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1 **Full title:** Chronic lung disease in patients with perinatally acquired HIV in England: a
2 retrospective case-note review.

3

4 **Short title:** Chronic lung disease in PA-HIV

5

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27

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32

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34

35 **Abstract**

36 Chronic lung disease (CLD) is common in individuals living with perinatally-acquired HIV
37 (PA-HIV) in southern/eastern Africa. Most of the UK PA-HIV population are African. We
38 conducted a case-note review of CLD in three UK PA-HIV cohorts (n=98). 8.1% had
39 bronchiectasis or obliterative bronchiolitis, 19.2% had ring/tramline opacities on chest x-ray.
40 There may be unrecognised and underdiagnosed CLD among PA-HIV in the UK.

41

42 **Key point of this research**

43

44 Adolescents in SE-Africa with perinatally-acquired HIV have a high prevalence of
45 chronic lung disease (CLD).

46 This case-note review addressed whether the phenomenon exists in the UK where
47 many with perinatally-acquired HIV are Africa-born.

48 The CLD prevalence was higher than expected and warrants further study to mitigate
49 any long-term consequences.

50 **Introduction**

51

52 Reports from southern and eastern (SE)-Africa describe high rates of chronic lung disease
53 (CLD) in children and adolescents living with perinatally acquired HIV (PA-HIV). These
54 identify phenotypes of chronic cough, breathlessness and hypoxia, underpinned by
55 radiographic abnormalities consistent with obliterative bronchiolitis (1,2,3). Although CLD
56 has been associated with delayed HIV diagnosis and later antiretroviral therapy (ART)
57 initiation, it is also prevalent in those established early on ART and “slow-progressors”
58 presenting in early adolescence (1,4,5).

59

60 It is not clear to what extent this CLD is driven directly by HIV-associated inflammation or
61 by the particular health-care availability, environmental exposures and socio-economic
62 conditions of sub-Saharan Africa (1). PA-HIV adolescents in the US have more obstructive
63 airways disease, but data from other high-income settings are limited (6). Those living with
64 PA-HIV in the UK may benefit from earlier diagnosis and ART initiation, better childhood
65 vaccination coverage, and reduced household air pollution and circulating respiratory
66 pathogen exposure than in SE-Africa (1). However, 56% of the UK PA-HIV population was
67 born abroad, three-quarters are Black African and many present late (7). The epidemiology of
68 CLD in the UK PA-HIV population is unknown. We set out to determine the prevalence and
69 phenotype of recorded CLD in patients living with PA-HIV attending 3 north of England
70 regional HIV centres.

71

72

73

74 Methods

75 A retrospective case-note review of respiratory diagnoses in 6-30 year-old PA-HIV patients
76 attending paediatric and transition HIV clinics in Sheffield, Liverpool and Newcastle. Local
77 clinical teams used a standardised protocol to extract demographic and HIV disease data,
78 respiratory diagnoses and verbatim chest radiology reports. We chose data items based on
79 those used in studies from SE-Africa (2,5). We considered CLD was present based on
80 documentation of a clinical diagnosis and/or chest radiographic changes. A standardised
81 definition of CLD in this population does not exist. The SE-Africa PA-HIV studies report
82 bronchiectasis and obliterative bronchiolitis as the principal CLDs (2,3). The majority did
83 not describe reversible airways disease. Adult HIV studies mainly report COPD,
84 bronchogenic carcinoma and pulmonary hypertension. We therefore defined a clinical
85 diagnosis of CLD as bronchiectasis, obliterative bronchiolitis and any other chronic lung
86 condition except asthma, tuberculosis, lymphocytic interstitial pneumonia (LIP) or any with a
87 clear a genetic aetiology. Informed by the African reports and Norton et al., we defined
88 radiographic changes of CLD as any report showing ring/tramline opacities, bronchial wall
89 thickening, a nodular/reticulonodular/reticular pattern, or moderate/severe atelectasis on chest
90 x-ray (CXR) and decreased attenuation consistent with small airway disease on high
91 resolution computed tomography (HRCT) (2, 3, 8, 9). Anonymised summary data from each
92 site were collated and analysed in Sheffield. Radiology reports were classified according to
93 the Fleischner Society Glossary of Terms by an independent consultant paediatric respiratory
94 radiologist. Where an individual had the same abnormality reported more than once, we only
95 counted a single instance. If a report recorded more than one type of abnormality, we counted
96 each separately. Informed by the non-parametric distribution of the data, the Mann Whitney
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97 U-test and Fisher's exact test were used to compare continuous and categorical data
98 respectively in SPSS. Sub-studies were registered and approved as service evaluations at
99 Sheffield Teaching Hospital NHS Foundation Trust (NFT), Sheffield Children's Hospital
100 NFT, Doncaster and Bassetlaw Teaching Hospitals NFT, Newcastle-Upon-Tyne Hospital
101 NFT, Liverpool and University Hospitals NFT and Alder Hey Children's NFT.
102

103 Results

104

105 98 individuals were included; 51 (52%) were female, median age was 17.9 (interquartile
106 range 14.1-21.4) years. 67 (68.4%) were Black African, 12 (12.2%) mixed African, 9 (9.2%)
107 White British and 9 (9.2%) other. 64 (65.4%) were non-UK born. Median age at HIV
108 diagnosis was 4.5 (1.9-9.0) years and 49/83 with available data initiated ART within a year of
109 diagnosis. Median nadir CD4 was 280.0 (149.5-462.5) cells/mm³; 73.5% had undetectable
110 viral loads and 82.7% had a CD4 > 350 cells/mm³ at last clinic visit.

111

112 27 (28%) had a significant lung disease documented in their clinical record, with
113 “bronchiectasis” and “community acquired pneumonia” most prevalent (Table 1). 8 (8.1%)
114 had bronchiectasis or obliterative bronchiolitis recorded and we considered these as
115 significant CLDs. They did not differ significantly by age, gender, UK birth, age at HIV
116 diagnosis, time to ART initiation or nadir CD4 from those without CLD. They were,
117 however, admitted to hospital with respiratory tract infection (RTI) significantly more often
118 than individuals without CLD; median 1.5 (0.8-2.3) vs 0.0 (0.0-0.3) events, p=0.012
119 respectively. There were trends for those with CLD to be more likely to have had any RTI
120 (88% vs 66%, OR 3.678, 95% CI 0.60 to 42.63, p=0.27) and a higher frequency of outpatient
121 RTI diagnosed (median 3.0 (0.5-12.75) vs 1.0 (0.0-3.0), p=0.096) (supplementary data table
122 S1).

123

124 73 individuals had CXR performed at least once, median 2 (1-4), 23 had no evidence of
125 imaging available and records were not accessible for 2. In total 57 of the 120 CXR reports
126 described abnormalities. 41 out of the 73 individuals had ≥1 abnormal CXR. The most
127 prevalent abnormality was ring/tramline opacities (19.2%) (Table 1). 8 individuals had a total

128 of 13 HRCT scans; 12 (92.3%) reported abnormalities, most often bronchiectasis. 7/8 had ≥ 1
129 abnormal HRCT.

130

131 Clinical diagnoses and radiological identification of CLD differed by place of birth. Among
132 sub-Saharan Africa-born compared to UK-born individuals, the prevalence of a clinical
133 diagnosis of bronchiectasis/obliterative bronchiolitis was 10.5% versus 3.6% ; CXR
134 ring/tramline opacities 36.4% versus 15.8% and HRCT bronchiectasis 83.3% versus 0.0%,
135 respectively (Table 1).

136

137 **Discussion**

138

139 We have found a high prevalence of radiological abnormalities suggestive of CLD in this
140 ART-era, UK-based cohort of individuals living with PA-HIV. 7 had a diagnosis of
141 bronchiectasis (6 supported by HRCT) and another obliterative bronchiolitis. These
142 diagnoses were also associated with increased RTI frequency.

143

144 A similar prevalence of CLD and chest radiographic abnormalities might be expected
145 nationally as our cohort appears representative of the UK PA-HIV population; in 2017 the
146 Collaborative HIV Paediatric Study (CHIPS) had a median age 14.9 years, 54% were female,
147 77% Black African and the 56% non UK-born had a median age at HIV diagnosis of 9-12
148 years (7).

149

150 The rate of bronchiectasis in our cohort is greater than expected given the UK incidence for
151 18-30 year-olds is 43.4 per 100,000 person-years (10), albeit data aren't available for the
152 general UK paediatric population. Indeed, it is similar to the 5.7% reported in a pre-2000
153 USA cohort of predominantly ART-naive individuals living with PA-HIV (11). However,
154 while in the pre-ART-era bronchiectasis was driven by *pneumocystis jirovecii* pneumonia
155 (PCP), TB and LIP, only a single individual with bronchiectasis in our study had such a
156 history. The ART-era, USA Paediatric HIV/AIDS Cohort Study (12) reported a higher rate of
157 PA-HIV cases 'using asthma medication' but a similar rate of 'diagnosed asthma' than
158 controls. Another US cohort found more fixed airflow obstruction in those with PA-HIV (6).
159 Both potentially indicate the existence of unrecognised CLD.

160

161 The combined prevalence of bronchiectasis, obliterative bronchiolitis and CXR ring/tramline
162 opacities in our population is 27.3%, considerably lower than the prevalence of CLD in SE-
163 African studies (1,2,3,4). Among those born in sub-Saharan Africa in our study, 10.5% had
164 bronchiectasis/obliterative bronchiolitis compared with only 3.6% of UK-born. Higher age at
165 HIV diagnosis, longer periods of uncontrolled HIV viremia, untreated lower RTIs and
166 environmental factors may drive the higher prevalence of CLD in that setting (2,3,5). The
167 association between inpatient RTI and CLD diagnoses suggest the severity of RTI may be an
168 important contributor to the development of CLD; a previously undocumented finding. Albeit
169 at lower rates than those living with PA-HIV, age-matched HIV-seronegative individuals
170 from SE-Africa also have some limitation in lung function further indicating a role for local
171 environment (5).

172 Importantly, irrespective of setting, those who acquire HIV in adulthood have increased risk
173 of CLD (13). Early life exposures will affect peak lung development and set an adult lung
174 function trajectory for obstructive airways disease (14). Thus, taken together with our
175 findings, it may be that early life exposures in sub-Saharan Africa and chronic HIV infection
176 will drive CLD in a proportion of the UK PA-HIV population who will be vulnerable to
177 further deterioration of respiratory function through adulthood.

178

179 This study is limited by the retrospective design and the incompleteness of case notes. Pre-
180 UK health care information for the 65.4% of individuals born outside the UK were also
181 unavailable. We did not search primary care records so could not evaluate RTIs managed in
182 the community. Diagnoses, radiology reports and other record data were not always
183 standardised and original radiology images were often unavailable. Not all imaging was
184 followed-up so we could not determine resolution or progression of changes. Thus, our
185 definition of CLD from radiographic findings was pragmatic and based on single reports (9).

186 We were unable to determine the duration of observation and timing of diagnoses precisely
187 enough to calculate CLD incidence or trends over time. As the median age at HIV diagnosis
188 was 4.5 years and a high proportion were born in sub-Saharan Africa, we cannot exclude a
189 role for undocumented, pre-UK arrival early life lung insults such as LIP in CLD
190 pathogenesis. While PA-HIV populations in other low- and middle-income regions will
191 share similar risks for CLD to those from SE-Africa, published data on CLD in these
192 populations are sparse. However, migrants from these areas are rare among the UK PA-HIV
193 population.

194

195 Our study detected a signal for a higher than expected prevalence of CLD in the UK PA-HIV
196 population. This may reflect the high proportion who spent their early years with
197 undiagnosed HIV in sub-Saharan Africa. Further investigation of ‘hidden’ and potentially
198 progressive CLD in UK PA-HIV cohorts is now required to understand its true prevalence,
199 change over time and optimal prevention and treatment to mitigate significant respiratory
200 disability.

201

202

203

204

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207

208 *Contributions:*

209 P.K.E., P.J.C., F.S., and K.U. contributed to conception and design. P.K.E., C.E. R., S.O., P.

210 B., A.R. and C.I.I. performed data collection. D.H. provided clinical advice on data

211 interpretation. P.K.E., and P.J.C. performed data analysis. All authors contributed to writing

212 the manuscript and approved final version.

213

214

215

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Table 1. Record of lung disease and prevalence of abnormalities on chest radiograph and high-resolution computed tomography, n (%)				
Diagnosis of lung disease as recorded in clinical notes:	UK Born n=28	SSA born n=57	Born elsewhere / unknown* n=13	Total n =98
Asthma	1 (3.6)	1 (1.8)	0 (0.0)	2 (2.0)
Bronchiectasis	0 (0.0)	6 (10.5)	1 (7.7)	7 (7.1)
Obliterative Bronchiolitis	1 (3.6)	0 (0.0)	0 (0.0)	1 (1.0)
LIP	1 (3.6)	1 (1.8)	2 (15.4)	4 (4.1)
PCP	4 (14.3)	0 (0.0)	1 (7.7)	5 (5.1)
Pneumonia	2 (7.2)	4 (7.0)	1 (7.7)	7 (7.1)
Pulmonary/Disseminated TB	0 (0.0)	6(10.5)	0 (0.0)	6 (6.1)
CXR	n =19	n =44	n = 10	n = 73
Atelectasis	1 (5.3)	0 (0.0)	1 (10.0)	2 (1.7)
Consolidation	8 (42.1)	4 (9.1)	3 (30.0)	15 (12.5)
Lymphadenopathy	0 (0.0)	2 (4.5)	0 (0.0)	2 (1.7)
Non-cavitating nodules	1 (5.3)	3 (6.8)	4 (40.0)	8 (6.7)
Reticular pattern	4 (21.1)	2 (4.5)	1 (10.0)	7 (5.8)
Ring/tramline opacities	3 (15.8)	16 (36.4)	4 (40.0)	23 (19.2)
Normal	9 (47.4)	37 (84.1)	7 (70.0)	53 (44.2)
No report available	3 (15.8)	7 (16.0)	0 (0.0)	10 (8.3)

HRCT	n = 0	n = 6	n = 2	n = 8
Atelectasis	0 (0.0)	1(16.7)	1(50.0)	2 (15.4)
Bronchiectasis	0 (0.0)	5 (83.3)	1(50.0)	6 (46.2)
Consolidation	0 (0.0)	1(16.7)	1(50.0)	2 (15.4)
Non-cavitating nodules	0 (0.0)	2 (33.3)	0(0.0)	2 (15.4)
Normal	0 (0.0)	1(16.7)	0(0.0)	1 (7.1)

CXR, chest x-ray; HRCT, high resolution computed tomography; IQR; interquartile range; LIP, Lymphocytic interstitial pneumonia; n, number of individuals with finding; PCP, pneumocystis jirovecii pneumonia; RTI, respiratory tract infection; TB, Tuberculosis. * 6 of these had unknown places of birth

Supplementary Table S1 Distribution of characteristics by diagnosis of bronchiectasis or obliterative bronchiolitis				
Sample, median (IQR) or n (%)				
Characteristic	Bronchiectasis or obliterative bronchiolitis (n=8)	No bronchiectasis or obliterative bronchiolitis (n=90)	Difference (Confidence Interval)	P value
Gender, female	2 (25.0)	49 (54.4)		0.469
Age	19.8 (17.0- 24.0)	17.45 (14.0-21.0)	0.99 (-3.1 to 4.8)	0.550
Born outside the UK [#]	7 (87.5)	57 (67.9)		0.428
Age at HIV Diagnosis [§]	4.3 (1.8-6.7)	4.5 (1.9-9.1)	- 0.6 (-4.9 to 2.8)	0.622
Years HIV Diagnosis to ART initiation [§]	0.1 (0.0-1.0)	0.1 (0.0-3.0)	0.0 (-3.0 to 0.2)	0.659
Nadir CD4 Cell count, cells/	265.0 (256.5- 456.5)	280.0 (143.0- 534.5)	105.0 (-60.0 to 246.0)	0.327
Number of outpatient RTI per patient	3.0 (0.5-12.75)	1.0 (0.0-3.0)	2.0 (0.0 to 3.0)	0.096

Number of times admitted to hospital for RTI	1.5 (0.8-2.3)	0.0 (0.0-0.3)	1.0 (0.0 to 2.0)	0.012
ART, antiretroviral therapy; IQR, interquartile range; RTI, respiratory tract infection; UK, United Kingdom				
# Data available for 92 individuals. §Data available for 90 individuals. \$Data available for 83 individuals				