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Persisting high prevalence of pneumococcal carriage among HIV-infected adults receiving antiretroviral therapy in Malawi: a cohort study

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Objective: HIV-infected adults have high rates of pneumococcal carriage and invasive disease. We investigated the effect of antiretroviral therapy (ART) on pneumococcal carriage in HIV-infected adults prior to infant pneumococcal conjugate vaccine (PCV) rollout.

Design: Observational cohort study.

Methods: We recruited HIV-infected adults newly attending a rural HIV clinic in northern Malawi between 2008 and 2010. Nasopharyngeal samples were taken at baseline and after 6, 12, 18 and 24 months. We compared pneumococcal carriage by ART status using generalized estimated equation models adjusted for $CD4^+$ cell count, sex, seasonality, and other potential confounders.

Results: In total, 336 individuals were included, of which 223 individuals started ART during follow-up. Individuals receiving ART had higher pneumococcal carriage than individuals not receiving ART (25.9 vs. 19.8%, $P = 0.03$) particularly for serotypes not included in PCV13 (16.1 vs. 9.6% $P = 0.003$). Following adjustment, increased carriage of non-PCV13 serotypes was still observed for individuals on ART, but results for all serotypes were nonsignificant [all serotypes: adjusted risk ratio (aRR) 1.22 (0.95–1.56); non-PCV13 serotypes: aRR 1.72, 95% CI 1.13–2.62].

Conclusion: Pneumococcal carriage in HIV-infected adults in Malawi remained high despite use of ART, consistent with failure of mucosal immune reconstitution in the upper respiratory tract. There was evidence of increased carriage of non-PCV13 serotypes. HIV-infected adults on ART could remain an important reservoir for pneumococcal diversity post infant pneumococcal vaccine introduction. Control of pneumococcal disease in African HIV remains a priority.

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Introduction

Streptococcus pneumoniae is a leading cause of morbidity and mortality worldwide. As a leading cause of bacterial pneumonia, meningitis and sepsis, the pneumococcus is estimated to cause 11% of all-cause mortality in children 1–59 months worldwide [1]. HIV-infected adults and children are at 20-fold to 100-fold higher risk of invasive

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pneumococcal disease (IPD) [2–4]. In sub-Saharan Africa, IPD in adults is strongly associated with HIV infection and has a high mortality rate [5–8].

Nasopharyngeal carriage of pneumococci is believed to be a prerequisite for IPD, although the underlying mechanisms remain to be established. Pneumococcal carriage is more common in HIV-infected than HIV-uninfected individuals [9–11]. The nasopharynx also acts as the main reservoir for pneumococcal transmission [12]. Exclusion of pneumococci from this site prevents transmission and is the mechanism underlying the herd protection generated by pneumococcal conjugate vaccines (PCVs).

Antiretroviral therapy (ART) reduces the incidence of IPD in HIV-infected adults [2] and there is a strong temporal relationship between large-scale ART introduction and declines in IPD in Malawi [13,14]. This population impact will be driven by immune reconstitution and/or immune maintenance at the individual level. However, HIV-infected individuals established on ART remain at much higher risk of IPD as compared with HIV-uninfected individuals [15]. This suggests immune reconstitution is incomplete; a finding supported by earlier work in Malawi suggesting that ART did not alter the risk of recurrent IPD events [16].

There is limited information on the effect of ART on pneumococcal carriage in HIV-infected adults. Three studies have reported carriage prevalence in ART-treated adults with diverging results. In two immunological studies on HIV-infected Malawian adults, carriage was highest in those receiving ART for more than 12 months [9,17]. The third study in HIV-infected Brazilian adults reported a lower risk of colonization in ART-treated individuals [18]. The major limitation in these three studies was the lack of control for potential confounders such as child contacts, whereas the studies in Malawi were not powered to investigate carriage epidemiology effectively. Based on the drop in IPD since introduction of ART in Malawi and the impact of immune reconstitution, we hypothesized that pneumococcal carriage in individuals would decrease when established on ART. Using a cohort design and recruiting attendees at a rural HIV clinic in northern Malawi, we investigated the impact of ART on pneumococcal carriage in Malawian adults infected with HIV. The study was undertaken prior to introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in the infant immunization schedule in October 2011.

Methods

Study design

This study is part of a cohort study on ART eligibility, adherence and outcomes, as described elsewhere [19]. The study was set in a rural HIV clinic within the area covered by the Karonga Health and Demographic Surveillance System (HDSS) in northern Malawi [20]. HIV prevalence in the area was estimated at 7.1% in men and 9.2% in women in 2008/2009 [21]. ART was available in the study clinic since 2006. At the time of the study, individuals were eligible for ART if they had clinical features consistent with WHO disease stage 3 or 4, or had a $CD4^+$ cell count of less than 250 cells/μl, as per government guidelines. All individuals attending ART clinic were offered cotrimoxazole prophylactic treatment. Pneumococcal vaccination was not provided to HIV-infected adults at the time of the study. All HIV-infected adults and adolescents (>15 years) living in the HDSS who newly attended the clinic and were not already taking ART were invited to participate in the cohort study from January 2008. Detailed clinical data were obtained at baseline and on follow-up visits every 3 months. $CD4^+$ cell counts were recorded at baseline and at 6 monthly intervals. Viral loads were recorded at baseline and at 6 months after treatment initiation. Individuals not qualifying for ART at baseline were assessed on subsequent visits for qualification. Treatment failure was assessed as a $CD4^+$ cell count less than 100 cells/μl or a fall of $CD4^+$ cell count below pretherapy baseline after at least 12 months on ART and/or a viral load more than 10 000 copies/ml after at least 6 months on ART despite good adherence. Poor adherence was defined as missing more than 3 days of therapy in 3 months.

This study on the effect of ART on pneumococcal carriage included all individuals recruited between February 2008 and May 2010. Nasopharyngeal samples were taken at baseline and at 6-monthly intervals from individuals returning to the HIV clinic until February 2011. We included all individuals with a baseline and at least one follow-up result in the analysis.

The cohort was established with the primary objective of understanding outcomes of HIV care delivery in adults resident in the HDSS. We expected to recruit 500 participants of whom 300 would be commenced on ART. Under these circumstances, we would have 80% power to detect a fall in nasopharyngeal carriage by 40% or more following ART initiation from a baseline prevalence of 25% (two-tailed alpha 0.05).

Laboratory procedures

Nasopharyngeal samples were collected and analyzed according to standard procedures [22]. A calcium alginate swab (Medical Wire & Equipment, Corsham, UK) was inserted into the posterior nasopharynx and transported in skim milk-tryptone-glucose-glycerol medium. Inoculated vials were stored at −20°C within 6 h of collection, and frozen at −80°C until tested. Samples were cultured on gentamicin blood agar and incubated overnight at 37°C with 5% CO_2. Pneumococci were identified by morphology and sensitivity for optochin. One colony was isolated and cultured in Todd–Hewitt broth. Pneumococci were serogrouped using latex agglutination and

serotyped by the Quellung reaction using standard antisera (Statens Serum Institut, Copenhagen, Denmark). Reagents were available to type 48 of the potential 92 serotypes, including the PCV13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F).

Data analysis

We compared pneumococcal carriage prevalence between individuals started on ART and individuals not started on ART. Individuals starting ART during the follow-up period contributed observation time to both non-ART and ART groups. Proportions of pneumococcal carriage were tested using the chi-square or Fisher's exact test as appropriate.

Crude and adjusted risk ratios (RR and aRR) for pneumococcal carriage by ART status were obtained by log-binomial regression using generalized estimated equations models with an exchangeable correlation structure and robust standard errors to account for any within-person clustering of the data [23]. Other factors considered were sex, age, $CD4^+$ cell count, cotrimoxazole use, WHO-defined clinical disease stage and household composition. For seasonality, parametric functions with different numbers of sin-cosine waves were examined. For instance, a model with two sin-cosine waves was specified as:

$$\begin{aligned} y_{i,t} = \quad & \alpha + \beta_1 \sin\left(\frac{2\pi t}{365}\right) + \beta_2 \cos\left(\frac{2\pi t}{365}\right) \\ & + \beta_3 \sin\left(\frac{4\pi t}{365}\right) + \beta_4 \cos\left(\frac{4\pi t}{365}\right) \\ & + \beta_5 ART_{i,t} + \beta_6 \ covariates_{i,t} \end{aligned}$$

where $y_{i,t}$ is the carriage in individual i on day of the year t, β_{1-4} terms are regression coefficients for each sine and cosine function, *ART* is a binomial variable of the individual's ART-status and *covariates* are other factors studied.

Sensitivity analyses

Missing $CD4^+$ cell count data were estimated for individuals with at least two $CD4^+$ cell counts available by simple linear regression on two $CD4^+$ cell counts closest in time to the missing data point. Sensitivity analysis was performed excluding individuals with poor adherence or treatment failure. A separate sensitivity analysis was performed including only those individuals that started ART at some point during follow-up.

Ethics

Informed written consent was obtained from all participants. Ethical approval was granted by the National Health Sciences Research Committee in Malawi and the London School of Hygiene and Tropical Medicine ethics committee.

Results

In total, 468 individuals newly attended the ART clinic between February 2008 and May 2010. Seventy-two individuals (15.4%) did not revisit the ART clinic because they died ($n = 22$) or departed from the study area ($n = 23$) within 6 months of recruitment or were lost to follow-up for unknown reasons ($n = 27$). At least one follow-up visit was recorded for 396 individuals (84.6%). At least two nasopharyngeal specimens (one at baseline, one at follow-up) were taken from 363 individuals (91.6%). For 26 individuals (7.2%) sample results were not available. One individual was excluded from the analysis because of unknown ART start date.

In total, 336 individuals were included in the analysis, of which 233 individuals started ART during follow-up (Table 1). Individuals completed on average 15.7 months of ART during the follow-up period (range 5–31 months). On average, three nasopharyngeal samples were available per person. The average number of samples was slightly higher in individuals who started ART during follow-up as compared with those who did not (3.1 vs. 2.9 samples, $P = 0.06$). More women (n = 207) than men ($n = 129$) attended the ART clinic and participated in the study ($P < 0.001$). Poor adherence was observed for five individuals (2.2%). Treatment failure was observed for 23 of 209 (11.0%) individuals with good adherence and

Table 1. Baseline characteristics of HIV-infected adults who started antiretroviral therapy during the follow-up period or not.

	Started ART during follow-up ($n = 233$)	Not started ART during follow-up ($n = 103$)
Female sex	131 (56.2%)	76 (73.8%)
Age, (mean, SD)	39.9, SD = 10.3	37.8, SD = 11.4
$CD4^+$ cell count (median, IQR)	174 cells/μl (86–280)	462 cells/μl (365–653)
WHO clinical disease stage	Stage 1: 31 (13.3%)	Stage 1: 34 (33.0%)
	Stage 2: 77 (33.0%)	Stage 2: 69 (67.0%)
	Stage 3: 101 (43.3%)	Stage 3: 0 (0%)
	Stage 4: 24 (10.3%)	Stage 4: 0 (0%)
Pneumococcal carriage	49 (21.0%) – all types	22 (21.4%) – all types
	26 (11.1%) – PCV13 types	10 (9.7%) – PCV13 types
	23 (9.9%) – non-PCV13 types	12 (11.7%) – non-PCV13 types

ART, antiretroviral therapy; IQR, interquartile range; PCV, pneumococcal conjugate vaccine; SD, standard deviation.

repeated $CD4^+$ cell count and/or viral load results available. Cotrimoxazole prophylactic treatment was reported to be taken during part or all of the follow-up period by 94.8% (221/233) of individuals receiving ART during follow-up and 81.5% (84/103) of individuals who did not receive ART during follow-up.

Pneumococcal carriage was detected in 232 out of 1027 samples (22.6%). Pneumococcal carriage prevalence at baseline was similar in individuals who subsequently received ART compared with those who did not (21.0 vs. 21.4%, $P=0.99$). Median $CD4^+$ cell count increased over time in patients started on ART, but no decrease in pneumococcal carriage was observed (Fig. 1). Individuals started on ART were more likely to have pneumococcal carriage than individuals not started on ART at all subsequent sampling points (25.6 vs. 17.9%, $P=0.03$) (Fig. 1). Among individuals on ART, carriage did not differ between those who had undetectable or low ($\leq$400 copies/ml) viral loads and those who had viral loads more than 400 copies/ml at 6 months after treatment initiation (26.1 vs. 23.3%, $P=0.84$). In the multivariable analysis including all samples, increased carriage was still observed for individuals on ART, but results were nonsignificant (aRR 1.22, 95% CI 0.95–1.56) (Table 2). Similar results were maintained when omitting results from individuals with treatment failure or poor adherence (aRR 1.25, 95% CI 0.96–1.63). In the sensitivity analysis with imputed $CD4^+$ cell count data a significant increase in carriage was observed for ART-treated individuals (aRR 1.29, 95% CI 1.03–1.62). Including only individuals who received ART during the follow-up period ($n=233$) resulted in a weaker association in the same direction (aRR 1.17, 0.86–1.60).

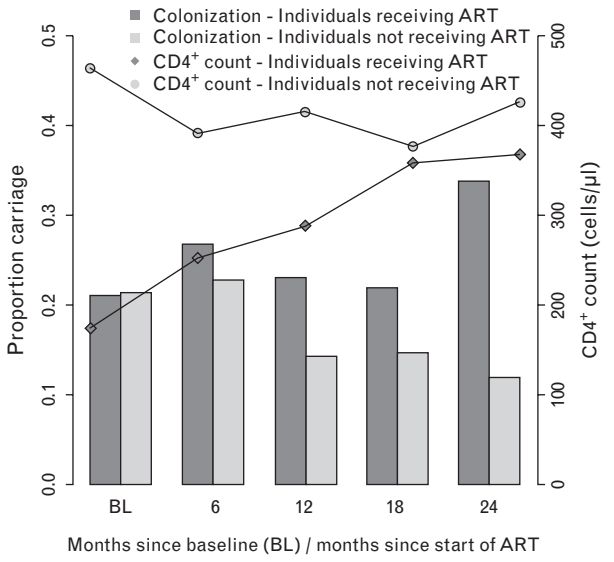

Fig. 1. Pneumococcal colonization and median $CD4^+$ cell count on baseline and by month since ART/month since baseline in patients receiving ART or not. ART, antiretroviral therapy.

There was no evidence that among individuals on ART pneumococcal carriage differed by duration of treatment (Table 2, Fig. 1).

Most common serotypes isolated were 3 (9.1% of isolates), 19F (6.5%), 6B (5.2%), 11 (4.7%) and 23F (4.7%) (Fig. 2). Sixty-six isolates (28.4%) could not be fully typed with the available reagents. There was weak evidence that the diversity of serotypes carried was greater in the ART-treated group than in the ART-untreated groups (32 serotypes in 87 typable isolates vs. 25 serotypes in 79 typable isolates): a comparison of bootstrapped Shannon diversity indices gave a simulated P value of 0.08. In a pooled analysis of all time points, carriage of PCV13 serotypes did not differ between individuals on ART or not (9.9 vs. 10.2%, $P=0.94$), but carriage of non-PCV13 serotypes was higher in individuals on ART (16.1 vs. 9.6% $P=0.003$). Carriage of non-PCV13 serotypes remained significantly higher in the ART-treated group after adjustment in the multivariable analysis (aRR 1.72, 95% CI 1.13–2.62) (Table 2).

Low $CD4^+$ cell count was associated with higher pneumococcal carriage prevalence (aRR 1.40, 95% CI 1.08–1.82 for $\leq$250 vs. >250 cells/μl). There was no evidence for an association between pneumococcal carriage and cotrimoxazole prophylactic treatment (aRR 0.95, 95% CI 0.68–1.34). Female sex was associated with higher pneumococcal carriage prevalence (aRR 1.74, 95% CI 1.26–2.40). Individuals living in large households seemed to be more likely to carry a pneumococcus than individuals living in small households (aRR 1.52, 95% CI 0.95–2.41 for 0–2 vs. 8–15 household members). There was no evidence for an association between pneumococcal carriage and living with children younger than 5 years of age (aRR 1.05, 95% CI 0.81–1.37). Pneumococcal carriage showed strong seasonality with a model with two sine-cosine pairs providing the best fit (Fig. 3). Carriage prevalence was higher in the cold (May-August) and hot (September-November) seasons as compared to the rainy season (December-April).

Discussion

This cohort study provides strong evidence that pneumococcal carriage in HIV-infected adults remains high during the first two years of ART use, with a tendency to increased carriage of non-PCV13 serotypes. Two immunological studies from Malawi have reported consistent findings [9,17], but this is the first cohort study that addresses important confounders for pneumococcal carriage and provides robust measures of association.

Several of our risk factors for carriage are well known. We found that females are at higher risk of pneumococcal carriage, consistent with their higher contact rates with

Table 2. Risk ratios and 95% confidence intervals of risk factors associated with pneumococcal carriage in HIV-infected adults.

		Carriage							
Risk factor	*n*	*n*	%	Crude RR	95% CI	*P*	aRR	95% CI	*P*
ART									
Carriage of all serotypes									
Not on ART	560	111	19.8	–			–		
On ART	467	121	25.9	1.29	1.02–1.62	0.03	1.22	0.95–1.56	0.12
Carriage of PCV13 serotypes									
Not on ART	560	57	10.2	–			–		
On ART	467	46	9.9	0.96	0.68–1.37	0.84	0.87	0.57–1.33	0.51
Carriage of non-PCV13 serotypes									
Not on ART	560	54	9.6	–			–		
On ART	467	75	16.1	1.64	1.19–2.27	0.003	1.72	1.13–2.62	0.01
Months on ART									
0 (at start ART)	233	53	22.7	–			–		
6	153	41	26.8	1.20	0.76–1.91	0.43	1.26	0.88–1.80	0.21
12	143	33	23.1	1.06	0.68–1.64	0.80	0.85	0.54–1.33	0.47
18	87	19	21.8	0.99	0.57–1.72	0.98	1.03	0.63–1.66	0.92
24	68	23	33.8	1.92	1.10–3.34	0.02	1.59	1.09–2.33	0.02
Sex									
Men	392	61	15.6	–			–		
Women	635	171	26.9	1.68	1.25–2.27	<0.001	1.74	1.26–2.40	<0.001
Age (years)									
<31	153	45	29.4	–			–		
31–40	424	99	23.3	0.80	0.58–1.10	0.18	0.84	0.60–1.17	0.30
41–50	262	56	21.4	0.76	0.53–1.08	0.13	0.85	0.60–1.21	0.38
>50	188	32	17.0	0.58	0.38–0.89	0.01	0.78	0.48–1.28	0.33
CPT									
Not on CPT	418	84	20.1	–			–		
On CPT	609	148	24.3	1.22	0.96–1.56	0.11	0.95	0.68–1.34	0.77
$CD4^+$ cell count (cells/μl)[a]									
>250	549	105	19.1	–			–		
≤250	320	84	26.3	1.35	1.03–1.77	0.03	1.40	1.08–1.82	0.01
WHO stage									
1	563	130	23.1	–			–		
2	324	71	21.9	0.92	0.71–1.18	0.50	1.13	0.85–1.49	0.40
3	112	29	25.9	1.06	0.75–1.50	0.76	1.15	0.80–1.66	0.45
4	28	2	7.1	0.34	0.12–0.99	0.05	0.37	0.10–1.45	0.15
Children <5 years in household[b]									
No	480	105	21.9	–			–		
Yes	470	109	23.2	1.03	0.79–1.33	0.85	1.05	0.81–1.37	0.70
Number of household members[b]									
0–2	248	52	21.0	–			–		
3–7	611	132	21.6	1.07	0.78–1.47	0.69	1.07	0.77–1.49	0.68
8–15	91	30	33.0	1.50	0.93–2.41	0.10	1.52	0.95–2.41	0.08
Year									
2008	179	33	18.4	–			–		
2009	452	95	21.0	1.13	0.81–1.56	0.47	1.03	0.72–1.48	0.87
2010	395	103	26.1	1.38	0.98–1.95	0.06	1.29	0.85–1.95	0.23

RRs were estimated from log-binomial regression models. Within-person clustering was adjusted for using the generalized estimating equations method. ART, seasonality (parametric spline fit), $CD4^+$ cell count and sex were included in the multivariable analysis. Analysis on all serotypes unless specified otherwise. aRR, adjusted risk ratio; ART, antiretroviral therapy; CI, confidence interval; CPT, cotrimoxazole prophylactic treatment; PCV, pneumococcal conjugate vaccine; RR, risk ratio.

[a]$CD4^+$ cell count missing for 158 observations (15.4%). Estimation by linear regression for 137 observations from individuals with at least two $CD4^+$ cell counts available resulted in an aRR for the association of ART with pneumococcal carriage of all serotypes of 1.29 (95% CI 1.03–1.62).

[b]Household information missing for 77 observations (7.5%).

young children in which pneumococcal carriage is greatest. However, household contact with children less than 5 years was not found to be independently associated with pneumococcal carriage in HIV-infected adults. A possible explanation for this inconsistency is that child contact may be universal amongst women and not determined by household contact only. Strong seasonality patterns were observed in this study, with lowest carriage observed in the rainy season. This finding is consistent with another household cohort study on pneumococcal carriage conducted in the same study area in 2009–2011 [24].

Our findings are consistent with two immunological studies of HIV-infected adults in Malawi which reported continued high pneumococcal carriage over a period of 12–18 months on ART [9,17]. Both studies reported failure of mucosal immune responses to normalize after initiation of ART. Similar incomplete mucosal $CD4^+$ T-cell immune reconstitution has frequently been

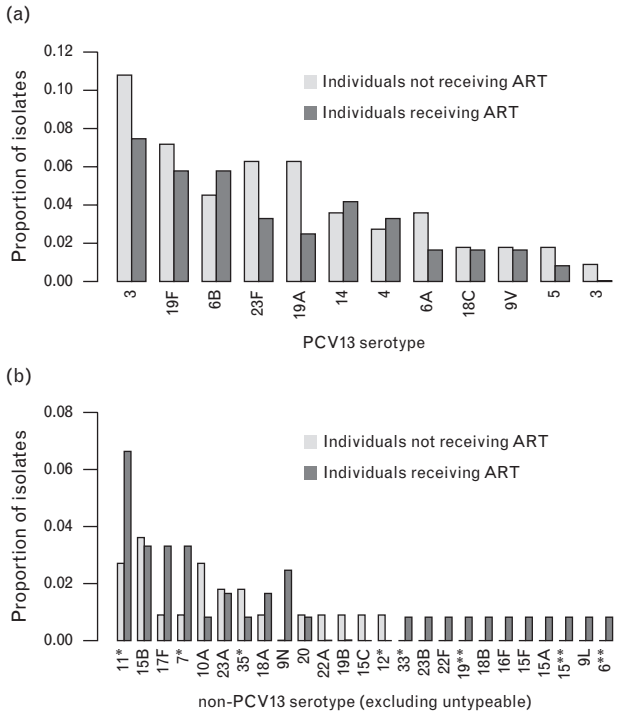

Fig. 2. Carriage of serotypes by ART status. (a) Serotypes included in PCV13. (b) Serotypes not included in PCV13. *Factor typing not done, **Not able to establish factor typing. ART, antiretroviral therapy; PCV, pneumococcal conjugate vaccine.

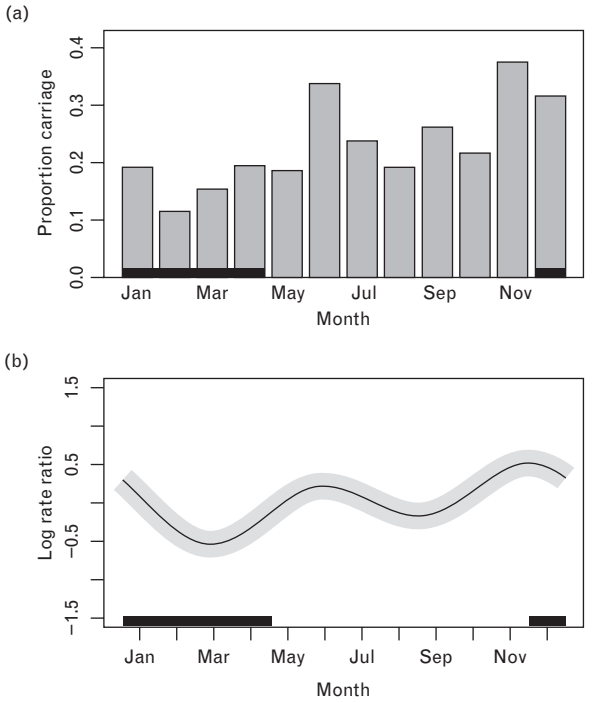

Fig. 3. Seasonality of pneumococcal carriage. (a) Crude carriage prevalence; (b) Fitted parametric spline from adjusted generalized estimated equations model. Grey area represents 95% confidence intervals. Black horizontal bars represent months in the rainy season (December–April).

reported in gut-associated lymphoid tissue [25]. Our findings differ from the two smaller Malawian studies in that we did not find a difference in pneumococcal carriage between symptomatic and asymptomatic HIV-infected adults. We did find evidence for higher carriage of non-PCV13 serotypes, providing further evidence for the hypothesis of 'loss of control' of pneumococcal carriage among ART-treated adults that was generated from the immunological studies [9,17]. A cross-sectional study from Brazil reported stable ART for 1 year or more was associated with lower odds of pneumococcal carriage [18]. This study was highly male biased (70% in Brazil vs. 38% in our study) and reported low household contact with young children (18% in Brazil vs. 50% in our study), representing different demography and risk factors from African HIV-infected populations.

A decrease in IPD has been observed since rollout of ART in Malawi [13], yet no decrease in pneumococcal carriage was observed in individuals established on ART. There are several possible explanations for this finding. At an individual level ART-mediated immune reconstitution may have a different impact on antipneumococcal mucosal responses than on systemic responses necessary for the control of IPD. Incomplete recovery of both mucosal and systemic response to the pneumococcus have been measured [9,17,26] and a mechanism for differential recovery mediated by T regulatory cells has been suggested from murine studies [27,28]. Behavioural changes as a result of improved well-being on ART may result in increased social mixing and thus more exposure to pneumococcal transmission. Extending this further, reduced use of antibiotics as a consequence of improved health may lead to less clearance of pneumococcal carriage. The latter explanation is unlikely given the lack of impact of cotrimoxazole on carriage observed in this study.

Several limitations can be identified for this study. Our two-tailed sample size calculations were limited by the geographical boundaries of the cohort and based on a hypothesized 40% change in pneumococcal carriage in ART-treated adults. We recruited less participants than anticipated: 336 were included in this study of which 233 started ART instead of an expected number of 500 participants of whom 300 would commence on ART. Despite this lower sample size than anticipated we can confidently refute our initial hypothesis and conclude that pneumococcal carriage does not decrease after ART initiation. Our study only included data from the first 2 years of ART initiation. It is possible that different results would be found for a prolonged time on ART. Despite adjusting for $CD4^+$ cell count, WHO-defined disease stage and other potential confounders, residual confounding must also be considered with individuals receiving ART differing from individuals not receiving ART during the study period. A self-controlled analysis including only the 233 individuals receiving ART during

follow-up found similar results as reported for the full cohort, suggesting major confounders were not missed. Our laboratory procedures did not allow for detection of simultaneous colonization with multiple serotypes. This will not have impacted our comparison of pneumococcal carriage by ART status but may have affected our conclusions over serotype diversity. Six-month sampling intervals are too long to study carriage duration and investigate whether our findings can be explained by similar carriage incidence but a prolonged carriage in HIV-infected adults on ART. We used a self-reported definition for poor adherence. Underreporting of poor adherence as a result of social desirability could have led to misclassification of patients. The impact of misclassification will have been minimized, however, as patients with unreported poor adherence are likely to have been classified under treatment failure, for which the definition relied on $CD4^+$ cell count and viral load measurements only. In the sensitivity analysis, similar results were maintained when omitting results from individuals with treatment failure or poor adherence.

These findings have implications for HIV care and potentially broader public health. The results indicate a continued respiratory mucosal immune defect after up to 2 years of ART and are consistent with the continued increased risk of IPD in this population. How long and why this defect persists merits further investigation through follow-up studies. In the meantime it is clear that prophylactic measures to prevent pneumococcal disease remain a priority and a better understanding of the burden of noninvasive pneumococcal disease is required. Rates of IPD have fallen, but pneumonia remains a common and serious problem in the HIV clinic and requires a renewed focus of attention.

Pneumococcal conjugate vaccination is known to work in this population. It has not been recommended for use on the expectation of HIV-infected adults benefiting from herd protection following the introduction of infant pneumococcal vaccination into the Malawi expanded programme on immunization schedule. However, the observed high rates of carriage in HIV-infected adults may have implications for pneumococcal transmission and consequently for the scale of herd protection. It is unclear how important HIV-infected adults are in pneumococcal transmission, but they represent a large reservoir of *S. pneumoniae* which is not reduced by ART in at least the first 2 years of treatment. Herd protection following infant PCV has to date been demonstrated in developed regions with low prevalence pneumococcal carriage in adults [29] and in African centres with low HIV prevalence [30–32]. In South Africa, declines in vaccine-type carriage [33] and IPD [34] in unvaccinated adults suggest indirect effects of PCV in the context of high HIV-burden, although it is difficult to distinguish vaccine effects from an ongoing background drop in pneumococcal carriage that predates the introduction of PCV. Surveillance of pneumococcal carriage as well as disease in HIV-infected adults during PCV rollout would be a prudent measure in Malawi and countries with similar generalized HIV epidemics. Vaccination of HIV-infected adults could be considered to provide both direct protection and maximize herd protection.

In summary, pneumococcal carriage in HIV-infected adults in Malawi remained high despite 2 years of ART, with evidence of increased carriage of non-PCV13 serotypes. Following PCV introduction monitoring of carriage in HIV-infected adults should be undertaken to determine whether they continue to be at risk of vaccine serotype pneumococcal disease and whether they constitute a reservoir for persisting vaccine serotype carriage and pneumococcal diversity.

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Conflicts of interest

N.F. has received grant income from Novartis and GlaxoSmithKline. His institution has received payment on his behalf for advisory panel membership from GlaxoSmithKline.

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