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## Pneumonia in HIV-Exposed and Infected Children and Association with Malnutrition

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### Abstract

We evaluated the association between HIV exposed-uninfected (HEU) status, malnutrition, and risk of death in Ugandan children hospitalized with pneumonia. Both HIV exposure and infection were associated with lower anthropometric indices on univariate analysis, and mid-upper arm circumference was significantly associated with overall mortality (OR 0.96) in a multivariable model. HIV infection (OR 5.0) but not HEU status was associated with overall mortality.

Malnutrition may contribute to poor pneumonia outcomes among HIV-infected and HEU children requiring hospitalization.

### Keywords

pneumonia; respiratory disease; pediatric; malnutrition; HIV

### Introduction

Pneumonia remains the leading infectious cause of death among those less than five years of age, and disproportionately affects children living in low and middle-income countries (LMIC). Malnutrition and HIV-exposed, uninfected (HEU) children have been associated with more severe, and poorer outcomes from, pneumonia.<sup>1, 2, 3</sup> Malnutrition may thus represent a pathway through which HIV exposure affects the severity and outcomes of children with pneumonia.

The association between malnutrition and HIV exposure, however, is not as well established. While some studies have shown a correlation between HIV exposure and malnutrition,<sup>4</sup> others have suggested that this exposure may be confounded by socioeconomic status.<sup>5</sup> Within the context of pneumonia, few data exist describing the relationship between HIV exposure, pneumonia severity and malnutrition, although each may independently increase mortality risk in hospital.<sup>2</sup>

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The objective of this study was to measure the association between HIV exposure/infection on malnutrition in children admitted to the hospital with pneumonia, as well as to examine the association between HIV exposure/infection on the severity of pneumonia on hospital admission and the risk of death during hospitalization. We hypothesize that HEU children hospitalized with pneumonia will be more malnourished (by anthropometric parameters) and have more severe disease (by clinical parameters) than HIV-uninfected children, although the difference will not be as marked as for HIV-infected children.

## Methods

We analyzed individual participant data from two prospective cohort studies performed in Uganda (Moschovis *et al*, manuscript under review).<sup>6, 7</sup> Both studies used the same inclusion criteria (children age 6–59 months admitted with any suspected infection) and neither included any in-hospital interventions. Subjects were enrolled at Mbarara Regional Referral Hospital and Holy Innocents Children’s Hospital, between November 2012 to December 2013, and November 2014 to January 2016. Further details of the studies have been previously reported.<sup>6, 7</sup>

We limited the analysis to children who were diagnosed with pneumonia by the treating physicians. We excluded subjects that had been previously enrolled, and subjects living outside the 10-district catchment area. All enrolled children had baseline clinical, laboratory and social characteristics measured. Maternal HIV status information was obtained by self-report; children were tested for HIV using rapid point-of-care tests using a serial algorithm. All positive tests on the Determine Antibody Test (Alere, Waltham, MA) were confirmed by a separate antibody test (UniGold, Trinity Biotech, Bray, Ireland). The StatPack test (Chembio, Medford, NY) was used as a tie-breaker. All positive tests in children less than 12 months of age were confirmed using PCR testing, which was used as the determining test. Anthropometric measurements were performed by trained study nurses. Mid-upper arm circumference (MUAC) was measured using a standardized MUAC tape. Weight was measured using a digital scale (Seca, Hamburg, Germany). Recumbent length was measured using a measuring tape in children <2 years; for children ≥ 2 years, standing height was measured using a Seca stadiometer. We calculated weight-for-height Z score, weight-for-age Z score, and height-for-age Z score using the WHO Child Growth Standards ([www.who.int/childgrowth/standards/en/](http://www.who.int/childgrowth/standards/en/)).

Primary outcome was overall mortality (death during hospitalization or the 6 months following discharge); secondary outcomes were clinical (temperature, respiratory rate, oxygen saturation, MUAC, hemoglobin, white blood cell count, Blantyre Coma Score) and anthropometric (MUAC, Z scores) parameters on admission. Statistical analysis was conducted using Stata 14 (StataCorp, LLC, College Station, TX). We compared the admission characteristics of HIV-infected vs. HEU vs. HIV-unexposed, uninfected (HUU) children using univariate linear regression. We examined the effect of HIV status on overall mortality using multivariable regression to adjust for known confounders (age, sex, oxygen saturation on admission, Blantyre Coma Score, maternal education, and number of household members). A  $p < 0.05$  was considered significant for all hypothesis testing.

Families of patients who participated in the studies provided written informed consent. The studies were approved by the Institutional Review Boards at Mbarara University of Science and Technology, the University of British Columbia and Massachusetts General Hospital/Partners Healthcare.

## Results

A total of 382 children with pneumonia were enrolled in the two cohort studies. Of these, 342 children (90%) had documented maternal and child HIV status (by self-report for mother and testing for child) and were included in this analysis (26 HIV-infected, 25 HEU, 291 HUU). Children with unknown maternal HIV status were on average 7 months older (20.2 months vs. 13.0 months) than those with known status, but were otherwise similar to those with known HIV status in terms of anthropometric and clinical parameters.

On univariate analysis, none of the clinical parameters obtained on admission were significantly associated with HEU status, although low hemoglobin was associated with HIV-infected children (mean difference  $-1.68$ ). Significant differences were seen between the three groups with MUAC ( $p<0.001$ ) and z scores ( $p<0.05$ ). HEU children hospitalized with pneumonia were more likely to have low MUAC (mean difference  $-8.25$ ), lower weight-for-age z scores (mean difference  $-0.99$ ) and height-for-age z scores (mean difference  $-0.98$ ), although not as low as HIV-infected children (mean difference  $-11.88$ ,  $-1.45$  and  $-1.49$ , respectively; Figure 1). In multivariable logistic regression, after controlling for potential confounders, overall mortality was significantly associated with low MUAC (OR 0.96,  $p<0.01$ ) and HIV infection (OR 5.0,  $p<0.01$ ), but not HEU status ( $p=0.75$ ).

## Discussion

While our results did not identify any significant association between pneumonia-related mortality and HEU status, we did note several statistically significant associations with anthropometric measures. The significantly lower MUAC, lower weight-for-age and height-for-age z scores among HEU children, although not as low as HIV-infected children, suggests that malnutrition is of concern not only in HIV-infected but also HEU children, and may be a contributing factor to the development of pneumonia requiring hospitalization.

Malnutrition has previously been implicated as a predisposing factor for severe pneumonia and associated morbidity and mortality. A Gambian study of 190 children hospitalized with hypoxemic pneumonia found nutritional status to be more predictive than the degree of hypoxemia of survival.<sup>8</sup> A study from Malawi analyzing over 100,000 episodes of pneumonia over an 11-year period found that those with severe undernutrition and with severe acute malnutrition had a 12% and 35% increase, respectively, in the odds of pneumonia mortality.<sup>1</sup> In a childhood pneumonia analysis combining 2,660 subjects from 16 LMIC sites, stunting was associated with longer course of recovery from illness.<sup>9</sup> In a cohort study of 4,184 Kenyan children  $<5$  years admitted with severe pneumonia, 25% had severe acute malnutrition, and this was strongly associated with 1 year post-discharge mortality.<sup>3</sup>

However, while HIV infection is a well-known risk factor for morbidity and mortality in pneumonia, the role of HIV exposure has been less well elucidated, and especially its relationship with malnutrition. Severe acute malnutrition independently predicted death in HIV-exposed Malawian children with pneumonia (OR 5.1), more so than HIV-infected children (OR 2.2).<sup>2</sup> In a South Africa child health study where none of the children were HIV-infected, HIV exposure was the strongest independent risk factor for severe pneumonia (incidence rate ratio 4.04), and both HIV exposure and malnutrition were associated with an increased incidence of pneumonia.<sup>1</sup>

Our study is limited by the relatively small amount of data available for HEU children. However, we did adjust for important social and environmental issues that could be confounders, such as number of household members and maternal education, and continued to find a consistent effect across anthropometric parameters. There is the possibility that other potential confounders or effect modifiers exist, such as breastfeeding,<sup>10</sup> that may not have been accounted for. Breastfed children were in the minority and hence were too small a group to perform a subgroup analysis. That HEU children have potentially modifiable factors that predispose them to illness does indicate the need for further research in this area. A high prevalence of stunting in HEU infants has been noted in other sub-Saharan Africa settings,<sup>11</sup> and this has been linked to post-discharge mortality.<sup>3</sup>

In conclusion, this study highlights the importance of the converging risk factors of HIV exposure/infection and malnutrition on inpatient and post-discharge mortality among children hospitalized for pneumonia. The success of prevention of mother-to-child transmission programs has resulting in a growing HEU population. It is therefore imperative that we understand how the clinical presentation, risk factors, and trajectory of HEU children are distinct from HIV-unexposed individuals, so that we can target this growing population for specific interventions.

## Acknowledgments

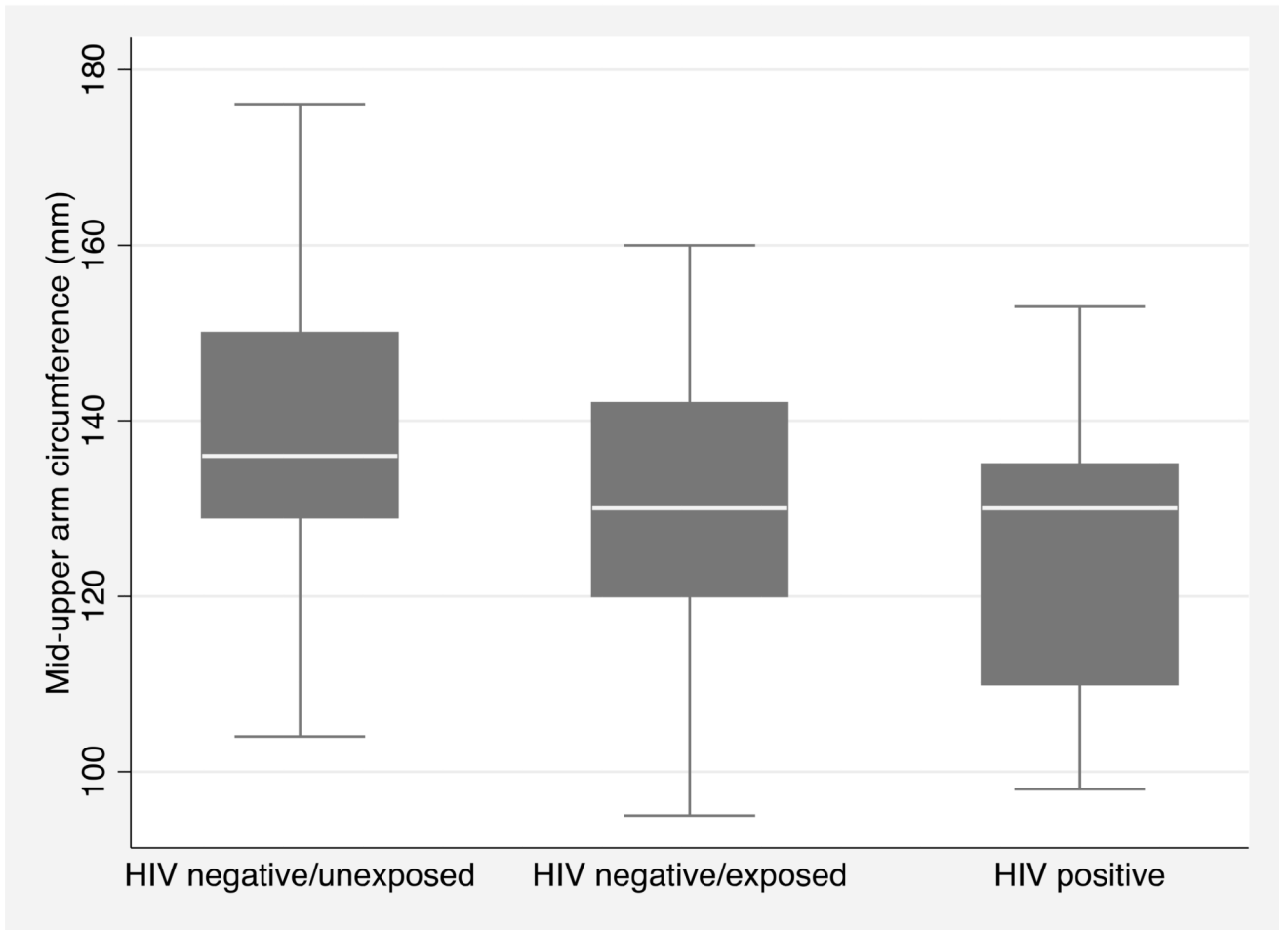
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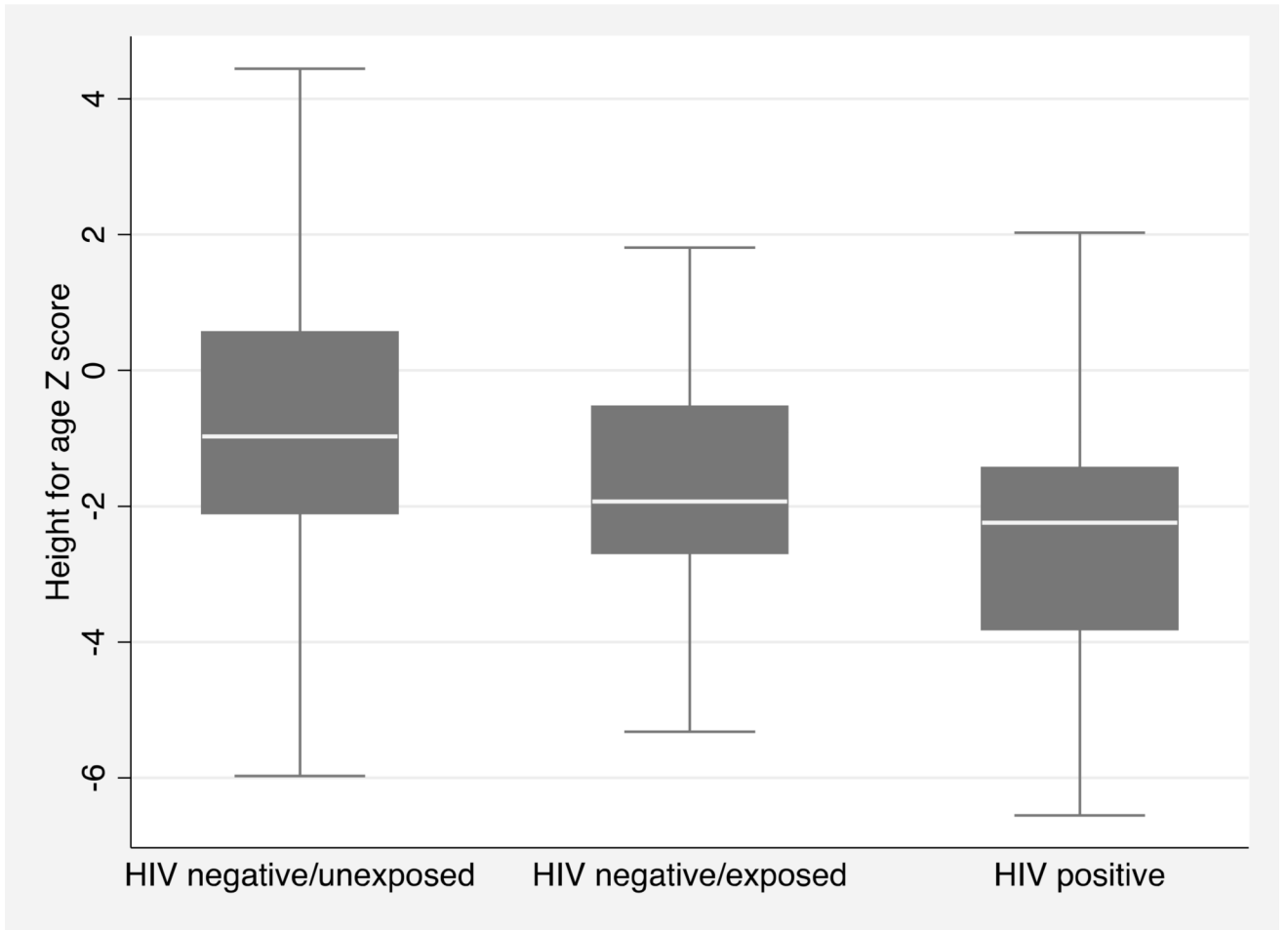
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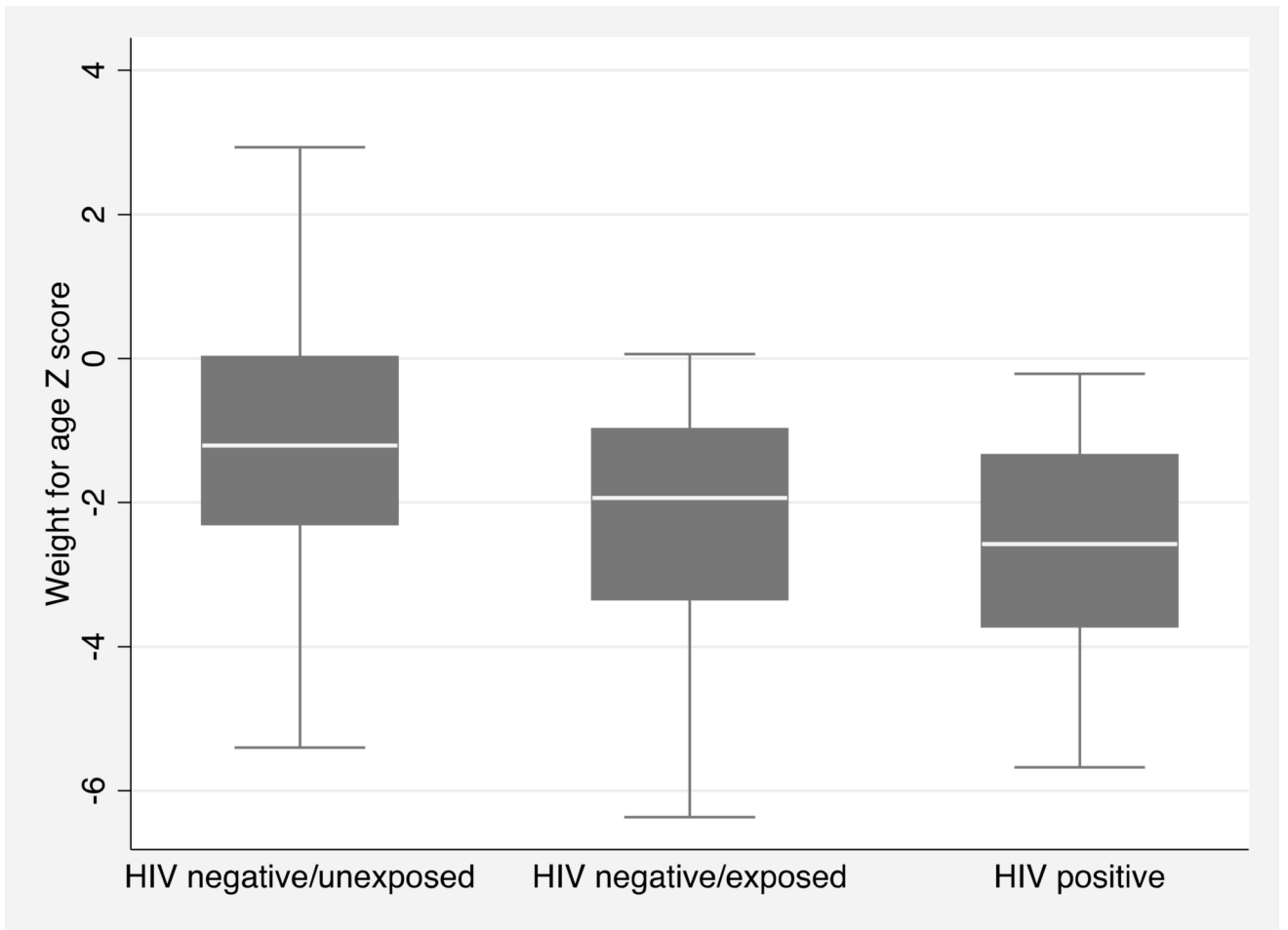
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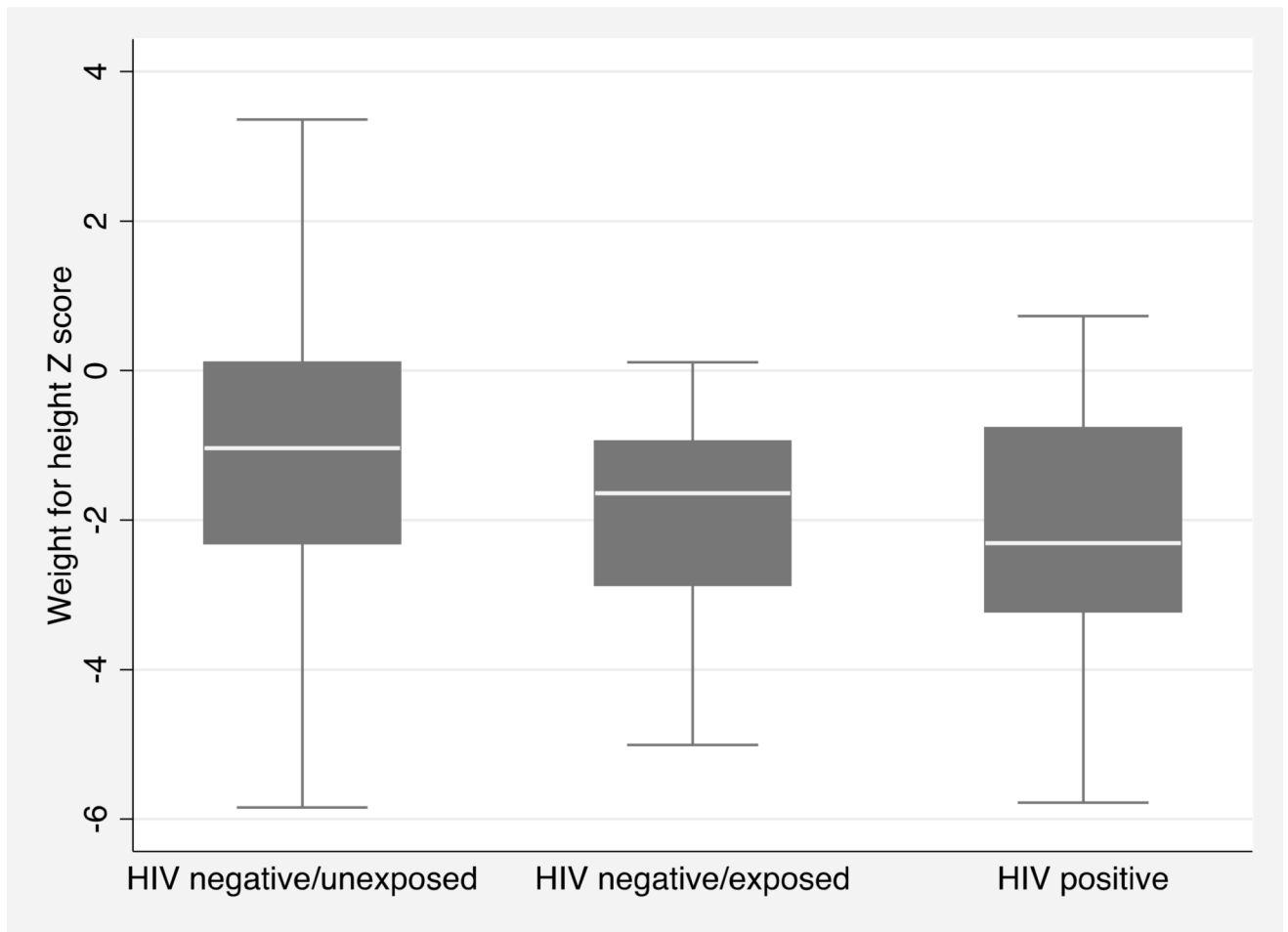
**B.**



C.





**D.****Figure 1.**

Box plot of distribution\* of hospitalized children with pneumonia diagnosis by HIV exposure/infection for (A) Mid-upper arm circumference; (B) Height-for-age Z score; (C) Weight-for-age Z score; (D) Weight-for-height Z score

\*Outliers not shown