic visit. CD4 count tests are done every six months and viral load testing is done 6 months after initiating treatment and annually thereafter. Patient records are routinely updated at every clinic visit including those that are lost-to-follow-up (LTFU), transferred in from other clinics/out to other clinics, or have died. Most deaths are reported by relatives, community health workers and volunteers. Since there is no death registry, for this study, we used the recorded date of death in the medical record.

Antiretroviral Therapy before and after July 2014

Prior to July 2014, ART initiation was recommended for PLWH with a CD4 cell count ≤350 cells/mm^3 or with advanced disease stage 3 or 4 as defined in the World Health Organization Clinical staging guidelines. This is referred to as “delayed ART” because the patient started ART at a certain level of disease severity (WHO guidelines). A patient with a higher CD4 count was more likely to be Stage I or II and was considered to be healthy and therefore did not need ART. However, a patient with a lower CD4 count was more likely to be Stage III and IV and therefore

needed ART to stop the disease progression. In resource-limited settings where CD4 testing was not widely available, clinical disease stage was the criteria used to initiate ART. Also, before 2014, priority for ART was given to children <5 years, pregnant women and very sick PLWH. Therefore, during this period, many young people did not start ART if they did not meet the eligibility criteria. Their ART was delayed in this context. Patients with WHO clinical stage I or II were given cotrimoxazole prophylaxis to reduce the risk of opportunistic infections and given medication for any other problems they had. All patients were assessed physically and immunologically on a monthly basis for signs of disease progression. In July 2014, Uganda adopted and implemented the 2013 WHO ART guidelines which recommended that ART be initiated for PLWH at CD4 cell count ≤500 cells/mm^3, referred to as "early ART initiation" because a higher CD4 count is indicative of a healthier person. This led to more PLWH started ART before getting to the advanced disease stages.

ART initiation in both time periods (pre- and post-July 2014) was administered using one non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs), as first line therapy. The NNRTIs included Efavirenz (EFV) or Nevirapine (NVP). The NRTIs were Zidovudine (AZT), Tenofovir (TDF), Lamivudine (3TC) or Emtricitabine (FTC). However, whereas pre-July 2014 the patients could be started on either AZT or TDF, post-July 2014 all patients had to be started on a TDF-based regimen, with Efavirenz (EFV) as the preferred option for the NNRTI. The ARV drugs are administered as a triple fixed dose combination, for example, TDF/3TC/EFV or as duo fixed dose e.g. TDF/3TC used with another separate ARV such

as EFV or NVP. The choice of regimen was guided by the patient's clinical condition, availability of drugs and presence of a contra-indication to any of the available drug options.

Study Sites

The research study was conducted in four tertiary level hospitals; one national and three regional referral hospitals, selected for their geographical representation. Each of these hospitals has a specialized HIV clinic for young people that is open all week days. Patients routinely receive a package of services that includes adherence assessment and support education and counseling, and clinical and laboratory monitoring for disease progression and opportunistic infections. A peer model in which young people are trained to identify fellow young people with adherence challenges and support them is used to foster adherence. Patients with poor adherence are each initiated on an intensive adherence counselling plan and followed up till they reach satisfactory levels before being reintegrated into routine clinical routines. Across all the four sites, ART and other forms of HIV treatment is free of charge with a centrally procurement and distribution system run by government warehouses. With the exception of the national referral hospital that has a computerized physician order entry system, regional referral hospital operates a paper based clinical notes system in which clinical findings and treatment procedures are summarized on a patient card during each follow up visit. These cards are kept at the health facility and later entered an EMR data base (District health information system [DHIS2]) for analysis and reporting.

Baylor College of Medicine Children's Foundation-Uganda (Baylor-Uganda)

Baylor-Uganda is located in Mulago National Referral Hospital in the central region, and also serves as a teaching hospital for medical professionals. An affiliate of the Baylor International Pediatric AIDS Initiative (BIPAI)'s network of clinics, Baylor-Uganda is the largest pediatric HIV clinic in Uganda and Africa that provides comprehensive HIV care and treatment services for children and adolescents infected with HIV/AIDS. The clinic has been in existence since 2003 and has an estimated daily attendance of about 200 patients with a total enrollment of 7000 patients. Over 1800 patients aged 15-24 years have been started on ART since 2011.

Fort Portal Regional Referral Hospital

The Fort Portal Regional Referral Hospital, located in Western Uganda, serves close to 500,000 people in the Rwenzori Region. The HIV clinic, founded in 2002 has a total enrollment of nearly 8000 patients in care with about 7000 started on ART between 2011 to date.

Mbale Regional Referral Hospital

The Mbale Regional Referral Hospital is located in Eastern Uganda. A cumulative total of about 6400 adults and children are currently receiving ART at the hospital's HIV clinic. Of these 400 adolescents and young adults have started ART since 2011.

Gulu Regional Referral Hospital

The Gulu Regional Referral Hospital, located in the northern region, offers comprehensive HIV services to the Acholi sub-region. Over 6000 patients with HIV infection are receiving ART at the HIV clinic, 786 of whom are adolescents and young adults.

STATEMENT OF THE PROBLEM

Although HIV infections have reduced tremendously in the last few decades, Uganda still has a high HIV-related disease burden with a prevalence rate of nearly 4% for young people, 15-24 years[3] . The number of children who were prenatally infected with HIV, who are surviving into adulthood is increasing. The rise in new infections and AIDS-related deaths among this age group is also a source of concern among health professionals and policy makers. The initiation of ART at a higher CD4 count threshold herein referred to as "Early ART", using more efficacious ARVs and a lower pill burden, it is believed will greatly reduce the number of infections and deaths[3-8]. However, the success of ART relies on sustaining high levels of ART adherence for viral suppression[9,10], which is a problem in this age group.

Early ART initiation also raises medication adherence concerns in a population that has been widely reported to have poor adherence[11-15]. The threat of poor adherence in this age group cannot be overlooked given that ART adherence rates are lower, mortality rates are not decreasing as in other age groups and there is a rise in new infections[8,16]. Between 2005 and 2012, the number of deaths among this age group increased by 50% whereas overall it had decreased by 30% [6]. In Uganda, a total of 5200 AIDS-related deaths were reported among young people 15-24 years in 2016[4]. The risk of drug resistance is increasing and this has implications on viral suppression. Young people are staying on treatment longer than adults leading to a higher treatment burden, it is therefore important to examine the implications of these policy changes on treatment outcomes.

Furthermore, most published literature focusses on children and adults, is mostly from high income countries, with this age-group aggregated as either children or adults, and therefore excluded in most of the statistical data analyses. More studies with better age disaggregation are needed.

Although a few studies have examined the effect of treatment guidelines in sub-Saharan Africa and Uganda, their main focus was drug efficacy, reducing morbidity and mortality. None of these studies have assessed the effect of the changing ART guidelines on adherence and treatment outcomes in this age group and the implications on future HIV programs. Therefore, in this study, we sought to assess the effect of changes in ART guidelines on ART adherence, opportunistic infections and survival among young people in Uganda, 15-24 years, who initiated ART before and after the implementation of the 2013 ART guidelines.

LITERATURE REVIEW

A considerable amount of literature has been published on treatment outcomes since the outbreak of the HIV epidemic. However, the limitations of current studies on adolescents and young adults, not limited to study designs, study populations, and mixed results underpinned the importance of this study. The benefits of ART on outcomes for people infected with HIV cannot be over emphasized and a substantial amount of literature has been published about it. However, only a few studies have been done in resource-limited settings like Uganda. There is even more paucity of information when it comes to adolescents and young adults.

A substantial amount of literature available for Sub-Saharan Africa is based on pre-2010 ART treatment guidelines that recommended ART initiation at a lower CD4 count threshold (<200cells/mm^3) and the available ARVs were less efficacious than those currently available. ART initiation is currently recommended at a higher CD4 count threshold (≤ 500cells/mm^3), using more potent ART regimens[5,7]. For this study, we sought to understand how newer (2013) guidelines impacted treatment outcomes in Uganda. We analyzed data from adolescents and young adults over time and believe that the results can be used to inform policy and improve effectiveness of ART among this population.

Early initiation of ART is associated with reduced mortality and morbidity caused by the HIV infection. Montaner et al. (2014) who sought to characterize the association of HAART with new AIDS cases and mortality, reported an 80% reduction in both AIDS incidence (from 6.9 to 1.4 per 100,000 population) and HIV-related mortality (from 6.5 to 1.3 per 100,000 population)[8].

Positive results have also been reported elsewhere. A multi-country study of 30 countries with the highest AIDS mortality burden found that access to ART averted about 1,051,354 and 422,448 deaths in South Africa and Nigeria and increasing coverage could avert 2.2 and 1.2 million deaths respectively [9,10].

ART among Adolescents and Young Adults

Considerable evidence shows that successful treatment of perinatally infected children, in addition to managing opportunistic infections and increasing ART coverage has led to an increase in the number of HIV-infected adolescents and young adults on ART[17,18] . Nachega et al. (2009) argued however, that despite the number of large studies that described virological outcomes of ART in adults and children, very few looked at adolescents and young adults per se. For example, the START Trial[11] that assessed the clinical outcomes of immediate versus delayed ART initiation did not include adolescents.

Adolescents are at risk of poor health outcomes and acquisition of new HIV infections as a result of poor use of ART. Mutevedzi and Newell (2014) reported a large number of new HIV infections showing up among adolescents and young adults. Data from the Global Health Observatory Data Repository supports this finding. Furthermore, adolescents have poor adherence rates compared to adults and children[12].

> "Over one third (38%) of adolescents globally are sub-optimally adherent to ART, with substantial regional variation"[13] .

"HIV infected adolescents and young adults on ART in Southern Africa have poor adherence rates and poor virologic outcomes than their adult counterparts"[14].

A review by Lowenthal et al. (2014) of the changing epidemiology of HIV among perinatally-infected adolescents in Sub-Saharan Africa also revealed increased risk of chronic lung disease, cardiac disease, skin, renal and bone disease. They also noted that growth failure was more pronounced during adolescence. All this affected adherence to treatment, education and the overall quality of life. They further argued that existing studies were cross-sectional in nature, had small sample sizes and lacked controls against which comparisons could be made. On the other hand, studies from high income settings lacked age-specific data. These mentioned limitations made generalizability of the results to HIV-infected adolescents and young adults in Uganda a challenge.

Ford, Mills and Egger (2014) in their editorial commentary argued that the meta-analyses such as the one done by Siedner et al. (2015), were prone to ecological biases because of the use of aggregated data. Similar studies like Ferrand et al. (2016) scored the quality of many of the studies used in their systematic review as low or moderate. They could not make accurate estimates about the effectiveness of ART on viral suppression because there was a lot of variation in the number of adolescents achieving viral suppression in the studies they reviewed. They also found that many of the studies did not stratify by duration of ART and none included age-specific analysis both of which were associated with treatment adherence. This was a gap that this study hoped to address.

It should also be noted that before 2010, only children 0-5 years were started on ART if they tested positive for HIV. Older children, adolescents and adults, started ART only if they had advanced disease, defined by the WHO as clinical disease stage III and IV or having a CD4 cell count below a recommended threshold. Therefore, newly diagnosed adolescents and young adults may not have been eligible for ART and thus were excluded from most studies. According to UNAIDS, in 2013 there were 200,000 young people (15-24 years) out of 1.2million PLWHA in Uganda. Of these 41% adults (15+years) were started on treatment. The number of young people 15-24 years is not disaggregated. This study sought to capture more of them and provide results that are more generalizable.

Adherence to ART

Early ART does not only have implications on costs, service delivery and access to care, but also on adherence. As earlier mentioned, long-term medication adherence is a challenge for any disease and HIV is not an exception. Added to this is the frequently required clinic visits which is still the case in Uganda as in many other Sub-Saharan African countries. Recent studies[15,16] in the US that underscored the importance of timely and uninterrupted care, also reported a high rate of missed clinic visits during the first year in HIV care. Furthermore, social and psychological factors, adverse side effects, drug toxicities, pill burden, daily doses and drug interactions are documented barriers to ART adherence. Although the current ARV drugs are more potent and effective[17], they still have minor adverse effects that PLWHA have to deal with.

Medication adherence is a major determinant of ART success. Several studies [13,18,19] found that non-adherence to ART treatment led to drug resistance, increased viral load, disease progression, decreased CD4 cell count and death. It was also argued that not all PLWHA took their medication as prescribed. Different approaches such as clinician documented prescription refills, directly observed therapy, self-report and microelectromechanical systems (MEMS) technology have been used to address this problem. However, non-adherence remains a major threat to the success of ART.

A meta-analysis by Stricker et al. (2014) found that on average 62% of patients reported ≥ 90% adherence. These findings are similar to those reported in an earlier study by Mills et al. (2006)[20]. However, a retrospective study done in Nigeria[19] that analyzed medication refill adherence found that refill adherence reduced with successive visits. This means that fatigue set in, which in turn affected adherence overtime. Even with the single once-daily fixed dose regimen that has reduced the pill burden tremendously, Gulick (2010)[21] found that only 60-80% of patients achieved complete viral suppression.

Concerning adolescents and young adults many study findings pointed to their poor adherence compared to children and adults. Findings from a systematic review by Kim, Gerver, Fidler and Ward (2014) found that almost 40% of adolescents who were eligible for or started ART were non-adherent to treatment. Nevertheless, they also noted that the studies in that analysis looked at the period before the CD4 count threshold for ART initiation was raised, the ART regimens were less potent and had unpleasant side effects. Therefore, analyses that are

more recent were needed to assess adherence among this population. They also noted considerable variation in the studies that were included in the review most of which were cross-sectional because the paucity of longitudinal studies. Also, countries like the United States, Brazil and South Africa were over-represented. Existing data is therefore incomplete and the magnitude of the problem of non-adherence is not really known. It is also likely that the incidence of medication non-adherence is actually higher than published. The methodological difficulties associated with measuring adherence may therefore be underestimating the extent of the problem.

In Uganda adherence is measured using pill counts and self-reports. At each clinic visit, the patient is asked to return with all medicine containers from the previous visit and a pill count is done and recorded in the patient HIV care/ART card. This card is a record of all patient information, including all follow-up visits and is kept at the health facility/clinic. Clinic visit reminders, and other information is recorded in the patient's book that acts as a copy of the patient's medical record that the patient has access to. However, research has shown that pill counts and self-reports are subjective and may be over reporting adherence and underestimating the problem of non-adherence. This may be associated with the increase in AIDS-related mortality, likelihood of OIs and new HIV infections among this population.

Furthermore, many factors affect adherence in this age group. Social and psychological factors[22], treatment fatigue[12], stigma and size of tablets[23], education[24] and transitioning from pediatric care to adultcare[25], and non-disclosure[20] have been documented in published

literature. The association between age and adherence has already been established. Adherence is reported to decline with age among adolescents and young adults[26]. The Pediatric AIDS Clinical Trial Group (PACTG 219C) found 76% adherence rates for ages 15-18 years compared to 83-89% in younger children[26]. Mekuria L.A et al. (2017), Auld et al. 2014 and Nachega et al. (2009) also found significant associations between age and suboptimal adherence.

We cannot overemphasize the need for more evidence-based literature. Most of the literature on ART adherence among adolescents and young adults is from high-income countries. The meta-analysis by Mills et al. (2006) that is cited in most literature did not include adolescent populations from Africa. Furthermore, very few longitudinal studies have been done in Sub-Saharan Africa. One longitudinal study done by Sasaki et al. (2012) in Zambia focused on a rural-based population sample using pre-2010 ART treatment guidelines. Current analyses, like this study, are therefore needed to assess factors associated with ART adherence and allow for more generalizable results.

Opportunistic infections (OI)

OIs are still a major threat to PLWHAs as they increase the risk of morbidity and mortality[19-22] . They negatively affect the quality of life and threaten the success of ART treatment. Findings from Rubaihayo et al. (2016) showed that OIs increased stigma, affected a patient's response to treatment and led to increased healthcare costs since the affected patient had to visit the health facility more frequently.

ART reduces the load of HIV in an infected person's body enhancing the person's ability to fight off OIs and live longer. A large cohort study by Guillen et al. (2010) reported that ART initiation led to a reduction in incidence and prevalence of OIs among children in high-income countries. In 2016, a systematic review by Drouin et al. (2016) focused on low- and middle-income countries (LMIC), found similar results except for bacterial pneumonia, tuberculosis (TB), and candidiasis. They however noted that many of the studies lacked lost-to- follow-up data that was key in incidence studies. They also lacked data on confounders such as CD4 cell count, age at ART initiation and use of cotrimoxazole prophylaxis, a key medication used to prevent OIs.

Poor adherence, a major determinant of treatment failure increases the risk for OIs[27]. Iroezindu and colleagues (2013) examined the OI prevalence and risk factors in patients on ART. They found that 22.4% had OIs despite reported good adherence rates among 78% of study participants. The study may have under- or over-estimated some infections because it lacked diagnostic test data.

Although the evidence supporting the success of ART in significantly reducing OIs and AIDS progression cannot be disputed, differences still exist in the burden of OIs between high-income countries (HIC) and LMIC settings. Prevalence and incidence rates also vary between and within countries - 22.4% was reported by one study in Nigeria[28], 30% in Senegal[29], and 47.6% in South Africa[30]. Studies done in Ethiopia[31] and West Africa[32] had similar findings. The endemicity of diseases such as tuberculosis and pneumonia in some areas may have influenced study findings. However, different CD4 count thresholds were used in each of these studies and that variation

should be accounted for when using the results. A systematic review by Low et al. (2014) that reviewed studies from Sub-Saharan Africa, Asia, Latin America and the Caribbean noted a 57% - 91% decline in risk of oral candidiasis, toxoplasmosis and Pneumocystis pneumonia (PCP), during the first year on ART. They still found a significant number of PLWHA presenting with advanced disease, an issue that cannot be overlooked in face all the achievements made by ART. However, they also noted that there was a lot of variability in study parameters such as reporting cotrimoxazole prophylaxis, ART regimens, and duration on ART, follow-up times and lack of information on important confounders like CD4 cell count.

As earlier noted, adolescents and young adults have been understudied. Most of the literature focuses on adults and children. According to Shroufi et al. (2013), many research programs put little emphasis on adolescents and young adults and concentrated more on infants and younger children. With reported poor adherence to ART, the risk of OIs among this subgroup is increased but it is not documented. An observational cohort study by Nachega et al. (2009) found that lower virologic suppression and immunologic recovery was common among adolescents and young adults because of poor ART adherence. This increases the risk of infections.

A few of the studies done in Uganda focused on children ≤ 15 years but with more emphasis on infants. Others focused on adults 18 years and above. Literature on adolescents and young adults is very limited. A prospective cohort study by Namutebi, Kamya and Byakika-Kibwika (2013) focused on the age group 28-40 years and found that though OIs had declined, they should

not be ignored because patients still present with advanced disease. Rubaihayo et al. (2016) assessed OIs before and after ART initiation and found that OIs accounted for 91% of all opportunistic events, the most common being diarrhea < I month and geohelminths. They also found that oral candidiasis was still present although not as highly prevalent as in previous years. These studies, however, used different study designs, had adults as their study population, and some lacked data on confounders like patient's CD4 counts, duration on ART and reported ART adherence.

It was therefore important to obtain updated analyses on the impact of ART on OIs, ever since the global scale-up of ART coverage and use of more potent ART regimens. Existing literature such as Holmes et al. (2003), Nachega et al (2009), and Hull, Phillips and Montaner (2008) preceded this period and/or addressed specific OIs and regions. Low et al. (2014) also argued that country-specific evidence-based assessment of prevalent OIs would help define local priorities and inform targeted expenditure on and procurement of relevant prophylaxis drugs, in addition to treatment of HIV-related comorbidities.

This longitudinal study sought to provide updated information by exploring the magnitude of OIs among young people in Uganda and identify the risk factors associated with them**.**

Survival and Predictors of Survival

The use of ART has been associated with improved survival among PLWH. It is one of the indicators, though difficult to measure, that is used to evaluate program performance. One of

the causes of death among PLWH is the presence of OIs. Patients with advanced HIV disease have a higher risk of OIs when initiated on ART, which in turn increases their risk of death. Results from a South African study showed that OIs and the Immune Reconstitution Inflammatory Syndrome (IRIS) were major causes of death after initiation of ART[33]. IRIS is a combination of clinical signs and symptoms considered to be associated with immune recovery brought about by a response to ART. It occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy.

Furthermore, patients with poor adherence have a higher risk of death because of poorly controlled viral load. Ayele, Mulugeta, Desta and Rabito (2015) found that the risk of death was nearly 3 times higher (HR: 2.9695, 95% CI: 1.396 – 5.203) among patients with poor adherence compared to those with good adherence. A similar study in Ethiopia by Hambisa, Ali and Dessie (2013) found that non-adherent patients were 27 (95% CI: 8.928, 86.8) times more likely to die than adherent patients were. However, the confidence interval was wide. A Ugandan study[34] reported that non-adherent patients were 2 times more likely to die compared to adherent patients. But as noted with many studies, the study by Hambisa et al. (2013) had a lot of missing data on OIs, an important determinant of mortality used in several studies.

According to the WHO and UNAIDS, adherence to ART is critical to the survival of PLWHA since poor adherence was the main reason for poor treatment outcomes[35].Early initiation of ART improves survival of PLWHA[7,23,24] and reduces the cost of healthcare. Cost-effectiveness studies such as Bendavid, Grant, Talbot, Owens and Zolopa (2011) found that a TDF regimen was

associated with highest survival (135.2 months of quality adjusted life expectancy), and fewer opportunistic infections [36].

Despite the benefits of ART in improving survival, patients still die when started on ART although the numbers as not as high as they used to be. The number of patients that died in the first year of ART was estimated to be between 8% - 26%[37]. Most of the deaths occurred in the first few months of ART. This may change as more updated analyses based on newer ART guidelines recommending earlier ART initiation at a higher CD4 count threshold and with more potent ARVs, become available. Amanzi, Michelo, Simoonga, Dambe and Chongwe (2016) reported low survival rates during the first year on ART, similar to findings from Tanzania[38] and Cameroun[39]. A patient with a lower CD4 count (≤200 cells/mm^3) had a lower chance of survival compared to one with a higher CD4 count (≤350 cells/mm^3) at the start of ART. The median survival found in a 5-year Tanzanian cohort was 24 months[40]. This was lower than was reported in an earlier Tanzanian cohort by Johannessen et al. (2008) and in Uganda[34]. The Cameroun study[39] also found patient characteristics, adherence and quality of healthcare were independent predictors of survival.

A 2015 retrospective cohort study done in Ethiopia found that 12.2% of the patients died during 5 years of follow-up, 68% of whom died in the first 6 months of ART initiation[41]. Mageda, Leyna and Mmbaga (2012) found that mortality was 4.3 per 100-person years with more deaths happening within the first 5 months following ART initiation. The authors noted however, that most patients had CD4 cell count less than 200 cells/mm^3. This variability could be explained by

the different time-periods, wide variation in age-range and different study designs, in addition to the low CD4 count. It should also be noted that highly active antiretroviral therapy (HAART) was not readily available in many African countries before 2012. Therefore, current analyses will significantly contribute to the body of knowledge since they are based on a higher CD4 cell count and more potent ARVs that are now available.

One can also argue that although Nachega et al. 2009 is one of the very few published studies reporting adolescent clinical outcomes in Africa, the causes of mortality among adolescents and young people was not well documented. This supports the argument that adolescents and young adults living with HIV have been understudied and yet available literature highlights their risk of poor health outcomes. This study sought to add to available research by providing adolescent and young adult-specific data that can be used to improve HIV interventions in this population.

Patient Factors

Uganda scaled up efforts to increase ART coverage countrywide in 2012 and with the reported success, it is easy to overlook what is happening over time. Studies also demonstrate that ART alone is not a sole determinant of mortality.

A patient's use of healthcare services is a function of predisposing, enabling, and need factors as demonstrated by the Andersen Behavioral Model. A substantial amount of studies found associations between these factors and ART use. Greer et al. (2015) examined the

association between new HIV patients and IOM treatment indicators and found that poverty was associated with poor adherence to ART and poor clinic appointment attendance. Age was also found to be significantly associated with ART use[26].

Furthermore, if patients are not ready to start ART, treatment initiation would be delayed, which in turn increased the risk of transmission, disease progression and even death. This is a serious concern for both patients and health providers. Many of the patients perceive ART as a death sentence[25,26] . Therefore, preparation and assessment of the patient's readiness has to be taken into consideration too.

This study sought to provide a deeper understanding of factors, specific to Uganda, that affect adherence to HAART among adolescents and young people living with HIV, to better develop interventions to improve adherence in this population and reduce barriers to HIV care and treatment.

PUBLIC HEALTH SIGNIFICANCE

The importance of documenting what happens to adolescents and young adults in order to design interventions that will effectively improve HIV treatment outcomes cannot be overlooked. The HIV epidemiology has changed and coupled with new antiretroviral treatments and treatment indications, there is need for more timely data. This study provides country-specific evidence-based assessment on occurrence of opportunistic infections, ART adherence and survival among adolescents and young adults. This information can be used to identify priority areas in HIV service provision and improve treatment outcomes especially as the country seeks to implement the latest guidelines aimed at further reducing the time between HIV diagnosis and ART initiation. This longitudinal analysis also provides policy makers with a deeper understanding of factors that are associated with early initiation of ART in this population. This information can then be used to target expenditure on, and the procurement of relevant prophylaxis drugs, in addition to treatment of HIV-related comorbidities. Furthermore, this study will contribute to the growing body of research[5], and in addition to ongoing trials to evaluate the impact of early ART initiation, barriers and drivers of adherence, and incidence of adverse events from increased exposure to ART. This study therefore provides updated information that can be used to improve ART adherence and treatment outcomes among young people in Uganda and thereby reduce barriers to HIV care and treatment.

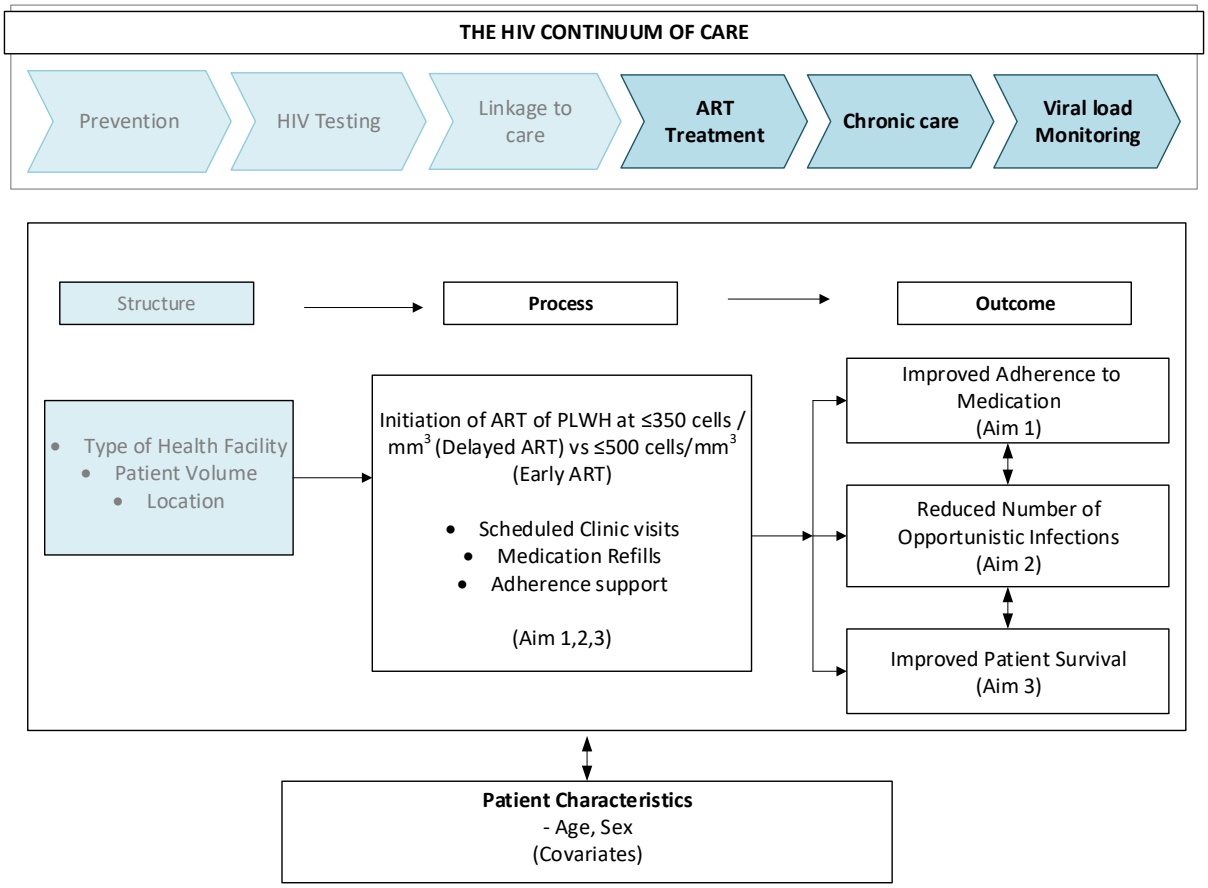
THE CONCEPTUAL FRAMEWORK

The conceptual framework that underpinned this study is a modified version using features from both the Donabedian Structure-Process-Outcome (SPO) model[42,43] and the Anderson Behavioral model (ABM)[44], underpinned by the HIV Care Continuum[45,46]. The SPO model illustrates the relationship between structure, process and outcome of the healthcare system, the ABM model incorporates the patient characteristics influencing that relationship.

The HIV Care Continuum (HCC) illustrates the stages of care a person living with HIV goes through from diagnosis to viral suppression. It is used globally to track the number of PLWH at each stage and identify priority areas to improve HIV delivery services. The stages, important in the fight against HIV, involve having adequate care provision conditions and resources to provide that care. On the other hand, however, the success of HIV care is also dependent on the patient's right and willingness to accept or defer treatment[5]. This is influenced by a number of factors illustrated by the ABM model in the literature as predisposing, enabling and need factors. This study focused on the predisposing factors of age and sex[27,28], and examined their association with the study outcomes. In the Donabedian model, structure is defined as "the conditions under which care is provided, including material resources, human resources, and organizational characteristics"[42]. In order to provide quality HIV treatment, adequate physical and human resources have to be available. For this study we operationalized structure as type of health facility, its location and patient volume. These were broadly defined since the detailed aspects are not the focus of this study. The process of providing HIV care includes ART treatment routine

clinic visits, drug refills and viral load monitoring, among other activities. Donabedian defined these as the "set of activities that constitute health care, including diagnosis, treatment, rehabilitation, prevention and patient education usually carried out by professional personnel"[42]. If the process is not working well, then the outcomes would not be desirable. This study operationalized the process as early initiation of ART for PLWH at CD4 cell count ≤500cells/mm^3 as recommended in the 2013 WHO guidelines. We examined the association between early ART initiation and study outcomes; (i) adherence to ART medication, (ii) occurrence of OIs and (iii) survival, among adolescents and young adults living with HIV in Uganda. These outcomes were defined to as "changes (desirable or undesirable) in individuals and populations that can be attributed to health care"[42]. Figure 1 shows the modified model that guided this study. It illustrates the relationship between the different components of this study.

Figure 1: Conceptual Framework



Adapted from Donabedian 2003 and Kane 1997; Andersen 1995 (Source: Begley et al 2008; Glanz 2008; R.M Andersen 1995) and modified by the Researcher

Hypothesis, Research Question and Specific Aims

Research Question

What is the effect of the changes in the WHO 2013 ART guidelines, herein referred to as early ART initiation and adopted in Uganda in 2014, on treatment outcomes among young people living with HIV in Uganda?

Overall Aim

The broad aim of this study was to assess the impact of changes in ART policies on patient outcomes, over time, among young people living with HIV, 15 - 24 years of age, in high-volume health facilities in Uganda. We hypothesized that young people who started ART after the policy changes were implemented would have better treatment outcomes compared to those who started ART before the policy changed.

Specific Aims

Aim 1: To assess the effect of changes in ART guidelines on ART adherence among young people 15 - 24 years, before and after the ART policy change.

Hypothesis: We hypothesized that young people would have better ART adherence after the policy change.

Aim 2: To assess the effect of changes in ART guidelines on Opportunistic Infections (OI) among young people 15 - 24 years, before and after the ART policy change.

Hypothesis: We hypothesized that there would be fewer OIs among young people who initiated ART after the policy changed compared to those who initiated ART before.

Aim 3: To assess the effect of changes in ART guidelines on survival and identify predictors of survival among Young people 15 - 24 years, the ART policy change.

Hypothesis: We hypothesized that young people who initiated ART after the policy changed would have a lower risk of death compared to those who initiated ART before the policy change.

METHODS

Study Design and Data source

We conducted a retrospective cohort study comparing young people who started ART in the period July 1st, 2014 to December 31st, 2016 to a historical cohort that was treated in January 1st, 2012 to 30th June 2014 before the policy change. We used administrative data from the District Health Information System (DHIS2) and the national referral hospital's EMR. This data, routinely collected from patients who receive HIV treatment at the health facilities during clinic visits, is used to plan and track a patient's treatment from the date of HIV diagnosis to the date he/she leaves the clinic either through transfer-out to another clinic, lost to follow-up (LTFU) or death.

For this study design we needed patient information over a period of time, which information was not readily available in most health facilities. This study was conducted in four tertiary level hospitals; one national and three regional referral hospitals, selected for their geographical representation. These hospitals have a high patient volume, have electronic medical records that covered the study period and therefore, provided an adequate sample population. These health facilities were also at the forefront of implementing the new ART guidelines before scale-up of services to lower-level health facilities.

Electronic Medical Records (EMR)

We used de-identified secondary data that was routinely collected from patients that received HIV treatment and recorded in the EMR. The Baylor-Uganda EMR was developed by

BIPAI in 2005 to manage real time registration, appointments and enhance tracking of patients. It is used in all BIPAI-affiliated COEs in more than 10 different countries worldwide.

The Regional Referral Hospitals (RRHs) started using EMRs in 2011 using an open source medical records system platform, OpenMRS which was developed for use in developing countries. The OpenMRS system, a collaboration between the Regenstrief Institute, a world-renowned medical informatics research institute, and Partners in Health a Boston-based organization, focused on health service delivery for the underprivileged worldwide. This was later revised and a newer platform, the District health information system [DHIS2]) was adopted at the national level for reporting and analysis. The databases contain information on patient demographics and clinical parameters, not limited to: date of diagnosis, ART initiation date, CD4 cell count, adherence, and presence/absence of OIs, stage of disease; registration date; and status of the patient.

These databases were appropriate for this longitudinal study design because of the ability to track a patient from the time of registration in the clinic, course of treatment, up till the time they exited the clinic due to death, transferred-out to other clinics or are lost-to-follow-up. It was therefore possible to follow-up the study participants over the study period.

Study Cohort

We defined the study population as young people aged 15-24 years. The study included all HIV-infected young people, 15-24 years at the time of ART initiation, who started ART between January 1, 2012 and December 31, 2016, regardless of the date of HIV diagnosis. We included those who were newly diagnosed with HIV and those who were diagnosed prior to the study

period but had not started ART. The cohort entry point was the date of ART initiation with each study participant contributing follow-up time to the study period. Young people had to have data for at least two follow-up visits, had to have started ART at the selected HIV clinics, and be on lifelong ART. Young people who were LTFU or transfer-out during the study period were included because they contributed time until the event happened. However, we excluded young people who were lost- to- follow-up at the start of study period; started ART for Pre-exposure prophylaxis (PrEP) because it is short term; had no records; and had started ART elsewhere because the data from the original health facility was not readily available. The study cohort was closed on December 31, 2017 to ensure that all study subjects had data for at least two follow-up visits.

For all the study participants that met the selection criteria, we extracted their pre-ART data. The patient information included socio-demographic characteristics, date of ART initiation, CD4 cell count, WHO clinical disease stage, cotrimoxazole prophylaxis, ARV regimen, number of ARV pills given per day and ARV refills, among other patient data that was relevant to the study.

Sampling Frame

The sampling frame used for this study was the Pre-ART and ART registers in which all patients diagnosed with HIV and received treatment at the selected health facilities are registered. The registers contain both baseline and follow-up information about each patient and are updated at every clinic visit.

Sample Size

The selection of study participants was not based on probability sampling. We included all patients that met the inclusion criteria in the analysis. However, we performed a power analysis to obtain an adequate number of subjects to detect a difference and be able to answer our research question. Literature on effect sizes used in HIV treatment outcomes research in Uganda is very limited and mixed. However, a randomized clinical trial[47] and case-control study[48] conducted in Kenya used 10% effect size, the smallest difference that would be of clinical importance in the HIV field. Results from meta-analyses (mean weighted ES) range from 0.10 – 0.79[49,50,50,50,50,50,50,50,50,50,50,50,50]. The total number of adolescents and young adults who were included in the analysis was 3084. This gave the study 80% power to detect an effect size of 0.08 based on a two-sided t-test at 0.05 significance level, assuming that the outcome variable at baseline was continuous and normally distributed.

Study Variables

Dependent Variables:

ART Adherence: The dependent variable "ART adherence" was defined as the percent adherence for each patient during the first 12 months of starting ART. This was coded as a binary variable, "1" if the patient had an adherence code corresponding to ≥95% adherence and "0" otherwise. An adherence rate of ≥95% is the threshold necessary for sustained clinical effectiveness of ART[9,29,30]. A young person was considered to be adherent if he/she had a code of "1" for all the months at 3, 6 and 12 months of follow-up. An individual was considered to be

less adherent if he/she had a code of "0" for any of the months at 3, 6 and 12 months of follow-up.

Opportunistic Infections (OI): We defined the dependent variable "opportunistic infection" as a disease event diagnosed during a clinic visit and recorded in the patient's medical record as an OI. The ART clinics use the WHO classification of OIs[5,31]. This was coded as a binary variable, "1" if the patient had an OI and "0" otherwise. A young person was considered to have an OI if he/she had a code of "1" for any of the months at 3, 6 and 12 months of follow-up. An individual who had an OI at 3 months, was considered to have an OI at 6 and 12 months.

Survival: We defined survival as the time between ART initiation and death or end of study period. For more comparable results the total follow-up time for each group was restricted to 36 months after starting ART. For young people in the pre-policy group, the censor date was December 2014 and for those in the post-policy group, the censor date was June 2017. Length of time was measured in months. The variable was coded as "1" if the patient died and "0" otherwise.

Independent Variables:

Policy change group (pre/post): The independent variable of interest was a binary time variable representing the before and after introduction of the guidelines (pre-policy=0, post-policy=1). The pre-policy group included young people who started ART before July 2014 (January 2012 – June 2014) and the post-policy group included young people who started ART after July

2014 (July 2014-December 2016). The ART start date was the date the patient was given a dose of ARVs.

Socio-demographic variables

Age: Age is a key predictor of ART adherence. ART Adherence has been reported to decline with age among young people[32].

Gender: Studies have reported that females are more likely to be adherent to ART compared to males. Females are disproportionately affected by HIV in this age group.

Health facility/ART clinic: The clinic providing the HIV treatment is important to this analysis because of the geographical representation and the differences in structure and clinical processes.

Clinical Characteristics

Weight: The weight of the patient is documented at each clinic visit so that any weight loss in a short time is immediately addressed. Extreme weight loss is indicative of treatment failure.

WHO clinical disease stage (coded as I, II, III and IV): The WHO clinical disease stage (I-IV) is an indicator of disease severity and in the absence of CD4 testing and more recently viral load testing, clinical stage was used as the eligibility criteria to assess for ART initiation.

CD4 count at ART start: CD4 count is a key indicator for both disease severity and virological failure. It was commonly used during the study period to assess eligibility for ART. The

change in ART policy raised the CD4 count threshold increasing the number of young people starting ART.

Treatment Characteristics

Duration in pre-ART care (coded as 0, 1)

Pre-ART care is the time between a positive HIV diagnosis and ART initiation. This duration defers from patient to patient depending on the health professional's assessment of the patient's readiness to start ART and availability of drugs among other factors. One of the changes in the guidelines has been the reduction of the pre-ART period.

ARV Drug regimen (coded as 0, 1)

This variable captured the ARV drug given to the patient at the start of ART. The regimen is not changed unless the patient shows signs immunological or virological failure. Prior to 2014 a patient could be started on either an AZT-based or a TDF-based regimen as first line. After 2014, for all patients TDF was the first line regimen. It should be noted that those that were doing well on other regimens prior to the change, were not switched to the new regimen. Among the ARV regimens are TDF-3TC-EFV, TDF-FTC-EFV, TDF-3TC-NVP, TDF-FTC-NVP, AZT-3TC-EFV, AZT-3TC-NVP, AZT-3TC-ATV, ABC-3TC-ATV, ABC-3TC-EFV, and other combinations.

Number of ARV pills per day (coded as 0, 1)

We derived the number of ARV pills per day given at ART start by dividing the number of ARV pills given by the total number of days the pills were given.

Cotrimoxazole Prophylaxis (coded as 0, 1)

Cotrimoxazole prophylaxis is given to all HIV positives patients irrespective of whether they started ART or not. This is a key medication for treatment of many bacterial infections that plague PLWH.

Table 1 below is a summary of the all variables and definitions that were used in this study.

Table 1: Measurement Matrix of the Study Variables

Measured Variable	**Aim**	**Definition**
Dependent Variables		
ART Adherence	Aim 1	Binary Outcome: 1= Adherent, 0=Less adherent
Opportunistic Infections	Aim 2	Binary category: 1 =" had an OI", 0= otherwise"
Survival time to death	Aim 3	Time from ART initiation to death/end of study period
Independent Variables		
Demographic characteristics		
Policy change group	All	Binary category: 1=Post-Policy, 0=Pre- policy
Year of ART Initiation	2	Categorical variable: 1=20 12, 2=2013, 3=2014, 4 =2015, 5=2016
Health facility	All	Categorical variable: 1=ART Clinic 1, 2= ART Clinic 2, 3= ART Clinic 3, 4 = ART Clinic 4
Age	All	Binary category: 1 =15-19, 0=20-24
Sex	All	Binary category: 1 =Female, 0=Male
Clinical Characteristics		
Weight	All	Continuous: weight at ART initiation (in kgs)
Had an OI at ART start	2,3	Binary category: 1= had an OI, 0=otherwise
WHO Disease Stage*	All	Categorical variable: 1 = Stage I, 2 = Stage II, 3 =Stage III & IV
Treatment Characteristics		
Duration in pre-ART care	All	Binary variable: 0=<1 month, 1=1 month or more
ARV regimen	All	Binary variable: 1= TDF-based, 0=Non-TDF,
ARV Pills Per Day	1	Binary variable: 1 = 1 pill, 0 =2 pills or more
Cotrimoxazole prophylaxis	1,2	Binary variable: 1= Yes CTX, 0 = otherwise
*This classification is based on the World Health Organization (WHO) clinical staging criteria		

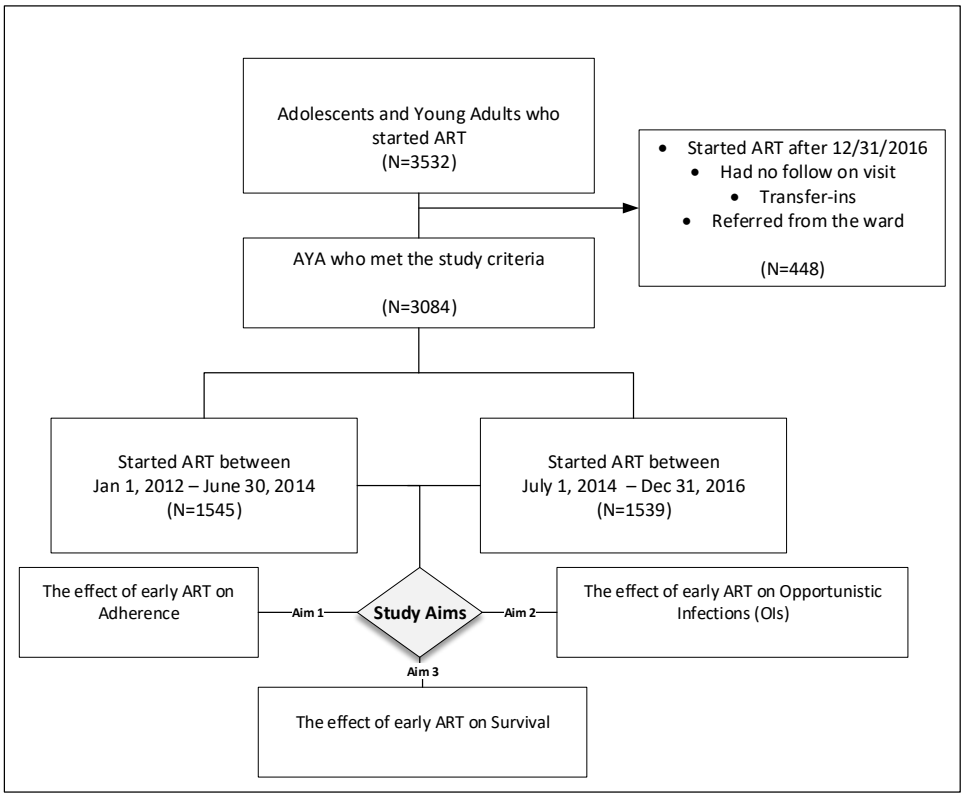
Data Supervision and Management

The dissertation committee provided the overall supervision and management of the study. The researcher supervised the data extraction exercise with the help of data specialists in health records and staff from the participating health facilities. The data was de-identified by generating new study IDs that were used in the analysis for all participants to ensure privacy and confidentiality of the patients' information. The patient clinic IDs were only used in the data cleaning process and quality checks. The data was cleaned using STATA 15.1 and re-coded by the researcher and a trained data manager, to create an analysis file. The abstracted data was encrypted and stored on a password-protected computer of the researcher. The back-up dataset was password-protected too and stored on the UTSPH server in Houston. All study records will be disposed of as required, using the records disposal policies of Baylor-Uganda, Ministry of Health - Uganda and UTSPH.

Data Collection

We extracted existing patient-level data from the electronic medical records databases of the selected health facilities into a Microsoft Excel spreadsheet. The starting point of the data extraction was the date the patient started ART. For those entered into the study cohort, we also extracted their Pre-ART data. The data extraction was done by a trained Health Information Technologist, using a data extraction tool (Appendix 1) and guided by the variables described in the measurement matrix. For quality assurance, we did a reliability check using a random selection of the patient charts. Figure 2 illustrates how the data was extracted.

Figure 2: Data Extraction Plan



Data for 3532 young people was extracted from the databases of one national and three regional referral hospitals. Out of these, 448 young people did not meet the inclusion criteria and were therefore excluded from the analysis. We extracted data on patient clinical information including sex, age, CD4 cell count, WHO disease stage, ARV regimens, ARV pills given per day, cotrimoxazole prophylaxis, and dates of clinic visits. Data on death, LTFU and transfer-outs was also extracted, in addition to data on ART adherence and opportunistic infections recorded during the follow-up clinic visits.

Data Analysis

All statistical analyses were performed using STATA 15.1 (StataCorp LP, College Station, TX, USA) and SAS 9.4 (SAS Institute Inc, Cary, NC, USA). We described patient baseline characteristics using frequencies and percentages for categorical variables, and means and standard deviation, for continuous variables. These were compared using T-tests and Pearson's chi-squared tests, respectively. All p-values were two-tailed and considered statistically significant at α=0.05. To assess associations of each independent variable with the dependent variables, univariable analyses were first performed. We conducted multivariable logistic regression analyses to determine the effect of the change in policy on the study outcomes, controlling for the independent variables at the start of ART. All variables that were statistically significant at p-value <0.25 or had prior clinical significance for the outcomes from the univariable analysis, were included in a multivariable regression model. We checked the correlation between the variables to ensure that none was highly correlated. Possible interactions were also checked. The variables that were included in each of the regression models are described under each aim.

Aim 1: The effect of ART guideline changes on antiretroviral adherence

All the young people who met the selection criteria were included in this analysis. We defined the dependent variable "ART adherence" as the percent adherence for each patient during the first 12 months of starting ART. This was coded as a binary variable, "1" if the patient had an adherence code corresponding to ≥95% adherence and "0" otherwise. An adherence rate of ≥95% is the threshold necessary for sustained clinical effectiveness of ART[9,29,30]. A young

person was considered to be adherent if he/she had a code of “1” for all the months at 3, 6 and 12 months of follow-up. An individual was considered to be less adherent if he/she had a code of “0” for any of the months at 3, 6 and 12 months of follow-up

The independent variable of interest was a binary time variable representing the before and after introduction of the guidelines (pre-policy=0, post-policy=1). The pre-policy group included young people who started ART before July 2014 (January 2012 – June 2014) and the post-policy group included young people who started ART after July 2014 (July 2014-December 2016). The patient **socio-demographic characteristics** included in the regression model were gender, age at ART initiation and health facility providing treatment. The **clinical characteristics** were weight, OI at ART start (Yes, No) and WHO clinical disease stage (I, II, III &IV) at ART start. **The treatment characteristics** included duration in pre-ART care (less than 1 month, 1 month or more), ARV drug regimen (TDF, Non-TDF), the number of ARV pills per day (1 pill, 2 pills or more) given at ART start, cotrimoxazole prophylaxis at ART start (Yes, No).

We used a multivariable Logistic regression model to examine the association between the changes of the ART guidelines and ART adherence. We adjusted the model for the independent variables described above. The variables were assessed at both univariable and bivariable levels to see which factors were associated with the study outcome before fitting them to the final multivariable model, using a p-value of <0.25 and clinical relevance. Possible interactions or effect modifiers were also assessed. The underlying assumptions of regression models were checked.

Aim 2: The effect of ART guidelines changes on opportunistic infections

All the young people who met the selection criteria were included in this analysis. The dependent variable was a disease event diagnosed during a follow-up clinic visit and recorded in the patient's medical record as an opportunistic infection (OI). This was coded as "1" if the patient had an OI during the months after starting ART and "0" if the patient did not have an OI during the months after starting ART. A young person was considered to have an OI if he/she had a code of "1" for any of the months at 3, 6 and 12 months of follow-up. An individual who had an OI at 3 months, was also considered to have an OI at 6 and 12 months.

The independent variable of interest was a binary time variable representing before and after the introduction of the guidelines (pre-2014 policy =0, post-2014 policy=1). The pre-policy group included young people who started ART before July 2014 (January 2012 – June 2014) and the post-policy group included young people who started ART after July 2014 (July 2014-December 2016). We adjusted the regression model for **socio-demographic characteristics** (age at ART start, gender and ART clinic), The **clinical characteristics** were weight, OI at ART start (Yes, No) and WHO clinical disease stage (I, II, III &IV) at ART start. The **treatment characteristics** included duration in pre-ART care (less than 1 month, 1 month or more), ARV drug regimen (TDF, Non-TDF), the number of ARV pills per day (1 pill, 2 pills or more) given at ART start, cotrimoxazole prophylaxis at ART start (Yes, No) and ART adherence (adherent, less adherent) at 3, 6 and 12 months on ART.

We fit a multivariable Logistic regression model to examine the association between the changes in the ART guidelines and occurrence of opportunistic infections. We adjusted the model

for the independent variables described above. We run three separate models at 3 months, 6 months and 12 months to see if early initiation of ART was successful in keeping the infections low. The variables were assessed at both univariable and bivariable levels to see which factors were associated with the study outcome before fitting them to the final multivariable model, using a p-value of <0.25 and clinical relevance. Possible interactions or effect modifiers were also assessed. The underlying assumptions of regression models were checked.

Aim 3: To assess the effect of ART guidelines changes of survival and identify predictors of Survival

Survival was defined as the time between ART initiation and death if it happened before the end of the study period for each group. Young people who were LTFU, transferred out or were alive at the end of the study period were censored. We restricted the follow up period to 36 months after starting ART for each cohort so as to have comparable results. For young people who started ART before the guidelines changed, the censor date was December 2014 and for those that started ART after the guidelines changed, the censor date was June 2016. The variable was coded as "1" if the patient died and "0" otherwise. The independent variable of interest was a time dummy variable representing the pre-and post-policy periods. We adjusted the regression model for **socio-demographic characteristics** (age at the time of death & Gender), **clinical characteristics** (weight, OI at ART start (Yes, No) and WHO clinical disease stage (I, II, III &IV) at ART start) and **treatment characteristics** (duration in pre-ART care (less than 1 month, 1 month or more), ARV drug regimen (TDF, Non-TDF), the number of ARV pills per day (1 pill, 2 pills or

more) given at ART start, cotrimoxazole prophylaxis at ART start (Yes, No). We tested the difference in survival functions of both groups using the log-rank test. We fit a Cox Proportional Hazards regression model to assess the association between ART policy changes and survival, adjusted for the independent variables above. We generated time-to-event data, in months, based on the date of death or end of study. Current age was derived from adding the duration in ART care to the age at ART start and used it as a time-varying variable. The variables were selected using a p-value of <0.25 and clinical relevance. We checked the underlying model assumptions of the proportional hazards model using the model-based test for time by log (t) interaction.

Human Subjects Considerations

Informed Consent/Assent was waived for this study because there was no contact with or direct participation of patients. A waiver of consent was obtained for the charts reviewed for quality assurance. Each study participant was assigned a de-identified unique number that was used for analysis. The study was approved by the Makerere University School of Public Health, Uganda National Council of Science and Technology, Baylor College of Medicine's Institutional Review Board, and Committee for the Protection of Human Subjects at the University of Texas Health Sciences Center at Houston.

JOURNAL ARTICLE 1

Effect of Antiretroviral Therapy Policy Change on ART Adherence among Young People living with HIV in Uganda.

Abstract

Objectives: Although changes in treatment policy has led to initiation of antiretroviral therapy (ART) before onset of advanced disease resulting in better treatment outcomes, it has implications on long term adherence among young people. We evaluated the effect of such a policy change on ART adherence among young people, aged 15-24 years in Uganda.

Methods: This retrospective analysis of young people living with HIV, 15-24years old, who started ART from January 2012 – December 2016 used administrative data from the District Health Information System (DHIS2) and the national referral hospital's EMR. Multivariable logistic regression was used to assess the effect of the changes in policy on ART adherence among those who started treatment before and after the guidelines changed.

Results: ART adherence was affected by the health facility providing ART and having an opportunistic infection at the start of ART. The policy change did not have an effect on ART adherence. Although the percentage of adherent young people decreased at 3, 6 and 12 months, it increased for the less adherent young people.

Conclusion: This study found that ART adherence among young people was mainly driven by differences between health facilities providing ART and having an OI at ART start. ART adherence declined over time. Therefore, whereas initiating treatment before onset of advanced disease is beneficial, the implications on long term adherence cannot be overlooked.

Introduction

The current decade has seen an exponential increase in the number of people on life saving anti-retroviral medication[1,3,33]**.** The WHO estimates that ART has saved 11.4 million lives worldwide over the last decade[34]. Despite these achievements, Uganda still has a high HIV-related disease burden with a prevalence rate of nearly 4% among young people 15-24 years[3]. There is also an increasing number of children who were prenatally infected with HIV, surviving into adulthood[17]. A rise in new infections and AIDS-related deaths among this age group became a concern among health professionals and policy makers. Within this context there were efforts to maximize ART for HIV treatment and improve patient outcomes by revising policies to initiate ART early in the course of the illness. With initiation at a higher CD4 count threshold, ART can prevent the majority of these infections and deaths given the evidence it has greatly reduced morbidity and mortality among HIV-infected individuals[3-8]. However, the success of ART relies on sustaining high levels of ART adherence for viral suppression[9,10].

Although high income countries adopted the "test and treat strategy" as early as the year 2000, low- and middle-income countries (LMICs) used a more gradual approach due to cost implications and projected demands on already weak healthcare systems. Uganda adopted the 2013 ART guidelines in July 2014 and started initiating ART for all young people at CD4 cell count ≤500 cells/mm^3, using a once-a day fixed-dose combination regimen. Despite increased ART coverage, the threat posed by a higher treatment burden cannot be overlooked[15, 20,31,49,50]. This also raises medication adherence concerns in a population that has been widely reported to have poor adherence[11-15]. This age group has lower ART adherence rates, mortality rates are not

decreasing as in other age groups and there is a rise in new infections[8,16]. Furthermore, knowing that early initiation means that young people are staying on ART longer than adults, it is important to examine the implications of these policy changes on their adherence.

Few studies have examined ART adherence among young people in sub-Saharan Africa and Uganda[15,35-37]**.** However, none of them have assessed the effect of the changes in ART policy on adherence in this age group and the implications on future HIV programs. We therefore assessed the effect of such a policy change on ART adherence.

Methods

Study Design and Data source

We conducted a retrospective cohort study comparing young people who started ART in the period July 1st, 2014 to December 31st, 2016 to a historical cohort that was treated in January 1st, 2012 to 30th June 2014 before the policy change. We used administrative data from the District Health Information System (DHIS2) and the national referral hospital's EMR. This data, routinely collected from patients who receive HIV treatment at the health facilities during clinic visits, is used to plan and monitor a patient's treatment from the date of HIV diagnosis to the date he/she leaves the clinic either through transfer-out to another clinic, lost to follow-up (LTFU) or death.

Study Cohort

All individuals that were 15-24 years old at the time of ART initiation were included in the study. We also included young people who had been diagnosed prior to or during the study period but had not started ART. They also had at least 2 visits of follow-up data, started ART at the selected ART clinics and were on lifelong ART. Patients who were LTFU or transferred-out were considered for the period when they were in care. We excluded patients who were lost-to- follow-up before the start of the study period, started ART for Pre-exposure prophylaxis (PrEP) because it is short term, had no records, and had started ART elsewhere (transfer-in) for lack of information from the referral health facility. We also excluded patients who had no follow up visit after ART initiation.

Dependent Variable

The dependent variable "ART adherence" was defined as the percent adherence for each patient during the first 12 months of starting ART. This was coded as a binary variable, "1" if the patient had an ART adherence code corresponding to ≥95% adherence and "0", otherwise. An adherence rate of ≥95% is the threshold necessary for sustained clinical effectiveness of ART[9,29,30]. A young person was considered to be adherent if he/she had a code of "1" for all the months at 3, 6 and 12 months of follow-up. An individual was considered to be less adherent if he/she had a code of "0" for any of the months at 3, 6 and 12 months of follow-up.

Independent Variables

The independent variable of interest was a binary time variable representing the before and after introduction of the guidelines (pre-policy=0, post-policy=1). The pre-policy group included young people who started ART before July 2014 (January 2012 – June 2014) and the post-policy group included young people who started ART after July 2014 (July 2014-December 2016). The socio-demographic variables were ART clinic, gender and age at ART start. The clinical characteristics were weight, OI at ART start (Yes, No) and WHO clinical disease stage (I, II, III &IV) at ART start. The treatment characteristics included duration in pre-ART care (less than 1 month, 1 month or more), ARV drug regimen (TDF, Non-TDF), the number of ARV pills per day (1 pill, 2 pills or more) given at ART start, cotrimoxazole prophylaxis at ART start (Yes, No).

Analysis

All statistical analyses were performed using STATA 15. The unit of analysis was the patient. We described and compared patient characteristics using T-tests and Pearson's chi-squared tests, respectively (Table 1). All p-values were two-tailed and considered statistically significant at $\alpha=0.05$. We examined the data to ensure that there were no sparse cells. The duration in pre-ART care was right-skewed and we categorized it to reduce on the wide variability between patients and have more interpretable cutoff points. To assess associations of each independent variable with the dependent variable, ART adherence, univariable analyses were first performed. We conducted multivariable logistic regression analyses to determine the effect of the change in policy on ART adherence, controlling for variables at the start of ART that

included age, sex, weight, WHO clinical disease stage, duration in pre-ART care, ARV regimen and ARV pills per day given. All variables that were statistically significant at p-value <0.25 or had prior clinical significance for ART adherence from the univariable analysis, were included in a multivariable regression model. We checked the correlation between the variables to ensure that none was highly correlated. Possible interactions were also checked and none of them was significant. We report the unadjusted and adjusted odds ratios, and 95% confidence intervals in Table 3.

IRB approval

The study was approved by the Makerere University School of Public Health, Uganda National Council of Science and Technology, Baylor College of Medicine's Institutional Review Board, and Committee for the Protection of Human Subjects at the University of Texas Health Sciences Center at Houston.

Results

Out of a total of 3532 young people who were initiated on ART in the study period across the four study sites, 448 did not meet the inclusion-exclusion criteria and were excluded from this analysis. Of the remaining 3084 patients, 50.1% started ART before and 49.9% started ART after the policy change. In both groups, young people were more likely to be female and of older age (20-24 years)**.** They were less likely to have an OI at the start of treatment, but the percentage was higher in the pre-policy group (23.54%) compared to the post-policy group (18.60%).

Although young people were more likely to be disease stage I or II at ART stage, the post-policy group had a bigger percentage of stage I and less stage II patients compared to the pre-policy group. The group differences were significant. Concerning treatment characteristics, starting treatment in less than a month of testing HIV positive was observed in both groups. However, the post-group had more numbers (93.17%) compared to the pre-group (88.23). On further analysis, 43.54% in the post-group started ART the same day they tested HIV positive compared to 29.12% in the pre-group. Post-policy young people were more likely to be given a TDF-based regimen (93%), one pill a day (86%) compared to the pre-policy group (66% & 45%, respectively). The pre-policy group was also more likely to be given non-TDF regimen (34.35%) and 2 or more pills per day (54.66%) compared to the post-group (7.41% & 14.43%, respectively).

Regarding our study outcome, we found that although overall more than 80% of young people were adherent at 3, 6 and 12 months of follow-up, we observed a gradual decline in both groups over time (Figures 3 & 4). There were no significant group differences at any of time points.

In both the unadjusted and adjusted models, the policy did not have an effect on ART adherence (Table 3). Age at ART start, WHO disease stage and the number of ARV pills per day were only statistically significant in the unadjusted models at all three time points. Gender did not have an effect on ART adherence, as were weight at ART start, and cotrimoxazole prophylaxis in all models. Younger age (15-19 years) was only significant in the unadjusted model and was associated with being less adherent. In the adjusted model, only the ART clinic providing the treatment had an effect on ART adherence at 3, 6 and 12 months on ART. In both the unadjusted

and adjusted model, young people in clinics 2, 3, and 4 more likely to be adherent compared to the young people receiving treatment in ART clinic 1. Also, after controlling for the independent variables in the model, young people who had an OI at ART start were more likely to be adherent compared to young people who did not have an OI at ART start, at 6 months (AOR 1.60, 95% CI: 1.16, 2.21) and 12 months (AOR 1.34, 95% CI: 1.01, 1.77) on ART. This result was statistically significant. Young people who had disease stage II, III and IV disease had lesser odds of being adherent compared to those with stage I at ART start. The odds reduced as severity of disease increased. Young people who were in pre-ART care for more than one month had a very significant effect on ART adherence only in the unadjusted models, similar to young people who were given one ARV pill per day.

Table 2: Descriptive Statistics of Young People who started ART before and after the Policy Change

Characteristic	Pre-2014 policy	Post-2014 policy
Total	**1546**	**1538**
Dependent Variable		
ART Adherence		
3 months		
Adherent	89.11%	88.46%
Less Adherent	10.89%	11.54%
6 months		
Adherent	85.98%	84.80%
Less Adherent	14.02%	15.20%
12 months		
Adherent	82.21%	79.43%
Less Adherent	17.79%	20.57%
Independent Variables		
Policy change group		
Pre-Policy	50.13%	
Post- Policy		49.87%
Year of ART initiation		
2012 (reference)	28.78%	
2013	47.54%	
2014	23.67%	27.57%
2015		36.74%
2016		35.70%
Socio-Demographic Characteristics		
Age at ART start in years (%)		
15-19	28.91%	28.67%
20-24	71.09%	71.33%
Gender (%)		
Male	14.81%	13.72%
Female	85.19%	86.23%

Characteristic	Pre-2014 policy	Post-2014 policy
Total	**1546**	**1538**
Weight at ART start in kgs (mean, SD)	55.26(10.15)	55.45(9.30)
Health Facility (%)		
ART clinic 1	15.46% *	16.64% *
ART clinic 2	39.72% *	31.99% *
ART clinic 3	10.93% *	10.14% *
ART clinic 4	33.89% *	41.22% *
Clinical Characteristics		
Had an OI at ART Start (%)		
Yes	23.54% *	18.60% *
No	76.46% *	81.40% *
WHO disease stage at ART start (%)		
Stage I	57.32% *	75.36%*
Stage II	32.25% *	17.30% *
Stage III & IV	10.43% *	7.34% *
Treatment Characteristics		
Duration in Pre –ART care in months (%)		
<1 month	88.23% *	93.17% *
1 month +	11.77% *	6.38% *
ARV regimen given at ART start (%)		
TDF	65.65% *	92.59% *
Non-TDF	34.35% *	7.41% *
ARV pills per day at ART start (%)		
1 pill	45.34% *	85.57% *
2 pills or more	54.66% *	14.43% *
Cotrimoxazole Prophylaxis at ART start (%)		
Yes	97.67% *	99.09% *
No (reference)	2.33% *	0.91% *

*Significant at P<0.05

Figure 3: Trends of Adherent Young by Year of ART Initiation, before and after Policy Change

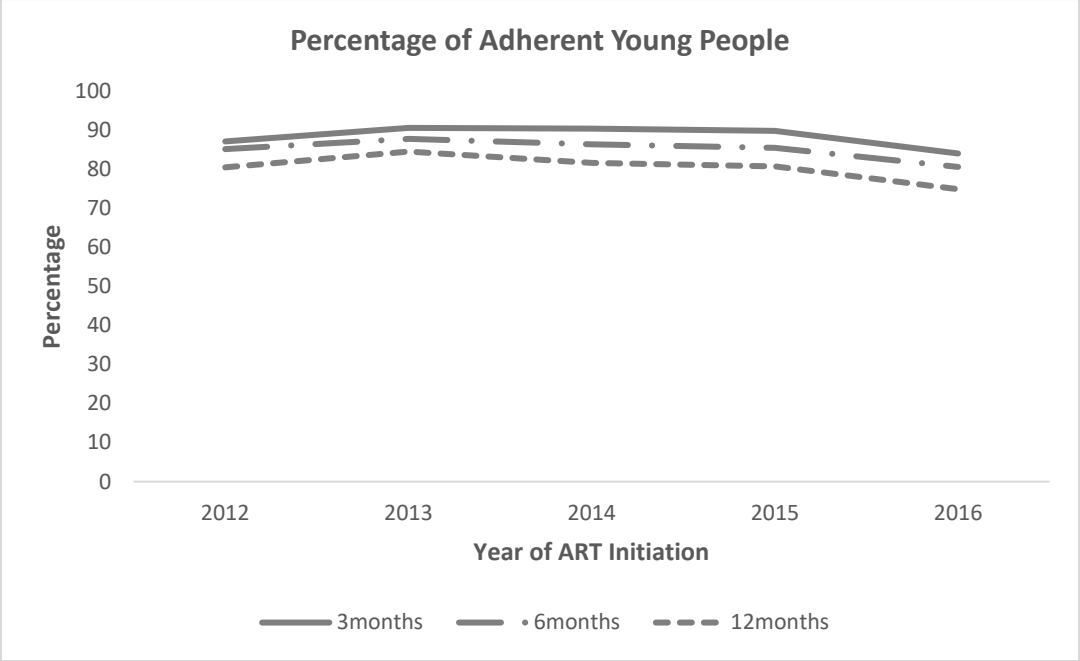


Figure 4: Trends of Less Adherent Young by Year of ART Initiation, before and after Policy Change

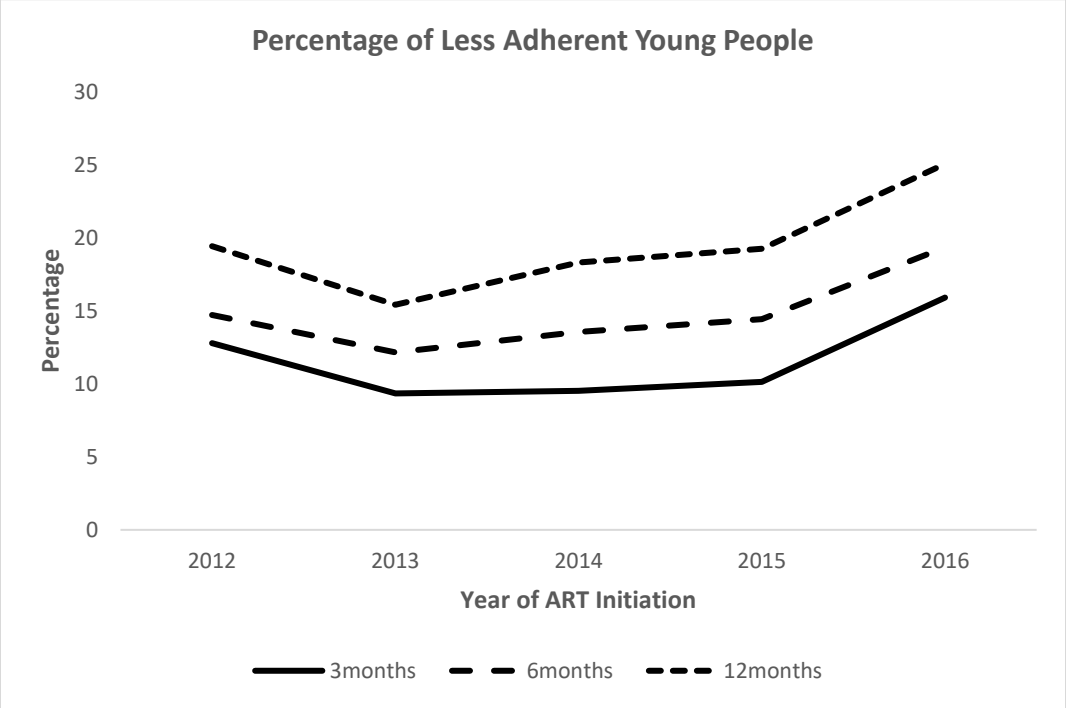


Table 3: The Effect of the Independent Variables on ART Adherence among Young People before and after the Policy Change

	3 months after ART start		6 months after ART start		12 months after ART start	
	Unadjusted Model OR (95% CI)	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**
Policy Change Group						
Pre/Post Group						
Pre-2014 policy	Reference	Reference	Reference	Reference	Reference	Reference
Post-2014 policy	0.95 (0.74, 1.21)	0.99 (0.73, 1.35)	0.92 (0.75, 1.14)	0.95 (0.73, 1.25)	0.84 (0.70, 1.02)	0.84 (0.66, 1.07)
Patient socio-demographic characteristics						
Age at Art start (years)						
15-19	**0.53 (0.41, 0.68) ****	1.13 (0.83, 1.55)	**0.57 (0.46, 0.71) ****	1.13 (0.85, 1.50)	**0.61 (0.50, 0.74) ****	1.12 (0.87, 1.45)
20-24	Reference	Reference	Reference	Reference	Reference	Reference
Gender						
Male	0.94 (0.67, 1.31)	1.11 (0.75, 1.64)	0.93 (0.69, 1.24)	1.09 (0.77, 1.55)	0.99 (0.76, 1.29)	1.18 (0.86, 1.63)
Female	Reference	Reference	Reference	Reference	Reference	Reference
ART Clinic						
ART Clinic 1	Reference	Reference	Reference	Reference	Reference	Reference
ART Clinic 2	**16.66 11.42, 24.31) ****	**21.98 (13.58, 35.59) ****	**16.48 (11.82, 22.99) ****	**22.67 (14.65. 35.07) ****	**16.81 (12.47, 22.67) ****	**25.23 (16.73, 38.03) ****
ART Clinic 3	**4.84 (3.02, 7.78) ****	**6.27 (3.50, 11.22) ****	**4.74 (3.19, 7.03) ****	**6.42 (3.89, 10.62) ****	**4.13 (2.94, 5.80) ****	**5.53 (3.53, 8.67) ****
ART Clinic 4	**11.37 (8.14, 15.87) ****	**14.25 (9.24, 21.97) ****	**8.49 (6.44, 11.20) ****	**11.47 (7.80, 16.85) ****	**7.86 (6.11, 10.10) ****	**11.14 (7.72, 16.07) ****
Patient Clinical Characteristics						
Weight at ART start	1.01 (1.00, 1.03)	1.00 (0.99, 1.02)	1.01 (1.00, 1.02)	1.00 (0.99, 1.01)	**1.01 (1.00, 1.02) ****	1.00 (0.99, 1.01)
Had an OI at ART Start						
Yes	1.15 (0.84, 1.56)	1.31 (0.92, 1.86)	1.25 (0.95, 1.64)	**1.60 (1.16, 2.21) ****	1.10 (0.87. 1.39)	**1.34 (1.01, 1.77) ***
No	Reference	Reference	Reference	Reference	Reference	Reference
WHO Disease Stage at ART start						
Stage I	Reference	Reference	Reference	Reference	Reference	Reference
Stage II	**0.67 (0.51, 0.89) ****	1.24 (0.88, 1.74)	**0.71 (0.56, 0.91) ****	1.21 (0.89, 1.64)	**0.72 (0.58, 0.90) ****	1.18 (0.89, 1.55)
Stage III & IV	**0.60 (0.40, 0.90) ****	0.90 (0.54, 1.50)	**0.58 (0.41, 0.83) ****	0.79 (0.50, 1.25)	**0.60 (0.43, 0.83) ****	0.76 (0.50, 1.16)

	3 months after ART start		6 months after ART start		12 months after ART start	
	Unadjusted Model OR (95% CI)	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**
Patient's Treatment Characteristics						
Duration in Pre-ART care						
< 1 month	Reference	Reference	Reference	Reference	Reference	Reference
One Month or more	**0.16 (0.12, 0.21) ****	1.28 (0.85, 1.94)	**0.17 (0.13, 0.22) ****	1.31 (0.88, 1.95)	**0.18 (0.14, 0.23) ****	1.42 (0.95, 2.12)
ARV Regimen at ART start						
TDF	0.83 (0.61, 1.13)	1.15 (0.75, 1.77)	0.87 (0.66, 1.13)	1.20 (0.82, 1.77)	0.87 (0.69, 1.10)	1.15 (0.81, 1.62)
Non-TDF	Reference	Reference	Reference	Reference	Reference	Reference
ARV Pills per day						
1 pill	**0.77 (0.59, 1.00) ***	1.03 (0.70, 1.52)	**0.78 (0.62, 0.98) ***	1.04 (0.73, 1.46)	**0.81 (0.66, 0.99) ***	1.20 (0.88, 1.63)
2 pills or more	Reference	Reference	Reference	Reference	Reference	Reference
Cotrimoxazole prophylaxis at ART start						
Yes	0.76 (0.23, 2.51)	0.57 (0.07, 4.39)	1.06 (0.44, 2.55)	0.94 (0.27, 3.28)	0.81 (0.36, 1.84)	0.76 (0.25, 2.29)
No	Reference	Reference	Reference	Reference	Reference	Reference

*Significant at p-value 0.05
**Significant at p-value 0.01

Discussion

This study gives an insight into the effect of 2014 ART policy change on ART adherence among young people, ages 15-24 years in Uganda. Our study found that ART adherence declined as the duration on ART increased. Whereas the percentage of adherent young people decreased at 3, 6 and 12 months, it increased for the less adherent young people (Figure 3 & 4). The increase is observed more in young people who initiated ART in 2015 and 2016. This could be attributed to inadequate preparation of young people for ART especially in the post-policy period where the duration between HIV diagnosis and ART initiation was reduced. Our study had more than 40% young people that started ART the same day they were diagnosed with HIV and could have contributed to this result. Given that the success of HIV care is dependent on the patient's right and willingness to accept or defer treatment[39], we can therefore argue that these young people may not have grasped the implications of the lifelong ART whose success depends on maintaining high levels of adherence to keep the viral load low. Our findings are similar to other studies that have reported poor ART adherence among relatively healthier patients starting ART early[40],[41,42]. We also know that one's attitude and perceptions have an effect on health behavior[43]. Some may not realize the importance of daily medication since they do not feel sick and some may still have the belief that starting ART is a death sentence as has been reported elsewhere[25,26]. Therefore, health professionals need to emphasize the importance of adhering to the daily medication and the benefits of ART when initiating treatment in young people.

Contrary to expectation, in our study the policy change did not have an effect on ART adherence. However, we found the ART clinic providing treatment was the main driver of ART

adherence at 3, 6 and 12 months. In the Donabedian model, structure is defined as "the conditions under which care is provided, including material resources, human resources, and organizational characteristics"[42]. In order to provide quality HIV treatment, adequate physical and human resources have to be available. Given that there was variability in how adherence is measured, staffing levels, infrastructure and location of the ART clinics involved in the study, though not the focus of this study, this may have influenced our results. In our study ART adherence differs by health facility and therefore more research is needed to identify those factors contributing to this result.

We also found that having an OI at ART start had an effect on ART adherence at 6 and 12 months, after adjusting for other variables in the model. Young people who had an OI at ART start had 60% and 34% higher odds of being adherent at 6 and 12 months on ART compared to young people who did not have an OI at ART start. Although having an OI at ART start increases the chances of complications that are common during the first months on ART[44], the desire to be healthier and stronger may be the motivation to adhere to treatment.

This study had a number of strengths. To our knowledge this is the first study to evaluate the effect of changes in ART policy on ART adherence among young people in Uganda. We had a large study cohort of young people from 4 large volume HIV clinics that are representative of the 4 geographical regions in Uganda. The different regions capture the regional variation and therefore increase generalizability of the study results. Our results must however be interpreted in light of several limitations. We did not capture socio-demographic data on education and marital status which may or may not have yielded different results given younger age was

associated with being in school and the older young people were more likely to be married. The variability in adherence measurement may have limited our ability to provide more generalizable results. Despite the limitations the study results are still generalizable to high volume health facilities in Uganda.

Conclusion

This study found that ART adherence among young people was mainly driven by differences between health facilities providing ART in Uganda and whether an individual had an OI at ART start. Although our study did not find an effect between policy change and ART adherence, young people starting ART much earlier will lead to a higher treatment burden, and this might negatively impact ART adherence over time. Therefore, whereas initiating treatment before onset of advanced disease is beneficial, the implications on long term adherence cannot be overlooked. We believe that there are factors influencing adherence that are not captured by our study, that need further investigation.

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JOURNAL ARTICLE 2

The Effect of Changes in Antiretroviral Therapy Policy on Opportunistic Infections among Young People living with HIV in Uganda.

Abstract

Objectives: For optimal benefits of life-saving antiretroviral therapy (ART) for people living with the Human Immunodeficiency Virus (HIV), the ART eligibility criterion has continually been revised to start treatment before advanced disease stages. We evaluated the effect of the changes in the ART policy on opportunistic infections among young people, aged 15-24 years.

Methods: This was a retrospective analysis of young people living with HIV, 15-24years old, who started ART from January 2012 – December 2016. This study used administrative data from the District Health Information System (DHIS2) and the national referral hospital. We compared young people who started ART before and after the policy change and assessed the effect of that change on opportunistic infections, using multivariable logistic regression.

Results: On average, young people who started ART after the policy change had lesser odds of having an OI compared to those who started ART before the policy at 3, 6 and 12 months on ART. Age, the health facility, weight, and WHO disease stage were also associated with having OIs, as well as duration in pre-ART care, ARV regimen and number of pills per day. Cotrimoxazole prophylaxis did not have an effect on OIs.

Conclusion: Post-Policy young people were less likely to have OIs compared those who started ART before the policy change. OIs declined over time. The positive trend is attributable to early ART initiation, with less advanced disease, in addition to the use of more potent ARVs. However,

there are still OIs that persist among PLWH and further research will help identify them and design interventions to mitigate the problem.

Introduction

Despite the introduction of life-saving antiretroviral therapy (ART) for treatment and prevention of the Human Immunodeficiency Virus (HIV), it continues to be a public health threat in sub-Saharan Africa. In Uganda, the 4% prevalence rate among young people, the increase in new infections and number of children who were perinatally infected with HIV becoming adolescents and adults, is a concern for health professionals and policy makers[3]. AIDS-related mortality is still high and opportunistic infections (OI) are still a major cause of death among those whose treatment is not keeping their viral load low enough to fight off infections. Between 2005 and 2012, the number of deaths among this age group increased by 50% whereas overall it had decreased by 30%[48]. It is within this context that efforts were made to maximize the benefits of ART by revising policies to initiate treatment before the onset of advanced disease. With initiation at a higher CD4 count threshold, ART can prevent the majority of these infections and deaths [3-8]. The WHO estimates that ART has saved 11.4 million lives worldwide over the last decade[34].

Whereas high income countries started initiating ART for all people living with HIV/AIDS immediately after diagnosis, as early as the year 2000, it was not the case for low- and middle-income countries (LMICs). LMICs adopted a more gradual approach to the test and treat strategy considering cost and demands it would place on already weak healthcare systems. In July 2014, Uganda adopted the 2013 ART guidelines. All young people were initiated on ART at CD4 cell

count ≤500 cells/mm^3 regardless of clinical disease stage, using once-a day fixed-dose combination regimens. Despite the increased ART coverage, the threat posed by a higher treatment burden in addition to poor adherence cannot be overlooked. Opportunistic infections still exist among young people and these negatively affect their quality of life and increase the risk of death[15,31,34,49,50]

Although several studies have assessed the OIs, they focused more on infants, children and adults and less on young people. In addition, OIs vary by region and age. Providing country-specific data will help define local priorities, reduce barriers to, and improve treatment outcomes. We therefore evaluated the effect of the changes in the 2014 ART policy on opportunistic infections among young people, aged 15-24 years in Uganda.

Methods

Study Design and Data Source

For this retrospective cohort study, we used administrative data from the District Health Information System (DHIS2) and the national referral hospital's EMR. We compared young people who started ART in the period July 1st, 2014 to December 31st, 2016 to a cohort that was treated in January 1st, 2012 to 30th June 2014 before the policy change. This data, routinely collected from patients who receive HIV treatment at the ART clinics during routine visits, is used to monitor a patient's treatment from the date of HIV diagnosis to the date he/she leaves the clinic either through transfer-out to another clinic, lost to follow-up (LTFU) or death.

Study Cohort

We included all individuals that were 15-24 years old at the time of ART initiation. Young people diagnosed prior to or during the study period but had not started ART, were also included in the study. Those who had at least 2 visits of follow-up data, started ART at the selected ART clinics and were on lifelong ART were included. Young people who were LTFU or transfer-out during the study period were included because they contributed time until the event happened. However, we excluded patients who were lost- to- follow-up before the start of the study period and those on Pre-exposure prophylaxis (PrEP) because it is short term. Individuals with no records, and had started ART elsewhere were excluded because of lack of information from the referral clinic. Patients who had no follow-up visit after ART initiation were also excluded.

Dependent Variable

We defined the dependent variable "opportunistic infection" as a disease event diagnosed during a clinic visit and recorded in the patient's medical record as an OI. This was coded as a binary variable, "1" if the patient had an OI during the months after starting ART and "0" otherwise. A young person was considered to have an OI if he/she had a code of "1" for any of the months at 3, 6 and 12 months of follow-up. An individual who had an OI at 3 months, was also considered to have an OI at 6 and 12 months.

Independent Variables

One of the independent variables of interest was a binary time variable (pre-2014 policy =0, post-2014 policy=1). The other independent variable of interest was the year of ART initiation (2012, 2013, 2014, 2015, 2016). The pre-policy group included young people who started ART from January 2012 – June 2014 and the post-policy group included those who started ART from July 2014-December 2016. The socio-demographic variables were ART clinic, gender and age at ART start. The clinical characteristics were weight, OI at ART start (Yes, No) and WHO clinical disease stage (I, II, III&IV) at ART start. The treatment characteristics included duration in pre-ART care (less than 1 month, 1 month or more), ARV drug regimen (TDF, Non-TDF), the number of ARV pills per day (1 pill, 2 pills or more) given at ART start, cotrimoxazole prophylaxis at ART start (Yes, No) and ART adherence (adherent, less adherent) during the follow-up time after starting ART.

Analysis

All statistical analyses were performed using STATA 15. We described and compared patient characteristics using T-tests and Pearson's chi-squared tests, respectively (Table 4). All p-values were two-tailed and considered statistically significant at $\alpha=0.05$. To assess associations of each independent variable with the dependent variable, opportunistic infection, univariable analyses were first performed. We conducted multivariable logistic regression analyses to determine the effect of the change in policy on opportunistic infections, controlling for all the independent variables mentioned above. All variables that were statistically significant at p-value <0.25 or had prior clinical significance for OIs from the univariable analysis, were included in the multivariable

regression models. We checked the correlation between the variables to ensure that none was highly correlated. Possible interactions were also checked and none of them was significant. We run three separate regression models at 3 months, 6 months and 12 months to see if the change in policy was successful in keeping the infections low. We report the unadjusted and adjusted odds ratios, and 95% confidence intervals in Table 2.

IRB approval

The study was approved by the Makerere University School of Public Health, Uganda National Council of Science and Technology, Baylor College of Medicine's Institutional Review Board, and Committee for the Protection of Human Subjects at the University of Texas Health Sciences Center at Houston.

Results

This analysis included data from 3084 young people who met the inclusion-exclusion criteria out of 3532. 50.13% of these started ART before and 49.87% started ART after the policy change. Although there were no significant group differences in age at ART start and gender, young people were more likely to be older (20-24 years) and female. The number of young people initiating ART was different between clinics, but within the clinics there was not much difference, pre- and post- policy. More than 76% of young people did not have an OI at ART initiation in both groups. But among those who had an OI, the pre-policy group was bigger (23.54%) compared to 18.60% in the post-policy group. 57% pre-policy and 75% post-policy young people started ART

with stage I disease. The pre-policy group had more young people (32%) starting ART with stage II disease compared to post-policy group (17%). In both groups, ART initiation was in less than a month of testing HIV positive. However, the post-policy group had a bigger percentage (93%) compared to the pre-policy group (88%). A sub-analysis showed that among those who started ART in less than a month, nearly 50% in the post-group and 30% in the pre-group started ART the same day they tested positive for HIV. More young people in the pre-policy group (11.77%) stayed in pre-ART care more than a month. Post-policy young people were more likely to be given a TDF-based regimen (93%) and one pill a day (86%). Almost all the young people in both groups were given cotrimoxazole prophylaxis at ART start.

With regards to our study outcome, there were significant group differences between young people who had an OI at 3, 6 and 12 months after starting ART. The percentage of young people with OIs declined especially after the policy changed in 2014 (Figure 5).

Starting ART pre-policy or post-post was significantly associated with having an OI at all three time points, in the unadjusted models at 3 and 6 months on ART and in both the unadjusted and adjusted models at 12 months on ART. Post-policy young people had less odds of having an OI after starting ART and these odds continued to decline over time (Table 5 and 6). Younger age (15-19 years) was associated with lesser odds of having an OI in all the three unadjusted models. But the odds did not change over time. Male young people had higher odds of having an OI in the unadjusted models. There were significant differences between the ART clinics providing treatment. Young people who received treatment at ART clinic 3 had lesser odds of OIs and those at clinics 2 and 4 had higher odds of OIs compared to those in clinic 1. Having an OI at ART start

increased the odds of having one after ART initiation in all 6 models. WHO disease stage was significant in all the models and at all the time points. Young people with disease stage II, III and IV at ART start had higher odds of having an OI compared to young people with stage I, and the odds declined over time. Young people who started ART a month or more after being diagnosed with HIV, had higher odds of having an OI compared to those with a shorter duration in pre-ART. Whereas ARV regimen and the number of pills per day given at ART start had an effect on OIs, cotrimoxazole prophylaxis did not.

Table 4: Descriptive Statistics of Young People who started ART before and after the Policy Change

Characteristic	Total	Pre-2014 policy	Post-2014 policy
	1546	**1546**	**1538**
Dependent Variable			
Had on OI			
3 months			
Yes		48.05%	35.84%
No		51.95%	64.16%
6 months			
Yes		54.02%	40.54%
No		45.98%	59.46%
12 months			
Yes		60.77%	44.97%
No		39.23%	55.03%
Independent Variables			
Policy change group			
Pre-Policy		50.13%	
Post- Policy			49.87%
Year of ART initiation			
2012 (reference)		28.78%	
2013		47.54%	
2014		23.67%	27.57%
2015			36.74%
2016			35.70%
Socio-Demographic Characteristics			
Age at ART start in years (%)			
15-19		28.91%	28.67%
20-24		71.09%	71.33%
Gender (%)			
Male		14.81%	13.72%
Female		85.19%	86.23%
Weight at ART start in kgs (mean, SD)		55.26(10.15)	55.45(9.30)
Health Facility (%)			
ART clinic 1		15.46% *	16.64% *
ART clinic 2		39.72% *	31.99% *

Characteristic	Pre-2014 policy	Post-2014 policy
Total	**1546**	**1538**
ART clinic 3	10.93% *	10.14% *
ART clinic 4	33.89% *	41.22% *
Clinical Characteristics		
Had an OI at ART Start (%)		
Yes	23.54% *	18.60% *
No	76.46% *	81.40% *
WHO disease stage at ART start (%)		
Stage I	57.32% *	75.36%*
Stage II	32.25% *	17.30% *
Stage III & IV	10.43% *	7.34% *
Treatment Characteristics		
Duration in Pre –ART care in months (%)		
<1 month	88.23% *	93.17% *
1 month +	11.77% *	6.38% *
ARV regimen given at ART start (%)		
TDF	65.65% *	92.59% *
Non-TDF	34.35% *	7.41% *
ARV pills per day at ART start (%)		
1 pill	45.34% *	85.57% *
2 pills or more	54.66% *	14.43% *
Cotrimoxazole Prophylaxis at ART start (%)		
Yes	97.67% *	99.09% *
No (reference)	2.33% *	0.91% *
ART Adherence at 3 months		
Adherent	89.11%	88.46%
Less Adherent	10.89%	11.54%
ART Adherence at 6 months		
Adherent	85.98%	84.80%
Less Adherent	14.02%	15.20%
ART Adherence at 12 months		
Adherent	82.21%	79.43%
Less Adherent	17.79%	20.57%

*Significant at P<0.05

Figure 5: Trends in Percentage of Young People with Opportunistic Infections at 3, 6 and 12 Months after ART Initiation

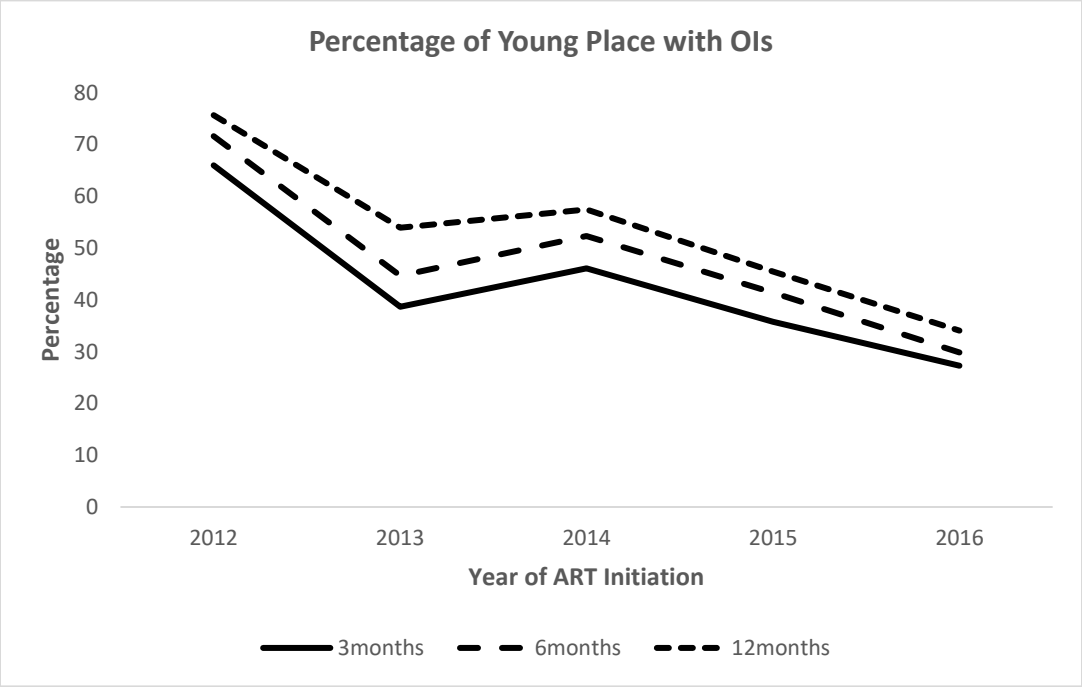

Table 5: The Effect of the Independent Variables on Opportunistic Infections among HIV Positive Young People on ART, before and after the 2014 ART Policy Change

	3 months after ART start		6 months after ART start		12 months after ART start	
	Unadjusted Model OR (95% CI)	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**
Policy Change Group						
Pre/Post Group						
Pre-2014 policy	Reference	Reference	Reference	Reference	Reference	Reference
Post-2014 policy	**0.60(0.52, 0.70) ****	0.85 (0.70, 1.05)	**0.58 (0.50. 0.67) ****	0.82 (0.67, 1.00)	**0.53 (0.46, 0.61) ****	**0.70 (0.58, 0.85) ****
Patient socio-demographic characteristics						
Age at Art start (years)						
15-19	0.88(0.75, 1.04)	**0.77 (0.63, 0.95) ***	0.88 (0.76, 1.03)	**0.77 (0.63, 0.95) ***	0.87 (0.74, 1.02)	**0.77 (0.63, 0.93) ****
20-24	Reference	Reference	Reference	Reference	Reference	Reference
Gender						
Male	**1.64 (1.34, 2.01) ****	1.12 (0.86, 1.47)	**1.66 (0.35, 2.04) ****	1.15 (0.89, 1.50)	**1.55 (1.26, 1.92) ****	1.10 (0.85, 1.42)
Female	Reference	Reference	Reference	Reference	Reference	Reference
ART Clinic						
ART Clinic 1	Reference	Reference	Reference	Reference	Reference	Reference
ART Clinic 2	**0.76 0.62, 0.95) ****	1.18 (0.80, 1.75)	**0.73 (0.59, 0.91) ****	1.25 (0.86, 1.84**)**	**0.73 (0.59, 0.91) ****	**1.08 (0.75, 1.56)**
ART Clinic 3	**0.38 (0.28, 0.52) ****	**0.43 (0.26, 0.70) ****	**0.40 (0.30, 0.54) ****	**0.51 (0.32, 0.81) ****	**0.43 (0.32, 0.58) ****	**0.52 (0.34, 0.82) ****
ART Clinic 4	0.92 (0.75, 1.14)	**1.88 (1.28, 2.78) ****	0.94 (0.76, 1.16)	**2.09 (1.43, 3.06) ****	0.98 (0.79, 1.21)	**1.81 (1.26, 2.61) ****
Patient Clinical Characteristics						
Weight at ART start	**0.97 (0.97, 0.98) ****	**0.99 (0.98, 1.00) ***	**0.97 (0.97. 0.98) ****	**0.99 (0.98, 1.00) ***	**0.98 (0.97, 0.99) ****	**0.99 (0.98, 1.00) ***
Had an OI at ART start						
Yes	**20.92 (16.00, 27.34) ****	**14.70 (11.09, 19.50) ****	**18.13 (13.67,24.05) ****	**12.96 (9.63, 17.43) ****	**15.60 (11.59, 21.00) ****	**10.92 (8.01, 14.88) ****
No		Reference				

	3 months after ART start		6 months after ART start		12 months after ART start	
	Unadjusted Model OR (95% CI)	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**
WHO Disease Stage at ART start						
Stage I	Reference	Reference	Reference	Reference	Reference	Reference
Stage II	**2.63 (2.21, 3.14) ****	**2.08 (1.65, 2.62) ****	**2.42 (2.03, 2.88) ****	**1.80 (1.44, 2.25) ****	**2.35 (1.97, 2.81) ****	**1.71 (1.37, 2.14) ****
Stage III & IV	**7.68 (5.59, 10.55) ****	**4.27 (2.88, 6.34) ****	**7.36 (5.25, 10.33) ****	**3.97 (2.65, 5.96) ****	**6.25 (4.40, 8.88) ****	**3.32 (2.20, 5.02) ****
Patient's Treatment Characteristics						
Duration in Pre-ART care						
< 1 month	Reference	Reference	Reference	Reference	Reference	Reference
One Month or more	**1.60 (1.25, 2.05) ****	**1.75 (1.12, 2.74) ***	**1.76 (1.37, 2.26) ****	**2.21 (1.42. 3.44) ****	**1.68 (1.30. 2.16) ****	**1.78 (1.16, 2.74) ****
ARV Regimen at ART start						
TDF	**0.45(0.38, 0.54) ****	**0.73 (0.56, 0.97) ***	**0.46 (0.38, 0.55) ****	**0.73 (0.55. 0.95) ***	**0.43 (0.36, 0.52) ****	**0.67 (0.51, 0.88) ****
Non-TDF	Reference	Reference	Reference	Reference	Reference	Reference
ARV Pills per day						
1 pill	**0.52 (0.44, 0.60) ****	**0.63 (0.49, 0.81) ****	**0.52 (0.45. 0.61) ****	**0.64 (0.50. 0.81) ****	**0.52 (0.45. 0.61) ****	**0.70 (0.55, 0.90) ****
2 pills or more	Reference	Reference	Reference	Reference	Reference	Reference
Cotrimoxazole prophylaxis at ART start						
Yes	0.88 (0.50, 1.56)	0.79 (0.33, 1.89)	0.66 (0.38, 1.17)	0.53 (0.23, 1.22)	0.70 (0.39, 1.25)	0.65 (0.28, 1.50)
No	Reference	Reference	Reference	Reference	Reference	Reference

*Significant at p-value 0.05
**Significant at p-value 0.01

Table 6: The Effect of Year of ART Initiation on Opportunistic Infections among HIV Positive Young People on ART

	3 months after ART start		6 months after ART start		12 months after ART start	
	Unadjusted Model OR (95% CI)	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**
Year of ART Initiation						
2012	Reference	Reference	Reference	Reference	Reference	Reference
2013	**0.32 (0.25, 0.41) ****	**0.41 (0.30, 0.57) ****	**0.32 (0.25, 0.41) ****	**0.45 (0.33, 0.61) ****	**0.37 90.29, 0.49) ****	**0.54 (0.39, 0.74) ****
2014	**0.44 (0.35, 0.56) ****	**0.62 (0.45, 0.85) ****	**0.43 (0.34, 0.56) ****	**0.67 (0.49, 0.92) ***	**0.43 (0.33, 0.56) ****	**0.65, (0.47, 0.90) ****
2015	**0.29 (0.22, 0.37) ****	**0.48 (0.34, 0.68) ****	**0.28 (0.22, 0.37) ****	**0.50, (0.35, 0.71) ****	**0.27 (0.21, 0.35) ****	**0.44 (0.31, 0.63) ****
2016	**0.19 (0.15, 0.25) ****	**0.28 (0.19, 0.41) ****	**0.17 (0.13, 0.22) ****	**0.25 (0.17, 0.36) ****	**0.16 (0.12, 0.22) ****	**0.24 (0.17, 0.35) ****
Patient socio-demographic characteristics						
Age at Art start (years)						
15-19	0.88(0.75, 1.04)	**0.77 (0.63, 0.96) ***	0.88 (0.76, 1.03)	**0.77 90.63, 0.95) ***	0.87 (0.74, 1.02)	**0.77 (0.63, 0.94) ****
20-24	Reference	Reference	Reference	Reference	Reference	Reference
Gender						
Male	**1.64 (1.34, 2.01) ****	1.10 (0.84, 1.44)	**1.66 (1.35, 2.04)** **	1.14 (0.88, 1.49)	**1.55 (1.26, 1.92) ****	1.09 (0.84, 1.42)
Female	Reference	Reference	Reference	Reference	Reference	Reference
ART Clinic						
ART Clinic 1	Reference	Reference	Reference	Reference	Reference	Reference
ART Clinic 2	**0.76 0.62, 0.95) ****	1.07 (0.72, 1.59)	**0.73 (0.59, 0.91) ****	1.10 (0.75, 1.63)	**0.73 (0.59, 0.91) ****	0.94 (0.64, 1.36)
ART Clinic 3	**0.38 (0.28, 0.52) ****	**0.38 (0.23, 0.63) ****	**0.40 (0.30, 0.54) ****	**0.45 (0.28, 0.72) ****	**0.43 (0.32, 0.58) ****	**0.45 (0.29, 0.71) ****
ART Clinic 4	0.92 (0.75, 1.14)	**1.68 91.13, 2.50) ****	0.94 (0.76, 1.16)	**1.84 (1.25, 2.72) ****	0.98 (0.79, 1.21)	**1.58 (1.09, 2.30) ***
Patient Clinical Characteristics						
Weight at ART start	**0.97 (0.97, 0.98) ****	**0.99 (0.98, 1.00) ****	**0.97 (0.97. 0.98) ****	**0.99 (0.98, 1.00) ***	**0.98 (0.97, 0.99) ****	0.99 (0.98, 1.00)
Had an OI at ART start						
Yes	**20.92 (16.00, 27.34) ****	**14.81 (11.14, 19.70) ****	**18.13 (13.67,24.05) ****	**13.12 (9.72, 17.73) ****	**15.60 (11.59, 21.00) ****	**10.94 (8.00, 14.96) ****
No	Reference	Reference	Reference	Reference	Reference	Reference

	3 months after ART start		6 months after ART start		12 months after ART start	
	Unadjusted Model OR (95% CI)	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**	**Unadjusted Model OR (95% CI)**	**Adjusted Model OR (95% CI)**
WHO Disease Stage at ART start						
Stage I	Reference	Reference	Reference	Reference	Reference	Reference
Stage II	**2.63 (2.21, 3.14) ****	**1.99 (1.58, 2.52) ****	**2.42 (2.03, 2.88) ****	**1.73 (1.37, 2.18) ****	**2.35 (1.97, 2.81) ****	**1.65 (1.31, 2.07) ****
Stage III & IV	**7.68 (5.59, 10.55) ****	**3.84 (2.58, 5.73) ****	**7.36 (5.25, 10.33) ****	**3.57 (2.36, 5.38) ****	**6.25 (4.40, 8.88) ****	**3.01 (1.98, 4.57) ****
Patient's Treatment Characteristics						
Duration in Pre-ART care						
< 1 month	Reference	Reference	Reference	Reference	Reference	Reference
One Month or more	**1.60 (1.25, 2.05) ****	1.43 (0.91. 2.25)	**1.76 (1.37, 2.26) ****	**1.79 (1.14, 2.80)***	**1.68 (1.30. 2.16) ****	1.46 (0.94, 2.26)
ARV Regimen at ART start						
TDF	**0.45(0.38, 0.54) ****	0.77 (0.58, 1.02)	**0.46 (0.38, 0.55) ****	**0.75 (0.57, 0.99) ***	**0.43 (0.36, 0.52) ****	**0.69 (0.52, 0.91) ****
Non-TDF	Reference	Reference	Reference	Reference	Reference	Reference
ARV Pills per day						
1 pill	**0.52 (0.44, 0.60) ****	**0.75 (0.58, 0.97) ***	**0.52 (0.45. 0.61) ****	**0.76 (0.59, 0.97) ***	**0.52 (0.45. 0.61) ****	0.83 (0.65, 1.06)
2 pills or more	Reference	Reference	Reference	Reference	Reference	Reference
Cotrimoxazole prophylaxis at ART start						
Yes	0.88 (0.50, 1.56)	0.94 (0.38, 2.31)	0.66 (0.38, 1.17)	0.60 (0.25, 1.42)	0.70 (0.39, 1.25)	0.73 (0.31, 1.73)
No	Reference	Reference	Reference	Reference	Reference	Reference

*Significant at p-value 0.05
**Significant at p-value 0.01

Discussion

In this study, our findings show that young people who started ART after the 2014 ART policy change were less likely to have OIs compared to those who started ART before the policy change, at all three time points (Table 5 & 6). The percentage of young people with OIs declined over time by year of ART initiation, as more young people were started on ART (Figure 5). Although the percentage declined between 2012 and 2013, there was an increase between 2013 and 2014. However, after 2014, a gradual decline is observed. This positive trend could be attributed to early ART initiation, with less advanced disease, which was consistent with the policy change, in addition to the use of more potent ARVs. In our study, young people were started on ART as soon as they are diagnosed with HIV to reduce the risk of infections and this could be the reason for the decline over time in OIs and the lesser odds of having one in the post-policy group. It is evident in the literature that the risk of getting an OI after starting ART are very low unless the patient is not adherent to medication[51]. Our results are not different from other studies done in Uganda and elsewhere in sub-Saharan Africa[31,52]. A systematic review of the literature found that the risk for all OIs in LMICs reduced to <2% during the first year on ART[31]. But they also noted that OIs still persist in PLWH even with ART, similar to what was reported elsewhere[20,50,53]. The fact that OIs still persist among PLWH could be the reason for the higher and increasing odds of having an OI in the pre-policy group. Our findings also show that OIs are still a burden for young people

living with HIV and more effort is needed to fully reap the benefits of ART in reducing such infections. It should be noted that our study did not disaggregate the OIs and therefore does not show the ones that have persisted in the study population.

Secondly, male young people were more likely to have OIs after ART initiation compared to female young people in the adjusted model and at all three time points. This is not surprising given that males have been found to be less adherent to ART and therefore at increased risk of getting OIs after starting ART. Poor adherence, a major determinant of treatment failure increases the risk for OIs[27]. This finding could be also be attributed to the gender differences in the prevalence of some OIs like tuberculosis with the men disproportionately affected compared to females as has been reported in the literature[51].

Furthermore, the ART clinic providing the ART treatment had a significant association with having an OI after ART initiation. Whereas young people who got their ART at clinic 3 had lesser odds of OIs, those who got their ART at clinic 4 had higher odds of OIs compared to young people at clinic 1. Health facility-based factors and the variation in the regional endemicity of certain OIs could be the contributing factor to this result. Though our study did not disaggregate OIs, our results are in line with findings by Rubaihayo et. al. (2016) who found that TB was endemic to the northern and eastern regions of the country compared to other geographical areas because of socio-economic disparities.

Our results also show that WHO disease stage at ART start was significantly associated with OI occurrence. Young people with stage II, III and IV disease were more likely to have an OI compared to those who had stage I disease. Although our study had a large number of young people who started ART with stage 1 disease in both groups, the decreasing odds of OIs for these advanced disease stages implies that the treatment is succeeding in reducing the infections over time. It is also not surprising that the higher odds of having OIs especially during the first months of treatment compared to those with less advanced disease were observed. PLWH who start ART with more advanced disease are more likely to have complications that are common during the first months on ART[44]. These start treatment with when they are too ill and have a bigger pill burden consisting of ARVs and other drugs given to treat opportunistic infections that are common with that disease stage. Our findings therefore support early initiation of ART before the onset of advanced HIV disease for better treatment outcomes on ART since it reduces morbidity and mortality among PLWHA[45] .

ART regimen also had an effect on OIs. Young people who were given TDF-based regimen had lesser odds of having an OI after ART initiation. TDF being a more potent ARV and the recommended first line regimen[7], is therefore effective in keeping the risk of OIs low. In line with this, is the finding that young people who were given one ARV pill per day had lesser odds of OIs. Therefore, the potency of the ARV drugs coupled with a lesser pill burden had a positive impact on reducing opportunistic infections among young people in Uganda.

Surprisingly cotrimoxazole prophylaxis (CTX) which is used to reduce on the risk of bacterial infections, did not have a significant effect on the dependent variable. This may not be surprising since CTX had been recommended for HIV-infected persons with CD4 counts <350 cells/mm^3 in resource-constrained areas [57]. We were limited by the lack of CD4 count data at ART start for all the young people in our sample. But for the few who had CD4 count data, the mean CD4 count was >500 cells/mm^3, and only 30% had <350 cells/mm^3. Therefore, CTX may not have an effect if a patient has a higher CD4 threshold and this could explain why we did not find a significant association. This finding is very useful in light of newer policies seeking to phase out cotrimoxazole prophylaxis among adherent PLWH.

Our study had several strengths. To our knowledge this is the first study to evaluate the impact of the changes in the 2014 ART guidelines, on OIs among HIV-infected young people living with HIV in Uganda. We had a large study cohort from 4 large volume ART clinics that are geographically representative. This regional variation increases the generalizability of the study results. This is also one of the few longitudinal studies that analyzed the effect of policy changes on OIs. Our results had some limitations. We lacked socio-demographic data on education and marital status. We also lacked data of CD4 count at ART initiation. Some unobserved measures may have affected our findings as is common in observational studies as well as some other factors that may be contributing to some of the positive trends

in declining OIs we observed in this study. However, the study findings are still generalizable to other high-volume HIV clinics in Uganda and useful for informing HIV interventions.

Conclusion

This study demonstrates that early ART initiation reduces morbidity due to HIV over time. Young people who initiated ART after the policy change were less likely to have an OI after starting treatment. However, there are still OIs that persist among PLWH and further research will help identify them and design interventions to mitigate the problem.

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JOURNAL ARTICLE 3

The Effect of Changes in Antiretroviral Therapy Policy on survival of Young People living with HIV in Uganda.

Abstract

Objectives: The introduction of life-saving antiretroviral therapy (ART) has prolonged the survival of people living with HIV. Despite this, HIV continues to threaten the survival of young people living with the virus. To mitigate this threat, the eligibility criteria was revised to start ART early but little has been documented about the effect of these changes. We evaluated the effect of the changes in Uganda's ART policy on survival of young people, aged 15-24 years.

Methods: This was a retrospective analysis of young people living with HIV, 15-24years old, who started ART between January 2012 and December 2016. This study used administrative data from the District Health Information System (DHIS2) and the national referral. We used multivariable Cox Proportional Hazards regression to examine the effect of the policy on survival.

Results: There was no significant difference in the survival probabilities and the hazard ratios of young people who started ART before and those who started ART after the policy changed. However, although not statistically significant, the risk of death among the post-policy group

was increased in the adjusted model. WHO disease stage, weight at ART start and ART adherence at the time of death had an effect on survival.

Conclusion: Young people had higher survival probabilities after ART initiation regardless of whether they started ART before or after the policy change. However, given that the risk of death among the post-policy group was higher and ART adherence had an effect on survival, more investigation is needed to identify factors influencing this.

Introduction

The introduction of life-saving antiretroviral therapy (ART) for treatment and prevention of the Human Immunodeficiency Virus (HIV) has saved lives and improved survival of people living with the virus (PLWH)[23,58]. The WHO estimates that ART has saved 11.4 million lives worldwide over the last decade[34]. Despite these achievements, HIV continues to be a public health threat in sub-Saharan Africa especially among young people. In Uganda, the HIV prevalence rate among young people is 4%. There has also been an increase in new infections. AIDS-related mortality is still high and opportunistic infections (OI) are still a major cause of death among those whose treatment is not keeping their viral load low enough to fight off infections. Between 2005 and 2012, the number of deaths among this age group increased by 50% whereas overall it had decreased by 30%[48]. It is within this context that efforts were made to maximize the benefits of ART for HIV treatment by revising policies to

initiate treatment early in the course of the illness. With initiation at a higher CD4 count threshold, ART can prevent the majority of these infections and deaths [3-8].

Although high income countries adopted the "test and treat strategy" as early as the year 2000, low- and middle-income countries (LMICs) used a more gradual approach due to cost implications and projected demands on already weak healthcare systems. Uganda adopted the 2013 ART guidelines in July 2014 and started initiating ART for all young people at CD4 cell count ≤500 cells/mm^3, using a once-a day fixed-dose combination regimen. Despite increased ART coverage, patients still die when started on ART and the threat posed by a higher treatment burden cannot be overlooked[15, 20,31,49,50].

Several studies have examined survival among PLWH, but very few have focused on young people. In addition, little is known about the effect of the changing ART policy on survival of young people in Uganda. Survival rates vary by region and age, and providing country-specific data will help define local priorities and reduce barriers to treatment. We therefore evaluated the effect of the 2014 policy ART changes on survival among young people, aged 15-24 years, initiating ART in Uganda.

Methods

Study Design and Data Source

We conducted a retrospective cohort study using administrative data from the District Health Information System (DHIS2) and the national referral hospital's EMR. We compared young people who started ART in the period July 1st, 2014 to December 31st, 2016 to a historical cohort that was treated in January 1st, 2012 to 30th June 2014 before the policy change. This data, routinely collected from patients who receive HIV treatment at the ART clinics during routine visits, is used to track a patient's treatment plan from the date of HIV diagnosis to the date he/she leaves the clinic either through transfer-out to another clinic, lost to follow-up (LTFU) or death.

Study Cohort

All individuals that were 15-24 years old at the time of ART initiation and on long-term ART, were included in the study. Patients who were LTFU or transferred-out were considered for the period when they were in care. We excluded patients who were lost- to- follow-up before the start of the study period, started ART for Pre-exposure prophylaxis (PrEP) because it is short term, had no records, and had started ART elsewhere (transfer-in) for lack of information from the referral health facility. We also excluded patients who had no follow up visit after ART initiation.

Dependent Variables

We defined survival as the time between ART initiation and death or end of study period. For more comparable results the total follow-up time for each group was restricted to 36 months after starting ART. For young people in the pre-policy group, the censor date was December 2014 and for those in the post-policy group, the censor date was June 2017. Length of time was measured in months. The variable was coded as "1" if the patient died and "0" otherwise.

Independent Variables

The independent variable of interest was a binary time variable (pre-2014 policy =0, post-2014 policy=1). The pre-policy group included young people who started ART before July 2014 (January 2012 – June 2014) and the post-policy group included young people who started ART after July 2014 (July 2014-December 2016). The socio-demographic variables were ART clinic, gender and age at ART start. The clinical characteristics were weight, OI at ART start (Yes, No) and WHO clinical disease stage (I, II, III) at ART start. The treatment characteristics included duration in pre-ART care (less than 1 month, 1 month or more), ARV drug regimen (TDF, Non-TDF), the number of ARV pills per day (1 pill, 2 pills or more) given at ART start, cotrimoxazole prophylaxis at ART start (Yes, No) and ART adherence (adherent, less adherent) at the time of death/end of study period.

Analysis

All statistical analyses were performed using STATA 15 and SAS 9.4. We described and compared patient characteristics using T-tests and Pearson's chi-squared tests, respectively (Table 1). All p-values were two-tailed and considered statistically significant at $\alpha=0.05$. To assess associations of each independent variable with the dependent variable, survival, univariable analyses were first performed. We conducted multivariable Cox Proportional Hazards regression analyses to determine the effect of the change in policy on survival, controlling for age at the time of the event, sex, OI at ART start, ARV regimen, ARV pills per day given and adherence at the time of death/send of study. All variables that were statistically significant at p-value <0.25 or had prior clinical significance for survival from the univariable analysis, were included in the multivariable regression model. We checked the correlation between the variables to ensure that none was highly correlated. Possible interactions were also checked and none of them was significant. We used the log-rank test to test the difference in survival functions between the two groups. We checked the underlying model assumptions of the proportional hazards model using the model-based test for time by log (t) interaction. The overall model fit was assessed using Cox-Snell residuals. We report both unadjusted and adjusted hazard ratios and 95% confidence intervals in Table 8.

IRB approval

The study was approved by the Makerere University School of Public Health, Uganda National Council of Science and Technology, Baylor College of Medicine's Institutional Review Board, and Committee for the Protection of Human Subjects at the University Of Texas Health Sciences Center at Houston.

Results

This analysis included data from 3084 young people who met the inclusion-exclusion criteria out of 3532. 50.13% of these started ART before and 49.87% started ART after the policy change. Although there were no significant group differences in age at ART start and gender, young people were more likely to be older (20-24 years) and female. The number of young people initiating ART was different between clinics, but within the clinics there was not much difference, pre- and post- policy. More than 76% of young people did not have an OI at ART initiation in both groups. But among those who had an OI, the pre-policy group was bigger (23.54%) compared to 18.60% in the post-policy group. 57% pre-policy and 75% post-policy young people started ART with stage I disease. The pre-policy group had more young people (32%) starting ART with stage II disease compared to post-policy group (17%). In both groups, ART initiation was in less than a month of testing HIV positive. However, the post-policy group had a bigger percentage (93%) compared to the pre-policy group (88%). A sub-

analysis showed that among those who started ART in less than a month, nearly 50% in the post-group and 30% in the pre-group started ART the same day they tested positive for HIV. More young people in the pre-policy group (11.77%) stayed in pre-ART care more than a month. Post-policy young people were more likely to be given a TDF-based regimen (93%) and one pill a day (86%). Almost all the young people in both groups were given cotrimoxazole prophylaxis at ART start. There were no group differences in the number of young people who died during the study period. However, those in the post-policy group were more likely to be LTFU (7.11%) or to transfer-out to another facility (19.32%) compared to those in the pre-policy group.

The survival probabilities of both groups were close to 1 (Figure 7). The log rank test (2.56) was not statistically significant (P <0.11) and there was not enough evidence to reject the null hypothesis that there is no difference in the survival probabilities of the two groups.

In the both the unadjusted and adjusted models there was no significant difference between the hazard ratios of young people who started ART before and those who started ART after the policy changed (Table 8). However, whereas the risk of death was lower in the unadjusted model (HR: 0.58, 95%CI: 0.29, 1.15), it was three times higher in the adjusted model (HR: 1.55, 95%CI: 0.46, 5.28), after controlling for age at the time of death/end of study period, gender, weight at ART start, OI at ART start, WHO disease stage at ART start, duration in pre-ART care, number of ARV pills per day and ART adherence at the time of death/end of

study period. Only weight at ART start, WHO disease stage and ART adherence at the time of death/end of study period had a significant effect of survival in the adjusted regression model. Young people who had stage II, III&IV at ART start had more than three times the risk of death (HR 3.88, 95%CI 1.01, 14.99 and 8.63, 95%CI: 2.48, 29.98, respectively) compared to those who had stage I at ART start. But the 95% CIs were wide. Those who were less adherent had lower odds of survival compared to those who were adherent. The difference was statistically significant.

Table 7: Descriptive Statistics of Young People who started ART before and after the Policy Change

Characteristic	Pre-2014 policy	Post-2014 policy
Total	**1546**	**1538**
Dependent Variable		
Deaths		
Yes	1.42%	0.85%
No	98.58%	99.15%
Independent Variables		
Policy change group		
Pre-Policy	50.13%	
Post- Policy		49.87%
Year of ART initiation		
2012 (reference)	28.78%	
2013	47.54%	
2014	23.67%	27.57%
2015		36.74%
2016		35.70%
Socio-Demographic Characteristics		
Age at ART start in years (%)		
15-19	28.91%	28.67%
20-24	71.09%	71.33%
Gender (%)		
Male	14.81%	13.72%
Female	85.19%	86.23%
Weight at ART start in kgs (mean, SD)	55.26(10.15)	55.45(9.30)
Health Facility (%)		
ART clinic 1	15.46% *	16.64% *
ART clinic 2	39.72% *	31.99% *
ART clinic 3	10.93% *	10.14% *
ART clinic 4	33.89% *	41.22% *

Characteristic	Total	Pre-2014 policy	Post-2014 policy
	1546	1546	1538
Clinical Characteristics			
Had an OI at ART Start (%)			
Yes		23.54% *	18.60% *
No		76.46% *	81.40% *
WHO disease stage at ART start (%)			
Stage I		57.32% *	75.36%*
Stage II		32.25% *	17.30% *
Stage III & IV		10.43% *	7.34% *
Treatment Characteristics			
Duration in Pre –ART care in months (%)			
<1 month		88.23% *	93.17% *
1 month +		11.77% *	6.38% *
ARV regimen given at ART start (%)			
TDF		65.65% *	92.59% *
Non-TDF		34.35% *	7.41% *
ARV pills per day at ART start (%)			
1 pill		45.34% *	85.57% *
2 pills or more		54.66% *	14.43% *
Cotrimoxazole Prophylaxis at ART start (%)			
Yes		97.67% *	99.09% *
No (reference)		2.33% *	0.91% *
Lost to Follow-up			
Yes		2.72*	7.22*
No		97.28*	92.78*
Transfer-Out			
Yes		8.02*	19.25*
No		91.98*	80.75*
Age at time of death/censor			
15-19		83.89% *	87.26% *
20-24		16.11% *	12.74% *
ART Adherence at time of death/censor			
Adherent		71.82%	71.05%
Less Adherent		28.18%	28.95%

*Significant at P<0.05

Figure 6: Trends in Deaths among Young People before and after the Policy Change

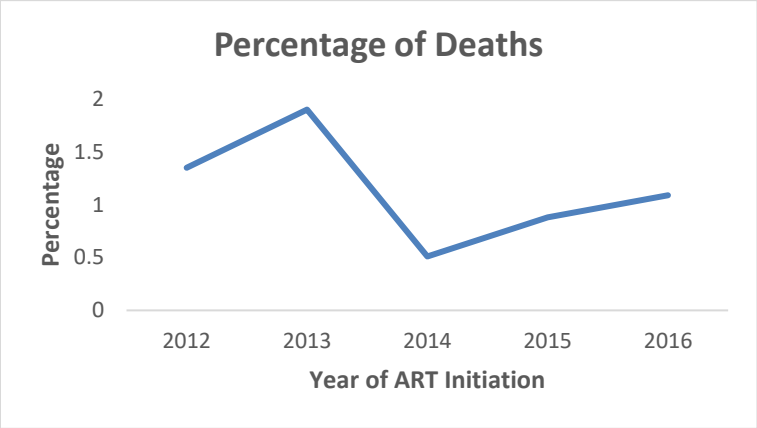

Figure 7: Comparison of Survival Probabilities of Young People before and after the 2014 ART Policy

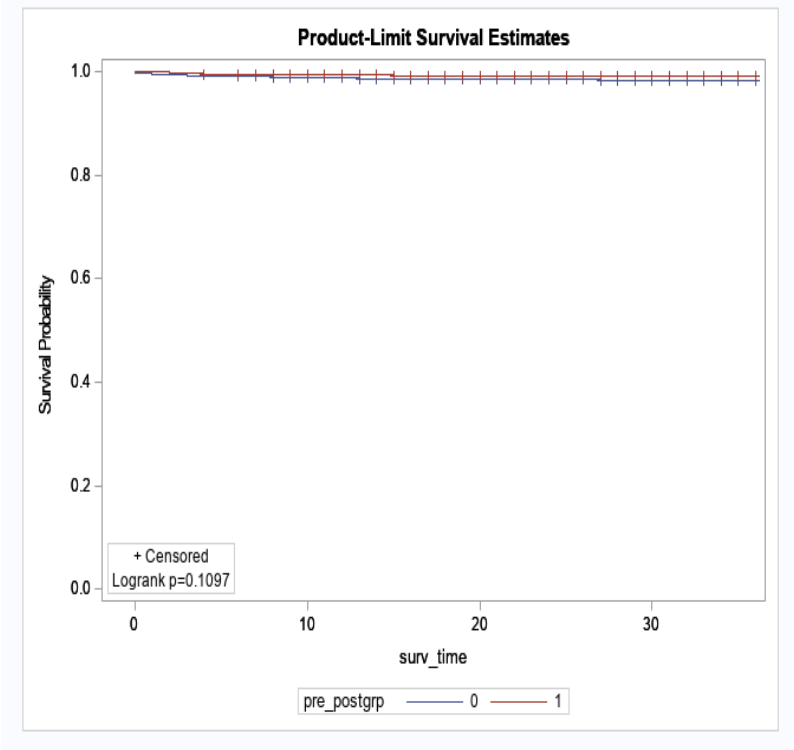

Table 8: The Effect of the Independent Variables on Survival among HIV Positive Young People, Before and After the 2014 ART Policy Change

Characteristic	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Pre/Post Group		
Pre-2014 policy	Reference	Reference
Post-2014 policy	0.58 (0.29, 1.15)	1.55 (0.46, 5.28)
Patient socio-demographic characteristics		
Age at time of time of death/censor		
15-19 years	1.84 (0.83, 4.08)	1.45 (0.49, 4.26)
20-24 years	Reference	Reference
Gender		
Male	**3.13 (1.56, 6.31) ****	1.15 (0.36, 3.60)
Female	Reference	Reference
Patient Clinical Characteristics		
Weight at ART start	**0.91 (0.89, 0.93) ****	**0.93 (0.89, 0.97) ****
Had an OI at ART start		
Yes	**3.12 (1.60, 6.07) ****	0.97 ((0.40, 2.33)
No	Reference	Reference
WHO disease stage at ART start		
Stage I	Reference	Reference
Stage II	**3.53 (1.23, 10.14) ***	**3.88 (1.01, 14.99) ***
Stage III & IV	**23.56 (9.48, 58.67) ****	**8.63 (2.48, 29.98) ****
Patient Treatment Characteristics		
Duration in PreART care		
< 1 month	Reference	Reference
One Month or more	0.30 (0.04, 2.14)	0.60 (0.08, 4.37)
ARV pills per day at ART start		
1 pill	**0.36 (0.19, 0.71) ****	0.41 (0.11, 1.47)
2 pills or more	Reference	Reference
Adherence at the time of death/censor		
Adherent	Reference	Reference
Less adherent	0.46 (0.16, 1.32)	**0.26 (0.09, 0.80) ***

*Significant at P<0.05

**Significant at P<0.01

Discussion

In this study we found that young people had higher survival probabilities after ART initiation regardless of whether they started ART before or after the policy change (Figure 7). Less than 2% (0.54 per 1000 person-months) died during the follow-up period which was lower than the 6.2 per 100 person years reported in a similar study done in Uganda[59]. Our sample had a very small number of deaths. The low number of deaths could be attributed to the increased ART coverage in the country that is prolonging the life of PLWHA given the strong and consistent evidence that ART improves survival[23,24].

This study did not find a significant association between the policy change group and survival of young people. With the small number of deaths in our sample, we may not have had an adequate number of deaths to detect a difference between the groups. Although the result was not significant, it was surprising that the risk of death increased in the post-policy group in the adjusted model. Whereas in the unadjusted model, the post-policy group had a lower hazard rate (HR: 0.58, 95%CI: 0.29, 1.15) compared to the pre-policy group, this changed (HR: 1.55, 95%CI: 0.46, 5.28) in favor of the pre-policy group in the adjusted model. It should also be noted that a bigger number of young people in the post-policy group had disease stage I at ART start and started ART in less than a month of being diagnosed. Therefore, there may by other factors driving this increased risk that need further research.

In addition, our study was limited by the lack of death registry data and a centralized database for PLWHA. There are unreported deaths in the community in general and also among young people who are lost or were transferred-out to other ART clinics for treatment. Therefore, this study could have underestimated death and overestimated survival.

It is evident in published literature that disease severity significantly increases the risk of death[61] among PLWH. Our study found that young people with disease stage II, III & IV at ART start had a significant effect on survival (HR 3.88, 95%CI 1.01, 14.99 and 8.63, 95%CI: 2.48, 29.98, respectively). Young people had more than three times the risk of death and nearly nine times higher risk compared to those with stage I at ART start, during the 36 months of follow-up. Other studies done in Africa have reported similar results that OIs and the Immune Reconstitution Inflammatory Syndrome (IRIS) were major causes of death after initiation of ART[61,62]. Our results could be attributed to the number of young people in our sample who had disease stage III and IV at the start of treatment. Overall nearly 40% of the young people had disease stage II, III & IV at ART start. In addition, 23% of that young people in the pre-policy group and 18% in the post-policy group had an OI at the start of ART. It should also be noted that although the prevalence of OIs is not as high as before the ART era, they still exist and there are some that still persist[50,52] . Therefore, their impact on survival cannot be overlooked or underestimated.

Our study also found that ART adherence at the time of death/study period had a significant effect on survival. It was surprising that less adherent young people had a lower hazard ratio compared to the adherent young people (HR:0.26, 95%CI: 0.09, 0.80). This was contrary to what we expected to find and what has been reported in published literature. Several studies have found that less adherent patients had a higher risk of death compared to adherent patients. Studies in Ethiopia, found that the risk of death was nearly 3 times higher (HR: 2.9695, 95% CI: 1.396 – 5.203) among patients with poor adherence[63]. In Uganda it has been reported that non-adherent patients were 2 times more likely to die compared to adherent patients[64]. Therefore, given that unexpected results, the existing literature, and the low number of deaths in the study sample, more investigation is needed into the survival of young people starting ART in the post policy era.

Among the strengths of this study is that this is the first study to evaluate the effect of the changes in ART policy on survival among young people in Uganda. This study had a large study cohort of young people from 4 large volume HIV clinics that are representative of the 4 geographical regions in Uganda. The regional variation increases generalizability of the study results. Our study also had some limitations. Our study may have misclassified the number of young people who were LTFU and transferred out as dead due to lack of tracking such patients. Adolescents who were perinatally infected with HIV may have introduced some survival bias in our analysis. Also common in such studies, some unobserved measures may

exist and could have affected our findings. However, our findings are unlikely to differ from other ART clinics in Uganda.

Conclusion

In conclusion therefore, young people are likely to survive longer after ART initiation regardless of whether they started ART before or after the policy changed. However, given that the risk of death among the post-policy group was higher and ART adherence had an effect on survival, more investigation is needed to identify factors that may be influencing this.

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CONCLUSION

This study found that ART adherence among young people was mainly driven by differences between health facilities providing ART in Uganda and whether an individual had an OI at ART start and not by policy change. Also, ART adherence declined over time. This study also found that the risk of OIs was lower among young who initiated ART after the policy change. Furthermore, young people are more likely to survive longer after ART initiation regardless of whether they started ART before or after the policy changed. Therefore, whereas initiating treatment before onset of advanced disease is beneficial to reducing HIV-related morbidity and mortality, the implications on long term adherence cannot be overlooked. Given our findings, we believe that there are factors influencing ART adherence, OIs and survival among young people that are not captured by our study, that need further investigation.

APPENDICES

Appendix 1: Data extraction tool

Qn.	Description	
	Information	**Response**
1.	Name of Health Facility	1=ART Clinic 1; 2= ART Clinic 2; 3 = ART Clinic 3; 4= ART Clinic 4
2.	Patient Name	Will only be used for data extraction and cleaning. A unique study ID will be generated for analysis
3.	Patient Clinic Number	Will only be used for data extraction and cleaning. A unique study ID will be generated for analysis
4.	Patient Study ID	This is the ID that will be used in the analysis
	Demographic and Baseline Information	
5.	Sex	0=Male 1=Female
6.	Date of Birth	dd/mm/yyyy
7.	Age	In years
8.	Date Patient started treatment at this health facility	dd/mm/yyyy
9.	Date patient was diagnosed with HIV	dd/mm/yyyy
10.	ART start date	dd/mm/yyyy
11.	ART regimen at ART start	
12.	Number of pills in a daily dose at ART start	
13.	Weight at ART start	in kilograms
14.	WHO clinic disease stage at ART start	1=Stage 1; 2=Stage 2; 3=Stage 3; 4=Stage 4
15.	TB status at ART start	1=No signs; 2=suspect; 3 =TB Rx
16.	New/Other OIs at ART start	1 =Yes, 0=No
17.	Name of new/other OIs at ART start	
18.	CD4 cell count at ART start	Cells/mm^3
19.	Pre-ART Opportunistic Infection (OI)	1 =Yes, 0=No
20.	Cotrimoxazole (CPT) dose at ART start	1 =Yes, 0=No
21.	Duration in Pre-ART care	In months

	Followup information – Repeat for every visit for the specified study duration	
22.	Visit date	dd/mm/yyyy
23.	Follow-up date	dd/mm/yyyy
24.	TB status	1=No signs; 2=suspect; 3 =TB Rx
25.	New/Other OIs at ART start	1 =Yes, 0=No
26.	Name of new/other OIs	
27.	WHO clinical disease stage	1=Stage 1; 2=Stage 2; 3=Stage 3; 4=Stage 4
28.	ARV adherence score	1=Adherent (≥ 95%), 0=Less Adherent (<95%)
29.	Transfer out date	dd/mm/yyyy
30.	Loss to follow up date	dd/mm/yyyy
31.	Date patient died	dd/mm/yyyy

Appendix 2: Research Approval – UTHealth

UTHealth
The University of Texas
Health Science Center at Houston

Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

Hilda Nakalema
UT-H – SPH – Student

NOTICE OF APPROVAL TO BEGIN RESEARCH **May 03, 2018**

HSC-SPH-18-0356 - EVALUATING THE IMPACT OF EARLY INITIATION OF ANTIRETROVIRAL THERAPY (ART) ON PATIENT OUTCOMES AMONG HIV-INFECTED ADOLESCENTS AND YOUNG ADULTS IN UGANDA

PROVISIONS: Ethics review and approval must be obtained and submitted for CPHS records before the research project can begin.

APPROVED: By Expedited Review and Approval

REVIEW DATE: 05/03/2018

APPROVAL DATE: 05/03/2018

EXPIRATION DATE: 04/30/2019

CHAIRPERSON: L. Maximilian Buja, MD L. Maximilian Buja

Subject to any provisions noted above, you may now begin this research.

CHANGES: The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. **ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.**

INFORMED CONSENT DETERMINATION:
Waiver of Consent Granted

INFORMED CONSENT: When Informed consent is required, it must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

RECORDS: The PI will maintain adequate records, including signed consent and HIPAA documents if required, in a manner that ensures subject confidentiality.

Appendix 3: Research Approval – Baylor College of Medicine

June 13, 2018

BCM
Baylor College of Medicine

SUSAN LANELLE GILLESPIE
BAYLOR COLLEGE OF MEDICINE
PEDIATRICS: RETROVIROLOGY

Baylor College of Medicine
Office of Research
One Baylor Plaza, 600D
Houston, Texas 77030
Phone: (713) 798-6970
Fax: (713) 798-6990
Email: irb@bcm.tmc.edu

H-41769 - EVALUATING THE IMPACT OF EARLY INITIATION OF ANTIRETROVIRAL THERAPY (ART) ON TREATMENT OUTCOMES AMONG HIV-INFECTED ADOLESCENTS AND YOUNG ADULTS IN UGANDA

APPROVAL VALID FROM 6/13/2018 TO 5/16/2019

Dear Dr. GILLESPIE

The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals (BCM IRB) is pleased to inform you that the research protocol named above was reviewed and approved by Expedited procedures on 6/13/2018 by Board 5.

The study may not continue after the approval period without additional IRB review and approval for continuation. You will receive an email renewal reminder notice prior to study expiration; however, it is your responsibility to assure that this study is not conducted beyond the expiration date.

Please be aware that only IRB-approved informed consent forms may be used when written informed consent is required.

Any changes in study or informed consent procedure must receive review and approval prior to implementation unless the change is necessary for the safety of subjects. In addition, you must inform the IRB of adverse events encountered during the study or of any new and significant information that may impact a research participants' safety or willingness to continue in your study.

The BCM IRB is organized, operates, and is registered with the United States Office for Human Research Protections according to the regulations codified in the United States Code of Federal Regulations at 45 CFR 46 and 21 CFR 56. The BCM IRB operates under the BCM Federal Wide Assurance No. 00000286, as well as those of hospitals and institutions affiliated with the College.

Sincerely yours,

JULIE PAMELA KATKIN, M.D.

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Full AAHRPP Accreditation

Appendix 4: Research Approval – UNCST

Study Approval - (HS218ES)

Research Management - UNCST <research@uncst.go.ug>

Thu 7/5/2018 1:17 AM

To Nakalema <Hilda.Nakalema@bcm.edu>;

Cc Nakalema, Hilda S <Hilda.N.Sekabira@uth.tmc.edu>;

Uganda National Council for Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Dear Hilda Nakalema,

I am pleased to inform you that on 05/07/2018, the Uganda National Council for Science and Technology (UNCST) approved your study titled, Evaluating the Impact of Early Initiation of Antiretroviral Therapy (ART) on Patient Outcomes Among HIV-Infected Adolescents and Young Adults in Uganda . The Approval is valid for the period of 05/07/2018 to 05/07/2019.

Your study reference number is HS218ES. Please, cite this number in all your future correspondences with UNCST in respect of the above study.

Please, note that as Principal Investigator, you are responsible for:

1. Keeping all co-investigators informed about the status of the study.
2. Submitting any changes, amendments, and addenda to the study protocol or the consent form, where applicable, to the designated local Research Ethics Committee (REC) or Lead Agency, where applicable, for re-review and approval prior to the activation of the changes.
3. Notifying UNCST about the REC or lead agency approved changes, where applicable, within five working days.
4. For clinical trials, reporting all serious adverse events promptly to the designated local REC for review with copies to the National Drug Authority.
5. Promptly reporting any unanticipated problems involving risks to study subjects/participants to the UNCST.
6. Providing any new information which could change the risk/benefit ratio of the study to the UNCST for review.
7. Submitting annual progress reports electronically to UNCST. Failure to do so may result in termination of the research project.

Please, note that this approval includes all study related tools submitted as part of the application.

Yours sincerely,

Musa Kwehangana
For: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

Appendix 5: Human Subjects Certification – CITI certificate

CITI PROGRAM

Completion Date 05-Jun-2017
Expiration Date 04-Jun-2020
Record ID 19030312

This is to certify that:

Hilda Nakalema

Has completed the following CITI Program course:

Biomedical Research - Basic/Refresher (Curriculum Group)
Biomedical Research - Basic/Refresher (Course Learner Group)
1 - Basic Course (Stage)

Under requirements set by:

Baylor College of Medicine

CITI

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