Respiratory Tract Infections and Household Fuel Use in HIV-Infected Kenyan Infants

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Abstract

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Background: Acute respiratory infections (ARIs) are the largest contributor to child morbidity and mortality worldwide. HIV-infected children are particularly susceptible to ARIs. Little data exists on the incidence and cofactors of ARIs in HIV-infected infants receiving early antiretroviral therapy (ART). Household air pollution from wood (high polluting), charcoal, or kerosene (both medium polluting) fuel may also exacerbate risk of ARIs in HIV-infected children compared to exposure to petroleum gas (low polluting). We examined the burden of fuel use and HIV infection on ARI risk in HIV-infected infants receiving ART.

Methods: HIV-infected infants initiated ART at ≤12 months of age and were followed monthly for 2 years in Nairobi, Kenya. AT 4-6 years post-ART initiation, fuel exposure was collected on the survivors within this cohort. ARI rates and cofactors were determined using Andersen-Gill models.

Results: Among 111 HIV-infected infants (49% male) initiating ART, the median age at ART initiation was 4.5 months. Pre-ART, the median CD4% was 19% and HIV-1 RNA was 6.6 $\log_{10}$ copies/ml. Most infants (29%) were wasted (weight-for-height Z-score <-2). At 2-years post-ART, upper respiratory infection (URI) and pneumonia rates were 118.9 and 32.7 per 100 person-years, respectively. In univariate analyses, lower monthly rent (<1000 Kenya Shillings), higher plasma HIV-RNA level (per 1 $\log_{10}$copies/ml increase) and wasting were associated with pneumonia (hazard ratio (HR) =3.62; p=0.0001; HR=1.91; p = 0.01 and HR=2.82; p=0.001, respectively), and these associations remained in adjusted models (HIV RNA, p=0.1; wasting, p=0.07; rent, p=0.01). At 2-years post-ART, URI and pneumonia rates in those infants for

whom fuel exposure data were collected (N=45) were 122.2 and 15.6 per 100 person-years respectively. Of these infants, 4.1% had wood, 64.6% had charcoal and/or kerosene, and 30.4% had liquid petroleum gas exposure, which was often used in combination with higher polluting fuels. In univariate analysis, lower monthly rent was associated with pneumonia (HR=7; p=0.02). Wood exposure was associated with higher risk of URI (HR=1.74; p = 0.004).

Conclusions: In early treated HIV-infected infants, lower monthly rent, and wasting prior to ART were independent risk factors for pneumonia, and infants with wood exposure had higher URI. Future effective strategies need to be implemented to decrease this ARI risk in HIV-infected infants.

I. Specific Aims

Aim 1: To characterize incidence and determine cofactors for acute respiratory infections (ARIs) in early treated Kenyan HIV-infected infants.

Hypothesis 1: Among early treated HIV-infected Kenyan infants, low CD4% and high HIV RNA viral load prior to antiretroviral therapy (ART) will be associated with higher incidence of respiratory tract infection post-ART treatment.

Aim 2: To characterize the prevalence of household fuel exposure and determine cofactors for use of high and medium polluting fuels versus low polluting fuels within households of Kenyan HIV-infected infants.

Hypothesis 2: Among HIV-infected infants, use of high (wood) and medium polluting fuels (charcoal and kerosene) will be common. Use of both of these fuels will be associated with lower socioeconomic status, as indicated by lower household monthly rent, fewer years of maternal education, smaller houses, and lack of flush toilets.

Aim 3: To characterize the relationship between household fuel exposure (high and medium polluting fuels versus low polluting fuels) and ARI risk among HIV-infected infants during 2 years of follow-up post-ART.

Hypothesis 3: Exposure to high and medium polluting fuels will be associated with higher incidence of respiratory tract infections, particularly pneumonia both prior to ART and while on ART.

II. Introduction

Contribution of Acute Respiratory Infections in Under 5 Mortality Globally

Globally, acute respiratory tract infections (ARIs) are the leading cause of under-5 child morbidity and mortality in developing countries.[1,2] The incidence of ARIs is 10 times greater in resource poor countries compared to resource rich countries.[3,4] In children under 5 years, pneumonia incidence in resource rich settings is 2.6 to 4.0 events per 100 child-years[3,4] compared to 29 per 100 child-years in resource poor settings.[3] ARIs, principally pneumonia[3], contribute to over 1.7 million deaths, which comprise a staggering 18% of childhood deaths worldwide.[5]

The majority of ARI-related deaths are concentrated in sub Saharan Africa,[7,6] a region of the world where 90% of HIV-infected children reside.[7] HIV-infected children have a 3-fold higher risk of ARI than HIV-uninfected children (RR: 3.0, 95%CI: 1.9, 4.8) [8,9,10,11,4,12] Globally, HIV-infected children are 6.5 times more likely to be hospitalized for pneumonia compared to HIV-uninfected children (95%CI: 5.9, 7.2) and have a 6-fold increased risk of mortality from pneumonia (95%CI: 2.7, 12.7).[13] Studies from South Africa and Malawi indicate an HIV prevalence of 45-62% among children hospitalized for severe pneumonia with case fatality rates 3-6 times higher in HIV-infected children.[11,14] HIV-infected children are at increased risk for bronchiolitis, bronchitis, lymphoid interstitial pneumonitis, tuberculosis, asthma, and other lower respiratory tract conditions which can lead to long term respiratory complications[15] contributing to chronic lung disease.[16] ARIs are associated with more severe disease in HIV-infected children as well as a higher case fatality rate.[17] In a South African study of HIV-infected infants, pneumonia accounted for 75% of mortality.[18] The pneumonia mortality rate in another study was 20.5% in untreated HIV-infected versus 8.1% in HIV-uninfected infants (p=0.008).[19] In Kenya, HIV and pneumonia are the top 2 causes of years of life lost (Global Burden of Disease 2013).[20] Kenya

is one of 15 countries with the highest number of under 5 childhood deaths due to pneumonia, with a pneumonia mortality rate of 50.3 per 10,000 in the under 5 population.[2] HIV is also a leading cause of mortality in Kenya.[21]

Continued ARI Burden despite Expanded Antiretroviral Treatment

With the advent of antiretroviral therapy (ART), hospitalizations of HIV-infected infants have decreased and survival has improved[22], however ARI burden persists.[23,24] Pneumonia rates in older HIV-infected children on ART[23,24,25] range from 2.1 per 100 person years[25] in the United States to 18.7 per 100 person years in Zambia.[26,27] Pneumonia rates decreased from 6.07 to 2.17 per 100 child-months following ART in a study from Cote d'Ivoire.[16] In one study, 36% of hospitalizations after ART were attributed to pneumonia.[28] Pneumonia also remains an important cause of mortality in children on ART.[22,29,30]

Early ART administered between 6-12 weeks of life resulted in 76% reduced mortality compared to infants with ART deferred until symptomatic in the CHER study from South Africa.[22] In this study, pneumonia rates were 12.2 per 100 person-years vs 26.5 per 100 person-years in the early ART vs deferred ART groups, respectively.[22,29,30] Unfortunately, around 70% of children do not receive ART due to delayed diagnosis or poor access, which increases the risk for long term airway destruction.[8,31]

ARI risk factors in general include low birth weight, malnutrition, lack of breastfeeding, crowding, and air pollution both indoors and outdoors.[1] Additional factors include low parental education, living under impoverished conditions, parental smoking, vitamin A and zinc deficiency, and shorter duration of mother's experience as a caregiver.[2,4,32] For HIV-infected children in

resource poor settings, ARI risk factors include low birth weight, absence of breastfeeding, poor nutrition, high viral load pre-ART, and low CD4% pre-ART.[25,33 16]

Household Indoor Air Pollution in Developing Countries

The WHO estimates that household air pollution (HAP) is responsible for 2 million child deaths in developing countries annually, half in children less than 5 years of age.[1,34,35,36] Three billion people worldwide rely on biomass fuel (animal dung, agriculture residues, wood, and charcoal – all solid fuels), coal, and kerosene [('paraffin' (non-solid fuel)] as their fuel source for cooking, heating, and lighting their homes. Greater than half of this population resides in developing countries with an estimated 90-95% of rural households using these fuels.[37,38] Since 2010, air pollution from solid fuels has been one of the three leading risk factors for childhood disease burden in Africa,[39] and has accounted for the third highest disability-adjusted life years for children 0 to 4 years of age.[40]

Household Air Pollution and Indoor Fuel Pollutants

Household air pollution (HAP) is comprised of particles and gases which are associated with multiple mechanisms of adverse effects on host defense against respiratory infections. Indoor pollutants arise from multiple sources such as the use of open fires or the combustion of biomass fuels, coal, and kerosene. The combustion of household fuels leads to toxic products such as particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), carbon monoxide (CO), nitrogen dioxide, sulfur dioxide, and nitrogenated compounds. Particulate matter is defined by the Environmental Protection Agency (EPA) as a mixture of small particles and liquid droplets composed of various components including nitrates, sulfates, organic chemicals, metals, and soil or dust particles.[41] Respirable PM includes PM_{10} (≤10μm) which can deposit in the upper respiratory tract and large airways, whereas $PM_{2.5}$ (≤2.5μm) may additionally penetrate terminal bronchioles and alveoli.[42] The pediatric respiratory toxicity of PM is well

established with smaller size fraction $PM_{2.5}$ considered the more toxic. PM is associated with respiratory illness, respiratory symptoms, asthma exacerbation, and reduced lung function development.

Polyaromatic hydrocarbons (PAHs) are among the most highly toxic components released during incomplete combustion of organic matter and associated with combustion related PM. Greater than 80% of PAHs result from combustion of biomass fuels[43,44] and kerosene used for cooking.[45] PAHs include fluorine, pyrene, benzanthracene, benzofluoranthene, and idenopyrene. These compounds lead to chronic inflammatory changes in the airways and alveoli[46-49] via neutrophil and macrophage activation. These effects may potentiate the inflammatory effects HIV has on the lung tissue, thus increasing the risk of lung damage in HIV-infected individuals.[50] Additionally, CO produced from the combustion of fuels has been implicated in having detrimental impacts on fetal development because the CO binds with hemoglobin to produce carboxyhemoglobin, which may reduce oxygen delivery to the developing fetus.[51] This depletion can lead to poor growth (low birth weight and long-term stunting)[52] and anemia,[53] which are each common in HIV-infected infants and children.[29,54]

Household Air Pollution and the Importance of Concentrations of Indoor Fuel Pollutants

Concentrations of the substances released during fuel combustion are important to classify the health impacts of indoor air pollution. The WHO ambient air guidelines and US Environmental Protection Agency regulatory standard for annual average PM_{10} is <50ug/m^3.[55] Individuals living in developing nations may be exposed to concentrations ranging from up to 200ug/m^3 to 5,000ug/m^3 or greater depending on the fuel and stove type used, and housing structure.[47,56] A child's risk of ARI from HAP exposure varies with the concentration of exposure to particulate matter with increased risk for exposures above 200ug/m^3. Children exposed to 200-500ug/m^3

have a 2.42 increased risk of ARI (95%CI: 1.53,3.83, p<0.001) and those exposed to 1000-2000ug/m^3 have a 4.30 increased risk of ARI (95% CI: 2.6, 7.04; p<0.001).[57]

Certain fuels emit higher concentrations of particulate matter, PAHs, and CO. Ranging from highest to lowest concentrations, these fuels include dung, crop residues, wood, charcoal, coal, paraffin, and liquid petroleum gas.[56,58] Classifying fuels by their PM concentrations serve as a basis as categorizing household air pollution into high polluting fuel (crop residues, dung, wood), medium polluting fuel (charcoal, coal, paraffin), and low polluting fuel (liquid petroleum gas).[59] Environmental sampling techniques may be used to measure HAP exposure by measuring amount of particulate matter, CO, and PAHs in air samples from homes; however several studies have utilized type of fuel use as a less resource intensive proxy for severity of HAP exposure.[56,59-61]

Multiple factors influence the level of HAP exposure, including the fuel-stove combinations, home characteristics, amount of time spent inside house, and cooking practices.[62] For example, pollutant exposure is higher among women who do most of the cooking and among children who stay indoors and are frequently carried on their mother's back or laps while cooking.[60] Exposures to these substances during a child's respiratory system development – which can occur up until the age of 8 – have adverse consequences on both the structure and function of their respiratory tracts.[63]

Impact of Household Air Pollution on Child Respiratory Health

Infants and young children are particularly vulnerable to the health impacts of household air pollution compared to adults. Children's higher respiratory rates accompanied with the smaller surface area of their lungs make it likely that the inhaled pollutant dose will have greater impacts

on their lungs. Furthermore, children's narrow airways relative to adults can cause significantly greater irritation with subsequent obstruction compared to the effects seen in adults' wider caliber airways.[64] Infants have increased airway edema than adults due to their larger mucous glands with increased secretions accompanied with less tightly adherent airway mucosa. In addition, infants' smaller quantity of interalveolar pores increase the susceptibility to hyperinflation and atelectasis.[63] Household air pollution emissions may also increase ARI risk by weakening defense mechanisms in the lung and weakening immune responses.[65] The emissions impact the respiratory tract's non-specific immune responses by weakening upper airway filtration mechanisms and the mucociliary apparatus. These emissions may also target specific humoral and cellular immunity, with a Chinese cross sectional study determining an association between charcoal use and lower serum IgG levels.[56,65] Another cross-sectional analysis found a relationship between higher carbon content of airway macrophages and decreased forced expiratory volume (FEV1), forced vital capacity (FVC), and forced expiratory flow (FEF) in children living in the US where the pollution was mostly due to emissions from road traffic.[66] Aggregates of fine carbon are thought to decrease the bactericidal activity of airway macrophages, thus decreasing their properties to kill bacterial pathogens that are the main culprit for many respiratory infections including pneumonia.[67] In addition, particulate matter triggers phagocytosis inhibition and oxidative burst impairment in alveolar macrophages, resulting in weakened defense against pathogens. Particulate matter also has a dose dependent inflammatory response in lung cells and macrophages. [68]

Impact of Household Air Pollution on Child Respiratory Health in Developing Countries

Several studies have demonstrated an association between HAP and increased risk of developing ARIs in HIV-uninfected populations less than 5 years of age. Among 3,559 Zimbabwean children, exposure to high and medium polluting fuels was associated with a two-

fold increased risk of ALRI.[60] In a longitudinal study of national surveys in India, high vs low polluting fuel exposure was significantly associated with ALRI (OR,1.53; 95% CI: 1.21-1.93) in children less than 3 years of age.[59] Another longitudinal study in India determined that children less than 6 years who lived in households using solid fuels were 1.78 (95%CI: 1.05-2.99) fold as likely to suffer from an ALRI as those living in households using other fuels (kerosene or liquid petroleum gas).[69] A meta-analysis of 9 studies found 2.5-fold increased risk of ALRI for children under 5 years with HAP exposure.[46] Studies also suggest a significant association between otitis media, a form of AURI, and smoke exposure.[70,51,70,71] Among 103 hospitalized Nigerian preschool-aged children, there was a 12-fold increased risk of ALRI-associated death for children in households with wood exposure compared with kerosene or gas ($p<0.0005$).[72] The 2008-2009 Kenya Demographic and Health Survey found respiratory infection symptoms in children less than 5 to be prevalent in 8% of children who lived in a home that used wood fuels for cooking, 8.7% in homes that used kerosene, 7% in homes that used charcoal, and 3.3% prevalent if from homes that used electricity or gas.[73] Within Kenya, the type of fuel used is associated with whether one lives in urban or rural households. In rural households, wood use predominates, whereas in in urban households charcoal use predominates.[73]

Rationale for Hypothesized Vulnerability of HIV-infected Infants to HAP related Respiratory Illness

Household air pollutants and the human immunodeficiency virus have individually both been shown to diminish the immune system's response to invading pathogens and enhance airway inflammatory responses. Similar to the pollutants from burning fuels, HIV targets the humoral and cell mediated immune responses. Host defenses in the lower respiratory tract are provided by alveolar macrophages, lymphocytes, and polymorphnuclear cells, which are all affected by HIV leading to compromised host defense functions.[67,68,74,75] These weakened immune responses along with persistent immune activation and inflammation despite sustained ART[76],

increases the lungs susceptibility to pathogens which cause respiratory infections in infants and children. If these cumulative effects of pollutants are compounded with sustained pulmonary inflammation in an HIV infected infant, [77,56,78] it is reasonable to believe this will lead to further increased risk of ARI as well as increased risk of chronic lung disease as these children age.[22,19]

The majority of HIV-infected children reside in sub-Saharan Africa, where respiratory tract infection and household indoor air pollution prevalence is very common. Given the elevated background rates of ARIs in HIV-infected children and the significant association of ARIs with HAP, it continues to be important to assess the association between HAP and ARI risk in the context of HIV-infected children. To our knowledge, the impact of fuel use in HIV-infected and treated infants has never been examined.[35] This retrospective study will examine the post-ART incidence rates of acute respiratory infections in a cohort of early-treated HIV-infected infants from Nairobi, Kenya. The prevalence and cofactors for fuel exposure in HIV-infected Kenyan infants will be determined. Finally, the relationship between fuel exposure and ARI in this cohort will be explored.

III. Methods

Study Populations and Follow-up

Infants included in this analysis participated in 2 randomized clinical trials involving ART initiation at the time of enrollment and 2 years of pre-randomization follow-up. Study participants were from Optimizing Pediatric HIV-Therapy (OPH) 03 and 612 cohorts, which took place in Nairobi Kenya. Enrollment for this study was from 2007-2009, and included 154 infants HIV-infected infants. These infants were identified at PMTCT (prevention of mother to child transmission) clinics or at the hospital wards, where they received infant HIV-1 DNA polymerase chain reaction tests and initiated ART immediately after HIV-diagnosis confirmation (Figure 1).

The details of the OPH 03 study enrollment have been described elsewhere.[29] The OPH 612 cohort included 34 infants between 6-12 months who were ART-naïve and immediately randomized to an ART regimen. These infants all had a history of PMTCT. The OPH03 cohort included 99 infants less than 4.5 months of age who were ART naive who were followed for 24 months on ART prior to randomization. Additional inclusion criteria were 1) HIV-DNA positive diagnosis, 2) no previous ART except for ART drugs used during PMTCT, and 3) caregiver planned to reside in Nairobi for 3 years. Before 2009, infants with suspected active tuberculosis were excluded from the OPH612 cohort. The original 2 randomized control trial studies were approved by Kenyatta National Hospital/University of Nairobi Ethical Review Board and University of Washington Institutional Review Board. This secondary analysis falls under the existing human subjects application.

Data Collection

Infants attended monthly follow up visits at which current and past respiratory illness/symptoms or hospitalization, and growth parameters were ascertained in clinic through questionnaires and a physical exam by trained personnel. Blood samples for ascertainment of 3-monthly plasma HIV RNA levels, and 6-monthly CD4 were obtained from participants during these visits. The CD4 counts and percentages were obtained with flow cytometry and plasma HIV RNA levels were determined with the Gen-Probe HIV Viral Load Assay.[79]

Respiratory Outcomes

Infants were evaluated for respiratory conditions at enrollment and at monthly visits thereafter via physician administered physical examination and ascertainment of respiratory signs/symptoms. Respiratory conditions assessed during these visits include upper respiratory infection, otitis media, bronchiolitis, pneumonia, and tuberculosis. For this study, acute

respiratory infection (ARI) will be subdivided into upper respiratory infection (URI) and acute lower respiratory infection (ALRI). The case definition of an URI and ALRI are similar to the World Health Organization (WHO) definitions.[56,80,45,81] however pneumonia, bronchiolitis, and tuberculosis will be the only ALRI outcomes assessed. In our study, these diagnoses were made by clinicians during monthly follow up visits. Acute upper respiratory infection and pneumonia are two outcomes which were focused on in depth in the analysis. The case definition of URI was a history of cough or runny nose with or without fever, with absent fast breathing and normal chest exam. The pneumonia case definition was given to an infant who presented with a cough, fever, and fast breathing, with possibility of respiratory examination consistent with tachypnea, lower chest in-drawing, nasal flaring, grunting, and coarse crackles on auscultation. The respiratory conditions will be collectively referred to as 'ARI' throughout our study.

Fuel Exposure

Type of fuel used in the household was ascertained at 4-6 years post-ART initiation for 60 HIV-infected children who were followed monthly following ART initiation as infants. Caregivers were asked the following question "What type of exposure is in the home? (tick all that apply)" and chose from the following responses: "cigarette smoke, charcoal stove, biomass (eg. dung) fuel, indoor firewood, paraffin stove, other (specify)". The majority of responses in the 'other' category was liquid petroleum gas or other forms of clean gas. In some analyses, classification of fuels for analysis was divided into those children exposed to 'any liquid petroleum gas' versus those children exposed to 'no liquid petroleum gas'. Additional analyses including indicator variables for exposure to each fuel type were also performed. These models included indicators for LPG, charcoal, paraffin and wood simultaneously.

Statistical Analysis

Incidence of respiratory infections post-ART initiation was calculated using Andersen-Gill models. Andersen-Gill model provided the benefit of calculating multiple events per infant over a longitudinal time period. Stata 13.1 software was used for statistical analysis. The association between ARI and various cofactors for ARI were determined using Andersen-Gill models. Multivariate analyses were performed to determine independent cofactors for respiratory tract conditions in infants. Primary cofactors of interest were higher plasma RNA level and lower CD4% pre-ART and fuel type infants were exposed to in their homes. Secondary cofactors of interest included low birth weight, poor growth outcomes at time of ART initiation, prior hospitalization, advanced WHO clinical stage, and socioeconomic status variables (years of caregiver education, household monthly rent, number of rooms in home). Prevalence and cofactors for fuel use were determined using chi square tests (for dichotomous variables) and Wilcoxon rank sum tests (for continuous variables). Primary cofactors of interest are socioeconomic status as indicated by monthly rent, number of rooms in house, level of education, and access to flush toilet.

IV. Results

Study Population

One hundred and eleven HIV-infected infants were enrolled in this study. The number of infants who remained in our study at 6 months, 12 months, and 24 months were 78, 75, and 71 respectively. Sixty infants had fuel exposure data (Figure 1) and forty-six of them had data for ARI incidence from the time of ART initiation. Among 111 HIV-infected infants (49% male) who initiated ART, the median age at ART initiation was 4.5 months (IQR, 3.7, 6.9) and median birth weight was 3 kg (IQR, 2.7, 3.4) with 12% <2.5kg at birth (Table 1). Infants overall were sick and had a median CD4% of 19% (IQR, 14, 25) with 28.2% infants with CD4% <15%, and a median

plasma HIV-1 RNA of 6.57 (log_{10}copies/mm^3). Almost half of all infants (46.8%) had WHO clinical stage III/IV and 58.6% had at least one prior hospitalization since birth. The majority of infants (82.5%) were ever breastfed and 43.2% were themselves or had mothers who were recipients of PMTCT. More than half of all infants (56.4%) were underweight (WAZ < -2), 50% were stunted (HAZ < -2), and 29.1% were wasted (WHZ <-2). All of the infants' caregivers were female and had a median age of 26 years (IQR, 23, 31) with 78.4% married. When looking at socioeconomic indicators for this cohort of infants, 68.2% of the infants' caregivers were employed and the median household monthly rent was 1500 KES (Kenya Shillings) (IQR, 1200, 2650). More than one third of caregivers (38.2%) had greater than a primary level education with median years of education of 8.5 years. About one fifth (18.9%) of these infants came from a household which used a flush toilet. About three-quarters (77.5%) of these infants were living in a home which had only one room, with a median of 4 people living in a home (IQR, 3, 5).

Respiratory Infection Burden

A total of 96 infants had at least one episode of upper respiratory tract infection (URI). Of these infants, 69 infants had more than 1 episode. A total of 35 infants had at least one episode of pneumonia and of these infants, 9 infants had more than 1 episode (Table 2a). The two year post-ART initiation URI incidence rate was 118.9 per 100 person-years (95% CI: 102.8, 137.4) and the two year pneumonia incidence rate was 32.7 per 100 infant years (95%CI: 24.7, 43.1) (Table 2b).

Cofactors of Upper Respiratory Tract Infection and Pneumonia

There were no cofactors associated with increased URIs except for prior PMTCT which was associated with a decreased URI incidence (HR=0.89; p=0.05) (Table 3a).

Pneumonia incidence was associated with several baseline factors, including higher plasma HIV RNA (per 1 $\log_{10}$copies/ml increase), wasting (WHZ<-2), lower WAZ, lower caregiver education, and lower monthly rent (<1000 Kenya Shilling <KES>) (Table 3b). For every 1 $\log_{10}$copies/mm^3 increase in plasma HIV-RNA, infants had a 2-fold increased risk of pneumonia (HR, 1.91, 95% CI: 1.15, 3.16; p=0.01). Infants who were wasted at baseline had a 3-fold increased risk of pneumonia (HR, 2.82, 95%CI: 1.54, 5.18; p=0.001). When analyzed as a continuous variable, lower WAZ was significantly associated with increased pneumonia risk (HR, 0.83, 95% CI: 0.69, 0.99; p<0.04). Infants were at 3.7-fold increased risk for pneumonia if they lived in a home that had a low monthly rent (HR, 3.69, 95%CI: 2.03, 6.72; p=0.0001). Each additional year increase in caregiver education led to decreased risk of pneumonia (HR, 0.86, 95%CI: 0.76, 0.97; p=0.01). WHO Stage 3 or 4 was also associated with a trend for increased risk of pneumonia (HR: 1.80, 95%CI: 0.94, 3.45; p=0.07) (Table 3b). In multivariate analysis controlling for viral load, wasting, and monthly rent, each of these associations with pneumonia remained significant suggesting independent effects on pneumonia risk (Table 4).

Prevalence of Fuel Use and Cofactors for Fuel Use

Sixty children had data for household fuel use. The predominant fuels used in each household were medium polluting fuels (charcoal, kerosene); 5.1% had wood, 64.6% had charcoal and/or kerosene, and 30.4% had liquid petroleum gas exposure, which was often used in combination with higher polluting fuels. The majority of these children were exposed to more than one type of household fuel (Figure 2). Cofactors for use of any liquid petroleum gas (LPG) included greater caregiver education (p=0.06), living in a home with more than 1 room (p=0.007) and a flush toilet (p=0.001). Infants with LPG exposure had a lower mean CD4% (16% vs 21%; p=0.03) and had a lower mean WHZ than those with no LPG exposure (WHZ: -1.8 vs -0.6; p=0.04) (Table 5).

Acute Respiratory Infection Burden in Infants Surviving to >4 years Post-ART

In analyses restricted to those infants who were still in follow-up at >4 years post-ART (for whom there was fuel exposure data), the 2 year URI rate was 122.2 per 100 infants years (95% CI: 101.4, 147.3) and the pneumonia rate was 15.6 per 100 infant years (95%CI: 9.2, 26.3) (Table 6).

Among this cohort of infants, infants exposed to LPG had a trend for lower URI incidence than those not exposed to LPG (75 versus 132.4 per 100 person years, p=0.2) (Table 7). Exposure to indoor firewood was associated with a significantly higher risk for URI compared to infants exposed to no firewood (HR 1.74; 95%CI 1.29, 2.52; p = 0.004) (Table 8b). This association remained after adjustment for caregiver education (Table 8b). Exposure to firewood was associated with increased pneumonia risk, but not significantly (HR 2.56, CI: 0.69, 9.54; p=0.2) (Table 8b).

Lower household monthly rent (<1000 KES) remained significantly associated with a 2 fold increased risk of URI (HR=1.49, 95%CI: 1.01, 2.21; p =0.04) and 7 fold increased risk of pneumonia (HR=7.00, 95%CI: 1.44, 34.1, p=0.02). WAZ<-2 and WHZ <-2 were each associated with a trend for increased pneumonia (Table 9).

V. Discussion

In this study of acute respiratory infections in HIV-infected infants in Kenya, the 2-year incidence rate for pneumonia was 32.7 per 100 person-years while the incidence rate for upper respiratory infection was 118.9 per 100 person-years. Cofactors associated with the higher risk of pneumonia in our entire cohort were higher viral load, wasting, lower caregiver education and

lower household rent. The majority of households used charcoal and/or kerosene. The risk of URIs in infants in households that use wood fuel was 2 times greater than infants in households that did not use wood fuel. Wood exposure was also associated with a trend for increased pneumonia risk. Collectively, our findings point to the high incidence of ARIs in ART-treated HIV-infected infants and HIV-related and sociodemographic factors that increase this risk, including household air pollution. There is need for future studies to explore the possible synergism between air pollution and HIV on risk of ARIs, and need for interventions to decrease indoor air pollution.

The pneumonia incidence rate in our study (32.7 per 100 person-years) is comparable to the under 5 year of age global pneumonia incidence rate of 28 events per 100 person-years reported by the World Health Organization for the general population.[3] Similarly, a Kenyan study that followed children for 2 years reported pneumonia incidence rates in children less than 5 years of age to be 21 per 100 person-years.[4,82] In a study of HIV-infected infants, pneumonia incidence was 12.2 per 100 person years among children receiving early ART versus 26.5 per 100 person years for the delayed treated children (median age of treatment at 5 months) in the CHER study in South Africa.[22] Our results are comparable to the deferred treated children in the CHER trial. Similarly, in Zambian ART-treated infants, URI incidence was 68.5 per 100 person years and pneumonia 24.9 per 100 person years.[83] In our study, the 2-year pneumonia incidence rate for the subset with prolonged follow up post-ART for at least 4 years was 15.6 per 100 person-years while the URI rate was 122.2 per 100 person-years. The pneumonia rate for this subset of infants is much lower compared to the overall cohort, likely due to survivorship bias.

We found that baseline higher plasma HIV viral load was associated with a 2 fold increased risk of pneumonia. Peak plasma virus levels are associated with HIV disease progression in

children.[84-90] A systematic review of 17 studies of treated HIV-infected children in sub-Saharan Africa reported high pre-ART viral load to be associated with mortality.[91] Pre-ART viral load has also been associated with risk of hospitalization in children.[28] Severe pneumonia has been found to be more prevalent in children with high baseline RNA viral loads.[33] In our study, more than half of infants were diagnosed with HIV at the hospital, and among these children, acute sickness, possibly pneumonia, led to their initial HIV diagnosis.

Prior studies have reported associations with immunosuppression and increased risk of pneumonia.[16,83] However, in contrast to plasma HIV RNA levels, we found no significant association between CD4% and pneumonia risk. Those most severely immunosuppressed may have died before an ARI could be diagnosed.[83]

Wasting (WHZ<-2) was significantly associated with a 3-fold increased risk of pneumonia. About one third (29%) of all infants were less than 2 standard deviations below their expected weight for height. Undernutrition has been shown in prior studies to be associated with ARIs in general.[92] A systematic review found a dose response relationship between decreasing WAZ and increasing risk of ALRI mortality.[93] Undernutrition is also a predictor of mortality in HIV-infected infants.[94,29] Undernutrition and HIV disease contribute to a vicious cycle which leads to further destruction of the immune system. Malnourished children have multiple vitamin and mineral deficiencies and also have reduced cell mediated immunity.[95] The combination of HIV and undernutrition places children at risk for ALRI, as was evident in our study. A systematic review of baseline cofactors and post-ART outcomes HIV infected children revealed associations between baseline CD4%, viral load, and low WAZ as a risk factor for mortality.[96] The interplay of these factors is complex and stresses the importance of continuous monitoring of HIV-infected infants to decrease their mortality risk.

Lower caregiver education and household rent was associated with a higher risk of pneumonia. In a 2015 systematic review of 14 studies on 26,130 HIV-negative children, low maternal education was associated with increased risk of ALRI mortality.[97] Another systematic analysis reported improvement in education level in women to be the main contributing factor to 50% reduction in the under 5 child mortality between 1970 and 2009.[98] This review reported low socioeconomic status (assessed via profession and income) to be associated with a 62% increased odds of mortality.[97] In our cohort, 68.2% of the infants' caregivers were employed and the median household monthly rent was 1500 KES (Kenya Shillings), a monthly rent comparable to the general Kenyan urban population.[99] Household crowding is another common cited risk factor for ARIs.[100-102] The majority of our cohort lived in a one room home, making it difficult to evaluate this as a risk factor for ARI in our study.

Air pollution, including indoor air pollution is a leading cause of respiratory infection in children. Worldwide, biomass fuel such as wood or dung contributes to the highest concentration of pollutants.[56,58] We found that the most households used charcoal and/or kerosene and only 5.1% of households used wood. These findings are consistent with the Kenya Demographic Health Survey which reported the predominant fuel in urban households to be charcoal and kerosene and in rural households to be biomass fuels.[73] LPG use was associated with better socioeconomic status, consistent with other studies.[72,103,59,59,72,60,59] Interestingly, in our study, LPG use was associated with lower baseline CD4%, perhaps as a result of late presentation due to stigma facing HIV diagnosis[104], in spite of financial ability to access health services. The failure to seek healthcare services may also explain why infants who had any LPG exposure were relatively more malnourished.

We found that wood exposure was associated with a 2-fold increased risk of upper respiratory tract infection. Contrary to other studies, there was no significant association between wood exposure and increased risk for pneumonia. This null finding may have been due to relatively low statistical power to find an association in the subset of infants with fuel use data. A study which assessed acute lower respiratory infections (ALRIs) such as pneumonia, in children living in India, found a 26.3 fold increased risk of infections in children living in households that use biomass compared to LPG.[105] In a Zimbabwean study, children living in households using wood, dung or straw for cooking, were at 2-fold increased risk of ALRIs.[60]

Our study had several strengths and limitations. To date, no studies have examined the combined effects of HIV and household air pollution on respiratory infection risk in HIV-infected infants. Our study included intensive monthly follow-up, which provided detailed data on ARI incidence. The infants in our study were overall relatively sick, as revealed by their malnutrition and immunocompromised status, both very common in infants in Africa.[79,94,106] Infants initiated ART by age <12 months. Only one other study to date has reported on ARI rates in early treated infants.[22] Other studies involved children who began ART only when they met the criteria for ART initiation according to the WHO guidelines. There were several limitations to our analysis. A lack of standardized protocol to diagnose respiratory infections may have led to over diagnoses or missed cases. Diagnosis of pneumonia was not distinguished from severe pneumonia. Distinguishing between these 2 classifications of pneumonia may have revealed more severe pneumonia to be associated with specific cofactors. Also, as infants were enrolled from 2007 to 2009, they had not yet received the pneumococcal conjugate vaccine, which is currently more commonly administered to HIV-infected infants. An additional limitation is that fuel exposure data may not reflect the true fuel exposure at the time of the infants' ARI illnesses, as fuel exposure ascertainment occurred 4 to 6 years after collection of ARI morbidity data.

Furthermore, fuel type was used as a proxy for HAP exposure, instead of quantification of HAP exposure Information such as primary source of cooking fuel versus less commonly used fuels were not obtained. Additional limitations include our study's limited power to detect an association between fuel type exposure and ARI due to a small sample size and low-exposure prevalence to the different fuel types, especially to wood. Lack of information on household cooking practices also has potential for diluting effect size seen between fuel exposure and ARIs as these practices have been shown to increase risk of childhood ARI.[45]

Our study also represents important findings of some other modifiable risk factors that may decrease the burden of ARIs among HIV-infected infants. Measures to improve nutritional status of HIV-infected infants, may be of benefit for decreasing respiratory morbidity. Vitamins and minerals are integral to immune support and function.[107,108] The infants in our study were supplemented with multivitamins and standard food supplements when indicated, however further support may be useful. An additional potentially modifiable risk factor is household air pollution. Wood exposure was associated with increased URIs. Cleaner cookstoves are more efficient and provide better ventilation than the current methods of indoor cooking used in many developing countries. The RESPIRE trial, a randomized control trial of clean cookstoves conducted in Guatemala revealed that the use of improved stoves led to a 33% decrease (in physician diagnosed severe pneumonia in children.[109]

Respiratory tract infection incidence rates in early-treated HIV infected infants continues to be high. Household air pollution is one of the many cofactors which increase the risk of respiratory tract infections in these infants, in addition to higher viral load, lower CD4%, wasting, and

poverty. Combined interventions are necessary to optimize long-term lung health in these children.

Figure 1: Flow chart of cohort of HIV-infected infants included in analysis

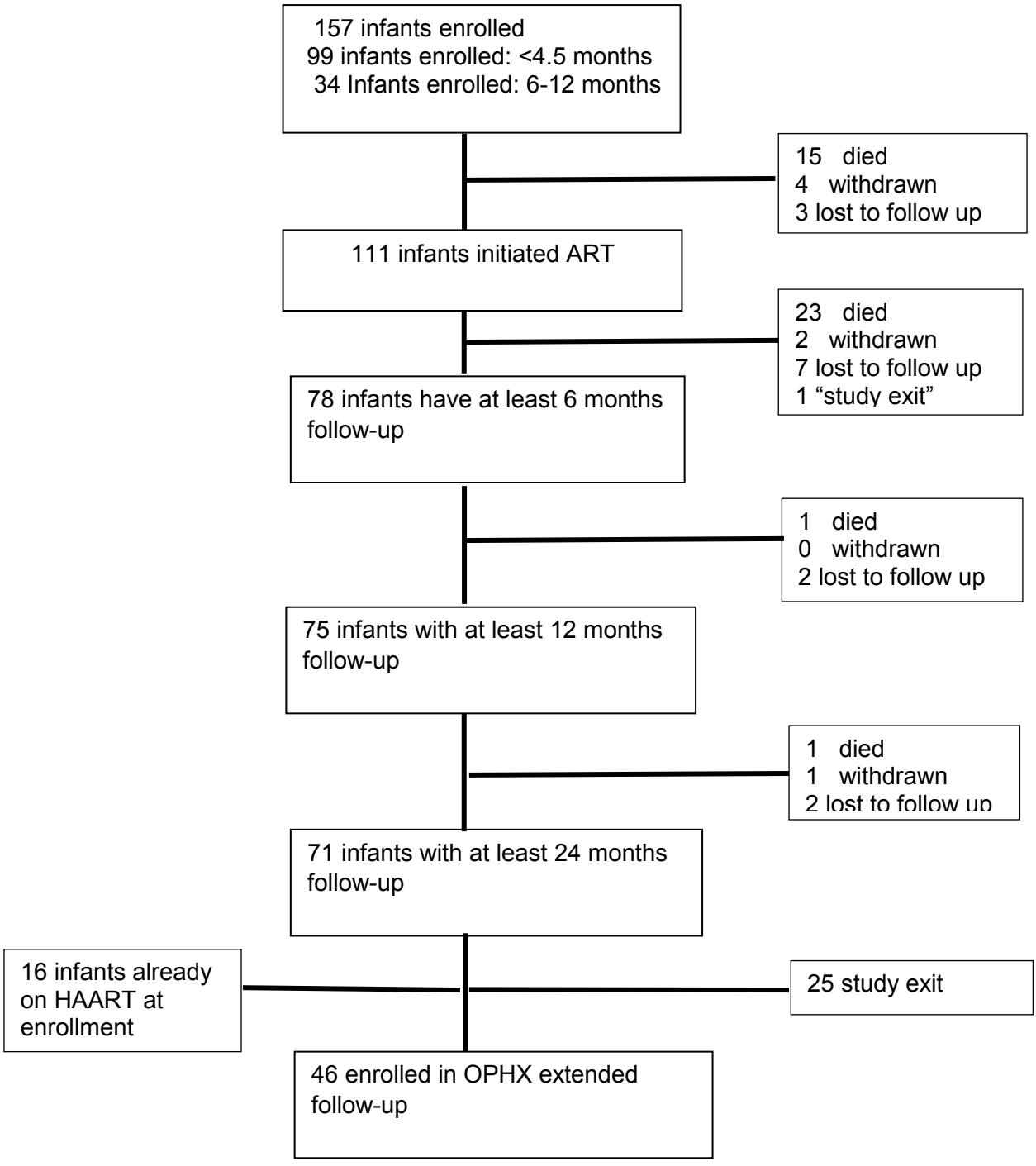
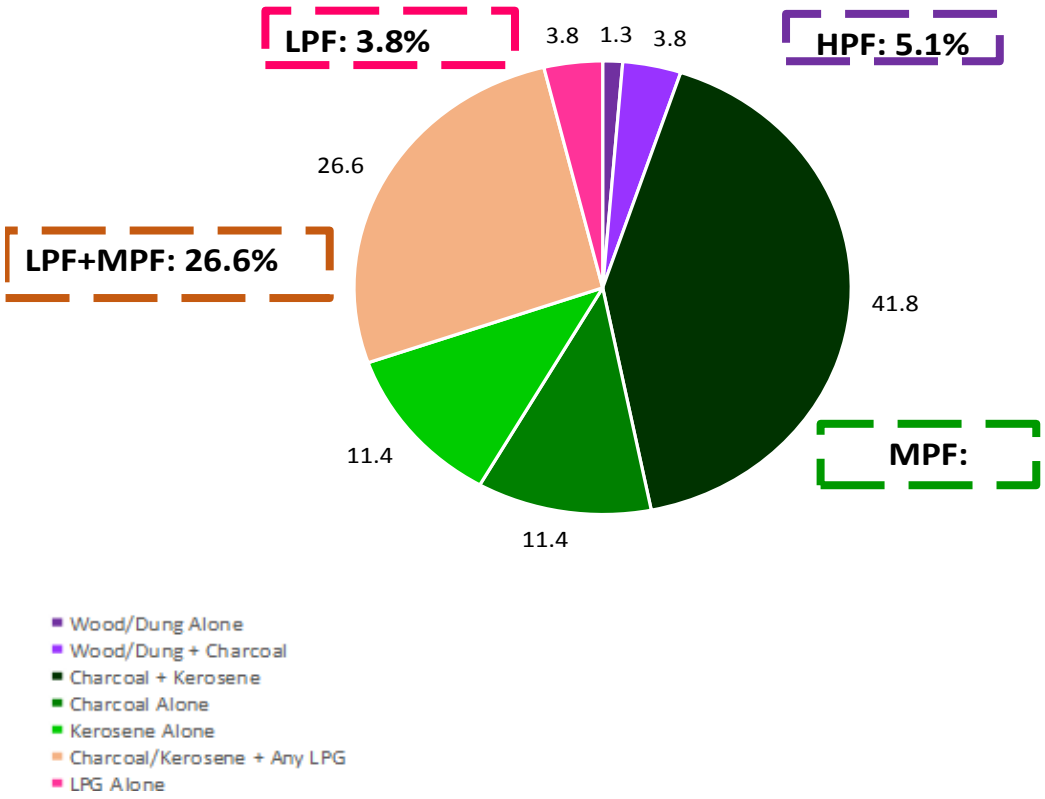


Figure 2: Prevalence of reported cooking fuel type in study sample of peri-urban HIV-infected children (N=60)



LPF (low polluting fuels) =liquid petroleum gas (LPG)
MPF (medium polluting fuels) =kerosene and charcoal
HPF (high polluting fuels) =wood+dung+charcoal

Table 1: Summary of baseline characteristics of infants

Characteristic	N=X	Median (IQR) or N (%)
Infant Birth and Pre-ART Clinical Characteristics		
Age at ART initiation (months)	111	4.5 (3.7, 6.9)
Gender (male)	111	54 (48.7)
Birth weight (kg)	107	3 (2.7, 3.4)
Birth weight (<2.5 kg)	107	13 (12.1)
CD4%	110	19 (14, 25)
CD4% < 15	110	31 (28.2)
Plasma HIV-1 RNA (log_{10}copies/mm^3)	105	6.57 (6.0, 7.0)
WHO clinical stage III/IV	109	52 (46.8)
Prior hospitalization since birth	111	65 (58.6)
Ever breastfed	103	85 (82.5)
PMTCT received by either? mother or infant	111	48 (43.2)
Pre-ART Growth Status		
WAZ	110	-2.3 (-3.8, -0.9)
WAZ < -2		62 (56.4)
HAZ	110	-1.96 (-3.1, -0.9)
HAZ < -2		55 (50)
WHZ	110	-0.8 (-2.3, -0.2)
WHZ < -2		32 (29.1)
HCZ (cm)	111	40.5 (39, 42)
Socioeconomic indicators		
Caregiver employed	110	75 (68.2)
Household monthly rent (KES)	106	1500 (1000, 2550)
Household monthly rent (US $)	106	22.7 (15.1, 38.3)
Caregiver education (years) *	96	8.5 (8, 11)
Social history of caregiver		
Age (years)	110	26 (23, 31)
Biological mother	111	108 (97.3)
Married	111	87 (78.4)
Home		
Flush toilet (%)	111	21 (18.9)
1 room house	111	86 (77.5)
Number of people in home	111	4 (3, 5)

*42/110 (38.2%) of caregivers had > primary level education
*WAZ: weight for age; HAZ: height for age; WHZ: weight for height; HCZ: head circumference

Table 2a: Burden of multiple respiratory infection events in HIV-infected infants

Number of respiratory events*	1	2	3	4	5	6	7	Total number of infants with ≥1 events	Total events
URI (N)	27	23	13	10	2	2	1	96	181
Pneumonia (N)	26	4	5	0	0	0	0	35	49

* Number of respiratory events in 2 year period; URI=Upper respiratory tract infection; N=total number of infants

Table 2b: Summary of 2 year incidence rates of respiratory infections in HIV infected infants initiating ART

Respiratory Conditions	Number of Events	Incidence/100 Person-Years (95% CI)
*URI	182	118.9 (102.8, 137.4)
Otitis media	23	15.03 (9.2, 22.6)
Bronchiolitis	9	5.9 (3.1, 11.3)
Pneumonia	50	32.7 (24.7, 43.1)
Tuberculosis	5	3.3 (1.4, 7.8)

Number of infants=103; Person-Years=153.1; *URI = Upper respiratory infection

Table 3: Cofactors for URI and pneumonia incidence

N: 103; Person-years: 146.7	URI Events=181**		Pneumonia Events=49**	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
CD4% €	1.01 (0.99, 1.03) €	0.4	0.98 (0.94, 1.01)	0.2
Plasma HIV RNA (per log_{10} increase) ¥	0.92 (0.76, 1.11) ¥	0.4	1.91 (1.15, 3.16) ¥	0.01
WHO stage 3/4	0.94 (0.70, 1.27)	0.7	1.80 (0.94, 3.45)	0.07
Gender (male)	1.01 (0.82, 1.47)	0.5	0.71 (0.37, 1.36)	0.3
Birthweight (kg) ◊	1.0 (0.74, 1.37) ◊	0.9	1.49 (0.76, 2.90) ◊	0.2
ART initiation age (months)	0.9 (0.91, 1.02)	0.2	1.13 (1.00, 1.28)	0.04
WAZ <-2 €	0.89 (0.66, 1.20) €	0.5	1.41 (0.74, 2.68)	0.3
HAZ < -2 €	0.83 (0.62, 1.12) €	0.2	0.97 (0.50, 1.85)	0.9
WHZ <-2 €	0.92 (0.63, 1.34) €	0.7	2.82 (1.54, 5.18)	0.001
Breastfed (past or current) ∓	1.02 (0.69, 1.51) ∓	0.9	0.91 (0.33, 2.47) ∓	0.9
PMTCT	0.89 (0.81, 0.99)	0.05	0.92 (0.74, 1.13)	0.4
Caregiver education (per year increase) ∞	0.96 (0.91, 1.01) §	0.1	0.86 (0.76, 0.97) ∞	0.01
Household Rent < 1000 KES per month *‡	0.93 (0.48, 1.79) *	0.8	3.69(2.03, 6.72) ‡	0.0001
One room home (vs > one room home)	1.09 (0.78, 1.51)	0.6	1.35 (0.63, 2.92)	0.4

N=Number of infants: 103 except for: *70; ∞89; ∓91; ¥97; ◊99; €102

Person-years: 146.7 except for: §126.7; ∓139.4; ¥138.9; ◊139.5; €144.8; *100.4; for URI; ‡137.6 for pneumonia

**Number of URI events: 181 except for: *133; §160; ∓171; ¥167; ◊170; €179

**Number of pneumonia events: 49 except for: ‡53 ∞44; ∓46; ¥45; ◊48

Weight for age z-score (WAZ) as continuous variable: significant association between higher Z score and decreased pneumonia risk 0.83 (0.69, 0.99) p<0.04

Table 4: Univariate versus multivariate models for cofactors of pneumonia incidence

	Univariate		Multivariate	
	Events/Person-time	HR (95%CI)	Events/Person-time	HR (95%CI)
Plasma HIV-1 RNA (per 1 log_{10}copies/mm^3 increase)	45/138.9	1.91 (1.15, 3.16) **	49/129.78	1.94 (1.17, 3.24)**
WHZ <-2	49/144.8	2.82 (1.54, 5.18)***	49/129.78	1.80 (0.95, 3.43)*
Household Rent < 1000 KES per month	53/137.6	3.62(1.68, 7.90)***	49/129.78	2.33 (1.20, 4.53)**

*P=0.07; **P=0.01; ***P=0.001

Table 5: Cofactors for type of household fuel used among HIV-infected children who remained in follow up for at least 4 years post ART

	N	Median (IQR) or N (%)	No Gas/LPG Median (IQR) or N(%)		Any Gas/LPG Median (IQR) or N(%)		P-value
			N		N		
Infant Birth and Pre-ART Clinical Characteristics							
Age at ART initiation (months)	61	4.9 (4.2, 7.5)	46	4.8 (4.2, 7.1)	15	7 (3.3, 9.2)	0.4
Gender (male)	61	33 (54.1)	46	21 (45.7)	15	12 (80)	0.02
Birth weight (kg)	58	3.2 (2.7, 3.5)	43	3.2 (2.7, 3.5)	15	3.2 (2.8, 3.6)	0.5
CD4%	60	18.5 (14, 23.5)	45	21 (15, 25)	15	16 (12, 21)	0.03
CD4%<15%	17	17 (28.3)	11	11 (64.7)	6	6 (35.3)	0.4
Plasma HIV-1 RNA (log_{10}copies/mm^3)	43	6.5 (5.8, 6.9)	36	6.4(5.6, 7.1)	7	6.7(6.6, 6.9)	0.2
WHO clinical stage at enrollment (III/IV)	22	22 (36.3)	16	16 (72.7)	6	6 (27.3)	0.8
*Prior hospitalization	61	38 (62.3)	46	26 (56.5)	15	12 (80)	0.1
Ever breastfed	59	54 (91.5)	45	41 (91.1)	14	13 (92.9)	0.8
Pre-ART Growth Status							
WAZ	57	-2.3 (-3.2, -0.9)	42	-1.9 (-3.2,-0.6)	15	-2.8 (-4.4, -1.7)	0.1
HAZ	57	-1.8 (-2.9, -0.9)	42	-1.8 (-2.7, -0.9)	15	-2.5 (-3.8, -0.9)	0.5
WHZ	57	-0.8 (-2.2, .1)	42	-0.6 (-1.4, -0.6)	15	-1.8 (-3.1, -0.5)	0.04
Socioeconomic Indicators							
*Caregiver employed	59	31 (52.5)	44	23 (52.3)	15	8 (53.3)	0.9
*Household monthly rent (USD)		31.4 (17.4, 69.8)		29.1 (17.4, 46.5)		58.1 (0, 17.4)	0.1
*Caregiver education (years)	56	9.5 (8, 12)	41	8 (7, 12)	15	12 (8, 12)	0.06
Social history of caregiver							
*Age (years)	57	32 (29, 38)	42	31 (28, 38)	15	33 (29, 40)	0.2
*Caregiver=biological mother	61	90 (98.4)	46	45 (97.8)	15	15 (100.0)	0.6
*Married	59	32 (54.2)	44	20 (45.5)	15	12 (80.0)	0.2
Home							
*Number of rooms in home	58	1 (1, 3)	44	1 (1, 2)	14	4.5 (2, 5)	0.001
*Number living in 1 room house	58	30 (51.7)	44	27 (61.4)	14	3 (21.4)	0.007
*Flush toilet	58	36 (62.1)	44	22 (50.0)	14	14 (100.0)	0.001

N = Number of infants; LPG = Liquid Petroleum Gas; *Variables ascertained during same time period as 'fuel use' ascertainment: 4-6 years after respiratory infection events in infants.

Table 6: Incidence rates of respiratory infections in HIV-infected infants who remained in follow up for at least 4 years post ART (N=45)

Respiratory Conditions	Number of Events	Incidence/100 Person-Years (95%CI)
URI	110	122.2 (101.4, 147.3)
Otitis media	11	12.2 (6.8, 22.1)
Bronchiolitis	5	5.6 (2.3, 13.3)
Pneumonia	14	15.6 (9.2, 26.3)
Tuberculosis	2	2.2 (0.6, 8.9)

N: Number of infants=45; Person-Years=90

Table 7: Incidence of respiratory infections by type of fuel exposure in HIV-infected infants who remained in follow up for at least 4 years post ART (N=45)

	URI		Pneumonia	
	Incidence/100 Person-Years	Events	Incidence/100 Person-Years	Events
No LPG/Gas (N=37)	132.4(108.6,161.4)	98	16.2(9.2,28.6)	12
Any LPG/Gas (N=8)	75(42.6, 132.1)	12	12.5(3.1,49.9)	2
Hazards Ratio (95% CI)	0.57 (0.23, 1.50)*		0.77(0.10, 5.40)**	

N: Number of infants=45; LPG=liquid petroleum gas;*P=0.2; **P=0.8

Table 8a: Unadjusted model for fuel use as cofactors for URI and pneumonia incidence in early-treated HIV infected infants who remained in follow up for at least 4 years post ART

	URI			Pneumonia		
	Events/ Person-Time (Years)	**Incidence/100 Person-Years (95% CI)**	**HR (95%CI)***	**Events/ Person-Time (Years)**	**Incidence/100 Person-Years (95%CI)**	**HR (95%CI)***
Indoor Firewood						
Exposure	8/4.0	200.0 (100.0, 399.9)	1.83 (1.45, 2.32) §	2/4.0	50.0 (12.5, 199.9)	3.50 (1.79, 6.86) §
No exposure	98/84.0	116.7 (95.7, 142.2)		12/84.0	14.3 (8.1, 25.6)	
Charcoal						
Exposure	83/70.0	118.6 (95.6, 147.0)	0.86(0.46, 1.64) ₸	10/70.0	14.3 (7.7, 26.6)	0.71 (0.24, 2.12) ₸
No exposure	27/20.0	135.0 (92.6, 196.9)		20/4.0	20.0 (7.5, 53.3)	
Kerosene						
Exposure	87/70.0	124.3 (100.7, 153.4)	1.16 (0.69, 1.92)¥	9/70.0	12.9 (6.7, 24.7)	0.51 (0.14, 1.94)¥
No exposure	23/20.0	115.0 (76.4, 173.1)		5/20.0	25.0 (10.4, 60.1)	
Gas/LPG						
Exposure	12/16.0	75.0 (42.6, 132.1)	0.58 (0.23, 1.46) ◊	2/16.0	12.5 (3.1, 49.9)	0.77 (0.11, 5.45)◊
No exposure	98/74.0	132.4 (108.7, 161.4)		12/74.0	16.2 (0.2, 28.6)	

*P-values: URI: § **<0.01;** ₸ 0.7; ¥ 0.6; ◊0.2; pneumonia: § **<0.01;** ₸ 0.5; ¥ 0.3; ◊0.8

Table 8b: Adjusted model for fuel use as cofactors for URI and pneumonia incidence in early-treated HIV infected infants who remained in follow up for at least 4 years post ART

	URI Events=109**		Pneumonia Events=14***	
	aHR (95%CI)	**P-value**	**aHR (95%CI)**	**P-value**
*Indoor firewood	**1.74 (1.20, 2.52)**	**0.004**	**2.56 (0.69, 9.54)**	**0.2**
Charcoal	0.96 (0.47, 1.95)	0.9	0.81 (0.23, 2.88)	0.7
Kerosene	1.13 (0.70, 1.81)	0.6	0.58 (0.11, 3.27)	0.5
Gas/LPG	0.62 (0.24, 1.61)	0.3	0.73 (0.07, 7.89)	0.8

*When adjusted for caregiver education, indoor firewood exposure remained statistically significant for URI (HR 1.56 (0.99, 2.43), p=0.05); caregiver education (HR 0.98 (0.89, 1.07) p=0.6) (95 events, 72.4 person time)

**Total URI events = 109; ***Total pneumonia events = 14; Totals from the chart above for URI and pneumonia are greater than the total # of events, since children could fall into multiple exposure groups

Table 9: Cofactors of URI and pneumonia incidence in infants who remained in follow up for at least 4 years post ART

	URI Events = 109**		Pneumonia Events = 14***	
	Hazard Ratio (95% CI)	**P-value**	**Hazard Ratio (95% CI)**	**P-value**
CD4%	1.01 (0.98, 1.04)	0.5	0.95 (0.87, 1.06)	0.4
Plasma HIV-1 RNA (per $\log_{10}$ increase) ¥	0.93 (0.74, 1.18) ¥	0.6	1.12 (0.45, 2.78) ¥	0.8
WHO stage ¾	0.98 (0.64, 1.50)	0.9	1.14 (0.35, 3.75)	0.8
Gender (male)	1.08 (0.72, 1.64)	0.7	0.69 (0.14, 1.64)	0.2
Birthweight ₸	1.06 (0.68, 1.66)₸	0.8	1.23 (0.45, 3.38)	0.7
HAART initiation age (months)	0.98 (0.89, 1.07)	0.7	1.06 (0.79, 1.43)	0.7
WAZ <-2◊	0.83 (0.54, 1.28) ◊	0.4	3.35 (0.96, 11.72)	0.06◊
HAZ < -2◊	0.75 (0.49, 1.14) ◊	0.2	1.2 (0.37, 3.93)	0.8◊
WHZ <-2◊	0.97 (0.52, 1.78) ◊	0.9	2.55 (0.75, 8.72)	0.1◊
Breastfed (past or current) ¥	0.99 (0.74, 1.32) ¥	0.9	0.98 (0.17, 5.53)	0.9
PMTCT	0.86 (0.74, 0.99)	0.05	0.89 (0.66, 1.22)	0.5
Caregiver education (per year increase)§	0.95 (0.89, 1.02) §	0.2	0.83 (0.69, 0.99)	0.05
Household rent < 1000 KES per month *	1.49 (1.01, 2.21)*	0.04	7.13 (1.44, 34.10)*	0.02
One room home (vs > one room home)	0.89 (0.59, 1.35)	0.6	0.55 (0.17, 1.79)	0.3
Number of rooms in home	--	--	1.36 (0.95, 1.96)	0.09

Number of infants = 45 except for: *30; §38; ₸42; ¥43; ◊44

Person-Years = 85.9 except for: *57.4; §72.5; ₸80.1; ¥82.4; ◊83.9

**Total URI events: 109 except for: *76; §95; ₸98; ¥99 for plasma HIV-1 RNA, 104 for breastfed; ◊107

***Total pneumonia events: 14 except for:*9; ¥11 for plasma HIV-1 RNA

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