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ORIGINAL ARTICLE

High Viremia and Wasting Before Antiretroviral Therapy Are Associated With Pneumonia in Early-Treated HIV-Infected Kenyan Infants

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Background. Human immunodeficiency virus (HIV)-infected children are particularly susceptible to acute respiratory infections (ARIs). We determined incidence and cofactors for ARIs in HIV-infected infants receiving antiretroviral therapy (ART).

Methods. Human immunodeficiency virus-infected infants initiated ART at ≤12 months of age and were observed monthly for 2 years in Nairobi. Acute respiratory infection rates and cofactors were determined using Andersen-Gill models, allowing for multiple events per infant.

Results. Among 111 HIV-infected infants, median age at ART initiation was 4.5 months. Pre-ART median CD4% was 19%, and 29% had wasting. During 24-months follow-up while on ART, upper respiratory infection (URI) and pneumonia rates were 122.6 and 34.7 per 100 person-years (py), respectively. Infants with higher pre-ART viral load (VL) (plasma HIV ribonucleic acid [RNA] ≥7 $\log_{10}$ copies/mL) had 4.12-fold increased risk of pneumonia (95% confidence interval [CI], 2.17–7.80), and infants with wasting (weight-for-height z-score < −2) had 2.87-fold increased risk (95% CI, 1.56–5.28). Infants with both high pre-ART VL and wasting had a higher pneumonia rate (166.8 per 100 py) than those with only 1 of these risk factors (44.4 per 100 py) or neither (17.0 per 100 py). Infants with exposure to wood fuel had significantly higher risk of URI (hazard ratio [HR] = 1.82; 95% CI, 1.44–2.28) and pneumonia (HR = 3.31; 95% CI, 1.76–6.21).

Conclusions. In early ART-treated HIV-infected infants, higher HIV RNA and wasting before ART were independent risk factors for pneumonia. Wood fuel use was associated with URI and pneumonia. Additional data on air pollution and respiratory outcomes in HIV-infected children may help optimize interventions to improve their lung health.

Keywords. acute respiratory infections; HIV; home air pollution; infants; pneumonia.

Globally, acute respiratory tract infections (ARIs) are a leading cause of under-5 child morbidity and mortality in developing countries [1–3]. In resource-poor settings, low birth weight, lack of exclusive breastfeeding, malnutrition, crowding, poor vaccine coverage, and indoor air pollution are each risk factors for ARIs and ARI-related mortality [2, 4, 5].

Most pediatric human immunodeficiency virus (HIV) and childhood pneumonia-related death is concentrated in Africa [3]. Before widespread antiretroviral treatment (ART), untreated HIV-infected children had 23.5 times higher hospitalizations for acute lower respiratory tract infections (ALRIs) compared with HIV-unexposed children [6]. A 2010 meta-analysis estimated a 6.5-fold higher risk of hospitalization for pneumonia and a 6-fold increased risk of mortality from pneumonia in HIV-infected children, who were often untreated [4].

In pediatric cohorts on ART, the ARI burden has persisted [7–10], with some evidence of decline. The pneumonia rate decreased from 50.6 to 18.1 per 100 person-years (py) after ART in Cote d'Ivoire [11]. The landmark Children with HIV Early Antiretroviral Therapy (CHER) trial demonstrated 76% reduced mortality in South African infants randomized to early (by age 6–12 weeks) versus deferred ART, and infants randomized to early ART also had lower severe pneumonia (12.2 vs 26.5 per 100 py) [12]. At the same time, a number of studies have implicated pneumonia in mortality and hospitalization in children on ART [12–15].

Older HIV-infected children and adolescents with either poor immune status before ART or poor response to ART have higher risk of ARIs [10, 16], and we hypothesize that a subset of treated infants may continue to have high risk of pneumonia, in spite of ART. Like HIV, indoor air pollution may compromise immune responses or contribute to inflammation [17], and

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the combined burden of exposure to indoor air pollution and severe HIV disease may be particularly harmful.

We examined the on-ART ("post-ART") incidence rates and cofactors for ARIs and pneumonia among HIV-infected infants receiving early ART. We hypothesized that infants with high viremia and poor immune status before ART would have higher ARIs. We also explored the relationship between indoor air pollution and risk of ARIs in this group.

METHODS

Study Populations and Follow-Up

Study participants were from Optimizing Pediatric HIV-1 Therapy (OPH) 03 (NCT00428116) and OPH 612 (NCT00427297) cohorts (2007–2010), both based in Nairobi Kenya. Infants were identified at prevention of mother-to-child transmission (PMTCT) clinics or in hospital wards as described previously [14, 18]. Both studies included only infants who initiated ART at <12 months of age. Infants were eligible for OPH612 if they had a prior nevirapine (NVP) exposure with no detectable resistance to nonnucleoside reverse-transcriptase inhibitors, based on an in-house population-based resistance test performed as described previously [19]. In brief, viral ribonucleic acid (RNA) was extracted from 140 μL plasma using a QIAmp viral RNA kit (QIAGEN, Valencia, California), amplified by reverse-transcription polymerase chain reaction, and sequenced on an ABI Prism 3100 in Nairobi. A consensus sequence was submitted to the Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu/) for interpretation of drug resistance profiles. Before 2009, infants with suspected active tuberculosis were excluded, and thereafter they were included. Infants in OPH03 were observed for a 2-year prerandomization phase on ART. Infants enrolled in OPH612 were randomized to either lopinavir-boosted ritonavir (LPV/r) or NVP-based ART regimen and followed thereafter. Studies were approved by Kenyatta National Hospital/University of Nairobi Ethical Review Board and University of Washington Institutional Review Board.

In accordance with World Health Organization (WHO) and Kenyan guidelines, infants received trimethoprim-sulfamethoxazole (co-trimoxazole) prophylaxis and received bacille Calmette-Guerin (BCG) at birth, pentavalent (for diphtheria, pertussis, tetanus, hepatitis B, and *Haemophilus influenza* type b) at 6, 10, and 14 weeks, and polio vaccinations at birth, 6, 10, and 14 weeks.

Data Collection

After enrollment, infants received a physical examination, and infants and biological mothers provided blood specimens. Caregivers provided sociodemographics. Infants attended monthly follow-up visits, at which time current respiratory illness and symptoms were ascertained through questionnaires and a physical exam. Infants also came in for unscheduled visits when ill, and clinical assessment and treatment were given by study clinicians. This analysis includes follow-up data for up to 2 years postenrollment, or until attrition.

Blood samples were ascertained for plasma HIV RNA using the Gen-Probe HIV Viral Load Assay [20], and CD4% and count levels were determined using flow cytometry. Among children still in follow-up in 2013 (4–6 years post-ART initiation), the type of fuel used in the household was determined (dung, firewood, charcoal, paraffin [kerosene], or liquid petroleum gas [LPG]). Usage of more than 1 fuel could be reported.

Respiratory Outcomes

Respiratory conditions (ARIs) assessed at enrollment and during monthly clinic visits included upper respiratory infection (URI), otitis media, bronchiolitis, pneumonia, and pulmonary tuberculosis (tuberculosis). Diagnoses were made by clinicians. The case definition of URI and pneumonia were based on WHO definitions [21] and were similar to definitions used in prior studies [22]. The case definition of URI was a history of cough or runny nose with or without fever, with absent fast breathing (defined as <60 breaths/minute [0–2 months], <50 breaths/minute [2–12 months], and <40 breaths/minute [12–59 months]) and normal chest exam. The pneumonia case definition was presentation with cough and fast breathing, with possibility of respiratory examination consistent with tachypnea, lower chest in-drawing, nasal flaring, grunting, or coarse crackles on auscultation. Clinicians used the Keith Edwards scoring system to diagnose tuberculosis [23], as per Kenyan Ministry of Health guidelines.

Statistical Analysis

Z-scores for weight-for-age (WAZ), height-for-age (HAZ), weight-for-height (WHZ), and head circumference-for-age (HCZ) were calculated using the 2006 WHO reference population [24]. Incidences of respiratory infections post-ART initiation were calculated, based on diagnoses made by clinicians at follow-up study visits, and excluding conditions present by ART initiation. The association between ARI and cofactors for ARI were assessed with Cox regression models using the Andersen-Gill method to allow for multiple events per infant over the study period. Primary cofactors of interest were pre-ART plasma HIV RNA and CD4% and home fuel exposure (using dichotomous indicators for any wood, charcoal, kerosene, or use of LPG, a low polluting fuel type). High pre-ART viremia was defined as plasma HIV RNA ≥7 $\log_{10}$ copies/mL, and definitions for underweight, stunting, wasting, and microcephaly were WAZ, HAZ, WHZ, and HCZ < −2, respectively. Multivariate analyses were performed to determine independent cofactors for respiratory tract conditions. Incidence rates were calculated for months 0–3, 3–6, 6–12, and 12–24 during ART. Indicators for socioeconomic status were not included in

multivariate analyses restricted to the 7 to 24-month timeframe due to co-linearity. Dichotomous indicators for fuel represented presence or absence of each fuel type, allowing for multiple fuel exposures. To further examine pneumonia, Kaplan–Meier survival methods were used to estimate time to first event, with ART initiation as the time origin. Cox proportional hazards regression was used to evaluate cofactors.

Secondary cofactors of interest included low birth weight, infant feeding practices, receipt of PMTCT (OPH03 only) nutritional status, prior hospitalization, advanced WHO clinical stage, and socioeconomic indicators. Cofactors for any LPG use were assessed using χ^2 or Fisher's exact tests (for dichotomous variables) and Wilcoxon rank–sum tests (for continuous variables). Stata 11 SE (StataCorp, College Station, Texas) was used for statistical analysis.

RESULTS

Study Population

Among 157 enrolled infants, 23 had initiated ART before enrollment, and 23 infants did not initiate ART (15 infants died, 3 infants were lost to follow-up, 4 infants withdrew, and 1 infant was exited due to early closure of the OPH612 study). One-hundred eleven infants initiated ART after enrollment at a median age of 4.5 months. Infants had a median CD4% of 19%, a median CD4 count of 1282 cells/μL, and a median plasma HIV-1 RNA of 6.6 $\log_{10}$ copies/mL (Table 1). Nearly half (46.9%) had a WHO clinical stage 3 or 4 diagnosis, and among these 52 infants, 64% had severe recurrent bacterial pneumonia. Other common diagnoses were unexplained moderate or severe malnutrition (17%) and unexplained persistent diarrhea (15%). Each of these diagnoses often occurred in combination with other diagnoses.

Most infants (89.5%) had breastfed, and 67.3% had received or had mothers who received PMTCT. Many infants (28.9%) had wasting (WHZ < −2). Nearly all infants had completed their expected immunizations by enrollment or shortly thereafter for BCG (110; 99%), polio (106; 96%), and pentavalent (106; 96%). Likewise, 110 (99%) infants had started co-trimoxazole prophylaxis before enrollment. Most caregivers (97.3%) were biological mothers. Most (77.5%) lived in a 1-room house.

Respiratory Infection Burden

Among 111 infants included in ART analysis, 103 provided post-ART morbidity data. The numbers remaining in follow-up at 6, 12, and 24 months were 78, 75, and 71, respectively. Among 81 survivors, the median follow-up time was 22.8 months (interquartile range [IQR], 22.6–23.2), and among 22 infants who died, median time to death was 2.3 months (IQR, 1.6–4.1). Seven infants were lost to follow-up at a median of 6.2 (IQR, 2.7–12.8) months.

Table 1. Summary of Baseline Characteristics of Infants Who Initiated ART

Characteristic	N = 111	Median (IQR) or N (%)
Infant Birth and Pre-ART Clinical Characteristics		
Male	111	54 (48.7)
Birth weight (kg)	107	3 (2.7–3.4)
Birth weight (<2.5 kg)	107	13 (12.1)
Ever breastfed	95	85 (89.5)
PMTCT received by mother or infant	107	72 (67.3)
HIV diagnosis in hospital	111	70 (63.1)
Age at ART initiation (months)	111	4.5 (3.7–6.9)
CD4%	111	19 (14–25)
CD4% <15	111	31 (27.9)
$CD4^+$ T-cell count (cells/μL)	111	1282 (750–1939)
Plasma HIV-1 RNA ($\log_{10}$ copies/mL)	105	6.6 (6.0–7.0)
WHO Stage 3 or 4	111	52 (46.9)
Prior hospitalization	111	65 (58.6)
Pre-ART Growth Status		
WAZ	111	−2.3 (−3.8 to −1.0)
Underweight (WAZ < −2)		63 (56.8)
HAZ	111	−2.0 (−3.1 to −0.9)
Stunted (HAZ < −2)		56 (50.5)
WHZ	111	−0.8 (−2.3 to 0.2)
Wasting (WHZ < −2)		32 (28.9)
HCZ	111	−0.9 (−1.7 to 0.4)
Microcephalic (HCZ < −2)		18 (16.2)
Socioeconomic Indicators		
Caregiver employed	110	75 (68.2)
Household monthly rent (KES)	100	1500 (1200–2500)
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		
One-room house	111	86 (77.5)
Number of people in house	111	4 (3–5)
Number of people per room	111	3.5 (3–5)

Abbreviations: ART, antiretroviral therapy; HAZ, height-for-age Z-score; HCZ, head circumference Z-score; HIV, human immunodeficiency virus; IQR, interquartile range; KES, Kenyan Shillings; PMTCT, prevention of mother-to-child transmission; RNA, ribonucleic acid; WAZ, weight-for-age Z-score; WHO, World Health Organization; WHZ, weight-for-height Z-score.

During 2 years of follow-up on ART, 78 (75.7%) infants had at least 1 episode of URI, and 50 (48.5%) infants had recurrent episodes. Thirty-six infants (35.0%) had at least 1 pneumonia, and 9 (8.7%) infants had recurrent episodes. Three (3%) infants had an episode of tuberculosis.

The overall URI incidence rate was 122.6 per 100 py, and the overall pneumonia incidence rate was 34.7 per 100 py (Table 2). Rates for otitis media, bronchiolitis, and tuberculosis were 15.7 per 100 py, 5.4 per 100 py, and 2.0 per 100 py, respectively. For each condition, rates were highest during the first 3 months on ART (Table 2). For example, pneumonia declined from 54.7 per 100 py during months 0–3 to 34.9 per 100 py during months 3–6.

Table 2. Incidence of Respiratory Conditions Among HIV-Infected Infants by Duration of ART, 24 Months ART, and Interim ART Periods 0–3, 3–6, 6–12, and 12–24 Months

Respiratory Conditions and Duration on ART	Number of Respiratory Events	Incidence/100 Person-Years[a] (95% CI)
URI		
Overall	180	122.6 (105.9–141.9)
0–3 months	36	151.4 (109.2–210.0)
3–6 months	28	139.5 (96.4–202.0)
6–12 months	42	111.7 (82.6–151.2)
12–24 months	74	113.2 (90.1–142.2)
Otitis media		
Overall	23	15.7 (10.4–23.6)
0–3 months	5	21.0 (8.8–50.5)
3–6 months	3	14.9 (4.8–46.3)
6–12 months	7	18.6 (8.9–39.1)
12–24 months	8	12.2 (6.1–24.5)
Bronchiolitis		
Overall	8	5.4 (2.7–10.9)
0–3 months	3	12.6 (4.1–39.1)
3–6 months	1	5.0 (.7–35.4)
6–12 months	3	8.0 (2.6–24.7)
12–24 months	1	1.5 (.2–10.9)
Pneumonia[b]		
Overall	51	34.7 (26.4–45.7)
0–3 months	13	54.7 (31.8–94.2)
3–6 months	7	34.9 (16.6–73.1)
6–12 months	15	39.9 (24.1–66.2)
12–24 months	16	24.5 (15.0–40.0)
Tuberculosis[c]		
Overall	3	2.0 (.7–6.3)
0–3 months	2	8.4 (2.1–33.6)
3–6 months	—	—
6–12 months	1	2.7 (.4–18.9)
12–24 months	—	—

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; URI, upper respiratory infection.

[a] Total person-years = 146.8.

[b] Pneumonia episodes include 1 episode that preceded a tuberculosis diagnosis.

[c] Tuberculosis episodes include 2 episodes with pulmonary tuberculosis diagnoses and 1 episode with concurrent pulmonary and extrapulmonary tuberculosis diagnoses.

Cofactors for Upper Respiratory Infection and Pneumonia During 2 Years Follow-Up on Antiretroviral Therapy

In analyses allowing for multiple events per infant, infants with high pre-ART plasma HIV RNA level had a higher risk of pneumonia (hazard ratio [HR] = 2.00; 95% confidence interval [CI], 1.20–3.34 per $\log_{10}$ copies/mL increase; $P = .008$) (Table 3), and those with high plasma viremia (HIV RNA ≥7 $\log_{10}$ copies/mL) had a 4-fold increased risk of pneumonia (HR = 4.12; 95% CI, 2.17–7.80; $P < .001$). Infants who had wasting before ART had a nearly 3-fold increased risk of pneumonia (HR = 2.87; 95% CI, 1.56–5.28; $P = .001$). Indicators of lower socioeconomic status, including lower monthly rent, and fewer years of caregiver education were each associated with higher risk of pneumonia. Results were similar in multivariate analyses adjusted for caregiver years of education (high viremia [HIV RNA ≥7 $\log_{10}$ copies/mL], adjusted HR [aHR] = 3.02, 95% CI, 1.58–5.78; $P = .001$; wasting, aHR = 3.14, 95% CI, 1.69–5.81; $P < .001$). In a multivariate model restricted to months 7-24, high pre-ART viremia and wasting were also associated with higher risk of pneumonia (high viremia, aHR = 2.90, 95% CI, 1.60–5.27; $P < .001$), wasting (aHR = 3.55, 95% CI, 1.91–6.57; $P < .001$). Lack of viral suppression (HIV RNA ≥3 $\log_{10}$ copies/mL, aHR = 3.01, 95% CI, 1.32–6.85; $P = .009$) and wasting (aHR, 1.93, 95% CI, 1.00–3.70; $P = .05$) at 6 months were each associated with higher pneumonia during months 7–24. In contrast to viremia, neither pre-ART nor 6-month CD4% were associated with pneumonia. Neither pre-ART growth, CD4%, nor plasma virus level were associated with URI incidence.

Infants with combined high pre-ART viremia and wasting had an extraordinarily high rate of pneumonia (166.8 episodes per 100 py; 95% CI, 96.9–287.3), representing a 10-fold increase (aHR = 9.48; 95% CI, 5.39–16.67; $P < .001$) in a model adjusted for caregiver education. The rate of pneumonia was lower in infants with either of these risk factors alone (44.4 per 100 py; 95% CI, 28.3–69.6), corresponding to a 3-fold increased risk in each case (high viremia and better nourished, aHR = 3.00, 95% CI, 1.23–7.30, $P = .02$; and lower viremia with wasting, aHR = 3.10, 95% CI, 1.22–7.90; $P = .02$). The rate was lower still in infants with neither risk factor (17.0 per 100 py; 95% CI, 10.2–28.2). Results were similar in survival analyses that allowed for 1 event per person (Figure 1).

Prevalence of Fuel Usage and Relation Between Fuel Use and Risk of Acute Respiratory Infection

Sixty-two children had data for household fuel use (46 who initiated ART at enrollment, and 16 who initiated before enrollment), a proxy for exposure to indoor air pollution. Four (6.5%) children lived in households with firewood or both firewood and dung exposure (both high polluting), 46 (74.2%) had charcoal exposure, 45 (72.6%) had kerosene exposure (both medium polluting), and 5 infants (8.1%) had neither charcoal nor kerosene. Fifteen (24.2%) infants lived in households with use of LPG (low polluting), which was generally used in combination with high or medium polluting fuels. Cofactors for use of any LPG included male infant (80% vs 46.8%; $P = .04$), higher education level (median = 12, IQR = 10–13 vs median = 10, IQR = 8–12; $P = .02$), living in a home with >1 room (66.7% vs 28.3%; $P = .01$), and HIV diagnosis in hospital (100% vs 52.6%; $P = .02$). Infants with LPG use had a lower CD4% before ART (median = 16%, IQR = 12%–21% vs median = 19%, IQR = 14%–25%; $P = .05$).

Forty-six infants had fuel exposure data, with 2 having exposure to wood and 44 infants without wood and with exposure to charcoal alone (N = 6), kerosene alone (N = 7), LPG alone (N = 2), or a combination of fuels (N = 29). Compared to other infants, infants with wood fuel exposure had significantly increased risk of URI (HR = 1.82; 95% CI, 1.44–2.28; $P < .001$) (Table 4) and pneumonia (HR = 3.31; 95% CI, 1.76–6.21; $P <$

Table 3. Univariate Analyses of Cofactors for URI and Pneumonia Incidence in Early-Treated HIV-Infected Infants

	URI[a]		Pneumonia[a]	
Potential Cofactor	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Infant Birth and Pre-ART Clinical Characteristics				
Male	1.08 (.81–1.45)	.6	0.72 (.37–1.40)	.3
Birth weight (per kg increase)[b]	1.0 (.74–1.38)	1.0	1.46 (.77–2.77)	.3
Ever breastfed[c]	1.02 (.69–1.51)	.9	0.93 (.34–2.53)	.9
Received PMTCT[d]	1.29 (.92–1.80)	.1	1.07 (.53–2.16)	.9
ART initiation age (per month in age)	0.96 (.91–1.02)	.2	1.16 (1.03–1.31)	.02
CD4% (per percentage increase)	1.01 (.99–1.03)	.4	0.98 (.94–1.01)	.2
Plasma HIV RNA (per $\log_{10}$ c/mL increase)[e]	0.94 (.79–1.12)	.5	2.00 (1.20–3.34)	.008
Plasma HIV RNA ≥7 $\log_{10}$ c/mL	0.96 (.67–1.36)	.8	4.12 (2.17–7.80)[f]	<.001
WHO Stage 3 or 4	0.98 (.72–1.33)	.9	1.92 (1.01–3.68)	.05
Pre-ART Growth Status				
Underweight (WAZ < –2)[g]	0.87 (.65–1.17)	.4	1.45 (.76–2.77)	.3
Stunted (HAZ < –2)	0.81 (.61–1.09)	.2	1.02 (.53–1.96)	1.0
Wasting (WHZ < –2)	0.95 (.65–1.38)	.8	2.87 (1.56–5.28)[f]	.001
Microcephalic (HCZ < –2)	0.93 (.54–1.63)	.8	0.56 (.22–1.45)	.2
Socioeconomic Indicators, Social History, and Home Characteristics				
Caregiver education (per year increase)[h]	0.97 (.92–1.02)	.2	0.85 (.75–0.96)	.007
Household rent (per 1000 KES increase)[i]	0.95 (.89–1.01)	.09	0.61 (.36–1.05)	.08
One-room house	1.04 (.75–1.46)	.8	1.41 (.65–3.05)	.4
People per room	0.99 (.90–1.08)	.7	1.15 (.90–1.47)	.3

Abbreviations: aHR, adjusted hazard ratio; ART, antiretroviral therapy; c, copies; CI, confidence interval; HAZ, height-for-age Z-score; HCZ, head circumference Z-score; HIV, human immunodeficiency virus; HR, hazard ratio; KES, Kenyan Shillings; OPH, Optimizing Pediatric HIV-1 Therapy; PMTCT, prevention of mother-to-child transmission; RNA, ribonucleic acid; URI, upper respiratory infection; WAZ, weight-for-age Z-score; WHO, World Health Organization; WHZ, weight-for-height Z-score.

[a]Number of infants = 103; total person-years = 146.8; no. URI events = 180; no. pneumonia events = 51, except as noted.

[b]Number of infants = 99; total person-years = 139.6; no. URI events = 169; no. pneumonia events = 50.

[c]Number of infants = 91; total person-years = 139.5; no. URI events = 171; no. pneumonia events = 47.

[d]Analyses restricted to infants in the OPH 03 cohort; no. infants = 70; total person-years = 102.1; no. URI events = 137; no. pneumonia events = 37.

[e]Number of infants = 97; total person-years = 139.0; no. URI events = 166; no. pneumonia events = 47.

[f]In multivariate analyses, adjusted for caregiver years of education, HIV RNA ≥7 $\log_{10}$ copies/mL (aHR = 3.02; 95% CI, 1.58–5.78; $P = .001$), wasting (aHR = 3.14; 95% CI, 1.69–5.81; $P < .001$).

[g]Pneumonia HR = 0.83 (95% CI, .69–.99) ($P = .04$) per unit increase in WAZ.

[h]Number of infants = 89; total person-years = 126.8; no. URI events = 160; no. pneumonia events = 47.

[i]Number of infants = 93; total person-years = 127.9; no. URI events = 160; no. pneumonia events = 44.

.001). Results were similar after adjusting for pre-ART HIV RNA level and WHZ (URI, aHR = 2.04, 95% CI, 1.55–2.67; $P < .001$ and pneumonia, aHR = 3.97, 95% CI, 1.83–8.58; $P < .001$). In adjusted models examining intervals of time during ART, the relation between wood fuel exposure and URI was only significant during months 7–24 (aHR = 2.31; 95% CI, 1.69–3.16; $P < .001$). There were no pneumonia episodes during months 0–6 among infants exposed to wood fuel; during months 7–24, these infants had a 5-fold increased risk of pneumonia (aHR = 5.35; 95% CI, 1.89–15.18; $P = .002$).

DISCUSSION

In this study of ARIs in HIV-infected infants in Kenya, the 2-year incidence rate for pneumonia was 34.7 per 100 py, and the incidence rate for URI was 122.6 per 100 py. Key cofactors associated with risk of pneumonia were pre-ART viremia and wasting. Infants with combined high plasma viremia and wasting had extremely high incidence of pneumonia—166.8 per 100 py. Infants with either high viremia or wasting had lower risk (44.4 per 100 py), whereas infants with neither risk factor had the lowest incidence of pneumonia (17.0 per 100 py). The moderate risk group had pneumonia incidence comparable to infants in the CHER cohort (44.3 per 100 py) who initiated ART at age 12 weeks and were not immunocompromised before ART [12]. Importantly, infants were enrolled before Kenyan rollout of pneumococcal conjugate vaccine. Rates of pneumonia in early-treated HIV-infected infants with access to this vaccine may be lower.

The overall pneumonia incidence in this study was 34.7 per 100 py over 24 months. Estimates for Kenya are similar: the WHO estimates that incidence of childhood (0–5 years) pneumonia in Kenya is 31–40 per 100 py [1]. The tuberculosis rate in this study was 2.0 per 100 py, substantially higher than estimates for the general population (167 cases of pediatric [0–14 years] tuberculosis per 100 000 in Kenya) [25]. Data for URI incidence in the general population in this region are scant; a cross-sectional study in rural Uganda found a prevalence of 37% among children age <2 years [26].

Table 4. Univariate Models for Fuel Use as Cofactors for URI and Pneumonia Incidence in Early-Treated HIV-Infected Infants

		URI			Pneumonia		
	N	Events/Person-Time (Years)	Incidence/100 py (95% CI)	HR (95%CI)	Events/Person-Time (Years)	Incidence/100 py (95% CI)	HR (95% CI)
Wood							
Yes	2	8/3.8	210.4 (105.2–420.7)	1.82 (1.44–2.28)[a]	2/3.8	52.6 (13.2–210.3)	3.31 (1.76–6.21)[b]
No	43	100/82.1	121.8 (100.1–148.1)		13/82.1	15.8 (9.2–27.3)	
Charcoal							
Yes	10	86/68.9	124.9 (101.1–154.3)	0.87 (.46–1.65)	11/68.9	16.0 (8.8–28.4)	0.76 (.27–2.18)
No	36	26/19.0	137.0 (93.3–201.2)		4/19.0	21.1 (7.9–56.2)	
Kerosene							
Yes	10	88/68.7	128.2 (104.0–158.0)	1.10 (.66–1.84)	10/68.7	14.6 (7.8–27.1)	0.56 (.15–2.04)
No	36	24/19.2	125.2 (83.9–186.8)		5/19.2	26.1 (10.9–62.7)	
Gas/LPG							
Yes	8	12/15.2	79.0 (44.9–139.2)	0.58 (.23–1.45)	2/15.2	13.2 (3.3–52.7)	0.56 (.10–5.10)
No	38	100/72.6	137.6 (113.1–167.5)		13/72.6	17.9 (10.4–30.8)	

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; LPG, liquid petroleum gas; py, person-years; URI, upper respiratory infection.
[a] $P < .001$.
[b] $P < .001$.

In this study, rates for upper and lower respiratory illnesses were highest during the first 3 months on ART. We previously observed that in older HIV-infected children initiating ART, pneumonia and tuberculosis were the most common morbidities [27], with the most severe morbidity occurring during first few months of ART, and likely before full immune reconstitution [27].

We found that infants with high viremia had a 4-fold increased risk of pneumonia. Peak plasma virus levels are associated with HIV disease progression and mortality in children [28–34]. Viremia before ART may be a key marker for risk of pneumonia in infants, who rapidly progress to severe HIV disease [30]. Prior studies have reported associations with immunosuppression and increased risk of pneumonia and opportunistic infections [10, 16]. However, we found no significant association between pre-ART CD4% and pneumonia risk.

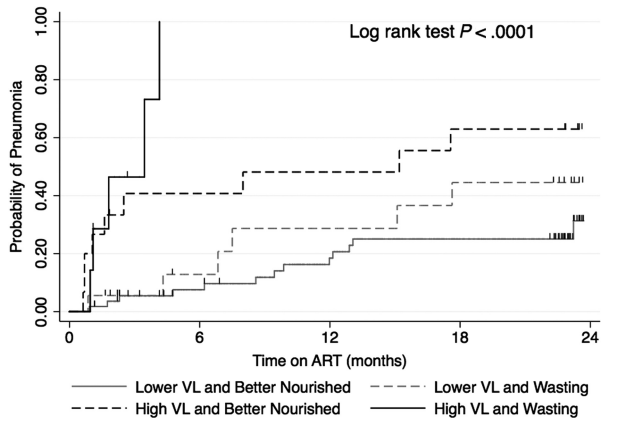

Figure 1. Kaplan–Meier curve depicting probability of pneumonia in early-treated human immunodeficiency virus (HIV)-infected infants by pre- antiretroviral therapy (ART) virological and nutritional status. In Cox proportional hazards models examining time to first event and adjusted for caregiver education, infants with high viremia with wasting had adjusted hazard ratio (aHR) = 8.48, 95% confidence interval (CI), 3.84–18.75; $P < .001$; high viremia and better nourished had aHR = 3.61, 95% CI, 1.30–9.99; $P = .01$; and lower viremia with wasting had aHR = 2.71, 95% CI, 1.12–6.57; $P = .03$, compared with those with lower viremia and better nourishment. Abbreviations: Better Nourished, WHZ ≥ –2; High VL, plasma HIV RNA ≥7 $\log_{10}$ copies/mL; Lower VL, plasma HIV RNA <7 $\log_{10}$ copies/mL; RNA, ribonucleic acid; VL, viral load; Wasting, WHZ < –2; WHZ, weightfor-height Z-score.

One-third of infants had wasting, which was associated with significantly higher pneumonia. Undernutrition is associated with ARIs in hospital- and community-based studies [35, 36]. Undernutrition is also associated with mortality in HIV-infected infants in this cohort and others [14, 37, 38]. Undernutrition may worsen immunosuppression or impede immune reconstitution. Malnourished children also have vitamin and mineral deficiencies, which contribute to poor immune function; reduced cell-mediated immunity is associated with higher risk of childhood ARIs [35].

We found that lower caregiver education and household rent were each associated with a higher risk of pneumonia. In HIV-uninfected children, poor maternal education and poverty have each been associated with increased risk of ALRI mortality [5]. Poverty is linked to household crowding, which is itself a commonly cited risk factor for ARIs [39–41]. The majority of infants in this cohort lived in a 1-room home, making it difficult to evaluate crowding as a risk factor in this study.

The majority of households (92%) in this periurban cohort used charcoal or kerosene for cooking, and fewer used wood fuel (6%). Twenty-four percent of households used at least some LPG for cooking. These proportions are consistent with recent Kenyan demographic survey data for urban households [42]. Use of LPG, a more expensive type of fuel than kerosene, charcoal or wood, was associated with living in a house with >1 room. Infants with lower pre-ART CD4% and infants who had their HIV diagnosis in hospital were each more likely to live in households with LPG,

perhaps because women with resources sought care at private clinics, which did not offer routine antenatal or infant HIV testing.

Wood fuel is associated with higher risk of respiratory illness than either charcoal or kerosene [17]. We observed significantly higher rates of URI and pneumonia among infants with wood exposure, in spite of small numbers. This study was limited to self-reported household fuel as a proxy for indoor air pollution exposure, and fuel usage was not quantified. Additional studies are needed to explore interactions between HIV, air pollution, and ALRI risk in children.

A strength of this study was the intensive monthly assessment of ARI incidence. To our knowledge, only 1 other study has reported ARI rates in empirically treated infants [12]. Previous studies involved older children [9, 11] or infants not provided with early ART [8, 10, 15]. Infants in our study were severely ill at enrollment, with severe malnutrition and immune compromise, both common in HIV-infected infants in Africa [37]. To date, no studies have examined the combined effects of HIV and household air pollution on respiratory infection risk in infants.

Nevertheless, this study was a secondary analysis, and it lacked a standardized protocol to diagnose respiratory infections, which may have led to missed or incorrect diagnoses. This study did not distinguish between severe and mild pneumonia. Many infants died before ART, limiting our ability to identify infant characteristics associated with higher ARI rates. Results presented here may not be generalizable to infants with access to the pneumococcal conjugate vaccine. Ascertainment of home air pollution exposure occurred 4–6 years after ascertainment of infant ARI outcomes.

CONCLUSIONS

In summary, ARI rates in early-treated HIV-infected infants may continue to be high during early months of ART. Infants with high viremia, wasting, or both are at particularly high risk, and careful monitoring of infants with these risk factors is warranted. The contribution of household air pollution to risk of ARI in HIV-infected children merits further study. Combined interventions such as nutritional support, early initiation of ART, and interventions to reduce home air pollution may optimize long-term lung health in these children.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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