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Exploring HIV infection and susceptibility to measles among older children and adults in Malawi: a facility-based study

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SUMMARY

Background: HIV infection increases measles susceptibility in infants, but little is known about this relationship among older children and adults. We conducted a facility-based study to explore whether HIV status and/or CD4 count were associated with either measles seroprotection and/or measles antibody concentration.

Methods: A convenience sample was recruited comprising HIV-infected patients presenting for follow-up care, and HIV-uninfected individuals presenting for HIV testing at Chiradzulu District Hospital, Malawi, from January to September 2012. We recorded age, sex, and reported measles vaccination and infection history. Blood samples were taken to determine the CD4 count and measles antibody concentration.

Results: One thousand nine hundred and thirty-five participants were recruited (1434 HIV-infected and 501 HIV-uninfected). The majority of adults and approximately half the children were seroprotected against measles, with lower odds among HIV-infected children (adjusted odds ratio 0.27, 95% confidence interval 0.10–0.69; $p = 0.006$), but not adults. Among HIV-infected participants, neither CD4 count ($p = 0.16$) nor time on antiretroviral therapy ($p = 0.25$) were associated with measles antibody concentration, while older age ($p < 0.001$) and female sex ($p < 0.001$) were independently associated with this measure.

Conclusions: We found no evidence that HIV infection contributes to the risk of measles infection among adults, but HIV-infected children (including at ages older than previously reported), were less likely to be seroprotected in this sample.

1. Introduction

Enormous progress towards measles control and elimination has been made in recent years, due largely to sustained efforts to increase vaccination coverage among children worldwide with a cheap, safe, and highly efficacious vaccine.[1–3] As a result, measles incidence and mortality in Sub-Saharan Africa decreased by approximately 90% between 2000 and 2010.[2,4,5] However, outbreaks continue to occur in areas where high vaccination coverage has not been achieved or maintained.[3,6–8] For example, in Malawi, following a reduction from 162 000 measles cases in 1980 to fewer than 200 per year between 2005 and 2009, a large outbreak occurred in 2010, with a reported 134 039 cases and 304 deaths.[8]

Although measles is typically a disease of young children (those aged less than 5 years),[6] an unexpected feature of this Malawian outbreak was that the majority of cases occurred among individuals aged 5 years and older, with 28% of cases among those aged 15 years and older.[8] A similar age distribution has been

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observed in other recent measles outbreaks in Sub-Saharan Africa.[5,7,9]

There are several possible explanations for this phenomenon, including low vaccination coverage in subpopulations despite high national coverage,[10] extensive vaccine failure (possibly due to the logistical difficulties of maintaining a functioning cold-chain in these contexts),[11] waning immunity among previously seroprotected individuals,[12] and impaired immunogenicity to measles vaccine due to health-related factors known to influence the immune response to vaccination, such as malnutrition.[13] Additionally, the reduction in circulating measles virus levels associated with successful measles control may limit or eliminate the immune-boosting effect of frequent re-exposure.

Another possible factor in the unusual age distribution could be the high prevalence of HIV infection in Malawi.[14] Several studies have reported associations between measles antibody concentration and HIV infection and exposure; for example, infants born to HIV-infected women have lower levels of measles-specific transplacental antibodies (which wane faster), potentially leaving these infants at greater risk of infection before they receive the scheduled measles vaccination at 9 months.[15–18] Other reports have shown that HIV infection is associated with greater severity of measles disease,[19] higher mortality from measles,[20] and prolonged measles virus shedding.[21]

Few studies have addressed the role of HIV infection in measles infection risk among adults and children after infancy:[18,22] one study concluded that measles vaccine-derived antibodies decline more rapidly in HIV-infected adults ($n = 48$);[23] a further three studies reported finding no difference in measles seropositivity between HIV-infected adults at different stages of disease progression (as measured by CD4 count).[24–26] A study among Kenyan adults in Nairobi found no statistical difference in measles IgG seroprevalence and concentration between HIV-infected and HIV-uninfected adults, and concluded that reduced immunity among HIV-infected adults was not a major contributor to measles resurgence in that country.[22]

An association between HIV infection and measles susceptibility in individuals over 18 months of age could have wide-ranging implications throughout areas of high HIV prevalence in Africa and Asia that remain at risk for measles outbreaks,[10] where achieving measles control goals may need to include specific guidance for HIV-infected individuals. To investigate this possible association, we assessed measles antibody levels according to HIV status and CD4 count among individuals presenting at a hospital-based outpatient clinic in a rural district of southern Malawi.

2. Materials and methods

2.1. Study design, setting, and participants

We investigated the relationship between HIV status (both serostatus and CD4 count) and measles antibody concentration. This cross-sectional study was conducted between January and September 2012 at Chiradzulu District Hospital in Malawi, the nominal catchment area of which includes all people living within Malawi's Chiradzulu District.

A convenience sample of HIV-uninfected participants was recruited from among individuals who voluntarily presented for HIV counselling and testing during the study period: all people who presented and who were subsequently found to be HIV-uninfected were referred to the study recruiters. Meanwhile, a convenience sample of HIV-infected participants was recruited from patients already on HIV treatment and who presented for follow-up care during the study period: all people who presented for such care were referred, after their medical consultation, to the study recruiters.

The study recruiters explained the study purpose and design to all individuals (or their guardians if they were younger than 18 years old) referred to them. Those who gave informed consent to participate were recruited into the study. Eligibility for inclusion was restricted to individuals aged 18 months or older at the time of recruitment to minimize the potential influence of maternal antibodies acquired either transplacentally or through breastfeeding.

2.2. Variables

The primary outcome measure of this study was measles seroprotection status (seroprotected vs. not seroprotected), and for this purpose, we set the seroprotected threshold (the antibody concentration considered protective against disease) at 330 mIU/ml.[27,28] The secondary outcome was measles IgG antibody concentration among HIV-infected participants only, measured as a continuous variable.

To explore predictors of measles seroprotection status, the exposure variable of interest was HIV infection status (HIV-infected vs. HIV-uninfected), while for measles antibody concentration among HIV-infected participants, the CD4 count was the exposure variable of interest. Additional predictors, potential confounders, and effect-modifiers included for both outcomes were age and sex,[27] time on highly active antiretroviral therapy (HAART),[18,27,29] and reported measles vaccination and infection status.[1]

2.3. Data sources and measurement

Samples of venous blood were collected from each participant for CD4 counts and measles serology. The manufacturer's instructions were followed for all analytical procedures. CD4 counts were determined on site by standard flow cytometry with Cyflow (Partec, Münster, Germany) analysis within 1–6 h of specimen collection.

Serum samples were obtained from whole blood and stored at −20 °C at Chiradzulu District Hospital until transfer to the National Institute for Communicable Diseases in South Africa, where measles serology was performed. Measles IgG antibody concentrations were assessed quantitatively by ELISA (Enzygnost Anti-Measles Virus IgG; Siemens, Marburg, Germany), using kit-dependent parameters.

For each participant, we recorded age, sex, reported measles infection status (ever having had measles), and reported measles vaccination status (ever having been vaccinated against measles). The treatment programme identification number of HIV-infected participants was also recorded to enable linking to the HIV treatment database to include duration of treatment on HAART in the analyses.

2.4. Bias

In order to limit potential sources of bias, all laboratory staff were blinded to the HIV status of participants.

2.5. Study size

Obtaining representative samples of hard-to-reach individuals is a major challenge for epidemiological studies and surveillance.[30] Traditional sampling methods often involve very large sample sizes, which are prohibitive due to operational and cost difficulties. Most importantly, carrying out home-based studies in this context is hindered by ethical considerations, as individuals may not disclose their HIV status, if known, to family members and friends. Like many other studies of this type, we used convenience

sampling and attempted to minimize bias by including a large sample size.[30] A 10% difference in the proportion of individuals with protective concentrations of measles antibodies (seroprotection) between HIV-infected and HIV-uninfected individuals was considered both realistic and of public health significance. Based on findings from Zambia,[31] we assumed these proportions to be 60% and 70% among HIV-infected and HIV-uninfected individuals, respectively. Assuming an alpha of 5%, power of 80%, and a laboratory test error proportion of 5%, we needed to recruit a total of 1424 individuals to detect this difference.

2.6. Statistical methods

We present the distributions of study participants by recruitment group (HIV infection status), according to age group (18 months to 17 years, and ≥18 years), sex, measles seroprotection status, and median time on HAART.

The association between HIV infection status and measles seroprotection was explored by fitting a log binomial generalized linear (logistic regression) model, while linear regression was used to model the association between HIV infection and log measles antibody concentration.[13,16,32] All regression models were adjusted for the potential risk factors and confounders for IgG concentration listed above.

As there is no clearly defined IgG threshold for measles seroprotection, and in order to explore the relationship between HIV status and possible vaccine failure (defined here as having a sufficient measles IgG concentration to be classified as seropositive but not sufficient to be classified as seroprotected), a sensitivity analysis was performed to explore the effect of using a different IgG threshold on our findings, using a commonly-defined measles IgG seropositivity threshold (≥120 mIU/ml).[16,32]

Confidence intervals (95% CI) and *p*-values are presented for all results.

Data were entered into EpiData 3.1 (EpiData Association, Odense, Denmark) and cleaned and analysed using R software version 3.0.3 (R Development Core Team, R Foundation for Statistical Computing; http://www.r-project.org).

2.7. Ethics statement

This project adhered to the Declaration of Helsinki. The study protocol received ethical approval from the National Health Sciences Research Committee of Malawi. The study was explained to all study participants (or their guardians if they were under the age of 18 years) in Chichewa, the local language, and all provided informed consent to participate. The confidentiality of participants was respected at every stage of this study, and all information was encoded with a non-nominative unique identification number. Participants were free to withdraw from the study at any time, and all participation was voluntary. Treatment and counselling were provided free of charge to all participants irrespective of study participation. We did not collect information on the numbers of individuals who refused to participate in this specific study.

3. Results

3.1. Descriptive analysis

One thousand nine hundred and sixty participants were recruited into the study, of whom 25 were excluded from the analysis because of quality issues with their blood samples. The remaining 1935 participants were included in the analyses, of whom 1434 were HIV-infected and 501 were HIV-uninfected (Table 1). Nearly two-thirds of participants (n = 1226, 63.4%) were female. The median age of the participants was 37 years (interquartile range 29–46 years), and 141 (7.2%) participants were children (aged 18 months to 17 years). The median age of the HIV-uninfected participants was 9 years younger than that of the HIV-infected participants (Figure 1). Information on the duration of treatment on HAART was available for 1049 (73.2%) HIV-infected participants.

While there was a clear difference between age groups in the distribution of the log measles IgG concentration, these were generally similar according to the other explanatory variables of interest (Figure 2).

3.2. Main results

More than half (58.9%) of the children and almost all (94.3%) of the adult participants (those aged ≥18 years) were seroprotected against measles (Table 2).

In the unadjusted analyses, HIV status, age, sex, and reported vaccination status were all significantly associated with measles seroprotection, while reported prior measles infection was not associated with this outcome (Table 3).

In the multivariate logistic model, age was found to interact with the association between HIV status and measles seroprotection ($p < 0.001$); therefore, we did an age-stratified analysis of this association.

Among children, HIV infection (adjusted odds ratio (OR) 0.27, 95% CI 0.10–0.69; p = 0.006) was associated with a decreased odds of being measles seroprotected (Table 3). However, among adults, HIV infection was not associated with measles seroprotection. Among adults, age was associated with an increased odds of being measles seroprotected (adjusted OR 1.12, 95% CI 1.08–1.15;

Table 1
Characteristics of HIV-uninfected and HIV-infected study participants, Chiradzulu District, Malawi, January to September 2012 (N = 1935)

Characteristic	HIV-uninfected (%)	HIV-infected (%)	Total
Age group			
18 months to 17 years	55 (11.0)	86 (6.0)	141 (7.3)
≥18 years	445 (89.0)	1347 (94.0)	1792 (92.7)
Sex			
Male	194 (38.9)	512 (35.7)	706 (36.5)
Female	305 (60.9)	921 (64.3)	1226 (63.4)
Measles seroprotection status[a]			
Not seroprotected	52 (10.4)	108 (7.5)	174 (9.0)
Seroprotected	449 (89.6)	1326 (92.5)	1761 (91.0)
Median IgG (IQR)	2301 (834–4873)	2956 (1238–5657)	2793 (1085–5400)
Time on HAART (n = 1049)			
Median number of days (IQR)	-	1721 (756–2575)	1721 (756–2575)
Total	501	1434	1935

IQR, interquartile range; HAART, highly active antiretroviral therapy.
[a] Measles seroprotection defined as IgG antibody concentration ≥330 mIU/ml.

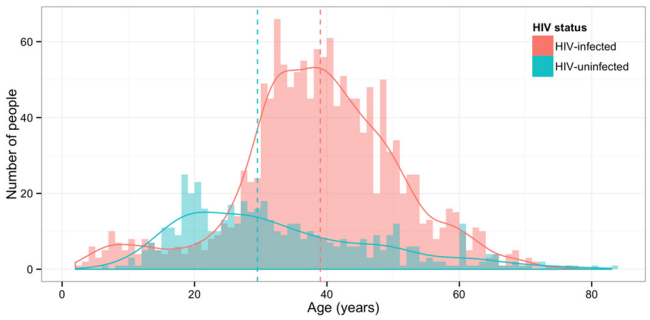

Figure 1. Age distribution of HIV-infected and HIV-uninfected study participants, Chiradzulu District, Malawi, January to September 2012. The dashed lines show the median ages of each group ($N = 1935$).

$p < 0.001$), while reported prior measles vaccination was associated with a lower odds of being measles seroprotected (adjusted OR 0.49, 95% CI 0.26–0.93; $p = 0.030$). In both age groups, neither sex nor reported prior measles infection was significantly associated with measles seroprotection, but this may have been due to the reduction in sample size in these stratified analyses.

In the log-linear regression model, neither CD4 count ($p = 0.16$) nor time on HAART ($p = 0.25$) was associated with measles antibody concentration among HIV-infected participants, while older age ($\beta = 0.04$; $p < 0.001$) and female sex ($\beta = 0.29$, $p < 0.001$) were positively associated with increasing measles antibody concentration.

We performed a sensitivity analysis to explore the effect of using an alternative IgG concentration on our results. This alternative threshold did not affect our findings (Table 3). In addition, we explored the relationship between vaccine failure (120 mIU/ml ≤ IgG < 320 mIU/ml) and HIV status, and found that HIV status was not associated with a likelihood of vaccine failure ($p = 0.39$), but males and younger participants were more likely to have such intermediate concentrations.

4. Discussion

In this study population, HIV status was associated with measles seroprotection status among children, but not among adults. CD4 count was not associated with measles antibody concentration among HIV-infected individuals. Older age and female sex were associated both with greater odds of measles seroprotection and higher measles antibody concentration.

The majority of the study participants were seroprotected against measles infection, and this was true of both HIV-infected and uninfected participants. Most participants aged ≥18 years were seroprotected against measles, but approximately half the children aged <18 years were vulnerable to measles infection.

A greater proportion of HIV-uninfected adults were measles seronegative compared to HIV-infected adults. This may be an artefact of the recruitment process: as HIV-uninfected participants were recruited while attending for HIV testing, they may have been experiencing ill-health at the time of recruitment; they may also have exhibited other risk factors, or there may have been other unknown differences between these two groups. As a result, the HIV-uninfected adults may not be comparable to HIV-infected adults in terms of their past or current health or health-seeking behaviour. On the other hand, as HIV-infected participants were recruited while attending regular treatment sessions, they may therefore have had more opportunities for vaccination during their regular clinic visits than their HIV-uninfected study counterparts at the time of recruitment, particularly as measles vaccination is recommended following the immune reconstitution that accompanies HAART.[18,33–36] A decreased likelihood that HIV-infected children are measles seroprotected (despite potential artefacts resulting from the recruitment procedure) has been reported elsewhere, but should be interpreted with caution, as the number

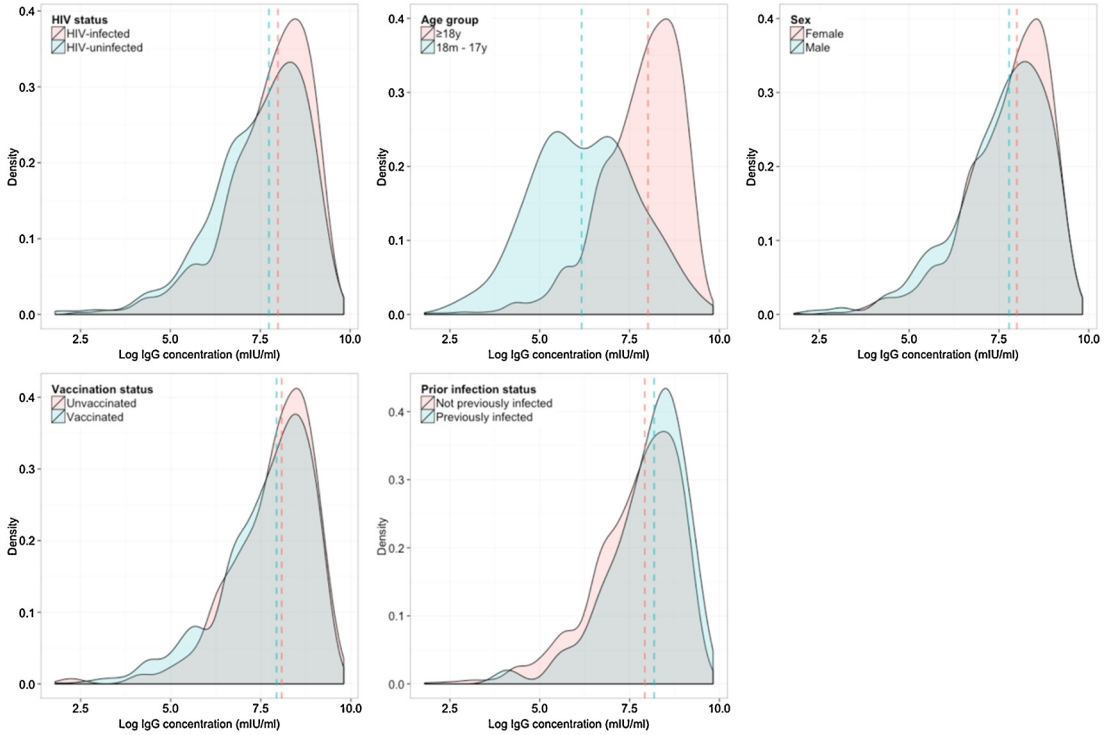

Figure 2. Distributions of, and median (dashed lines), measles antibody log concentrations among the study population, according to baseline characteristics, Chiradzulu District, Malawi, January to September 2012 ($N = 1935$).

Table 2
Distribution of study participants according to measles seroprotection status and HIV infection status, among children (aged 18 months to 17 years) and adults (aged ≥18 years), Chiradzulu District, Malawi, January to September 2012 (N = 1935)

Seroprotection status[a]	Children (n = 141)		Adults (n = 1792)	
	HIV-uninfected (%)	HIV-infected (%)	HIV-uninfected (%)	HIV-infected (%)
Not protected	13 (23.6)	45 (52.3)	39 (8.8)	63 (4.7)
Protected	42 (76.4)	41 (47.7)	406 (91.2)	1284 (95.3)

[a] Measles seroprotection defined as IgG antibody concentration ≥330 mIU/ml.

of children in the study (n = 141) represented a relatively small proportion of the total sample size.

We found that prior vaccination was independently associated with a lower odds of measles seroprotection, which is counterintuitive, as measles vaccination should boost the immune response. This finding is hard to explain, but we suspect that it may have derived from two possibilities: either from the recruitment procedure itself and/or poor recall of prior vaccination, which for many participants would have occurred in their distant past.

The absence of an association between CD4 count and measles antibody concentration was previously reported among HIV-infected adults in the USA[25] and among HIV-infected Kenyan children[36] and adults.[22] Further, the antibody response to measles vaccine was not associated with CD4 count in HIV-infected Zambian children.[37] However, a low CD4 count was associated with both a lower measles antibody concentration and a worse response to revaccination with measles vaccine among HIV-infected children in Central Africa.[38] One study found no difference in the initial immune response to measles, mumps, and rubella vaccine between HIV-infected adults on HAART and HIV-uninfected adults, but reported more rapid waning of these antibodies among HIV-infected adults, despite high CD4 counts.[23] Therefore, if HIV infection does influence susceptibility to measles infection among adults, it may operate through a mechanism unrelated to CD4 count.

Overall, these results support the idea that ensuring adequate vaccination coverage may be the most important factor in the control and elimination of measles.[6] We found no evidence that HIV infection among adults contributed to the risk of measles infection in this sample, but we did find that HIV-infected children were less likely to be seroprotected against measles infection. Previously, this had been demonstrated from infancy up to age 36 months,[13,37–39] but we report that this may also be true for older children, up to 17 years old. Our results also suggest that, if HIV status does contribute to measles infection risk, it may not be due to low CD4 count.

Although protection against measles infection was high among adults in this sample, the level may be insufficient to prevent periodic outbreaks.[6] Vaccination of HIV-infected adults who are not seroprotected against measles has been recommended.[25] As approximately 10% of HIV-uninfected adults were also not seroprotected against measles, revaccination of these vulnerable adults would provide individual and public health benefits. The current target age range for supplementary immunization activities in Sub-Saharan African countries identified for measles elimination strategies is 9 months to 14 years; to strengthen the attainment of elimination goals, the age range could be widened to include vulnerable older children and young adults. However, such a strategy would require substantial resources, and would need to be weighed against other potential interventions.

A large proportion of children were not seroprotected against measles, and HIV-infected children were at greater risk of having a sub-protective level of measles antibodies. Current World Health Organization (WHO) recommendations include the administration of a supplementary measles vaccination at age 6 months to HIV-infected infants in addition to the regular Expanded Programme on Immunization schedule, unless otherwise indicated.[40] Our results suggest that HIV-infected children may be less protected against measles infection than uninfected members of their cohort at older ages than previously reported, and this supports the proposal that measles vaccination should be reinforced for all HIV-infected children, irrespective of age, by offering at least one further opportunity for measles vaccination after successful immune reconstitution with HAART.[18,33–36] Furthermore, in such a context, in which one quarter of HIV-uninfected and half of HIV-infected children were not seroprotected against measles, we also recommend offering additional opportunities for measles vaccination for all children, to reduce the risk at both the individual level (through immunity boosters) and community level (through the effect of herd immunity).

As antiretroviral therapy becomes more widely available, thereby increasing the longevity of HIV-infected individuals, the

Table 3
Unadjusted and adjusted associations between measles seroprotection and various exposure variables, Chiradzulu District, Malawi, January to September 2012 (N = 1935)

Exposure variable	Unadjusted analysis		Adjusted analysis			
			Children		Adults	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
HIV status						
HIV-uninfected	Ref.		Ref.		Ref.	
HIV-infected	1.42 (1.00–2.01)	0.047	0.27 (0.10–0.69)	0.006	1.08 (0.61–1.93)	0.79
Age						
Per additional year	1.11 (1.09–1.13)	<0.001	1.06 (0.95–1.17)	0.33	1.12 (1.08–1.15)	<0.001
Sex						
Male	Ref.		Ref.		Ref.	
Female	1.60 (1.15–2.21)	0.005	1.91 (0.88–4.14)	0.10	1.54 (0.94–2.52)	0.09
Reported vaccination status						
Unvaccinated	Ref.		Ref.		Ref.	
Vaccinated	0.45 (0.26–0.79)	0.005	0.49 (0.09–2.71)	0.41	0.49 (0.26–0.93)	0.030
Reported infection status						
Never infected	Ref.		Ref.		Ref.	
Previously infected	1.91 (0.77–4.76)	0.17	2.21 (0.37–13.42)	0.39	1.95 (0.56–6.82)	0.29

OR, odds ratio; CI, confidence interval.

quality of the immune responses of these individuals to measles vaccine and infection will become increasingly important for measles control.[36,41] This study suggests that HIV-infected children up to the age of 18 years may be less likely to be seroprotected against measles, and therefore represent a potential pool of susceptible individuals who could contribute to propagating transmission and sustaining outbreaks of measles, thereby compromising the WHO Expanded Programme on Immunization. In high HIV prevalence settings, where the control and elimination of measles is a key public health goal and where a substantial proportion of the population is aged less than 18 years, vaccination strategies may need to be adapted to address adequately the additional potential risk posed by this high-risk section of the population. More population-based research is needed to elucidate further the age range at which this risk is elevated.

The principal limitation of this study is that the cross-sectional, convenience sampling design precludes making causal inferences between HIV infection status and measles serostatus. In addition, we recruited study participants from among routine attendees at Chiradzulu District Hospital, as we could not ethically justify the recruitment of HIV-uninfected participants who had not themselves taken the initiative to find out their own HIV status. Although we considered this appropriate for an explorative, hypothesis-generating study, this non-population-based convenience sampling method did not permit selection according to baseline characteristics of the participants in each recruitment group, and may have introduced various forms of selection bias. Future research could explore these issues by use of a population-based recruitment procedure, thereby ensuring greater similarity in these characteristics between recruitment groups. Population-based studies of this nature are often prohibitive, but additional research would be essential in order to provide more robust evidence.

A limit to the generalizability of our findings is that fact that we enrolled only HIV-infected individuals already on HAART, and whose immune system has likely been reconstituted and who have subsequently been offered additional opportunities for measles vaccination. These findings may therefore apply only to a narrow range of circumstances in Sub-Saharan Africa, i.e. where access to HIV treatment is high.

Because of the recruitment procedure, few infants and young children were recruited into this study, as children aged <18 months were excluded, and relatively few young children either present for HIV testing or are on HIV treatment. Young children are the most vulnerable to measles infection, and it is among these individuals that HIV status has been reported to influence measles antibody concentrations through a variety of mechanisms.[29,31,42] However, our primary objective was to explore the relationship of HIV status and measles seroprotection among older children and young adults, among whom the attack rate of the 2010 measles epidemic was surprisingly high and for whom research on the impact of HIV on susceptibility to measles has been identified as a priority.[10]

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Ethical issues: This project adhered to the Declaration of Helsinki. The study protocol received ethical approval from the National Health Sciences Research Committee of Malawi.

Conflict of interest: We declare that we have no conflict of interest.

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