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Medically Attended Respiratory Illness (MARI) among HIV-infected and HIV-uninfected Patients in Ghana

By

Neha Balachandran

Degree to be awarded: Master of Public Health

Epidemiology

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By

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Bachelor of Medicine and Bachelor of Surgery

Mahatma Gandhi Mission's Medical College

2015

Thesis Committee Chair: Dr. Kevin Ward, MPH, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2018

ABSTRACT

Medically Attended Respiratory Illness (MARI) among HIV-infected and

HIV-uninfected Patients in Ghana

By

Neha Balachandran

Background: Although seasonal influenza, including the influenza A (H1N1) pdm09, is a common cause of respiratory illness in HIV-infected adults, there are few data describing the relationship between HIV infection and influenza.

Methods: This was a prospective study conducted in Shai-Osudoku and Ningo Prampram (SONP) districts located in Ghana, with a target sample size of 300 HIV-infected and 600 HIV-uninfected persons. Participants were matched by age, district and sex in a 1:2 ratio and followed for 12 months. Incidence rates of medically attended respiratory illness (MARI) and influenza-associated MARI were calculated. Poisson regression analysis was conducted to compare the incidence density ratios of MARI among HIV-infected patients compared to HIV-uninfected patients, controlling for education status, occupation, pre-existing medical condition, smoking status and presence of children less than 5 years of age in the household.

Results: A total of 266 HIV-infected and 510 uninfected participants were enrolled. We observed 40 and 98 MARI episodes among infected and uninfected persons, respectively. The overall rate of MARI among HIV infected was 1504 (95% CI: 1038-1970 per 10,000 PY) per 10,000 PY while that among HIV-uninfected was 1922 per 10,000 PY (95% CI: 1541-2302 per 10,000 PY). In univariate analyses, the incidence of MARI was higher among those who were uneducated (IDR: 1.09), had pre-existing medical conditions (IDR: 1.44), and reported at least one child <5 years of age in the household (IDR: 1.17) but these associations were statistically not significant ($p>0.05$). After assessing for interaction and confounding, the final model included HIV status, education status and its interaction terms. The incidence of MARI among uneducated HIV-infected participants was 47% (IDR: 0.53, 95% CI: 0.31-0.89) lower than that among HIV-uninfected participants and the incidence of MARI among educated HIV-infected participants was 23% (IDR:1.23, 95% CI: 0.64-2.36) higher than that among HIV-uninfected participants.

Conclusion: This study showed a higher incidence of MARI among HIV-uninfected individuals, which was contrary to previous literature. Due to small numbers, few significant associations were observed. Additional more robust studies should take place in West Africa to examine the relationship between HIV infection and influenza infection.

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my thesis field advisor,
Ms. Jazmin Duque for her continuous support throughout the thesis development process. She steered me in the right direction whenever I had questions regarding various aspects of my thesis.

I would like to thank my faculty thesis advisor, Dr. Kevin Ward for his guidance and support. I am gratefully indebted to his valuable comments and advice on this thesis.

Finally, I must express my profound gratitude to my husband and my parents for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This thesis would not have been possible without them. Thank you.

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BACKGROUND AND LITERATURE REVIEW

INFLUENZA AS A PUBLIC HEALTH PROBLEM

Acute respiratory infections (ARIs) remain a leading cause of morbidity, mortality and economic loss worldwide (1). In 2015, lower respiratory infections caused 2.74 million deaths and 103 million DALYs (Disability Adjusted Life Years) (2). Up to 650,000 deaths annually are associated with respiratory diseases from seasonal influenza, according to new estimates by the United States Centers for Disease Control and Prevention (US-CDC), the World Health Organization (WHO) and global partners (3). In addition to the largely predictable threat of seasonal influenza, pandemics may occur as a result of the emergence of a new and efficiently transmitted strain of influenza A virus into the population. The first pandemic of the 21st century occurred in 2009 when a novel influenza virus emerged in the human population infecting more than 622,482 people worldwide with more than 7,820 deaths as of November 22, 2009 (4). It has been shown that infection with HIV increases a person's susceptibility to respiratory infections and is a risk factor for influenza illness (5).

Influenza-Like Illness (ILI) And Severe Acute Respiratory Illness (SARI)

Influenza infection causes a clinical syndrome that is not easily distinguished from other respiratory infections. To best monitor influenza cases, WHO recommends surveillance of influenza-like illness (ILI) and severe acute respiratory illness (SARI) (6). ILI and SARI are the most commonly used proxy respiratory syndrome indexes of influenza surveillance (7). ILI is generally intended for use in outpatient settings and SARI is used to capture severe hospitalized patients.

Surveillance Case Definitions

The WHO defines a case of ILI as an acute respiratory infection with measured fever of $\geq$38 C° and cough with illness onset within the last 10 days (8). A case of SARI is

defined by WHO as fever of ≥38 C° and cough with illness onset within the last ten days and requiring hospitalization (8). The case definitions for ILI and SARI are not necessarily intended to capture all cases but to describe trends over time and characterize circulating viruses. In this study, medically attended respiratory illness (MARI) was defined as either an ILI or a SARI episode.

HIV IN WEST AFRICA

According to UNAIDS statistics, there were approximately 36.7 million people worldwide and 6.1 million people in Western and Central Africa, living with HIV/AIDS in 2016 (2).West and Central Africa contain around 7% of the global population but are home to 17% of the world's population living with HIV and 30% of the world's AIDS-related deaths in 2016 (2).

HIV IN GHANA

Human immunodeficiency virus (HIV) is the etiologic agent for the acquired immunodeficiency syndrome (AIDS). In March 1986, the first case of AIDS was reported in Ghana. Three hundred and thirty-three people were identified as HIV-infected by the end of March 1988, and by April 1990, a of total 2,744 people had been identified (9). Though the first HIV/AIDS cases in Ghana were diagnosed in 1986, efforts to track prevalence were not instituted until 1990 when the Ministry of Health implemented the national HIV Sentinel Surveillance (HSS) system (10). The HSS is responsible for annual HIV sentinel survey at antenatal care (ANC) clinics for pregnant women and sexually transmitted infection (STI) centers for patients with STIs (11). In the 21st century, the government of Ghana adopted a multisectoral approach to HIV/AIDS programming, and in September 2000, the Ghana AIDS/STI Commission

(GAC) was established as a supraministerial and multisectoral body under the leadership of the President to direct and coordinate all HIV/AIDS-related activities in the country (10).

The estimated national HIV prevalence for 2016 was 1.6% with an estimated 260,000 persons living with HIV and AIDS (12). The UNAIDS Ghana fact sheet states that in 2016 of all the people living with HIV only 34% currently receive antiretroviral treatment (12). The HIV epidemic in Ghana continues to be a generalised epidemic with a prevalence of more than 1% in the general population. (WHO definition for a generalised epidemic is when the prevalence is 1% or greater in the general population) (13).

HIV AND OPPORTUNISTIC INFECTIONS

Human immunodeficiency virus (HIV) is the virus that causes Acquired Immune Deficiency Syndrome (AIDS). HIV destroys the biological ability of the human body to fight off infections. An individual is said to have developed AIDS when he or she presents with a combination of signs and symptoms and has a positive HIV antibody test (11). These are grouped into major and minor signs and symptoms. The major signs and symptoms include prolonged fever (more than a month), prolonged and chronic diarrhoea (usually over a month) and significant weight loss over a period of time (more than 10% of body weight). The minor signs and symptoms include, persistent cough for more than one month, persistent skin infection, aggressive skin cancer (Kaposi Sarcoma), oral thrush (Candidiasis), recurrent shingles ("Ananse") and enlargement of the lymph glands. An individual with two of these major signs and symptoms and two of the minor signs and symptoms plus a positive HIV antibody test is said to have the disease AIDS (11).

Opportunistic infections during HIV infection are often described as secondary infections. Individuals infected with HIV are at increased risk for opportunistic infections such as Pneumocystis carinii pneumonia and disseminated Mycobacterium avium complex, as well as common pathogens such as pneumococcal pneumonia and tuberculosis. It has often been assumed that HIV-infected individuals are at increased risk for acquisition of influenza and complications related to infection with influenza (14). Although seasonal influenza and 2009 H1N1 pandemic influenza A (H1N1pdm) are both common causes of respiratory illness in HIV-infected adults (15), there are few data describing the relationship between HIV infection and influenza (16).

INFLUENZA SUSCEPTIBILITY AND SEVERITY IN HIV-INFECTED PATIENTS

Biological Aspect

HIV infection is associated with deficiencies in both humoral and cell mediated immunity that can potentially alter the course of and severity of common infections (5). CD4 T cells are important in anti-influenza defence as they stimulate B cells, which lead to production of antibodies necessary to complete viral clearance (17). They also promote the generation of memory influenza-specific CD8 T cells which help in clearing secondary influenza infections (18). Asymptomatic HIV-infected African adults have considerable signs of immune dysregulation with influenza specific CD4 T cell response in the lung (19). In a study conducted by Jambo et al. in 2012, the influenza specific proliferative CD4 T-cell responses in the HIV-infected adults with CD4 count greater than 350 were lower than those of HIV-uninfected individuals (1.44%[0.5–2.9] vs. 4.78%[1.4–10.9]; $p = 0.03$) (20).

Epidemiological Aspect

Recent studies have shown that persons with HIV are at higher risk of developing influenza than people without HIV infection. A prospective study conducted by Ho et al. (21) showed that in a setting with a high HIV prevalence, HIV infection is an important risk factor for acquiring influenza infection and for severe presentation. The rate of occurrence of influenza among HIV-infected patients was 2.7 times (95% CI=1.02, 7.44) higher than that among HIV un-infected patients, adjusted for age, gender, household crowding and food security. Another prospective surveillance study conducted by Cohen et al. (22) found that HIV-infected individuals experienced a 13-19 time ($p<0.001$) greater incidence of severe acute respiratory illness (SARI) than HIV-uninfected individuals.

Klein et al conducted a prospective surveillance study (15) in 2007 to examine the effect of influenza vaccination and influenza infection in HIV-infected patients. The study included 50 HIV-uninfected outpatients who consulted with health care providers at a large university-based HIV clinic in Montreal, Canada, for fever and respiratory symptoms. They found that 42% of HIV-infected patients had influenza A and B even though 76% had been vaccinated. However, the lack of HIV-uninfected control group limited the ability to determine how the detection rates of the respiratory pathogen in the study sample differs from the general population.

Oliviera et al., in 2009 reported that in Brazil, 1.3% (25/5747) of laboratory-confirmed influenza A(H1N1) pdm09 cases were HIV-infected whereas the HIV prevalence among the population was 0.6% (23). Ope et al. conducted a case control study to look at the risk factors for hospitalized seasonal influenza in rural western Kenya in 2011 (24). The study suggested that HIV-infection was associated with hospitalization due to influenza [adjusted Odds Ratio (aOR) 3.56, 95% CI 1.25-10.1]. Another study

showed that influenza-associated lower respiratory tract infection incidence was 4-8 times greater among HIV-infected (186-228/100,000) than HIV-uninfected persons (26-54/100,000) (25). Hence, all the above studies show that HIV-infected individuals have higher risk of influenza than HIV non- infected patients.

On the other hand, a prospective study conducted by the Pulmonary Complications of HIV Study Group examined the types of respiratory disorders that occur across the full range of HIV disease and found that HIV-infection does not increase the risk of being infected by influenza, as 4.2% of both their HIV-infected and uninfected study participants developed influenza infection (26).

SEVERITY OF CLINICAL ILLNESS

Some case series analyses have shown that persons with HIV develop more severe and/or prolonged influenza illnesses. For example, Safrin et al. described influenza infection in 6 patients who were HIV-infected in 1988 and suggested that HIV-infected patients possibly have more prolonged viral shedding and duration of illness (27). A study by Cohen et al. in 2013, investigated the incidence of hospitalization for influenza-associated acute lower respiratory tract infection and the clinical course of the illness in persons with and without HIV infection in South Africa (25). The study suggested that compared to controls, HIV-infected patients with influenza were at higher risk of developing pneumococcal infection (OR 2.3, 95% CI 1.0–5.0), longer hospitalization (OR 2.8 95% CI 1.5–5.5) and deathfrom the illness. A case series by Bogoch et al. suggested that among HIV-infected patients, those who had a lower CD4 count were at a higher risk of being hospitalized for influenza (median 240 versus 585 cells/mL; P = 0.009) (28). Moreover, Radwan et al. described how influenza infection might lead HIV-infected individuals to suffer considerable morbidity from pneumonia

due to influenza (29). The study included 80 specimens from 73 patients, out of whom 14 (19.1%) were positive for influenza A and 7 (50%) out of 14 patients were HIV-infected, and 4 out of 7 HIV-infected patients had suffered from influenza-associated pneumonia. Finally, a study in South Africa reported a much greater influenza mortality rate among adults with AIDS (defined at CD4 count <200) compared to HIV-uninfected adults (30).

In contrast, a systematic review conducted in 2011 included 11 studies that assessed the susceptibility and severity of influenza in HIV-infected patients. The study suggested that HIV infection does not appear to significantly increase the susceptibility to seasonal influenza virus but also mention that some case series and retrospective cohort studies from the Pre-HAART (HIV antiretroviral treatment) era have demonstrated an increased illness severity among HIV-infected adults, particularly, those with AIDS (16).

RISK FACTORS OF INFLUENZA

Tempia et al. conducted active syndromic surveillance of SARI and ILI patients in two provinces in South Africa in 2017 and showed that the risk of influenza associated SARI hospitalization was higher in younger age groups below 6 months of age [adjusted odds ratio, 37.6] and older ages from 6-11 months [aOR, 40.7] (31). Underlying medical condition like asthma (aOR, 3.6), diabetes (aOR, 7.1), chronic lung diseases (aOR, 10.7), chronic heart diseases (aOR, 9.6), and obesity (aOR, 21.3) also increased the risk for influenza associated hospitalization(31). A study by Campbell et al. found that the risk of a severe outcome was associated with the presence of one or more underlying medical conditions (32). Another study suggested that HIV-infected patients with severe influenza infection had comorbid conditions like obesity, chronic

obstructive disease, asthma and active smoking (28). Fezeu et al. conducted a meta-analysis showing that severely obese patients with influenza A (H1N1) (body mass index ≥ 40 kg m(-2), n = 804) were twice as likely to be admitted to ICU or die (odds ratio: 2.01, 95% confidence interval: 1.29-3.14, P < 0.002) compared with influenza A (H1N1) patients who were not severely obese (33).

Smoking causes structural changes in the respiratory tract and decrease in the immune response and hence, influenza risk is several fold higher and much more severe in smokers than non-smokers (34). HIV-infected smokers have a higher risk of severe influenza infection (35). A study by Mdodo et al in 2015 suggested that adults with HIV were nearly twice as likely to smoke and less likely to quit smoking than the general population (36). Lower risk of severe influenza is seen in people with higher education level (35).

A report published by Archer et al. in 2009, on pandemic influenza A (H1N1) virus infections in South Africa suggested that high fatality from influenza A (H1N1) was attributable to HIV infection, most of whom had active tuberculosis (37). Another study by Walaza et al. in 2015 found that among individuals with symptoms lasting more than 7 days, tuberculosis and influenza co- infection was associated with increased risk of death (adjusted relative risk ratio (aRRR=6.1, 95% confidence interval (CI) 1.6-23.4) compared to tuberculosis only infection (38). A study by Clément Méda et al. found that the risk of tuberculosis in HIV-infected patients increases due to factors like CD4 counts below 200/ul, a history of sexually transmissible infections, and a past or present history of asthma, lack of education and arterial hypertension, past or present history of cardiovascular diseases (39).

Other risk factors for influenza include environmental risk factors, such as crowded living conditions and exposure to indoor air pollution, as well as biological risk factors,

such as malnutrition and underlying infections (40). Lower risk of lower respiratory tract infection is seen in people with higher education level (35). Antiretroviral treatment can also protect against comorbidities in HIV-infected patients. Iwuji et al. in 2011 conducted a longitudinal study of a population-based cohort in Uganda that showed that individuals who had been on anti-retroviral treatment (ART) for longer than 12 months had a substantially lower rate of morbidities than those not yet on ART (41).

RATIONALE

The incidence and severity of respiratory illness and influenza infection have not been studied widely in West Africa. Data is particularly lacking for developing countries, specifically in Ghana where the prevalence of HIV infection is high and access to antivirals and medical care may be limited. This study will help understand the incidence and severity of medically attended respiratory illness (MARI), which included ILI or SARI episodes, and influenza infection among HIV-infected and uninfected individuals matched by sex, age and district of residence.

METHODS

OVERVIEW

The study was conducted in Shai-Osudoku and Ningo Prampram districts (SONPD) located in the south-eastern part of Ghana, West Africa. These districts are in the greater region of Accra, Ghana's capital. This was a prospective cohort study that aimed to determine the incidence of influenza among HIV-infected and HIV-uninfected patients over a 12-month period. The target sample size was 300 HIV-infected and 600 HIV-uninfected persons (total 900 persons).

STUDY ELIGIBILITY AND RECRUITMENT PROCESSES

Eligible participants were residents of SONPD at least 18 years of age. Residents of other districts, pregnant women, and persons who declined to undergo HIV testing were excluded from the study. HIV-infected participants were recruited from the Antiretroviral Therapy (ART) Centers of the Shai-Osudoku District Hospital, Akuse Government Hospital and Battor Catholic Hospital over a 3-month period. Study staff at the ART Centers identified HIV-infected SONPD residents during a regular medical visit and invited them to participate in the study. A Know Your HIV Status campaign was conducted in the communities of the two districts to recruit HIV-uninfected persons as controls to match HIV-infected persons. The campaign was organized by the district health administration in conjunction with the Noguchi Memorial Institute for Medical Research (NMIMR) and the National AIDS/STI Control Program from Ghana Health Service. Two HIV-uninfected individuals were matched with one HIV-infected person by age (±5 years), district of residence (either Shai-Osudoku or Ningo Prampram) and sex. The two cohorts were matched within the same week of recruitment to enable follow up of the matched pairs during the same period.

DISEASE MONITORING

Both HIV-infected and HIV-uninfected participants were monitored for influenza-like illness (ILI) and severe acute respiratory illness (SARI) over a period of 12 months. Study staff called participants every 2 weeks to ask them about respiratory symptoms. If a participant reported an ILI or SARI, the study staff asked them to go to a nearby health facility that was part of the surveillance platform or an ART center for follow-up. For the purposes of this study, ILI was defined as a respiratory illness with a history of fever or measured axillary temperature ≥37.5 °C and cough with illness onset within the last 10 days. SARI was defined as an ILI requiring hospitalization. Medically attended respiratory illness (MARI) was defined as either an ILI or SARI episode.

When a participant attended a nearby health facility or ART center after reporting an ILI or SARI episode, he/she was interviewed and asked provide either a nasopharyngeal (NP) or oropharyngeal (OP) swab for laboratory testing. They were also given medical treatment as necessary.

LABORATORY METHODS

The study was designed to collect blood samples upon recruitment, at 6 months and at 12 months. At baseline, the blood samples were tested to confirm HIV status (negative or positive), HIV-positive type (HIV 1 or 2), CD4 count and HIV-1 viral load. Blood samples collected from the HIV-uninfected participants were meant to confirm HIV-negative status.

Nasopharyngeal (NP) or Oropharyngeal (OP) swabs were obtained from all participants at recruitment by a doctor or a trained medical professional for Real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) test for influenza virus. Subsequent OP/NP swabs were collected and tested for influenza virus by RT-PCR

whenever a participant was suspected of having ILI symptoms. RT-PCR testing was conducted according to standardized protocols by the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.

OUTCOME VARIABLES AND COVARIATES

Participants who met the ILI or SARI case definitions were grouped as patients with medically attended respiratory illness (MARI) while those who did not satisfy the definition were grouped as patients without MARI. MARI patients with an influenza-positive PCR result were considered influenza-associated infections.

In order to describe the study population, counts and percentages of demographic and health covariates were calculated. These included educational status, smoking status, pre-existing medical conditions, employment status, type of housing and presence of children less than 5 years old in the household. Educational status was categorized into two groups: patients who had no education or had completed only preschool education, were classified as illiterate while patients with some education including primary, secondary, tertiary schooling and above were classified as literate. Individuals with unknown education status or missing education status were considered missing. Smoking status was categorized into two groups. Patients who reported 'Never' or had no smoking status information were categorized as non-smokers while patients who reported 'Yes', 'Yes, regularly', 'Yes, irregularly' or 'Yes, in the past' were categorized as smokers in the study. Pre-existing conditions included asthma, diabetes, hypertension, and congenital heart disease. Other pre-existing conditions for HIV-infected patients included congestive heart failure, chronic liver disease, cystic fibrosis, fibroids, stomach ulcer and hepatitis B while those for HIV-uninfected included peptic

ulcer disease, hepatitis B, knee pain, typhoid and sickle cell anemia. Pre-existing conditions were categorized into two groups: people who reported any one or more of the above pre-existing conditions, and participants who did not report any pre-existing conditions. Employment status included a wide range of occupations and was categorized as employed for those who had a job, unemployed for those who did not have a job. Type of housing was categorized as compound and self-contained. Children less than 5 years of age in the household were categorized into two groups- Patients who had one or more children less than 5 years old in their household and patients who did not have any child less than 5 years old in the household. For HIV-infected patients baseline CD4 count, antiretroviral therapy and tuberculosis infection were considered to determine if the incidence of MARI and influenza is higher among HIV-infected patients with low CD4 counts, without antiretroviral therapy and who are infected with TB. Baseline CD4 counts were classified into two categories: ≤500 and >500. Antiretroviral therapy (ART) was classified as HIV-infected patients undergoing ART and those not undergoing ART. There was no case of tuberculosis (TB) infection in HIV-uninfected patients. Hence, under HIV-infected patients, those with TB infection were categorized as positive and those without TB infection were categorized as negative for TB.

DATA ANALYSIS

All data analyses were performed using SAS® 9.4 statistical software. Participants who died during the study period were excluded and only participants who completed follow-up were included in the preliminary analysis. Participants who sero-converted from being HIV-uninfected to HIV-infected were also excluded from the analysis. Incidence rates were calculated for medically attended respiratory illness (MARI) and

influenza-associated MARI among HIV-infected and HIV-uninfected per 10,000 person-years to determine the outcome variable to be used. Person-time for HIV-infected and HIV-uninfected cohorts was calculated using the following formula:

Person-time = Number of at-risk persons in the population under study* Time period during which the events are observed.

Each study participant was followed for 12 months; thus, the total number of person-years was equal to the total number of HIV-infected or HIV-uninfected patients in the study. Overall rates and 95% confidence intervals of MARI and influenza-associated MARI were calculated for each covariate, stratifying by HIV infection status. For patients with multiple MARI episodes over the study period of 12 months, every episode of MARI was taken into account in the analysis.

STATISTICAL ANALYSIS

Descriptive characteristics of each covariate along with their chi-square p-values were determined among HIV-positive and HIV-uninfected patients. The association between HIV status and MARI episodes was examined using unadjusted and adjusted Poisson regression. Univariate analysis was done to assess the significance of each of the covariates with the outcome. Interaction was assessed using the deviance test as well as by backward selection procedure. Confounding was established using the 10% change-in-estimate rule by comparing the incidence density ratios with and without the confounder in the model. All the statistical analysis was performed using complex survey procedures in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

STUDY CHARACTERISTICS

286 HIV-infected and 513 matched HIV-uninfected participants who completed 12 months of follow-up were included in this study to measure the incidence of influenza-like illness (ILI), severe acute respiratory illness (SARI) and associated influenza infection. The median age for both HIV-infected and HIV-uninfected patients was 39 years. Overall, 80% of the HIV-infected and 78% of the HIV-uninfected patients were female. Among HIV-infected patients, 42% were from Ningo-Prampram district and 58% were from Shai-Osudoku district; among HIV-uninfected patients, 43% were from Ningo-Prampram district and 57% were from Shai-Osudoku district (Table 1). Since the HIV-infected and uninfected participants were matched by age, district and sex in a ratio of 1:2 at recruitment, similar proportions were observed in each of these categories. Among HIV-infected patients, 11% were unemployed, 32% were uneducated, 80% lived in a compound house, 4% were smokers, 12% had pre-existing medical conditions and 50% had young children less than 5 years of age in the household. Among HIV-uninfected patients, 3% were unemployed, 22% were uneducated, 80% lived in a compound house, 2% were smokers, 15% had pre-existing medical conditions and 39% had young children less than 5 years of age in the household. There was a statistically significant association between HIV status and occupation (p value= <0.001), literacy (p value= <0.001) and presence of young children in the household (p value= <0.002). The association was not significant for pre-existing medical condition, type of house, smoking status, ILI/SARI episodes with HIV status.

There were 40 (15%) medically attended respiratory illness (MARI) episodes among HIV infected participants and 4 (10%) were influenza-positive. Among HIV-uninfected participants, there were 98 MARI episodes and 11 (11%) participants tested positive for influenza. Among HIV-infected patients, 49% had their CD4 count less than 500 while 50% had counts higher than 500, 5% were positive for TB and 81% were on antiretroviral treatment (Table 2).

INCIDENCE RATE OF MARI (ILI/SARI EPISODES)

The overall rate of MARI among HIV infected was 1504 (95% CI: 1038-1970 per 10000 PY) per 10,000 person-years while that among HIV-uninfected was 1922 per 10000 PY (95% CI: 1541-2302 per 10,000 PY) (Table 3). Among HIV-infected, the rate of MARI was higher among uneducated (2099 per 10,000 PY) compared to educated participants (1065 per 10000 PY), participants with pre-existing medical conditions (3226 per 10,000 PY) compared to people without pre-existing medical conditions (1277 per 10,000 PY), among patients with at least one child less than or equal to 5 years (1880 per 10,000 PY) compared to those without children less than 5 years in household (1128 per 10,000 PY) and among participants with tuberculosis (2143 per 10,000 PY) compared to those without TB (1420 per 10,000 PY). On the contrary, the rate of MARI was lower among participants who smoked (1000 per 10,000 PY) compared to those who didn't (1523 per 10,000 PY), participants living in self-contained house (769 per 10,000 PY) compared to those living in a compound house (1731 per 10,000 PY) and participants using anti-retroviral therapy (1349 per 10,000 PY compared to those who did not (2157 per 10,000 PY). Among HIV-uninfected participants, the rate of MARI was higher among participants with pre-existing medical conditions (2027 per 10,000 PY) compared to people without pre-existing medical

conditions (1904 per 10,000 PY), participants living in self-contained house (2222 per 10,000 PY) compared to those living in a compound house (1875 per 10,000 PY) and among patients with at least one child less than or equal to 5 years (1980 per 10,000 PY) compared to those without children less than 5 years in household (1885 per 10,000 PY). The rates of MARI were lower among participants who smoked (1667 per 10,000 PY). None of the unemployed participants, whether HIV-infected or –uninfected, reported MARI (Table 3).

INCIDENCE RATE OF INFLUENZA-ASSOCIATED MARI

The overall rate of influenza-associated MARI among HIV infected was 150 (95% CI: 3-298 per 10,000 PY) per 10,000 person-years while that among HIV-uninfected was 216 per 10000 PY (95% CI: 88-343 per 10,000 PY) (Table 4). Among HIV-infected, the rate of influenza was higher among uneducated (247 per 10,000 PY) compared to educated participants (118 per 10000 PY) and participants with TB compared to those without (114 per 10,000 PY). Among HIV-uninfected, the rate of influenza was higher among uneducated (270 per 10,000 PY) compared to educated participants (203 per 10000 PY), among those who lived in a self-contained house (404 per 10,000 PY) compared to those living in a compound house (175 per 10,000 PY), participants who smoked (833 per 10,000 PY) compared to those who didn't (201 per 10,000 PY) and participants with TB compared to those without (114 per 10,000 PY); the rates were lower for participants with children less than 5 years in the household (203 per 10,000 PY) compared to those who didn't (224 per 10,000 PY). The incidence of influenza-associated MARI among HIV-infected persons without pre-existing medical conditions was 170 per 10,000 PY, for persons living in a compound house was 192 per 10,000 PY, for persons who were employed was 180 per 10,000 PY, for those who had CD4

count less than 500 was 308 per 10,000 PY and for those who used antiretroviral therapy (183 per 10,000 PY). The incidence of influenza-associated MARI among HIV-infected persons without pre-existing medical conditions was 252 per 10,000 PY and for those who were employed was 220 per 10,000 PY.

DETERMINATION OF OUTCOME VARIABLE

The numbers for patients with PCR-confirmed influenza infection were very small, which resulted in undefined incidence rates and wide confidence intervals for many covariates. In stratified analyses, several cell values were equal to zero. For example, no influenza MARI episodes were observed among HIV-infected persons with pre-existing medical conditions. The same held true for persons living in self-contained houses, persons who were unemployed, persons with CD4 counts >500 and those who were not on antiretroviral treatment. Thus, we decided to use MARI as the main outcome of interest.

REGRESSION ANALYSIS

In univariate analyses, HIV infection was not significantly associated with MARI incidence (p=0.19). Overall, HIV-infected individuals had a lower rate of MARI than HIV-uninfected (incidence density ratio [IDR]= 0.78, 95% CI 0.54-1.13). This association was not statistically significant, with a corresponding p-value of 0.19. None of the other covariates had a statistically significant association with MARI episodes (p>0.05). (Table 5). Although statistically insignificant, the incidence of MARI was higher among those who were uneducated (IDR: 1.09, 95% CI: 0.74-1.60), had pre-existing medical conditions (IDR: 1.44, 95% CI: 0.94-2.20), and reported at least one child <5 years of age in the household (IDR: 1.17, 95% CI: 0.84-1.63). The point

estimates for MARI incidence were lower among smokers (IDR: 0.76, 95% CI: 0.24-2.39), persons who lived in a self-contained house (IDR: 0.94, 95% CI: 0.62-1.45), and unemployed (IDR: 0.41, 95% CI: 0.13-1.28).

Despite having no statistically significant association with the outcome, we included all the covariates in the full model to assess interaction and confounding. Interaction assessment by each covariate with the exposure, using the deviance method, showed significant interaction between HIV status and education status (p=0.048). For this reason, the gold standard final model to assess confounding included HIV and education status and the corresponding interaction term. None of the variables were found to be confounders in the association between HIV status and MARI. Therefore, our final model included HIV status, education status and its interaction with the exposure.

The incidence of MARI among uneducated HIV-infected participants was 47% (IDR: 0.53, 95% CI: 0.31-0.89) lower than that among HIV-uninfected participants. This association was statistically significant (p=0.016). The incidence rate of MARI among HIV-infected educated participants was 23% (IDR:1.23, 95% CI: 0.64-2.36) higher than that among HIV-uninfected participants. However, this association was not statistically significant (p=0.54).

DISCUSSION

This study did not find an increase in the incidence of MARI or influenza among HIV-infected patients. This is consistent with Judd et al.'s finding that HIV status did not affect the likelihood of being an influenza index case (42). Another study by Sheth et al. reviewed the literature and found that susceptibility to influenza virus-infection is not increased in HIV-infected patients unless they have advanced immunosuppression (43). A study assessing the seroincidence of influenza among HIV-infected and uninfected men who have sex with men in Thailand found that there was no difference in the rate of seroconversion to influenza A(H1N1) pdm09 (44). A study by Safrin et al. suggested that neither clinical presentation of influenza nor rate of secondary complications appeared to be altered in HIV- infected individuals compared to HIV-uninfected (27).

Analysis adjusted for education status revealed that HIV-infected uneducated participants were less likely to develop MARI than uneducated HIV-uninfected participants and this association was statistically significant. Our study did not find a significant association between HIV status and MARI when controlled for other factors like pre-existing medical conditions, smoking, occupation status, living in a compound house and presence of children less than 5 years of age in the household A few studies suggest a high incidence of influenza-associated MARI among people who smoke or have pre-existing medical conditions (28, 35). The crude incidence of MARI among HIV-uninfected was found to be higher than that among HIV-infected patients and this association was not statistically significant.

This study found that educated patients who were HIV-infected were more likely to develop MARI. There could also be selection bias in recruitment of the HIV-uninfected population as not all HIV-uninfected persons in the community had an equal chance

of participating in the study. It could also reflect a reporting bias as people who were educated could have been more likely to report a respiratory illness.

Strengths and Limitations

There is a need to better understand the epidemiology of influenza in West African countries like Ghana. This study, aimed at measuring the incidence of influenza-associated MARI among a population infected with HIV, is the first of its kind in the region. The investigators could share their lessons learned to better design similar future studies.

The study has some limitations. The main limitation is that not all of the information was collected electronically and the call logs were filled out manually and kept in paper form. This made it difficult to count the exact number of weeks (person-time) that each participants contributed to the study. In addition, some of the data were incomplete or missing and this could have also biased the results. SARI episodes were very low which could be due to patients misdiagnosed as malaria, as is common where the disease is prevalent. Diagnostic testing for influenza in clinical settings is not a routine practice in Ghana. This could have also impacted this study. The major limitation of this study is that details relating to an outcome (e.g., date of death or seroconversion) were not available for participants who did not complete all 12 months of follow-up. Had there been enough information about person-time and MARI episodes among patients who died, a better association between HIV status and MARI could have been established.

FUTURE DIRECTIONS

Although this study has many limitations, it can be used to set the direction for future studies of a similar kind in Ghana. Studies on the burden and incidence of influenza can be used to better inform prevention and control strategies. Hence, additional more robust studies with a larger cohort and longer follow-up times in West Africa to examine the relationship between HIV infection and influenza are recommended.

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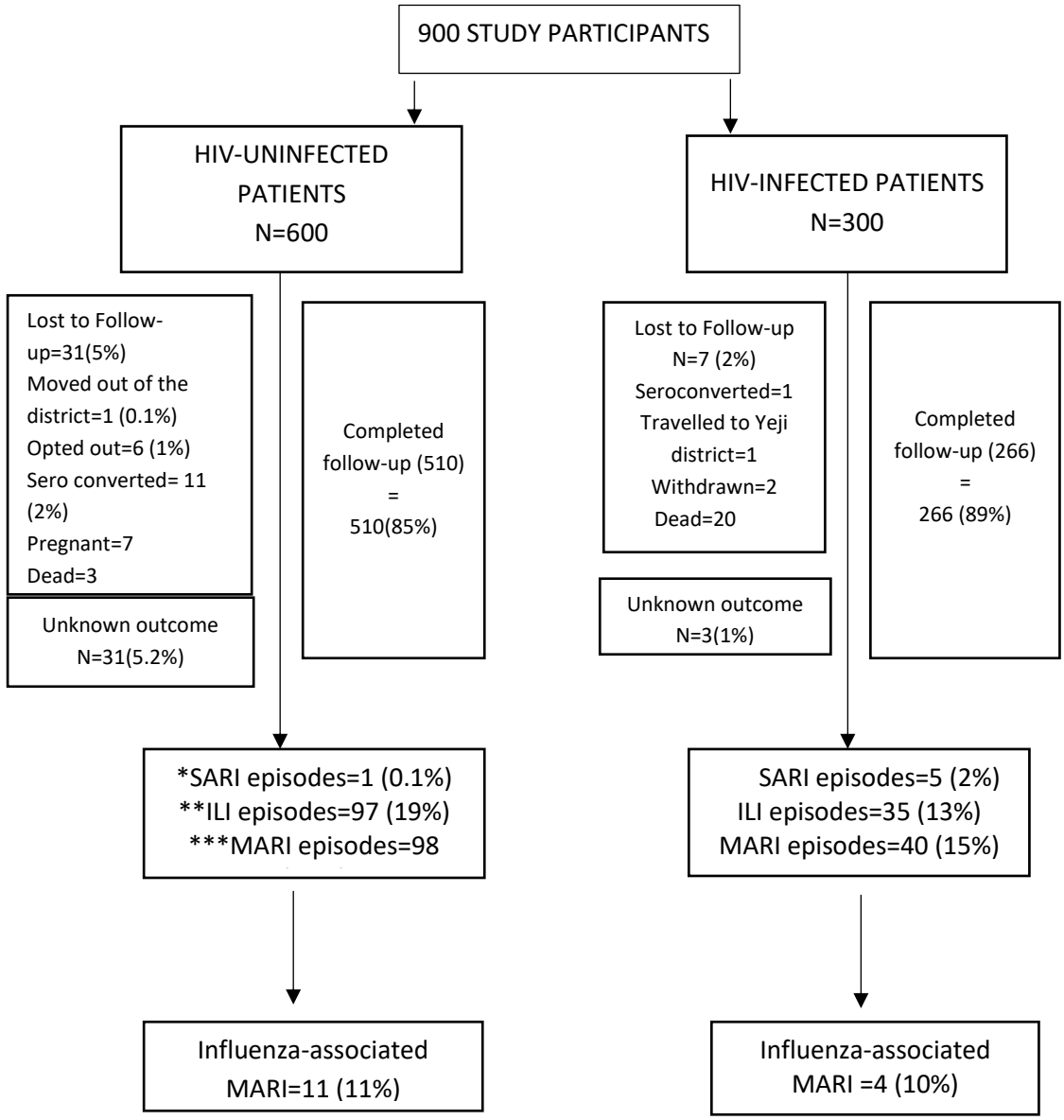
Figure 1. Total Influenza-associated MARI (medically attended respiratory illness) identified among HIV-infected and HIV-uninfected participants



*Severe acute respiratory illness
**Influenza-like illness
***Medically attended respiratory illness

Table 1. Participant characteristics among HIV-infected and HIV-uninfected participants

Characteristics	HIV-infected n(%)	HIV uninfected n(%)	P-value
Total (N)	266	510	
Age in years, median(range)	39 (33-46)	39 (33-46)	0.5689
Sex			
Female	214 (80)	397 (78)	0.5852
District			
Ningo-Prampram	111 (42)	218 (43)	0.7858
Occupation*			
Employed	222 (89)	455 (97)	<0.001
Unemployed	27 (11)	13 (3)	
Education**			
Illiterate	81 (32)	111 (22)	<0.001
Literate	169 (68)	395 (78)	
Type of House***			
Compound	208 (80)	400 (80)	0.9581
Self-contained	52 (20)	99 (20)	
Smoking Status			
Smoker(past & current)	10 (4)	12 (2)	0.2635
Non-smoker	256 (96)	498 (98)	
Preexisting Medical Condition	31 (12)	74 (15)	0.27
Asthma	7 (23)	11 (15)	
Congenital heart disease	7 (23)	25 (34)	
Diabetes	0	5 (7)	
Hypertension	10 (31)	18 (24)	
Other†	7 (23)	15 (20)	
TB	14 (5)	0 (0)	
ILI/SARI episodes	40 (15)	98 (19)	0.15
ILI	35 (88)	97 (99)	
SARI	5 (12)	1 (1)	
Influenza-positive	4 (2)	11 (2)	
Antiretroviral Therapy			
ART	215 (81)	N/A	
no ART	51 (19)	N/A	
CD4 Count at Baseline‡			
<=500	130 (49)	N/A	
>500	132 (50)	N/A	
Young Children in Household			0.002
At least one child <5years old	133 (50)	197 (39)	
No children <5 years old	133 (50)	313 (61)	

*Missing data: HIV neg=42, HIV pos=17, **Missing data: HIV neg=4, HIV pos=16, ‡Missing: 4.

Table 2a. Total medically attended respiratory illness and influenza-associated MARI episodes with person-years for each covariate among HIV-infected participants.

HIV-INFECTED PATIENTS			
	MARI (Medically attended respiratory illness)episodes (n)	**Influenza-positive MARI episodes (n)**	**Person Years**
Overall	40	4	266
Education Status			
Uneducated	17	2	81
Educated	18	2	169
Preexisting medical condition			
Yes	10	0	31
No	30	4	235
Smoking Status			
Yes	1	0	10
No	39	4	256
Types of House			
Self-contained	4	0	52
Compound	36	4	208
Occupation			
Unemployed	3	0	27
Employed	35	4	222
CD4 count at baseline			
≤500	21	4	130
>500	19	0	132
Antiretroviral Therapy			
Yes	29	4	215
No	11	0	51
Young children in household			
At least one child <5years old	25	2	133
No children <5 years old	15	2	133
Tuberculosis			
Yes	3	1	14
No	25	2	176

Table 2b. Total medically attended respiratory illness and influenza-associated MARI episodes with person-years for each covariate among HIV-uninfected participants.

HIV-UNINFECTED PATIENTS			
	MARI (Medically attended respiratory illness)episodes(n)	**Influenza-positive MARI episodes (n)**	**Person Years**
Overall	98	11	510
Education Status			
Uneducated	19	3	111
Educated	79	8	395
Preexisting medical condition			
Yes	16	0	74
No	83	11	436
Smoking Status			
Yes	2	1	12
No	96	10	498
Types of House			
Self-contained	22	4	99
Compound	75	7	400
Occupation			
Unemployed	0	0	13
Employed	89	10	455
CD4 count at baseline			
≤500	NA	NA	NA
>500	NA	NA	NA
Antiretroviral Therapy			
Yes	NA	NA	NA
No	NA	NA	NA
Young children in household			
At least one child <5years old	39	4	197
No children <5 years old	59	7	313
Tuberculosis			
Yes	0	0	0
No	0	0	510

Table 3. Incidence of medically attended respiratory illness (MARI) among HIV-infected and HIV-uninfected participants.

	HIV-INFECTED PATIENTS	HIV-UNINFECTED PATIENTS
	Rate of MARI (Medically attended respiratory illness) episodes (n)(Per 10000 PY)	**Rate of MARI (Medically attended respiratory illness) episodes (n)(Per 10000 PY)**
Overall	1504 (1038-1970)	1922 (1541-2302)
Education Status		
Uneducated	2099 (1101-3096)	1712 (942-2481)
Educated	1065 (573-1557)	2000 (1559-2441)
Preexisting medical condition		
Yes	3226 (1227-5225)	2162 (1103-3222)
No	1277 (820-1733)	1904 (1494-2313)
Smoking Status		
Yes	1000 (0-2960)	1667 (0-3976)
No	1523 (1045-2002)	1928 (1542-2313)
Types of House		
Self-contained	769 (154-1523)	2222 (1294-3151)
Compound	1731 (1165-2296)	1875 (1451-2299)
Occupation		
Unemployed	1111 (0-2368)	0 (0-0)
Employed	1577 (1054-2099)	1956 (1550-2362)
CD4 count at baseline		
≤500	1615 (925-2306)	NA
>500	1439 (792-2087)	NA
Antiretroviral Therapy		
Yes	1349 (858-1840)	NA
No	2157 (882-3431)	NA
Young children in household		
At least one child <5years old	1880 (1143-2616)	1980 (1358-2601)
No children <5 years old	1128 (557-1699)	1885 (1404-2366)
Tuberculosis		
Yes	2143 (0-4568)	0
No	1420 (864-1977)	0

Table 4. Incidence of influenza-associated MARI episodes in HIV-infected and HIV-uninfected participants

	HIV-INFECTED PATIENTS	HIV-UNINFECTED PATIENTS
	Rate of influenza positive MARI episodes (Per 10000 PY)	**Rate of influenza positive MARI episodes (Per 10000 PY)**
Overall	150 (3-298)	216 (88-343)
Education Status		
Uneducated	247 (0-589)	270 (0-576)
Educated	118 (0-282)	203 (62-343)
Preexisting medical condition		
Yes	0 (0-0)	0 (0-0)
No	170 (3-337)	252 (103-401)
Smoking Status		
Yes	0 (0-0)	833 (0-2467)
No	156 (3-309)	201 (76-325)
Types of House		
Self-contained	0 (0-0)	404 (8-800)
Compound	192 (4-381)	175 (454-305)
Occupation		
Unemployed	0 (0-0)	0 (0-0)
Employed	180 (4-357)	220 (84-356)
CD4 count at baseline		
≤500	308 (6-609)	NA
>500	0 (0-0)	NA
Antiretroviral Therapy		
Yes	186 (4-368)	NA
No	0 (0-0)	NA
Young children in household		
At least one child <5years old	150 (0-359)	203 (4-402)
No children <5 years old	150 (0-359)	224 (580-389)
Tuberculosis		
Yes	714 (0-2114)	0
No	114 (0-271)	0

Table 5. Univariate analysis of exposure and covariates to assess their association with outcome.

	IDR	95% CI	P value
HIV STATUS			
HIV-infected	0.78	(0.54-1.13)	0.19
HIV-uninfected	1		
EDUCATION STATUS (EDU)			
Illiterate	1.09	(0.74-1.60)	0.66
Literate	1		
PRE-EXISTING MEDICAL CONDITIONS (MED)			
Yes	1.44	(0.94-2.20)	0.09
No	1		
SMOKING STATUS (SMOKE)			
Yes	0.76	(0.24-2.39)	0.64
No	1		
TYPE OF HOUSE (HOUSE)			
Self-contained	0.94	(0.62-1.45)	0.79
Compound	1		
OCCUPATION (OCCU)			
Unemployed	0.41	(0.13-1.28)	0.13
Employed	1		
YOUNG CHILDREN <5 YEARS IN THE HOUSEHOLD (KIDS)			
At least one child < 5 years old	1.17	(0.84-1.63)	0.36
No children < 5 years old	1		

Table 6. Interaction assessment of each covariate with exposure.

	TYPE OF MODEL	MODEL CONTENTS	DEVIANCE	DEGREES OF FREEDOM	P VALUE*
PRE-EXISTING MEDICAL CONDITIONS (MED)	FULL MODEL	HIV,MED, HIV*MED	553.4049	772	0.053
	REDUCED MODEL	HIV,MED	557.1334	773	
EDUCATION STATUS (EDU)	FULL MODEL	HIV, EDU, HIV*EDU	537.0266	752	0.048
	REDUCED MODEL	HIV,EDU	540.9317	753	
YOUNG CHILDREN <5 YEARS IN THE HOUSEHOLD (KIDS)	FULL MODEL	HIV,KIDS, HIV*KIDS	557.0068	772	0.227
	REDUCED MODEL	HIV, KIDS	558.4629	773	
OCCUPATION (OCCU)	FULL MODEL	HIV,OCCU, HIV*OCCU	509.3438	713	0.099
	REDUCED MODEL	HIV,OCCU, HIV*OCCU	512.1055	714	
SMOKING STATUS (SMOKE)	FULL MODEL	HIV,SMOKE, HIV*SMOKE	559.3481	772	0.822
	REDUCED MODEL	HIV,SMOKE, HIV*SMOKE	559.3988	773	
TYPE OF HOUSE (HOUSE)	FULL MODEL	HIV,HOUSE, HIV*HOUSE	548.8143	755	0.068

*****P value calculated using deviance of reduced model - deviance of full model) and degrees of freedom of reduced model-full model

Table 7. Confounding assessment using 10% change in estimate method.

MODEL	Variable dropped	IDR	Within 10% limits	Confounding by variable
HIV, PREEXISTING MEDICAL CONDITION (MED), EDUCATION STATUS (EDU), YOUNG CHILDREN IN HOUSEHOLD (KIDS), OCCUPATION (OCCU), SMOKING STATUS(SMOKE), TYPE OF HOUSE(HOUSE), HIV*EDU	Gold standard	0.55 (10% change in estimate limits (0.50,0.61)	-	-
HIV, PREEXISTING MEDICAL CONDITION (MED), EDUCATION STATUS (EDU), YOUNG CHILDREN IN HOUSEHOLD (KIDS), OCCUPATION (OCCU), SMOKING STATUS(SMOKE), HIV*EDU	TYPE OF HOUSE(HOUSE)	0.55	Yes	No
HIV, PREEXISTING MEDICAL CONDITION (MED), EDUCATION STATUS (EDU), YOUNG CHILDREN IN HOUSEHOLD (KIDS), OCCUPATION (OCCU), HIV*EDU	SMOKING STATUS(SMOKE)	0.55	Yes	No
HIV, PREEXISTING MEDICAL CONDITION (MED), EDUCATION STATUS (EDU), YOUNG CHILDREN IN HOUSEHOLD (KIDS), HIV*EDU	OCCUPATION (OCCU)	0.52	Yes	No
HIV, PREEXISTING MEDICAL CONDITION (MED), EDUCATION STATUS (EDU), HIV*EDU	YOUNG CHILDREN IN HOUSEHOLD (KIDS)	0.54	Yes	No
HIV, EDUCATION STATUS (EDU), HIV*EDU	PREEXISTING MEDICAL CONDITION (MED)	0.53	Yes	No

Table 8. Incidence density ratios of HIV-infected participants compared to HIV-uninfected patients controlling for education status.

Final Model	HIV-infected	HIV-uninfected	P-value
	IDR	IDR	
Education Status =0	0.53 (0.31-0.89)	1	0.016
Education Status=1	1.23 (0.64-2.36)	1	0.542

*Final model controlled for education status and its interaction with HIV status.