Risk factors for hypoxia and tachypnea among adolescents with vertically-acquired HIV in Nairobi

Engi F. Attia

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington
2015

Committee:
Noel S. Weiss
Michael H. Chung
Kristina Crothers
Timothy Eoin West

Program Authorized to Offer Degree:
Public Health

University of Washington

Abstract

Risk factors for hypoxia and tachypnea among adolescents with vertically-acquired HIV in Nairobi

Engi F. Attia

Chair of the Supervisory Committee:
Professor Noel S. Weiss, MD DrPH
Epidemiology

Background

Chronic lung diseases are increasingly recognized as a complication of vertically-acquired HIV among adolescents in sub-Saharan Africa. These lung diseases may manifest with low oxygen saturation (hypoxia) or elevated respiratory rate (tachypnea). We sought to determine the prevalence of and risk factors for hypoxia and tachypnea among adolescents with vertically-acquired HIV in Nairobi, Kenya.

Methods

We performed a cross-sectional analysis of 258 adolescents (10-16.9 years old) with vertically-acquired HIV who were initiating care at the Coptic Hope Center for Infectious Diseases in Nairobi from January 2004 through June 2013. Adolescents with documented pneumonia were excluded. Hypoxia was defined as resting oxygen saturation ≤92%, and tachypnea was based on the 99th percentile of age-appropriate normal respiratory rates. Logistic regression models determined crude and adjusted odds ratios (ORs) for risk of hypoxia and tachypnea associated with potential risk factors, including age, gender, advanced HIV (WHO clinical stage 3/4), low CD4+ count (<200 cells/μL), current antiretroviral therapy (ART) and co-

trimoxazole use, and BMI-for-age and height-for-age *Z*-scores <-2 (malnutrition and stunting, respectively). Final models included adjustment for demographics and HIV severity.

Results

Overall, 11% of adolescents with vertically-acquired HIV had hypoxia and 55% had tachypnea at rest. Among those with hypoxia, 12 of 22 (55%) had advanced HIV and 10 of 22 (45%) had low CD4+ cell count. Advanced HIV (adjusted OR [aOR] 2.41) and low CD4+ (aOR 1.74) were associated with greater risk for hypoxia, but confidence intervals (CI) were wide and included the null (*95% CI* 0.93-6.23 and 0.69-4.39, respectively). Low CD4+ (aOR 2.45, *95% CI* 1.39-4.32), current ART use (aOR 0.48, *95% CI* 0.27-0.86) and stunted growth (aOR 3.46, *95% CI* 1.94-6.18) were associated with tachypnea risk.

Conclusions

Hypoxia and tachypnea were common among adolescents with vertically-acquired HIV. There was a suggestion that advanced HIV and low CD4+ count were associated with a greater risk of hypoxia. Low CD4+, lack of ART use and stunted growth were risk factors for tachypnea. Our results point to potentially important risk factors that may provide mechanistic insights into the development of hypoxia and tachypnea. Further studies are needed to understand the clinical implications of these respiratory abnormalities.

INTRODUCTION

Over 3 million HIV-infected children and adolescents live in sub-Saharan Africa, and nearly all of them acquired HIV by means of vertical mother-to-child transmission.[1] Lung diseases, such as lymphocytic interstitial pneumonia, recurrent pneumonia, tuberculosis and bronchiectasis, are well-described amongst HIV-infected children under 10 years of age in sub-Saharan Africa[2] and may also affect adolescents. The spectrum of pulmonary complications amongst HIV-infected adolescents in these settings additionally includes the chronic lung diseases – obliterative bronchiolitis, pulmonary hypertension and asthma.[3,4] Scarce availability of chest radiography and lung function testing outside of research and academic centers limits the definitive diagnosis of chronic pulmonary complications.[5,6]

Non-specific respiratory signs, such as hypoxia and tachypnea, are often a manifestation of lung disease,[7,8] and their presence may aid in identifying HIV-infected adolescents with chronic lung diseases. A study of adolescents with vertically-acquired HIV who had no acute respiratory symptoms demonstrated that 13% had low oxygen saturation at rest and 28% had an elevated respiratory rate.[3] Over 40% of adolescents in this cohort had lung function abnormalities or radiographic evidence of chronic lung disease. However, risk factors for chronic lung diseases and, specifically, their manifestations are not well defined among adolescents with vertically-acquired HIV in resource-limited settings. As oxygen saturation and respiratory rate are frequently measured in routine outpatient clinic visits, we sought to determine: a) the prevalence of hypoxia and tachypnea among adolescents with vertically-acquired HIV initiating care at the Coptic Hope Center for Infectious Diseases, an HIV clinic in Nairobi, Kenya;[9] and b) risk factors for the presence of hypoxia and tachypnea among these patients.

METHODS

Study design and population

We performed a cross-sectional analysis of adolescents with vertically-acquired HIV who were initiating medical care at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya from January 2004

through June 2013. We restricted the age range to 10-16.9 years because data supporting vertical transmission of HIV were available for this age group. Because we were interested in identifying baseline respiratory abnormalities, we excluded adolescents with documented pneumonia at the initial clinic visit as well as those in whom the respiratory rate was not documented (Figure 1). Of eligible adolescents, 56 did not have recorded oxygen saturation. We retained these adolescents in our overall cohort as baseline characteristics of adolescents with and without documented oxygen saturation were generally similar, except that those with missing oxygen saturation were more likely to have an elevated respiratory rate and stunted growth (Supplemental Table 1).

The Coptic Hope Center is an urban clinic that provides comprehensive HIV-related medical care and free antiretroviral therapy (ART) to HIV-infected individuals of all ages according to Kenyan national guidelines, and has been described elsewhere.[10,11] The University of Washington and Kenyatta National Hospital Institutional Review Boards approved this study.

Outcome variables: respiratory abnormalities

Hypoxia and tachypnea were documented during the initial clinic visit. We defined hypoxia as resting oxygen saturation ≤92% on ambient air measured using a non-invasive finger probe.[12] As normal respiratory rates vary by age among adolescents, we defined tachypnea as a respiratory rate greater than the 99th percentile of age-appropriate normal values reported in an international systematic review (Table 1).[13] Few published clinical guidelines define hypoxia and tachypnea at Nairobi's altitude of approximately 1,700 meters;[14] therefore, we also considered more conservative cutoffs for oxygen saturation and respiratory rate. Our conservative cutoff for hypoxia was oxygen saturation ≤90%, and for tachypnea, we added 2 breaths per minute to the respiratory rate cutoff for each age group (Table 1).

Exposure variables: potential chronic lung disease risk factors

Demographic characteristics

Baseline demographics, including age, gender and monthly household income in Kenyan shillings (Ksh), were based on self-report at initiation of care at the Coptic Hope Center. Information about region of

residence, specifically whether individuals resided in Kibera (a large urban slum settlement), was also self-reported.

HIV-related variables

HIV disease severity was categorized per World Health Organization (WHO) clinical staging criteria during the initial clinic visit.[15] Advanced HIV was defined as WHO HIV clinical stages 3 and 4. WHO clinical stage 3 includes history of any of the following diagnoses: chronic diarrhea, persistent fever, severe weight loss, pulmonary tuberculosis, bacterial pneumonia, other bacterial infections. Stage 4 diagnoses include: wasting, central nervous system toxoplasmosis, *Pneumocystis* pneumonia, extrapulmonary tuberculosis, recurrent severe bacterial pneumonia, other AIDS-defining illnesses. Current ART and co-trimoxazole use was also based on self-report. CD4+ cell count (cells/μL) was measured by the Coptic Hope Center laboratory within 30 days of initiation of care.

Clinical data

Malnutrition and stunted growth were defined as body mass index (BMI)-for-age and height-for-age *Z*-scores < -2, respectively, as measured during the initial clinic visit. We calculated *Z*-scores using the WHO Child Growth Standards to standardize anthropometric measurements of adolescents in our cohort to values of adolescents of the same age and gender in a reference population generated by the WHO.[16-18] *Z*-scores quantify how many standard deviations anthropometric measurements from individuals in our cohort vary from the mean (*Z*-score=0 or 50th percentile) of this age- and gender-adjusted reference population. Exposure to indoor biofuel burning was based on self-reported use of wood, charcoal and kerosene as an energy source for cooking within the adolescent's home.

Statistical analysis

Bivariate logistic regression models determined crude odds ratios (ORs) for risk of each of hypoxia and tachypnea associated with potential risk factors, and *95% confidence intervals* (*CI*) were computed for each OR. When age is analyzed as a continuous variable, the OR represents the odds of having hypoxia or tachypnea at a particular integer age compared to the odds of having hypoxia or tachypnea at one year of age less (i.e. when the OR is <1, each year of increased age is associated with a decreased risk of the

outcome). Multivariable logistic regression models were generated to determine the independent associations of each of the covariates listed in Tables 2 and 3 with hypoxia and tachypnea. Each of the final models included age (as a continuous variable) and gender in order to take into account potential confounding by these demographic factors. We also adjusted each model for WHO HIV clinical stage to minimize the potential selection bias that may be inherent in our study design, as HIV-infected adolescents who are ill tend to be more likely to present for medical evaluation than those who are well.[19] We repeated these analyses using conservative cutoffs for hypoxia and tachypnea.

All analyses were performed using Stata 13 (Stata Corp., College Station, TX). *P*-values <0.05 were considered statistically significant.

RESULTS

Cohort characteristics

Most adolescents with vertically-acquired HIV initiating care at the Coptic Hope Center were at the lower end of the age range included in this study (51% were 10-12.9 years old), and 49% were male. Overall, 34% met criteria for WHO Stage 3/4 HIV, 28% reported current ART use and 51% reported taking co-trimoxazole. Median CD4+ cell count was 326 cells/μL (*interquartile range [IQR],* 125-549), and 33% had a low CD4+ count (<200 cells/μL). Based on anthropometric measurements at care initiation, 19% were malnourished and 40% had stunted growth.

A substantial proportion of data were missing for exposure to indoor biofuel burning, household earnings and region of residence. Among adolescents for whom data were available for these variables, 53% reported exposure to indoor biofuel burning, 81% had monthly household earnings of ≤2,000 Ksh, and 13% lived in Kibera.

Overall, 22 of 202 (11%) of adolescents with vertically-acquired HIV had hypoxia defined as oxygen saturation ≤92%, and 143 of 258 (55%) had tachypnea as defined based on results of the aforementioned

international systematic review of respiratory rates (Table 1). When applying conservative definitions of hypoxia and tachypnea, 13 (6%) had oxygen saturation ≤90% and 60 (23%) had respiratory rates greater than the conservative cutoffs listed in Table 1.

Risk factors for hypoxia

On average, adolescents with hypoxia were younger than those without hypoxia (per year of age, aOR 0.81, *95% CI* 0.66 – 0.99; Table 2). Of those with hypoxia, 73% were in the youngest age group while only 4% were in the eldest group, compared to 47% and 22% of those without hypoxia, respectively. Adolescents with hypoxia were also more likely to be male. Advanced HIV was associated with greater risk for hypoxia: it was present in 55% of adolescents with hypoxia but only 31% of those without hypoxia (aOR 2.41, *95% CI* 0.93 – 6.23). Ten of the 22 adolescents with hypoxia (45%) had a CD4+ of <200 cells/μL, in contrast to 31% of those without hypoxia. This association persisted after adjustment for demographic characteristics and WHO HIV clinical stage (aOR 1.74), but the small number of subjects led to a statistically imprecise result (*95% CI* 0.69 – 4.39). Other clinical and anthropometric characteristics differed little between adolescents with and without hypoxia.

In sensitivity analyses, using oxygen saturation ≤90% as the outcome, the association with advanced HIV was further attenuated (aOR 1.49, *95% CI* 0.65 – 4.45), while the association with low CD4+ was not substantially changed (aOR 1.96, *95% CI* 0.63 – 6.05). The association with younger age also remained similar (aOR 0.68, *95% CI* 0.53 – 0.87).

Amongst adolescents for whom data were available, those with hypoxia were more likely to report exposure to indoor biofuel burning and living in Kibera compared to adolescents without hypoxia (70% *vs* 50%; and 23% *vs* 13%, respectively). However, the small number of subjects who provided data on indoor biofuel burning, household earnings and living in Kibera prohibited any meaningful conclusions to be drawn.

Risk factors for tachypnea

Adolescents with tachypnea were younger on average than those without tachypnea (per year of age, aOR 0.80, *95% CI* 0.70 – 0.91; Table 3); 55% of adolescents with tachypnea were 10-12 years old and

15% were 15-16 years old compared to 47% and 32% of those without tachypnea, respectively. The gender distribution was similar between groups. The prevalence of advanced HIV was 34% among those with and without tachypnea, and approximately one-half of adolescents with and without tachypnea were on co-trimoxazole prophylaxis. Only 22% of adolescents with tachypnea were currently using ART compared to 36% of those without tachypnea (aOR 0.48, *95% CI* 0.27 – 0.86). A greater proportion of adolescents with tachypnea had CD4+ <200 cells/μL compared to adolescents without tachypnea (40% *vs* 25%; aOR 2.45, *95% CI* 1.39 – 4.32). Additionally, 51% of adolescents with tachypnea had stunted growth compared to 26% of those without tachypnea (aOR 3.46, *95% CI* 1.94 – 6.18), though the prevalence of malnutrition did not differ to any substantial degree.

When generating multivariable logistic regression models using conservative cut-offs for tachypnea, the associations with low CD4+ (aOR 2.41, *95% CI* 1.31 – 4.44), current ART use (aOR 0.26, *95% CI* 0.11 – 0.62) and stunted growth (aOR 3.78, *95% CI* 1.98 – 7.22) were largely unchanged, but the association with age was diminished (aOR 0.95, *95% CI* 0.82 – 1.10).

Of adolescents with available data, exposure to indoor biofuel burning and living in Kibera was more prevalent among those with tachypnea compared to those without tachypnea. The extent of missing data for indoor biofuel burning, household earnings and living in Kibera again precluded our ability to draw meaningful conclusions in regard to tachypnea risk.

DISCUSSION

In this cohort of adolescents with vertically-acquired HIV initiating care at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya, we observed that hypoxia and tachypnea were common respiratory abnormalities. There was a suggestion that the presence of advanced HIV and a low CD4+ cell count <200 cells/μL were associated with a greater risk of hypoxia, and that a low CD4+, lack of ART use and stunted growth were risk factors for tachypnea. Further, we detected an association between younger age and both hypoxia and tachypnea. To minimize the likelihood that our definitions of these

outcomes resulted in misclassification of adolescents with normal oxygen saturation and respiratory rate into the groups with hypoxia and tachypnea, respectively, we repeated our analyses with conservative definitions of hypoxia and tachypnea, obtaining very similar results.

The diagnosis of advanced HIV, which we defined as WHO HIV clinical stages 3 and 4, is based on the prior presence of severe and AIDS-defining illnesses, such as opportunistic infections including bacterial, *Pneumocystis*, fungal and viral pneumonia as well as pulmonary tuberculosis. Pulmonary pathogens are thought to trigger local inflammation, which is linked with destructive lung lesions in advanced HIV.[20] This destruction of the pulmonary parenchyma can result in pulmonary gas exchange impairment and hypoxia.[7] Because WHO clinical stages 3/4 also encompass non-pulmonary diagnoses and HIV disease severity over extended periods of time, it is unclear from this cross-sectional study if advanced HIV does indeed predispose to hypoxia, and whether it is because of prior pulmonary infections or greater immune dysfunction.

The association between CD4+ <200 cells/μL and tachypnea persisted despite adjusting for age, gender and WHO clinical stage. Current severe immunosuppression is reflected by CD4+ cell count <200 and imparts a greater risk of opportunistic infections as well as non-infectious comorbid diseases.[21-23] Studies in adult populations suggest that HIV infection itself is associated with chronic lung diseases,[21,24] and destructive lung lesions were reported in HIV-infected adults without prior pneumonia or opportunistic infections.[25,26] Longstanding, untreated HIV infection in children during critical periods of immune system and organ development is likely to influence organ injury, including that of the lungs.[3,27,28] Uncontrolled HIV may also increase the risk of chronic lung diseases among adolescents who acquired HIV perinatally. Though we were unable to access CD4+ measures prior to care initiation at the Coptic Hope Center, it is possible that current CD4+ reflects a degree of immunosuppression that has persisted for many weeks, months or even years. If so, current CD4+ may serve as a valuable marker for risk of chronic lung diseases that might present with tachypnea.

We detected an association of current ART use with lower tachypnea risk. Despite continued limited access, ART scale-up over the last decade in sub-Saharan Africa has led to dramatic declines in morbidity and mortality.[1] However, ART initiation at advanced HIV stages or lower CD4+ may attenuate

the risk reduction that we observed for tachypnea, as immune function defects and pulmonary parenchymal damage may not be completely reversible.[3,28-31] Because adolescents in our study who were on ART received it elsewhere prior to initiating care at the Coptic Hope Center, it was not possible to determine duration of or past adherence to ART. Although current ART and co-trimoxazole use were moderately collinear in this study, we did not detect associations of co-trimoxazole with hypoxia or tachypnea. Co-trimoxazole has important antimicrobial properties and some immunomodulatory activities, contributing to the declining morbidity and mortality of HIV-infected populations.[32] The effects of ART and co-trimoxazole on the lung are not fully understood, but the association of ART with tachypnea may suggest that pulmonary infection mitigation and immune modulation by ART has important implications for pulmonary pathophysiology.

We also found that stunted growth was a strong predictor of tachypnea. In our cohort, 40% of adolescents had stunted growth, which has been reported in as many as 50% of HIV-infected children and is linked with the presence of advanced HIV.[33] HIV-infected adolescents with stunted growth who acquired HIV perinatally may have impaired lung development, as lung development is physiologically associated with growth velocity and height attainment.[34] Additionally, recent data suggest that if adequate growth attainment does not occur by the age of five years, adult lung function may be impaired.[35] This raises the concern that sequelae of stunted growth identified during adolescence may be irreversible. Malnutrition has also been linked with impaired lung function, and is common in regions of sub-Saharan Africa.[36,37] Yet, malnutrition was not associated with either hypoxia or tachypnea in our study. Current BMI may be a marker of more recent nutritional status, while height attainment likely reflects longer term exposures.

Finally, we found that, on average, younger age was associated with greater risk of hypoxia and tachypnea above and beyond the influence of HIV severity. This may suggest a survivor bias. In sub-Saharan Africa, adolescents with delayed diagnosis of vertically-acquired HIV or delayed ART initiation often present at advanced stages of HIV[19] with stunted growth, frequent infections and chronic respiratory abnormalities.[38,39] This subset of HIV-infected adolescents comprises up to 36% of infants with vertically-acquired HIV, and emerging data suggest that these “slow progressors” may survive a median of 16 years in the absence of ART.[40] Importantly, fewer than 40% of eligible HIV-infected children and

adolescents access ART in sub-Saharan Africa.[1,41] Consistent with these estimates, only 28% of our cohort was on ART upon care initiation at the Coptic Hope Center. As adolescents with untreated HIV have a high mortality risk,[19] many with advanced, undiagnosed or untreated HIV will have died, some with respiratory abnormalities, prior to initiating care at an outpatient HIV clinic. However, we pose this hypothesis with caution as the association with age was attenuated when the data were analyzed using conservative cutoffs for tachypnea (though the association remained for hypoxia).

To our knowledge, no clinical consensus guidelines have designated cutoffs for abnormal oxygen saturation or respiratory rate at Nairobi's moderate altitude of ~1700 meters. However, a systematic review aimed to define altitude-specific hypoxia models a mean oxygen saturation of ~97% and a hypoxia threshold of ~95% at this altitude.[12] Our reported hypoxia prevalence defined as oxygen saturation ≤92% is unlikely to be impacted by this altitude and is in line with the 13% prevalence of hypoxia among adolescents with vertically-acquired HIV in Zimbabwe.[3] We observed tachypnea among 55% of adolescents in our cohort as compared to 28% in the Zimbabwean study, which defined tachypnea as >25 breaths per minute regardless of age. Applying this cut-off in our cohort would have resulted in a tachypnea prevalence of 42%. We applied different cutoffs for respiratory rate by age because respiratory rate is known to decrease with increasing age in adolescence.[13] Even so, consistent clinical definitions for age-appropriate normal values for respiratory rates are lacking, so we based our definition of tachypnea on values that represented the 99th percentile of respiratory rates by age reported by an international systematic review.[13,42] It remains possible, though unlikely, that Nairobi's altitude may impact respiratory rate sufficiently to account for the greater prevalence of tachypnea in our cohort. Notably, at a similar altitude in Denver, Colorado (U.S.), no adjustment based on altitude is made when evaluating for tachypnea (personal communication, Dr. Leland Fan).

Our study has several other limitations. First, the sample size was relatively small, representing only adolescents initiating care at the Coptic Hope Center who met criteria for vertically-acquired HIV. Second, criteria for vertically-acquired HIV were based on self-reported information about family members with HIV and exposure history to HIV risk factors, which may have resulted in some degree of misclassification. However, the median age for sexual debut in Kenyan youth is reported to range from 16.5 to 24.3 years,[43]

supporting that the vast majority of adolescents in our cohort likely acquired HIV via vertical mother-to-child transmission. Third, there was a substantial proportion of missing data for risk factors such as indoor biofuel burning and indicators of socioeconomic status (i.e., household income and living in Kibera), limiting our ability to draw conclusions about any associations. Finally, despite controlling for potential confounding factors, there may still be residual confounding of the associations with hypoxia and tachypnea.

In conclusion, hypoxia and tachypnea were common among adolescents with vertically-acquired HIV initiating care at the Coptic Hope Center. The association of advanced HIV, CD4+ <200 cells/μL and lack of ART with greater risk of hypoxia or tachypnea suggests that sequelae of uncontrolled HIV may contribute to pulmonary parenchymal damage. Stunted growth, especially in the context of HIV infection, may impact lung maturation and development of tachypnea. As the prevalence of adolescents with vertically-acquired HIV in sub-Saharan Africa is projected to remain sustained for at least another decade,[27,40] further studies are needed to understand the clinical implications of these respiratory abnormalities and to determine whether they can be systematically utilized to identify chronic lung diseases among HIV-infected adolescents in resource-limited settings.

ACKNOWLEDGEMENTS

We thank the adolescents whose data were analyzed for this study and their caregivers. We also thank the staff of the Coptic Hope Center for Infectious Diseases in Nairobi for providing dedicated patient care, and the staff of the University of Washington Teaching, Research and Expert Education (TREE) program for data and project management.

REFERENCES

1. UNAIDS. 2014 Progress Report on the Global Plan: Towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva. 2014:1-36.
2. Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. *Pediatr Pulmonol* 2008;43:1-10.
3. Ferrand RA, Desai SR, Hopkins C, Elston CM, Copley SJ, Nathoo K, Ndhlovu CE, Munyati S, Barker RD, Miller RF, Bandason T, Wells AU, Corbett EL. Chronic lung disease in adolescents with delayed diagnosis of vertically acquired HIV infection. *Clin Infect Dis* 2012;55:145-152.
4. Miller RF, Kaski JP, Hakim J, Matenga J, Nathoo K, Munyati S, Desai SR, Corbett EL, Ferrand RA. Cardiac disease in adolescents with delayed diagnosis of vertically acquired HIV infection. *Clin Infect Dis* 2013;56:576-582.
5. Mehrotra A, Oluwole AM, Gordon SB. The burden of COPD in Africa: a literature review and prospective survey of the availability of spirometry for COPD diagnosis in Africa. *Trop Med Int Health* 2009;14:840-848.
6. Weber HC, Gie RP, Cotton MF. The challenge of chronic lung disease in HIV-infected children and adolescents. *J Int AIDS Soc* 2013;16:18633.
7. Young IH, Bye PT. Gas exchange in disease: asthma, chronic obstructive pulmonary disease, cystic fibrosis, and interstitial lung disease. *Compr Physiol* 2011;1:663-697.
8. Khirani S, Nathan N, Ramirez A, Aloui S, Delacourt C, Clément A, Faroux B. Work of breathing in children with diffuse parenchymal lung disease. *Respir Physiol Neurobiol* 2015;206:45-52.
9. Teaching, Research and Expert Education. Coptic Hope Center for Infectious Diseases. http://www.tree4health.org/?q=treatment/coptic-hope-center-infectious-disease. [Accessed 2015 June 5].
10. Chung MH, Drake AL, Richardson BA, Reddy A, Thiga J, Sakr SR, Kiarie JN, Yowakim, John-Stewart GC. Impact of prior HAART use on clinical outcomes in a large Kenyan HIV Treatment Program. *Curr. HIV Res* 2009;7:441-446.
11. Republic of Kenya Ministry of Medical Services. Guidelines for antiretroviral therapy in Kenya. 4th edition 2011. nascop.or.ke/library/artconference/Kenya_Treatment_ Guidelines.pdf. [Accessed 2015 May 10].
12. Subhi R, Smith K, Duke T. When should oxygen be given to children at high altitude? A systematic review to define altitude-specific hypoxaemia. *Arch Dis Child* 2009;94:6-10.
13. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, Maconochie I, Tarassenko L, Mant D. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet* 2011;377:1011-1018.
14. National Geographic Traveler. Kenya Facts. http://travel.nationalgeographic.com/travel/ countries/kenya-facts/. [Accessed 2015 June 8].
15. World Health Organization. Interim WHO Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions for Surveillance: African Region. 2005; www.who.int/hiv/pub/guidelines/clinicalstaging.pdf.
16. de Onis M and Blossner M. WHO global database on child growth and malnutrition: Programme of Nutrition World Health Organization; 1997.
17. WHO reference 2007 STATA macro package. 2007. Available from: www.who.int/ growthref/tools/ readme_stata.pdf. [Accessed October 19, 2014].
18. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization, 2006.
19. Shroufi A, Ndebele W, Nyathi M, Gunguwo H, Dixon M, Saint-Sauveur JF, Taziwa F, Viñoles MC, Ferrand RA. Risk of death among those awaiting treatment for HIV infection in Zimbabwe: adolescents are at particular risk. *J Int AIDS Soc.* 2015;18:19247.
20. Guillemi SA, Staples CA, Hogg JC, Le AN, Lawson LM, Schechter MT, Montaner JSG. Unexpected lung lesions in high resolution computed tomography (HRTC) among patients with advanced HIV disease. *Eur Respir J* 1996;9:33-36.
21. Hull MW, Phillips P, Montaner JS. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. *Chest* 2008;134:1287-1298.

22. Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, Cavert WP, Henry WK, Neaton JD. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* 2008;22:841-848.
23. Hirschhorn LR, Kaaya SF, Garrity PS, Chopyak E, Fawzi MC. Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. *AIDS* 2012;26 Suppl 1:S65-75.
24. Crothers K, Thompson BW, Burkhardt K, Morris A, Flores SC, Diaz PT, Chaisson RE, Kirk GD, Rom WN, Huang L; for the Lung HIV Study. HIV-associated lung infections and complications in the era of combination antiretroviral therapy. *Proc Am Thorac Soc* 2011;8:275-281.
25. Diaz PT, Clanton TL, Pacht ER. Emphysema-like pulmonary disease associated with human immunodeficiency virus infection. *Ann Intern Med* 1992;116:124.
26. Ramaswamy G, Jagadha V, Tchertkoff V. Diffuse alveolar damage and interstitial fibrosis in acquired immunodeficiency syndrome patients without concurrent pulmonary infection. *Arch Pathol Lab Med* 1985;109:408-412.
27. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, Chapman J, Goldrath K, Ferrand RA. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *Lancet Infect Dis* 2014;14:627-639.
28. Lahuerta M, Ue F, Hoffman S, Elul B, Kulkarni SG, Wu Y, Nuwagaba-Biribonwoha H, Remien RH, El Sadr W, Nash D. The problem of late art initiation in sub-Saharan Africa: A transient aspect of scale-up or a long-term phenomenon? *J Health Care Poor Underserved* 2013;24:359-383.
29. Pitcher RD, Lombard CJ, Cotton MF, Beningfield SJ, Workman L, Zar HJ. Chest radiographic abnormalities in HIV-infected African children: a longitudinal study. *Thorax* 2015. doi: 10.1136/thoraxjnl-2014-206105. [Epub ahead of print]
30. Siddique MA, Hartman KE, Dragileva E, Dondero M, Gebretsadik T, Shintani A, Peiperl L, Valentine F, Kalams SA. Low CD4+ T cell nadir is an independent predictor of lower HIV-specific immune responses in chronically HIV-1–infected subjects receiving highly active antiretroviral therapy. *J Infect Dis* 2006;194:661-665.
31. Kalayjian RC, Machekano RN, Rizk N, Robbins GK, Gandhi RT, Rodriguez BA, Pollard RB, Lederman MM, Landay A. Pretreatment levels of soluble cellular receptors and interleukin-6 are associated with HIV disease progression in subjects treated with highly active antiretroviral therapy. *J Infect Dis* 2010;201:1796-1805.
32. Church JA, Fitzgerald F, Walker AS, Gibb DM, Prendergast AJ. The expanding role of co-trimoxazole in developing countries. *Lancet Infect Dis* 2015;15:327-339.
33. Arpadi SM. Growth failure in children with HIV infection. *J Acquir Immune Defic Syndr.* 2000;25 Suppl 1:S37-42.
34. Wang X, Dockery DW, Wypij D, Gold DR, Speizer FE, Ware JH, Ferris BG Jr. Pulmonary function growth velocity in children 6 to 18 years of age. *Am Rev Respir Dis* 1993;148:1502-1508.
35. Suresh S, O'Callaghan M, Sly PD, Mamun AA. Impact of childhood anthropometry trends on adult lung function. *Chest* 2015;147:1118-1126.
36. Bhutta ZA, Salam RA, Das JK. Meeting the challenges of micronutrient malnutrition in the developing world. *Br Med Bull* 2013;106:7-17.
37. Dias CM, Pássaro CP, Cagido VR, Einicker-Lamas M, Lowe J, Negri EM, Capelozzi VL, Zin WA, Rocco PR. Effects of undernutrition on respiratory mechanics and lung parenchyma remodeling. *J Appl Physiol (1985)* 2004;97:1888-1896.
38. Ferrand RA, Munaiwa L, Matsekete J, Bandason T, Nathoo K, Ndhlovu CE, Munyati S, Cowan FM, Gibb DM, Corbett EL. Undiagnosed HIV infection among adolescents seeking primary health care in Zimbabwe. *Clin Infect Dis* 2010;51:844-851.
39. Ferrand RA, Bandason T, Musvaire P, Larke N, Nathoo K, Mujuru H, Ndhlovu CE, Munyati S, Cowan FM, Gibb DM, Corbett EL. Causes of acute hospitalization in adolescence: Burden and spectrum of HIV-related morbidity in a country with an early-onset and severe HIV epidemic: A prospective survey. *PLoS Med* 2010;7:e1000178.
40. Ferrand RA, Corbett EL, Wood R, Hargrove J, Ndhlovu CE, Cowan FM, Gouws E, Williams BG. AIDS among older children and adolescents in southern Africa: projecting the time course and magnitude of the epidemic. *AIDS* 2009;23:2039-2046.
41. Republic of Kenya Ministry of Health. *Kenya HIV Estimates: June 2014*. Nairobi, 2014: p. 1-28.

42. Smyth RL. Evidence-based measures of normal heart and respiratory rates in children differ significantly with existing published data. *J Pediatr* 2011;159:515-516.
43. Kenya National Bureau of Statistics, ICF Macro 2010. Kenya Demographic and Health Survey 2008-2009. Calverton, Maryland (USA): Kenya National Bureau of Statistics, ICF Macro.

Figure 1. Cohort development

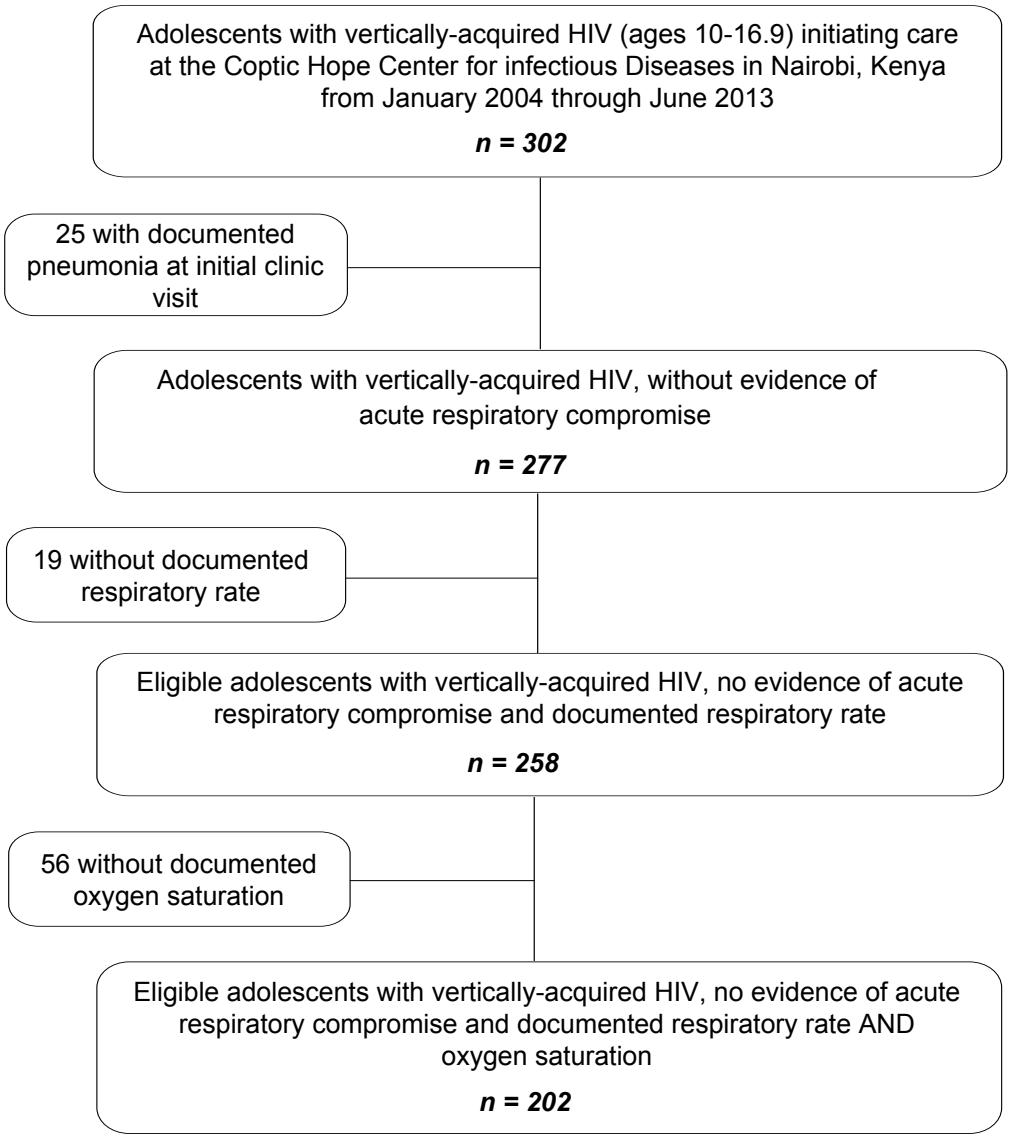

Table 1. Definition of tachypnea (in breaths per minute)		
Age group (years)	**Elevated respiratory rate based on respiratory rate >99th percentile of age-appropriate normal values***	**Conservative cutoffs for elevated respiratory rate (used in sensitivity analysis)**
10 – 12	>25	>27
13 – 14	>23	>25
15 – 16	>22	>24
*based on international systematic review of resting respiratory rates of children and adolescents[13]		

Table 2. Prevalence of demographic and other characteristics among adolescents with and without hypoxia

	Hypoxia (*n* = 22)		No hypoxia (*n* = 180)		Crude OR (*95% CI*)	aOR – adjusted for age, gender and WHO HIV Clinical Stage (*95% CI*)
	n	**%**	***n***	**%**		
Age* (years), median (IQR)	12.6 (11.0 – 13.1)		13.2 (11.4 – 14.7)		0.79 (0.64 – 0.96)	0.81 (0.66 – 0.99)
Age (years), by category						
10 – 12.9	16	73%	84	47%	Referent	Referent
13 – 14.9	5	23%	56	31%	0.47 (0.16 – 1.36)	0.52 (0.18 – 1.51)
15 – 16.9	1	4%	40	22%	0.13 (0.02 – 1.03)	0.15 (0.02 – 1.21)
Gender						
Male	14	64%	89	49%	1.79 (0.71 – 4.48)	1.45 (0.55 – 3.79)
Female	8	36%	91	51%	Referent	Referent
WHO HIV Clinical Stage						
Stage 3/4 (advanced HIV)	12	55%	55	31%	2.71 (1.10 – 6.65)	2.41 (0.93 – 6.23)
Stage 1/2	10	45%	124	69%	Referent	Referent
Missing	0	--	1	--		
CD4+ cell count						
<200 cells/μL	10	45%	54	30%	1.91 (0.78 – 4.71)	1.74 (0.69 – 4.39)
≥200 cells/μL	12	55%	124	70%	Referent	Referent
Missing	0	--	2	--		
Current co-trimoxazole use						
Yes	12	55%	94	52%	1.10 (0.45 – 2.68)	0.85 (0.34 – 2.14)
No	10	45%	86	48%	Referent	Referent
Current ART use						
Yes	7	32%	50	28%	1.21 (0.47 – 3.16)	0.91 (0.35 – 2.35)
No	15	68%	130	72%	Referent	Referent
BMI-for-age *Z*-score						
< -2 (malnutrition)	6	27%	32	19%	1.59 (0.58 – 4.41)	1.22 (0.46 – 3.25)
≥ -2	16	73%	136	81%	Referent	Referent
Missing	0	--	12	--		
Height-for-age *Z*-score						
< -2 (stunted growth)	9	41%	60	36%	1.26 (0.51 – 3.12)	1.21 (0.50 – 2.89)
≥ -2	13	59%	109	64%	Referent	Referent
Missing	0	--	11	--		
Indoor biofuel burning						
Yes	7	70%	40	50%	2.33 (0.56 – 9.75)	1.81 (0.43 – 7.62)
No	3	30%	40	50%	Referent	Referent
Missing	12	--	100	--		
Monthly household earnings						
≤2,000 Ksh	11	85%	103	79%	1.44 (0.30 – 6.93)	2.05 (0.39 – 10.8)
>2,000 Ksh	2	15%	27	21%	Referent	Referent
Missing	9	--	50	--		
Living in Kibera						
Yes	3	23%	16	13%	1.95 (0.48 – 7.90)	1.78 (0.38 – 8.46)
No	10	77%	104	87%	Referent	Referent
Missing	9	--	60	--		

*OR per 1 year increase in age

Table 3. Prevalence of demographic and other characteristics among adolescents with and without tachypnea

	Tachypnea (*n* = 143)		No tachypnea (*n* = 115)		Crude OR (*95% CI*)	aOR – adjusted for age, gender and WHO HIV Clinical Stage (*95% CI*)
	n	**%**	***n***	**%**		
Age* (years), median (IQR)	12.7 (11.0 – 14.0)		13.2 (11.8 – 15.4)		0.81 (0.72 – 0.92)	0.80 (0.70 – 0.91)
Age (years), by category						
10 – 12.9	78	55%	54	47%	Referent	Referent
13 – 14.9	44	31%	24	21%	1.27 (0.69 – 2.33)	1.22 (0.66 – 2.26)
15 – 16.9	21	15%	37	32%	0.39 (0.21 – 0.74)	0.38 (0.20 – 0.72)
Gender						
Male	71	50%	56	49%	1.04 (0.64 – 1.70)	0.93 (0.55 – 1.56)
Female	72	50%	59	51%	Referent	Referent
WHO HIV Clinical Stage						
Stage 3/4 (advanced HIV)	48	34%	38	34%	1.00 (0.59 – 1.68)	0.96 (0.56 – 1.65)
Stage 1/2	95	66%	75	66%	Referent	Referent
Missing	0	--	2	--		
CD4+ cell count						
<200 cells/μL	57	40%	28	25%	2.01 (1.17 – 3.47)	2.45 (1.39 – 4.32)
≥200 cells/μL	86	60%	85	75%	Referent	Referent
Missing	0	--	2	--		
Current co-trimoxazole use						
Yes	71	50%	60	52%	0.90 (0.55 – 1.48)	0.83 (0.49 – 1.39)
No	72	50%	55	48%	Referent	Referent
Current ART use						
Yes	32	22%	41	36%	0.52 (0.30 – 0.90)	0.48 (0.27 – 0.86)
No	111	78%	74	64%	Referent	Referent
BMI-for-age *Z*-score						
< -2 (malnutrition)	27	21%	18	17%	1.31 (0.68 – 2.54)	1.24 (0.62 – 2.50)
≥ -2	104	79%	91	83%	Referent	Referent
Missing	12	--	6	--		
Height-for-age *Z*-score						
< -2 (stunted growth)	70	51%	28	26%	3.07 (1.78 – 5.30)	3.46 (1.94 – 6.18)
≥ -2	66	49%	81	74%	Referent	Referent
Missing	7	--	6	--		
Indoor biofuel burning						
Yes	26	59%	24	47%	1.63 (0.72 – 3.69)	1.72 (0.73 – 4.07)
No	18	41%	27	53%	Referent	Referent
Missing	99	--	64	--		
Monthly household earnings						
≤2,000 Ksh	62	82%	74	80%	1.08 (0.49 – 2.35)	1.25 (0.54 – 2.90)
>2,000 Ksh	14	18%	18	20%	Referent	Referent
Missing	67	--	23	--		
Living in Kibera						
Yes	11	16%	8	10%	1.81 (0.68 – 4.81)	1.64 (0.62 – 4.38)
No	57	84%	75	90%	Referent	Referent
Missing	75	--	32	--		

*OR per 1 year increase in age