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Immunization of HIV-infected adults in the UK with Haemophilus influenzae b/meningococcal C glycoconjugate and pneumococcal polysaccharide vaccines --Manuscript Draft--

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Abstract:	Objectives To compare the antibody response to a licenced polysaccharide and glycoconjugate vaccine against encapsulated bacteria in HIV-infected and HIV-uninfected adults in the UK. Design Prospective cohort study. Setting UK teaching hospital. Participants 211 HIV-infected adults and 73 HIV-uninfected adults. Entry criteria: over 18 years of age. Exclusion criteria: previous pneumococcal, Hib or MenC vaccination. Interventions Vaccination with a 23-valent pneumococcal polysaccharide vaccine (PPV) and Haemophilus influenzae b/meningococcal C polysaccharide-tetanus toxoid conjugate vaccine (Hib/MenC-TT). ISRCTN registry (www.isrctn.com), ISRCTN95588307. Main outcome measures Concentration of IgG antibody responses to 12 pneumococcal, Hib and MenC polysaccharides and percentages of participants protected post-vaccination in HIV-infected participants compared with HIV-uninfected participants. Results Median IgG responses to Hib/MenC-TT were not significantly different between HIV-infected (3.74 and 2.88 g/ml) and HIV-uninfected groups (4.85 and 4.56 g/ml). PPV induced median IgGs above a 1.3 g/ml threshold for 10/12 serotypes among HIV-uninfected, and 5/12 in HIV-infected participants. HIV-uninfected adults had higher median post-vaccination IgGs than HIV-infected for serotypes 1, 7F, 18C and 23F ($p<0.001$). Median antibody levels to TT increased three-fold post-vaccination. Diphtheria toxoid antibody levels in HIV-infected subjects remained low. There was a lack of significant association between vaccine responses and CD4 count or viral suppression. Conclusions In a UK adult HIV-infected population, Hib/MenC-TT induced similar IgG responses to HIV-uninfected adults, while PPV induced comparatively poor responses. Lack of association with CD4 count or viral load supports early immunization. Further studies are required to guide vaccination policy in HIV-infected patients.
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The Editor,
JAIDS.

3rd September 2015.

Dear Editor,

**Re: Immunization of HIV-infected adults in the UK with *Haemophilus influenzae* b/
meningococcal C glycoconjugate and pneumococcal polysaccharide vaccines**

We would be grateful if you would consider the above manuscript for publication in JAIDS. As you will appreciate, HIV-infected individuals have increased susceptibility to a range of infections, including encapsulated bacteria for which a number of licensed vaccines are available. Although responses to vaccination are often impaired in this group, there are still limited data on which to base guidelines for vaccination policy and optimal policy for the UK may be different from that in other countries.

Studying immune responses following the implementation of vaccines recommended by the British HIV Association in a UK adult HIV-infected cohort, we found evidence of IgG antibody responses to the Hib/MenC-TT glycoconjugate vaccine similar to those in HIV-uninfected subjects, but comparatively poor responses to pneumococcal polysaccharide vaccine. Of importance for clinical practice, we did not find clear correlations between vaccine-induced antibody responses and either CD4 count or viral load suppression. This arguably supports the concept that immunization against encapsulated bacteria should be given early following a diagnosis of HIV infection.

The manuscript has not been submitted or accepted elsewhere. All authors fulfil the criteria for authorship, and have contributed to, seen, and approved the final, submitted version of the manuscript. No writing assistance was involved in the preparation of this manuscript.

Yours sincerely,

A handwritten signature in blue ink, appearing to read 'C.A. MacLennan', followed by a horizontal line.

Calman A. MacLennan
DPhil, FRCP, FRCPATH

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1 **Immunization of HIV-infected adults in the UK with *Haemophilus influenzae* b/**
2 **meningococcal C glycoconjugate and pneumococcal polysaccharide vaccines**

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4 Running title: Bacterial immunization in HIV infection

5
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70 to HIV-uninfected adults, while PPV induced comparatively poor responses. Lack of association
71 with CD4 count or viral load supports early immunization. Further studies are required to guide
72 vaccination policy in HIV-infected patients.

73 **Key words** HIV; vaccines; bacteria; pneumococcus; *Haemophilus influenzae* b; meningococcus

Introduction

There is an increased risk of disease and death due to vaccine-preventable infections among HIV-infected individuals compared with the general population. Incidence and mortality from bacterial pneumonia are both greatly increased among HIV-infected subjects and inversely correlate with CD4 count.¹ *Pneumococcus* and *Haemophilus influenzae* are most commonly isolated.¹ HIV-infected subjects are also at increased risk of invasive disease from these pathogens, despite a fall in incidence with use of highly-active antiretroviral therapy (HAART)² and implementation of childhood vaccination against pneumococcus.³ HIV-infected individuals are also at a higher risk of meningococcal disease than those living without HIV.⁴

Multiple observational studies have shown that 23-valent polysaccharide pneumococcal vaccine (PPV, Pneumovax[®]) protects against all-cause pneumonia^{5,6} and pneumococcal disease⁷⁻⁹ in HIV-infected individuals. Where this has been examined in relation to CD4 count, findings vary with some studies indicating a benefit at all CD4 counts⁹ while others detect a benefit only with CD4 counts above a certain threshold.⁸ The only randomized placebo-controlled trial of PPV in HIV-infected subjects was conducted in Uganda and found an increase in all-cause pneumonia in the vaccine arm.¹⁰

The British HIV Association (BHIVA) national guidelines recommend a decreased threshold for offering HIV-infected subjects vaccination.¹¹ However, the basis for many of these guidelines is empirical, owing to the lack of controlled studies investigating the impact of vaccination in HIV-infected subjects. BHIVA recommends PPV for all HIV-infected adults and *Haemophilus influenzae* b (Hib) and meningococcal vaccines may be considered when HIV-infected adults are scheduled to receive other vaccines. The guidelines acknowledge patients may have reduced response to vaccination and that higher doses may be required. Also, the duration of responses may be shortened requiring booster doses. Patients attending the University Hospital Birmingham adult

100 HIV outpatient clinic are routinely offered Hepatitis B and annual influenza vaccinations. From
101 September 2009, patients were offered PPV and a combined *Haemophilus influenzae* b and
102 meningococcal C polysaccharide-tetanus toxoid glycoconjugate vaccine (Hib/MenC-TT,
103 Menitorix[®]).

104

105 To better understand the effect of HIV infection on responses to these vaccines, vaccine-specific
106 antibodies were measured before and after immunization, and compared with those in a cohort of
107 HIV-uninfected adults.

108 **Methods**

109 **Study design**

110 The study was conducted at the University Hospitals Birmingham NHS Foundation Trust (UHBFT).
 111 HIV-infected patients commence HAART in accordance with national guidelines. At the time of the
 112 study, HAART most commonly consisted of a non-nucleoside reverse transcriptase inhibitor
 113 backbone of tenofovir and emtricitabine, with efavirenz as third agent. The study was part of a
 114 larger ongoing study, the AIR Study (Assessment of Immune Responses to Routine Immunisations
 115 in HIV-infected Adults, ISRCTN95588307) which began in September 2009, with HIV-infected
 116 adults offered enrolment and immunization with BHIVA-recommended vaccines, and serum
 117 antibody responses monitored before and four to six weeks after immunization. Clinic attendees
 118 declining the study are also offered the vaccinations. To reduce bias among the HIV-infected and -
 119 uninfected participant groups, HIV-uninfected participants were enrolled from UHBFT
 120 genitourinary medicine clinic attendees testing negative for HIV infection.

121

122 The study was conducted between September 2009 and December 2010, with AIR Study
 123 participants offered PPV (Merck, one 0.5 ml dose) and Hib/MenC-TT (GlaxoSmithKline, one 0.5
 124 ml dose) vaccines at the same time. Inclusion criteria were consented AIR Study participants,
 125 proven HIV infection or absence of HIV infection (for control group) and age over 18 years.
 126 Individuals who had previously been vaccinated with pneumococcal, MenC or Hib vaccines were
 127 excluded. Demographic data, including age, sex and ethnic group, were collected.

128

129 **Investigations**

130 HIV antibody testing (Abbott) and HIV-1 viral load measurement (Abbott) were performed.
 131 Participants were venesected for IgG screening before vaccination and four to six weeks post-
 132 vaccination. IgG antibody levels to 19 vaccine antigens: 12 PnPS (serotypes 1, 3, 4, 5, 6B, 7F, 9V,
 133 14, 18C, 19A, 19F and 23F), four Men PS (serogroups A, C, W and Y), Hib PS, tetanus toxoid (TT)

and diphtheria toxoid (DT), were measured in serum using a 19-plex fluorescence microbead assay [12]. The recommended post-vaccination threshold for protective IgG antibody levels against Hib and Men C are 1.0 and 2.0 $\mu\text{g/ml}$ respectively,¹² while two levels have been proposed for Pn serotypes: 1.3 $\mu\text{g/ml}$ by the American Association of Asthma Allergy and Immunology (AAAAI) for the prevention of colonization and infection,^{13,14} and 0.35 $\mu\text{g/ml}$ by the WHO, used primarily as the correlate of protection for assessment of vaccine responses in infants.¹⁵ Unless otherwise stated, 1.3 $\mu\text{g/ml}$ was used as the threshold level. For tetanus and diphtheria, long-term protective levels are 0.1 IU/ml.¹² CD4 counting was performed by TruCount assay (Becton Dickinson). HIV-infected participants were stratified into four groups by CD4 count, <350, 350-490, 500-690 and ≥ 700 cells/ μl .

Statistical Analysis

IgG antibody levels were initially treated as continuous variables, and compared across HIV status, use of HAART, as well as categories of CD4 count and viral load. Due to the level of skew in the IgG antibody levels, and truncated of some levels by the limits of measurement of the assay, a non-parametric analytical approach was employed. Comparisons between groups were performed using Mann-Whitney and Kruskal-Wallis tests, as appropriate, with the data summarized using medians and quartiles. The data were also analyzed treating the IgG antibody levels as a binary variable, specifying whether patients were above stated thresholds for each antigen, with comparisons across groups made using Fisher's exact test.

For both versions of the dependent variable, three sets of comparisons were made: pre-and post-vaccine IgG antibody levels, fold change in IgG levels and proportion of previously unprotected patients reaching threshold IgG levels post-vaccination. Since for each set of analyses, 19 antigens were considered, the effect of multiple comparisons on the type one error rate needed to be accounted for. Therefore, the critical p-value was Bonferroni-corrected for 57 comparisons (19

160 antigens by 3 outcomes). Hence $p < 0.0009$ was considered significant throughout. All analyses were
161 performed using IBM SPSS 19, with graphics produced using Graph-Pad Prism.

162

163 **Ethical Approval**

164 The study was approved by the North Staffordshire Research Ethics Committee of the National
165 Research Ethics Service, REC reference 09/H1204/53. All participants gave informed written
166 consent before taking part.

Results

Patient Population

Of 263 HIV-infected and 119 HIV-uninfected individuals enrolled into the AIR study, respectively 211 and 73 received PPV and Hib/MenC-TT at the same time, completed post-vaccination follow-up and were included in the analysis (S Fig. 1). No vaccine-related serious adverse events were reported following immunization. Ineligibility to receive PPV owing to prior vaccination was common in the HIV-infected group, while declining PPV led to a loss of subjects from the control group. Median age (35 and 40, $p=0.10$) and gender ratio (55% and 64% male, $p=0.16$) were similar between both groups (S Table 1). Among the HIV-infected subjects, 83% (176) were receiving HAART and 73% (128) of these had VL<50 copies/ml. Median CD4 count was 500 cells/ μ l (inter-quartile range, IQR 350-630 cells/ μ l) and stratification by CD4 count gave four subgroups of around 50 subjects. For the 62 HIV-infected participants with detectable viral load (>50 copies/ml), the median was 5,060 copies/ml (IQR 482-51,933 copies/ml). There was a small amount of missing data, namely 10 MenY measurements and one MenA and Pn1 measurement, in the HIV-negative group. These values were excluded from their respective analyses, with all available data included in the other analyses.

Low prevaccination specific antibody levels, particularly among HIV-infected participants

Median specific IgG levels in HIV-infected and HIV-uninfected groups against the 19 bacterial target antigens were below their respective thresholds, except for TT in both groups and PnPS 14 in the HIV-infected group (Table 1 and 2, Fig. 1). Levels were significantly lower in the HIV-infected group compared with the HIV-uninfected group for Hib, MenC, TT, DT and PnPS 7F ($p<0.001$ for all comparisons). There was no statistically-significant difference for the other eleven PnPS tested.

Equivalent response to Hib/MenC-TT among HIV-infected and HIV-uninfected individuals

Both HIV-infected and HIV-uninfected subjects mounted IgG antibody responses to the Hib/MenC conjugate vaccine with median fold increases of 9.28 and 34.08, and 5.70 and 13.22 respectively. Median post-vaccination IgG antibody levels for the HIV-infected group (3.74 and 2.88) were not statistically different from those for the HIV-uninfected group (4.85 and 4.56) (Table 1). Threshold antibody levels against Hib and MenC were achieved in 68% (108/160) and 56% (106/188) of HIV-infected, and 77% (30/39) and 65% (37/57) of HIV-uninfected subjects with levels previously-below the threshold (Table 3).

Poor response to PPV among HIV-infected individuals

Vaccination with PPV induced a median four-fold or greater increase in IgG antibody levels for four Pn serotypes (1, 5, 7F, and 18C) among HIV-uninfected subjects, while a four-fold increase was only achieved for Pn serotype 5 in the HIV-infected group. Median post-vaccination levels reached the 1.3 µg/ml threshold for ten of twelve Pn serotypes in the HIV-uninfected group, but only five Pn serotypes in the HIV-infected group. Significantly higher median post-vaccination IgG antibody levels were found in the HIV-uninfected compared with HIV-infected group for PnPS1, 7F, 18C and 23F ($p < 0.001$ for all comparisons). Response to Pn3 was universally poor with less than a two-fold median increase in both groups (Table 2). The proportion of individuals previously below the 1.3 µg/ml threshold who attained 1.3 µg/ml post-vaccination ranged from 13% (Pn13) to 75% (Pn7F) for the HIV-uninfected groups, and from 12% (Pn4) to 44% (Pn7F) in the HIV-infected group (Table 4). When the less-stringent WHO Pn IgG threshold of 0.35 µg/ml was used, these proportions increased to 35% and 75% for HIV-uninfected group and 30% to 78% for the HIV-infected group (S Table 2).

219 *Large increase in antibody levels to TT, but low antibody levels to DT*

220 Median pre-vaccination IgG levels against TT were above the long-term protective level (0.1 IU/ml)
 221 for both HIV-infected and control groups, but below this level (0.1 IU/ml) for DT, with levels
 222 significantly higher among HIV-uninfected compared with HIV-infected participants ($p < 0.001$,
 223 Table 1). A marked fold increase in median antibody levels to tetanus toxoid (3.58 and 3.45 for both
 224 HIV-infected and HIV-uninfected groups) was observed post-vaccination, while antibody levels to
 225 diphtheria toxoid remained unchanged.

226

227 *Influence of CD4 count and viral load on vaccine responses*

228 Among HIV-infected participants, there was a lack of significant association between pre-
 229 vaccination, post-vaccination or fold change in antibody levels, and CD4 count subgroup, full VL
 230 suppression or taking HAART (S. Table 3 and 4). The closest association was between fully-
 231 suppressed VL and fold change in antibody to TT (4.27 compared with 2.48 for $VL \geq 50$, $p = 0.002$).
 232 To investigate the effect of optimal response to HAART on vaccine response, we compared
 233 subjects with both $CD4 \geq 500$ cells/ μ l and fully-suppressed VL with all other HIV-infected subjects
 234 (S. Table 5 and 6). Again, there was little difference between the two HIV-infected groups divided
 235 in this way. However, borderline significance was reached for fold change increase of the three
 236 vaccine components of Hib/MenC-TT (TT 4.58 and 3.24, $p = 0.007$; MenC 59.25 and 29.22, $p = 0.026$;
 237 Hib 18.75 and 7.70, $p = 0.099$).

Discussion

The main conclusions of the study are that, although HIV-infected adults have relatively low antibody levels against encapsulated bacteria, they achieve similar levels of immunity to HIV-uninfected individuals through vaccination with glycoconjugates against Hib and MenC. In contrast, vaccination with pneumococcal polysaccharide results in poor responses compared with HIV-uninfected individuals. In general, there was a lack of association between response to vaccination and CD4 count, VL or HAART. An unanticipated finding was a boost in post-vaccination antibody levels to TT, likely due to the TT carrier component of the Hib/MenC vaccine, but overall low antibody levels to DT.

Previous studies of vaccine immunogenicity in HIV-infected individuals have tended to focus on one vaccine. Lack of consistency between findings from various vaccine studies emphasizes the importance of conducting such work in the population of interest and studies of vaccine immunogenicity among HIV-infected adult cohorts in the UK are currently lacking. A study from 1995, investigating response to PPV and Hib-CRM₁₉₇ among 20 recent HIV-seroconverters and 15 HIV-uninfected individuals found similar responses in both groups¹⁶. Conclusions from other studies with PPV have been mixed, with some investigators finding a strong response among HIV-infected adults,^{17,18} while others reported a poor response.^{19,20} Where response was compared with CD4 count, some studies found no correlation with antibody response,^{18,20} while others reported low CD4 count being associated with a poor response.^{19,21} A lack of effect of HAART on antibody response to PPV has been described.²¹ A recent study found no serological benefit from delaying administration of PPV in newly-diagnosed HIV-infected adults until after 6-12 months of HAART.²²

Fewer studies have been conducted on responses to Hib conjugate vaccines. These have generally reported a good response compared with controls, though not among individuals with low CD4

counts.²³⁻²⁵ In our study, all subgroups of HIV-infected subjects responded to the three components of Hib/MenC-TT, although individuals with CD4 counts >500 cells/ μ l and fully suppressed VL had borderline larger responses to all three components of this vaccine compared with all other HIV-infected individuals. The relatively small numbers in our study may have prevented us from detecting such differences as being significant, though no such borderline significant differences were detected for responses to PPV. It is intuitive that T-dependent antibody responses to Hib/MenC-TT should benefit from CD4 T-cell reconstitution more than the T-independent responses of PPV. Nevertheless, the lack of clear association between response to vaccination and CD4 count and viral load, all support a policy of early vaccination once diagnosis of HIV infection has been made. These findings indicate the need for further functional studies of CD4⁺ T cells and B cells, which are dysfunctional in HIV infection,²⁶ in order to better understand immune reconstitution in HIV infection beyond what can be discerned from the CD4 count alone.

The enhanced response to glycoconjugate MenC/Hib vaccination compared with that to PPV suggests that a similar strategy may overcome the lack of immunogenicity when vaccinating with pneumococcal conjugate vaccine (PCV). However, these different polysaccharide antigens may not be recognized in the same way by the immune system. HIV-infected children mount poor antibody responses to Pn PS even after systemic pneumococcal illness,²⁷ suggesting that these polysaccharides are inherently non-immunogenic, particularly to an immune system compromised by HIV infection. Immunogenicity studies in settings where patients have access to HAART have found a higher antibody response to PCV than PPV.^{28,29} A 9-valent PCV has been shown to protect HIV-infected South Africa children against pneumonia and invasive pneumococcal disease.³⁰ To date, the only randomized placebo-controlled trial of PCV in HIV-infected adults, from Malawi, showed enhanced protection against recurrent pneumococcal infection.³¹ Vaccination with PCV for HIV-infected adults was recommended in the US by the Advisory Committee on Immunization Practices in 2012.³² Meanwhile in the UK, in 2013 the Joint Advisory Committee on Vaccination

290 and Immunisation advised against the introduction of PCV in the UK³³ on grounds of lack of cost
291 effectiveness.³⁴

292

293 The large proportions of HIV-infected individuals in our study who failed to exceed threshold
294 antibody levels post-vaccination, particularly with PPV, suggests that single vaccine doses against
295 encapsulated bacteria are insufficient in this population. Furthermore, even with HAART,
296 maintenance of antibody responses to PPV over a 5-year period is a problem for HIV-infected
297 adults, particularly where CD4 counts are low.³⁵ Mixed vaccination regimes with conjugated and
298 unconjugated pneumococcal polysaccharide vaccines have been tested. Vaccination with a PCV7-
299 PCV7-PPV schedule has been shown to establish memory in HIV-infected children, as judged by
300 the response to a subsequent booster vaccination five years later.³⁶ Similar benefits have been found
301 in HIV-infected adults revaccinated with PPV after 5 years on HAART,³⁷ although there is the risk
302 that multiple doses of polysaccharide vaccines will result in hyporesponsiveness.³⁸ A recent study
303 using three doses of PCV13 in HIV-infected adults previously vaccinated with PPV found a rise in
304 pneumococcal antibody concentrations after each immunization compared with prevaccination
305 levels before, but overall levels after each dose were similar.³⁹ One dose of MenC/Hib conjugate
306 vaccines failed to induce threshold antibody levels in approximately a third of HIV-infected
307 subjects previously below these thresholds, indicating the need to investigate the use of multiple
308 doses of this vaccine too.

309

310 The low levels of antibodies to DT in HIV-infected individuals are a cause for concern as they
311 identify a potential risk of diphtheria outbreak among HIV-infected adults. A possible solution is to
312 vaccinate with glycoconjugates that use DT or CRM₁₉₇ (non-toxic recombinant form of diphtheria
313 toxin) as carrier protein, thereby providing a diphtheria booster. Although there were no serious
314 adverse events, it is important to be vigilant for episodes of clinical pneumonia among HIV-infected
315 subjects, particularly following the increased number of cases of pneumonia in the Ugandan PPV

316 trial.¹⁰ In addition to the use of fixed vaccine doses without booster vaccinations, limitations of our
317 study include the lack of clean matching between ethnic background of HIV-infected and HIV-
318 uninfected groups which could introduce a potential source of bias in the results. Uncertainty also
319 comes from a recent study of PCV13 in infants that questions our current understanding of
320 correlates of protection for pneumococcal vaccines.⁴⁰ Serotype-specific correlates of protection
321 were found to range widely for IgG levels and opsonophagocytic antibody titers, with an overall
322 aggregate correlate of protection of 0.98 µg/ml IgG against the 13 serotypes of PCV13 (range: 0.14
323 µg/ml for Pn18C to 2.83 µg/ml for Pn3).

324

325 The main unanswered clinical question from the study and subject for future research is how to
326 robustly induce sustained protective antibody levels against encapsulated bacteria among HIV-
327 infected adults in high-income countries such as the UK. While use of pneumococcal
328 glycoconjugate vaccine is an obvious step, differences in quantity of vaccine used and dosing
329 schedule may also be important. The lack of improved vaccine responses at high CD4 counts
330 indicates that physicians should remain vigilant for clinical presentations of bacterial pneumonia
331 and invasive disease, even in HIV-infected patients who have apparently normal immunity or
332 reconstituted immunity on HAART.

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335 and Clinical Immunology Service, University of Birmingham for their support.

336

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452 **Figure legends**

453 **1. Vaccine-specific antibody levels pre- and post-vaccination with PPV and Hib/MenC-**

454 **TT**

455 Each point represents one subject. Solid horizontal lines indicate medians. Dotted horizontal
456 lines indicate thresholds for protective post-vaccination antibody responses. Pn
457 pneumococcal; Men meningococcal; Hib *Haemophilus influenzae* b; TT tetanus toxoid; DT
458 diphtheria toxoid

1 **Table 1. Median IgG antibody levels to meningococcal and Hib capsular polysaccharides, tetanus and diphtheria toxoid in study**
2 **participants according to HIV status**

Pre-Vaccine		Hib	MenC	TT	DT	MenA	MenW	MenY
HIV Status	HIV-	0•94 (0•21-2•01)	0•23 (0•06-1•73)	1•60 (0•48-3•46)	0•08 (0•03-0•21)	1•77 (0•83-5•18)	0•09 (0•03-0•22)	0•50 (0•18-1•97)
	HIV+	0•24 (0•07-0•92)	0•06 (0•02-0•22)	0•51 (0•15-1•56)	0•02 (0•01-0•07)	0•81 (0•38-2•32)	0•04 (0•01-0•10)	0•20 (0•06-0•48)
		<i>p</i>	<i><0•001**</i>	<i><0•001**</i>	<i><0•001**</i>	<i><0•001**</i>	<i><0•001**</i>	<i><0•001**</i>
Post-Vaccine		Hib	MenC	TT	DT	MenA	MenW	MenY
HIV Status	HIV-	4•85 (1•99-13•72)	4•56 (1•90-15•00)	7•59 (3•18-10•00)	0•11 (0•04-0•35)	3•77 (1•39-7•98)	0•17 (0•06-0•28)	0•87 (0•42-2•16)
	HIV+	3•74 (1•08-14•46)	2•88 (0•90-8•94)	2•94 (0•68-7•57)	0•03 (0•01-0•08)	1•47 (0•59-3•33)	0•06 (0•02-0•17)	0•31 (0•10-0•70)
		<i>p</i>	<i>0•064</i>	<i><0•001**</i>	<i><0•001**</i>	<i><0•001**</i>	<i><0•001**</i>	<i><0•001**</i>
Fold Change		Hib	MenC	TT	DT	MenA	MenW	MenY
HIV Status	HIV-	5•70 (1•67-21•25)	13•22 (4•41-52•67)	3•45 (1•82-6•92)	1•10 (0•77-1•78)	1•37 (0•97-2•23)	1•24 (1•00-2•00)	1•43 (1•09-2•19)
	HIV+							

<i>HIV+</i>	9•28 (2•68-34•00)	34•08 (9•87-96•00)	3•58 (1•63-8•62)	1•00 (1•00-1•50)	1•31 (1•00-2•04)	1•25 (1•00-2•00)	1•35 (1•00-2•20)
<i>p</i>	0•071	0•003*	0•656	0•621	0•983	0•682	0•619

3 *Data reported as: "Median (Quartiles)"*

4 *p-values from Mann-Whitney tests*

5 **Significant at $p<0.05$*

6 ***Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at $p<0.00088$*

7 *Hib Haemophilus influenzae b; Men meningococcus; TT tetanus toxoid; DT diphtheria toxoid*

8

9

10 **Table 2. Median IgG antibody levels to pneumococcal polysaccharides in study participants according to HIV status**

Pre-Vaccine		Pn1	Pn3	Pn4	Pn5	Pn6B	Pn7F	Pn9V	Pn14	Pn18C	Pn19A	Pn19F	Pn23F
HIV Status	HIV-	0.24 (0•10-0•76)	0•29 (0•10-1•78)	0•14 (0•07-0•33)	0•38 (0•19-1•06)	0•36 (0•14-1•49)	0•77 (0•39-1•49)	0•52 (0•18-1•33)	1•03 (0•32-3•94)	0•44 (0•18-1•95)	0•78 (0•25-2•71)	0•63 (0•19-2•26)	0•55 (0•22-1•60)
	HIV+	0•24 (0•08-0•67)	0•24 (0•08-0•78)	0•12 (0•04-0•35)	0•24 (0•09-0•72)	0•32 (0•10-1•12)	0•35 (0•15-1•07)	0•25 (0•10-0•70)	1•51 (0•23-5•65)	0•43 (0•08-1•52)	0•66 (0•15-2•23)	0•40 (0•14-1•38)	0•31 (0•10-0•96)
	<i>p</i>	0•782	0•446	0•398	0•015*	0•600	<0•001**	0•002*	0•516	0•168	0•243	0•146	0•005*
Post-Vaccine		Pn1	Pn3	Pn4	Pn5	Pn6B	Pn7F	Pn9V	Pn14	Pn18C	Pn19A	Pn19F	Pn23F
HIV Status	HIV-	2•74 (0•93-10•00)	0•49 (0•16-3•93)	0•36 (0•21-1•06)	4•63 (0•58-10•00)	1•67 (0•41-5•72)	5•24 (2•43-10•00)	1•89 (0•82-10•00)	7•76 (1•22-10•00)	5•96 (1•13-10•00)	3•72 (1•00-8•50)	2•19 (0•57-7•08)	2•35 (0•79-6•69)
	HIV+	1•11 (0•46-3•55)	0•53 (0•20-2•10)	0•30 (0•10-0•79)	1•34 (0•41-5•55)	0•97 (0•25-3•20)	1•51 (0•65-4•75)	1•15 (0•35-3•82)	5•12 (1•38-10•00)	2•01 (0•29-9•48)	2•19 (0•57-6•97)	1•07 (0•30-4•32)	1•08 (0•31-2•72)
	<i>p</i>	<0•001**	0•791	0•044*	0•003*	0•031*	<0•001**	0•002*	0•255	<0•001**	0•035*	0•008*	<0•001**
Fold Change		Pn1	Pn3	Pn4	Pn5	Pn6B	Pn7F	Pn9V	Pn14	Pn18C	Pn19A	Pn19F	Pn23F
HIV Status	HIV-	8•01 (3•92-16•67)	1•63 (1•00-3•95)	2•65 (1•60-5•93)	4•15 (2•07-12•88)	2•20 (1•30-10•02)	5•56 (2•15-11•88)	2•81 (1•58-11•25)	3•43 (1•27-8•19)	5•47 (2•17-16•66)	3•31 (1•29-6•22)	2•94 (1•52-6•19)	2•55 (1•80-8•91)
	HIV+	3•42 (1•54-10•32)	1•79 (1•00-3•90)	2•00 (1•24-4•08)	4•00 (1•62-11•07)	1•87 (1•18-4•69)	3•50 (2•00-7•65)	3•82 (1•57-8•29)	1•99 (1•00-4•63)	3•35 (1•56-7•30)	2•00 (1•20-5•58)	2•06 (1•29-4•82)	2•40 (1•40-5•56)
	<i>p</i>	<0•001**	0•387	0•030*	0•299	0•156	0•060	0•863	0•017*	0•013*	0•181	0•060	0•126

11 *Data reported as: "Median (Quartiles)"*12 *p-values from Mann-Whitney tests*

- 13 **Significant at $p < 0.05$*
- 14 ***Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at $p < 0.00088$*
- 15 *Pn pneumococcal*
- 16

17 **Table 3. Rates above nominal IgG protection levels against meningococcus, Hib, tetanus and diphtheria in study participants according to**
 18 **HIV status**

Pre-Vaccine		Hib	MenC	TT	DT	MenA	MenW	MenY
HIV Status	HIV-	34/73	16/73	70/73	34/73	32/73	3/73	18/73
		47%	22%	96%	47%	44%	4%	25%
	HIV+	51/211	23/211	173/211	42/211	58/211	7/211	22/201
		24%	11%	82%	20%	27%	3%	11%
<i>p</i>		<0.001**	0.028*	0.003*	<0.001**	0.013*	0.721	0.007*
Post-Vaccine		Hib	MenC	TT	DT	MenA	MenW	MenY
HIV Status	HIV-	64/73	53/73	72/73	40/73	48/73	3/73	21/73
		88%	73%	99%	55%	66%	4%	29%
	HIV+	159/211	129/211	198/211	50/211	80/210	7/211	22/202
		75%	61%	94%	24%	38%	3%	11%
<i>p</i>		0.031*	0.090	0.126	<0.001**	<0.001**	0.721	0.001*
Absolute Increase		Hib	MenC	TT	DT	MenA	MenW	MenY
HIV Status	HIV-	30/73	37/73	2/73	6/73	16/73	0/73	3/73
		41%	51%	3%	8%	22%	0%	4%
	HIV+	108/211	106/211	25/211	8/211	22/210	0/211	0/201

		51%	50%	12%	4%	11%	0%	0%
	<i>p</i>	-	-	-	-	-	-	-
Protection for Previously								
	Unprotected Patients[‡]	Hib	MenC	TT	DT	MenA	MenW	MenY
HIV Status	HIV-	30/39	37/57	2/3	10/39	16/41	0/73	4/55
		77%	65%	67%	26%	39%	0%	7%
	HIV+	108/160	106/188	25/38	13/169	26/152	0/204	3/179
		68%	56%	66%	8%	17%	0%	2%
	<i>p</i>	0•333	0•285	1•000	0•003*	0•005*	1•000	0•055

19 *Data reported as the numbers and proportions of patients with antibody levels above the protection thresholds (Hib=1 µ/ml, Men=2 µ/ml, DT/TT=0.1 IU/ml)*

20 *p-values from Fisher's Exact tests*

21 **Significant at p<0.05*

22 ***Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at p<0.00088*

23 *#Patients with 8 Pn antibodies above the thresholds*

24 *‡The proportion of patients with antibody levels below the threshold pre-vaccine, who had levels above the thresholds post-vaccine*

25 *Hib Haemophilus influenzae b; Men meningococcus; TT tetanus toxoid; DT diphtheria toxoid*

26

27 **Table 4. Rates above nominal IgG protection levels against pneumococcus, in study participants according to HIV status**

Pre-Vaccine		Pn1	Pn3	Pn4	Pn5	Pn6B	Pn7F	Pn9V	Pn14	Pn18C	Pn19A	Pn19F	Pn23F	8 Pn's [#]
HIV Status	HIV-	15/73	20/73	2/73	14/73	20/73	22/73	19/73	33/73	21/73	30/73	23/73	21/73	9/73
		21%	27%	3%	19%	27%	30%	26%	45%	29%	41%	32%	29%	12%
	HIV+	37/211	42/211	12/211	32/211	47/211	42/211	36/211	113/211	60/211	74/211	54/211	39/211	15/211
		18%	20%	6%	15%	22%	20%	17%	54%	28%	35%	26%	18%	7%
<i>p</i>		0.600	0.191	0.530	0.462	0.424	0.076	0.121	0.225	1.000	0.398	0.360	0.069	0.220
Post-Vaccine		Pn1	Pn3	Pn4	Pn5	Pn6B	Pn7F	Pn9V	Pn14	Pn18C	Pn19A	Pn19F	Pn23F	8 Pn's [#]
HIV Status	HIV-	48/73	26/73	16/73	47/73	40/73	60/73	48/73	54/73	53/73	51/73	45/73	46/73	39/73
		66%	36%	22%	64%	55%	82%	66%	74%	73%	70%	62%	63%	53%
	HIV+	99/210	68/211	35/211	108/211	92/211	115/211	97/211	159/211	117/211	131/211	94/211	91/211	69/211
		47%	32%	17%	51%	44%	55%	46%	75%	55%	62%	45%	43%	33%
<i>p</i>		0.007*	0.665	0.376	0.057	0.104	<0.001**	0.004*	0.876	0.012*	0.259	0.014*	0.004*	0.002*
Absolute Increase		Pn1	Pn3	Pn4	Pn5	Pn6B	Pn7F	Pn9V	Pn14	Pn18C	Pn19A	Pn19F	Pn23F	8 Pn's [#]
HIV Status	HIV-	33/73	6/73	14/73	33/73	20/73	38/73	29/73	21/73	32/73	21/73	22/73	25/73	30/73
		45%	8%	19%	45%	27%	52%	40%	29%	44%	29%	30%	34%	41%
	HIV+	62/210	26/211	23/211	76/211	45/211	73/211	61/211	46/211	57/211	57/211	40/211	52/211	54/211
		30%	12%	11%	36%	21%	35%	29%	22%	27%	27%	19%	25%	26%

<i>p</i>		-	-	-	-	-	-	-	-	-	-	-	-	
Protection for Previously														
Unprotected Patients [‡]		Pn1	Pn3	Pn4	Pn5	Pn6B	Pn7F	Pn9V	Pn14	Pn18C	Pn19A	Pn19F	Pn23F	8 Pn's [#]
HIV- Status HIV+	HIV	33/58	7/53	14/71	33/59	21/53	38/51	30/54	21/40	32/52	22/42	22/50	26/52	30/64
		57%	13%	20%	56%	40%	75%	56%	53%	62%	51%	44%	50%	47%
	HIV+	64/173	28/169	24/199	76/179	46/164	74/169	61/175	46/98	57/151	57/137	42/157	55/172	54/196
		37%	17%	12%	43%	28%	44%	35%	47%	38%	42%	27%	32%	28%
<i>p</i>		0•009*	0•669	0•116	0•097	0•126	<0•001**	0•010*	0•578	0•004*	0•294	0•034*	0•021*	0•005*

28 Data reported as the numbers and proportions of patients with antibody levels above the protection thresholds (Pn=1.3 µ/ml)

29 *p*-values from Fisher's Exact tests

30 *Significant at $p < 0.05$

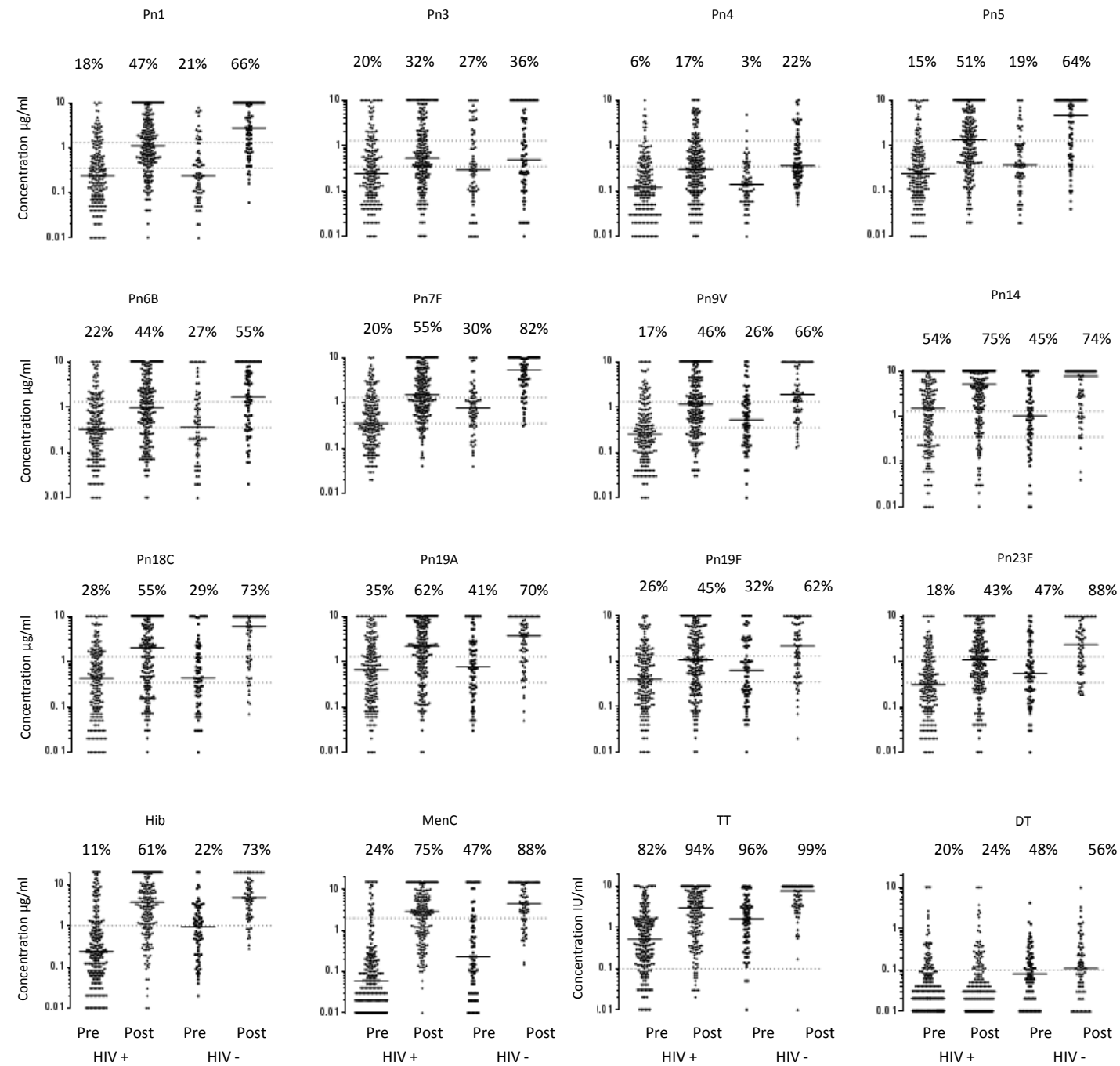
31 **Significant after Bonferroni correction for 57 comparisons (19 antibodies by 3 measures) at $p < 0.00088$

32 [#]Patients with 8 Pn antibodies above the thresholds

33 [‡]The proportion of patients with antibody levels below the threshold pre-vaccine, who had levels above the thresholds post-vaccine

34 Pn pneumococcal

Figure 1



S Fig 1

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