

# Incidence and Risk Factors for Invasive Pneumococcal Disease and Community-acquired Pneumonia in Human Immunodeficiency Virus–Infected Individuals in a High-income Setting

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(See the Editorial Commentary by Jenny-Avital on pages 51–2.)

**Background.** Although people living with human immunodeficiency virus (PLWH) are at increased risk of invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP), it is unclear whether this remains the case in the setting of early initiation of combination antiretroviral therapy (cART), at high CD4 cell counts. This is important, as pneumococcal vaccination coverage in PLWH is low in Europe and the United States, despite longstanding international recommendations.

**Methods.** We identified all CAP and IPD cases between 2008 and 2017 in a cohort of PLWH in a Dutch HIV referral center. We calculated incidence rates stratified by CD4 count and cART status and conducted a case-control study to identify risk factors for CAP in PLWH receiving cART.

**Results.** Incidence rates of IPD and CAP in PLWH were 111 and 1529 per 100 000 patient-years of follow-up (PYFU). Although IPD and CAP occurred more frequently in patients with CD4 counts <500 cells/ $\mu$ L (incidence rate ratio [IRR], 6.1 [95% confidence interval, 2.2–17] and IRR, 2.4 [95% confidence interval, 1.9–3.0]), the incidence rate in patients with CD4 counts >500 cells/ $\mu$ L remained higher compared with the general population (946 vs 188 per 100 000 PYFU). All IPD isolates were vaccine serotypes. Risk factors for CAP were older age, CD4 counts <500 cells/ $\mu$ L, smoking, drug use, and chronic obstructive pulmonary disease.

**Conclusions.** The incidence of IPD and CAP among PLWH remains higher compared with the general population, even in those who are virally suppressed and have high CD4 counts. With all serotyped IPD isolates covered by pneumococcal vaccines, our study provides additional argumentation against the poor current adherence to international recommendations to vaccinate PLWH.

**Keywords.** HIV; pneumococcal disease; community-acquired pneumonia; epidemiology; vaccination.

People living with human immunodeficiency virus (PLWH) are at increased risk of both invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* [1]. Pneumococcal disease (PD; ie, IPD and pneumococcal CAP), in PLWH often requires hospitalization, and mortality rates range up to 25% [2, 3]. In addition, the recurrence rate of PD is high [4]. Therefore, PD remains an important problem in PLWH, contributing significantly to disease burden and healthcare

costs [5, 6]. Pneumococcal vaccination is recommended for all PLWH by most international guidelines [7–9]. However, despite longstanding recommendations, pneumococcal vaccine uptake is low [5, 10–12]. This is worrying, as a recent meta-analysis showed that the incidence rate of IPD remains approximately 30 times higher among PLWH compared to the general population in the modern era of combination antiretroviral therapy (cART)—that is, in the period from 2000 onward, when effective cART was available [2]. An oft-mentioned argument against pneumococcal vaccination in all PLWH is that cases of PD represent an untreated or severely immunocompromised subgroup [13]. Unfortunately, most individual studies on the incidence of PD in the late cART era are based on bacterial surveillance data and lack clinical information on CD4 cell counts, cART use, viral load, and other risk factors [2, 14]. In addition, many of these study data originate from before 2015, when early start of cART, irrespective of CD4 count and viral load, became the cornerstone of human immunodeficiency virus (HIV) care [15, 16].

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Thus, it is yet unclear whether the risk of PD in the growing group of PLWH with high CD4 counts who started cART shortly after their HIV diagnosis has declined to the level of the non-PLWH, or whether it is still substantially increased, which may provide more compelling evidence for the recommendation of universal vaccination in PLWH.

The purpose of this cohort study was to determine the incidence of IPD and CAP in PLWH stratified to CD4 cell count and treatment status, between 2008 and 2017. Additionally, we aimed to identify risk factors for pneumococcal disease in PLWH.

## METHODS

### Cohort Study

We identified all IPD and CAP cases from June 2008 until December 2017 in PLWH who received care at the Amsterdam University Medical Center (UMC), location Academic Medical Centers (AMCs). Within this cohort, we calculated incidence rates of CAP and IPD stratified by CD4 cell count and cART status.

### IPD Case Definition and Identification

We defined a case of IPD as a culture-proven (blood or cerebrospinal fluid) infection with *S. pneumoniae*. All IPD cases occurring in the Amsterdam UMC-AMC are reported to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) as part of a national pneumococcal surveillance system [14]. For the years 2008–2016, the HIV status of all IPD cases reported to the NRLBM was collected as part of another study [14] and Vestjens et al, unpublished data). We appended data for 2017 to this dataset.

We counted infections within 30 days in the same patient as a single case. The NRLBM used co-agglutination and the Quellung method for serotyping of pneumococcal isolates from IPD cases [17].

### CAP Case Definition and Identification

The Dutch HIV Monitoring Foundation (Stichting HIV Monitoring [SHM]) prospectively collects data of PLWH in the Netherlands (the AIDS Therapy Evaluation in the Netherlands [ATHENA] cohort). The ATHENA cohort was initiated in 1998 and captures data, including cART use, HIV type 1 viral loads, CD4 cell counts, and opportunistic infections, from >98% of all PLWH in the Netherlands [18, 19]. An episode of CAP is registered in the ATHENA database if it is mentioned in the electronic patient file. The SHM provided us with all registered cases of CAP in PLWH in care of the Amsterdam UMC-AMC between June 2008 and December 2017.

For all registered ATHENA cases of CAP, we reviewed the electronic patient file. A case of CAP was confirmed and included in our study if it was community-acquired (>60 days after discharge if a patient was previously admitted to a hospital), diagnosed on clinical, microbiological, and/or radiological grounds, and required antibiotic treatment.

Based on the microbiologic results, we divided all CAP cases into 3 subgroups: (1) pneumococcal CAP, if there was at least 1 positive culture for *S. pneumoniae* in sputum and/or blood; (2) “unspecified CAP,” when no pathogen was cultured; (3) “other pathogen (OP) CAP,” when we found documentation of 1 or more cultured pathogen(s) other than *S. pneumoniae*.

### Case-control Study

We performed a nested case-control study to identify risk factors for pneumococcal and unspecified CAP in PLWH receiving cART. For each case, 1 control matched for year of HIV diagnosis was selected. Controls were not matched for cART use to avoid overmatching. For the case-control study, we excluded CAP cases in which another pathogen was cultured (OP), as this subgroup’s complexity was beyond the scope of our study. Each control had to be in care at the Amsterdam UMC-AMC in the year the linked case was diagnosed with CAP.

### Data Extraction and Analysis

We collected clinical and demographical data of all cases and controls from the electronic patient file and online vaccination registry (Orion Globe, Assen, the Netherlands) using a standardized case report form. Data items collected were date of HIV diagnosis; ethnicity; mode of HIV acquisition; viral load; CD4 and nadir CD4 cell counts; cART use; comorbidities; smoking, alcohol, or drug use; pneumococcal vaccination status and vaccination date; mortality; and duration of hospital admission.

Longitudinal data collected by SHM on all PLWH in care in the Amsterdam UMC-AMC were used to calculate cumulative patient-years of follow-up (PYFU) from 1 June 2008 until 31 December 2017. HIV PYFU was stratified by calendar year, CD4 cell count, and treatment status.

We calculated the incidence rates (IRs) of IPD, pneumococcal CAP, PD (pneumococcal CAP + IPD), and all CAP in total and per subgroup, based on CD4 count (<500 cells/ $\mu$ L and  $\geq$ 500 cells/ $\mu$ L), cART treatment status, and the occurrence of the disease before or after 2015. If an IPD episode originated from CAP, this case was only counted once in incidence calculations for pneumococcal disease. We calculated incidence rate ratios (IRRs) per subgroup with 95% confidence intervals (CIs).

For the incidence calculations, we excluded patients with a newly diagnosed HIV infection, defined as date of HIV diagnosis within 60 days of the IPD or CAP episode, because the IPD or CAP episode in these cases was often the trigger for establishing the HIV diagnosis, and could thus not have been prevented by vaccination.

For statistical analyses, we used SPSS statistical software, version 25 (IBM SPSS, Armonk, New York). We applied an  $\alpha$  level = .05 for significance. We performed multivariable conditional regression analysis to identify risk factors for pneumococcal/unspecified CAP in PLWH receiving cART. In our initial model, we included the covariates age, sex, mode of HIV

acquisition, viral load, CD4 cell count subgroups, smoking, alcohol, chronic obstructive pulmonary disease (COPD), kidney diseases, cardiovascular diseases, asthma, drug use, malignancies, and hepatitis B and C coinfection. Covariates were excluded from the model using the stepwise backward selection method based on *P* value <.05. We performed a subgroup analysis excluding cART-discordant case-control pairs to assess if this would change the effect size of our results.

### Ethical Considerations

For this noninterventive study, an exemption was granted by the local medical ethics committee on 29 June 2018 (W18\_204; document with the authors).

## RESULTS

From June 2008 to December 2017, during 18 898 PYFU, we observed 24 cases of IPD in 21 PLWH and 318 episodes of CAP in 215 PLWH. In 18 of 24 (75%) IPD cases, patients initially presented with the clinical diagnosis of CAP, and were consequently classified as having bacteremic pneumococcal CAP, resulting in a total of 324 episodes of IPD and/or CAP.

Of all 318 cases of CAP, 36 (11%) were culture-proven pneumococcal infections; in 214 (67%) cases, no pathogen was identified (unspecified CAP); and in 68 cases (21%), a different pathogen was identified (OP CAP). The case fatality rates were 8.3% and 3.5% for IPD and CAP, respectively. Baseline characteristics of all cases are shown in Table 1. Baseline characteristics differed between the different CAP subgroups. Compared with pneumococcal CAP and unspecified CAP, the OP CAP group was the most severely immunocompromised, with the lowest median and nadir CD4 counts, the fewest patients on cART, the fewest patients with an undetectable viral load, and the highest proportion of patients with comorbidities. The majority of cases in the OP group (54%) met the criteria of AIDS at the time of CAP diagnosis, and 15 of 70 (22%) were newly diagnosed with HIV (Table 1).

### Incidence Rates

The overall IRs of IPD, CAP, and pneumococcal CAP were 111, 1529, and 159 per 100 000 PYFU, respectively. We found no differences in IRs before and after 1 January 2015 for CAP, pneumococcal CAP, and IPD (Supplementary Table 1).

Incidence rates of IPD stratified to cART treatment and CD4 cell count are depicted in Figure 1. The incidence of IPD was the highest in patients without cART (490/100 000) or with a CD4 count <500 cells/ $\mu$ L (246/100 000) compared with patients with cART (80/100 000) or patients with a CD4 count >500 cells/ $\mu$ L (40/100 000) (Figure 1).

Similarly, for both CAP and PD (Figures 2 and 3), IRs were the highest in those without cART, combined with a CD4 count <500 cells/ $\mu$ L (8023/100 000 for CAP and 1189/100 000 for PD). Incidence rates were significantly lower in those receiving cART

and with a CD4 count >500 cells/ $\mu$ L (946/100 000 for CAP and 69/100 000 for PD).

### Microbiology Data

*Streptococcus pneumoniae* was the most commonly identified pathogen of CAP (30%). An overview of cultured pathogens is provided in Table 2. The serotype distribution of the pneumococcal isolates causing IPD is depicted in Figure 4. Data on microbial resistance of *S. pneumoniae* were available in 30 cases. In 2 (6.7%) cases, *S. pneumoniae* was penicillin-resistant, of which 1 strain was also resistant to amoxicillin and clavulanic acid, trimethoprim-sulfamethoxazole, and tetracyclines.

### Case-control Study

Baseline characteristics of CAP cases and controls can be found in Table 3. Median age was higher in cases, whereas CD4 counts were significantly lower in cases. Significant risk factors for CAP in multivariable analysis were age >60 years, CD4 counts 200–500 cells/ $\mu$ L and <200 cells/ $\mu$ L, COPD, smoking, and drug use. Pneumococcal vaccination coverage was very low in both cases (7.4%) and controls (3.7%), with no significant difference (Table 4).

## DISCUSSION

We found that the incidence of IPD in PLWH was >7 times higher compared to the general Dutch population (14.9/100 000) [20] and >20 times higher than the incidence of IPD in healthy adults in the Netherlands (5/100 000) [14]. Compared to previous studies in high-income countries such as Denmark and the United Kingdom, we found lower incidence rates for IPD in PLWH [21, 22]. This may be due to the higher cART coverage and higher CD4 cell counts in our study. The incidence of CAP among PLWH in our study was >8 times higher compared to the general Dutch population (188/100 000) [23]. Incidence rates of CAP found in our study were comparable to previous studies in PLWH in high-income settings [24–26].

No surveillance data on PD (pneumococcal CAP + IPD) are available from the Netherlands. Based on the rate of pneumococcal infections reported in the Community-acquired Pneumonia Immunization Trial in Adults trial [27] and the overall incidence rate of CAP in the Netherlands [23], we estimate that the incidence of PD in PLWH is 5 times higher compared with the general population.

Among PLWH, we did not observe a decline in incidence of IPD, pneumococcal CAP, and CAP since 2015, when immediate initiation of cART was introduced [15]. However, this is not surprising, because even in current practice—when cART is immediately initiated in newly diagnosed PLWH, irrespective of the CD4 cell count—many patients still present late with significant immunodeficiency (CD4 count <350 cells/ $\mu$ L) or even with AIDS-defining opportunistic infections (45% in 2017 in the Netherlands). In addition, in 2017, 25% of all Dutch PLWH receiving cART were still immunocompromised, with a CD4 count <500 cells/ $\mu$ L [18].

**Table 1. Baseline Characteristics of All Included Episodes of Invasive Pneumococcal Disease and Community-acquired Pneumonia**

Characteristic	All Cases (N = 324)	IPD (n = 24)	CAP				P Value <sup>a</sup>
			All CAP (n = 318)	Pneumococcal CAP (n = 36)	Undefined Pathogen CAP (n = 214)	Other Pathogen CAP (n = 68)	
Male sex	222/324 (68)	15/24 (63)	218/318 (69)	23/36 (64)	154/214 (72)	41/68 (60)	.51
Age, y, median (IQR)	50 (41–60)	41 (29–55)	50 (41–60)	43 (35–53)	51 (43–60)	50 (39–61)	<b>.01</b>
Mode of HIV acquisition							.35
Sex (heterosexual)	122/299 (41)	10/23 (44)	122/293 (42)	20/34 (59)	74/200 (37)	28/59 (48)	
Intravenous drug use	30/299 (10)	3/23 (13)	30/293 (10)	5/34 (15)	17/200 (9)	8/59 (14)	
MSM	137/299 (46)	8/23 (35)	133/293 (45)	9/34 (27)	101/200 (51)	23/59 (39)	
Mother to child	8/299 (2.7)	2/23 (8.7)	6/293 (2.0)	0/34 (0)	6/200 (3)	0/59 (0)	
Blood transfusion	2/299 (0.7)	0/23 (0)	2/293 (0.7)	0/34 (0)	2/200 (1)	0/59 (0)	
Ethnic group							.15
White European	189/315 (60)	10/22 (46)	187/310 (60)	19/35 (54)	132/209 (63)	36/66 (55)	
Asian	12/315 (3.8)	0/22 (0)	12/310 (3.9)	0/35 (0)	9/209 (4.3)	3/66 (4.5)	
Black African	93/315 (30)	11/22 (44)	90/310 (29)	15/35 (43)	51/209 (25)	24/66 (36)	
Hispanic	21/315 (6.7)	1/22 (4.5)	21/310 (6.8)	1/35 (2.9)	17/209 (8.2)	3/66 (4.5)	
Nadir CD4 count, No.; median (IQR)	321; 180 (70–290)	24; 265 (115–403)	315; 180 (70–290)	36; 220 (103–347)	211; 180 (80–300)	68; 145 (33–227)	<b>.03</b>
Date of diagnosis							.16
Before 1 January 2015	229/324 (71)	20/24 (83)	224/318 (70)	29/36 (81)	142/214 (66)	53/68 (78)	
After 1 January 2015	95/324 (29)	4/24 (17)	94/318 (30)	7/38 (19)	72/214 (34)	15/68 (22)	
Newly diagnosed HIV infection <sup>b</sup>	29/324 (9)	3/24 (13)	29/318 (9.1)	6/36 (17)	8/214 (3.7)	15/68 (22)	.53
Duration of HIV, mo, median (IQR)	120 (49–215)	63 (9–124)	121 (49–217)	76 (9–196)	143 (60–221)	90 (7–175)	<b>.02</b>
CD4 count at time of diagnosis, median (IQR)	440 (220–670)	345 (235–470)	445 (220–670)	345 (240–478)	490 (300–715)	290 (40–532)	.18
CD4 count at time of diagnosis							<b>.03</b>
<200 cells/μL	70/324 (22)	4/24 (17)	68/318 (21)	6/36 (17)	36/214 (17)	26/68 (38)	
200–499 cells/μL	123/324 (38)	15/24 (63)	121/318 (38)	22/36 (61)	75/214 (35)	24/68 (35)	
≥500 cells/μL	131/324 (40)	5/24 (21)	129/318 (41)	8/36 (22)	103/214 (48)	18/68 (27)	
Undetectable viral load at time of diagnosis	193/324 (60)	10/24 (41)	188/318 (59)	14/36 (39)	148/213 (69)	26/68 (38)	.06
AIDS at time of diagnosis	86/334 (27)	6/24 (25)	84/318 (26)	9/36 (25)	38/214 (18)	37/68 (54)	.86
cART at time of diagnosis	224/324 (69)	14/24 (58)	218/315 (69)	20/36 (56)	168/213 (79)	30/66 (46)	.39
Duration of cART, mo, No.; median (IQR)	224; 102 (32–175)	14; 54 (19–144)	218; 102 (32–178)	20; 68 (29–166)	168; 106 (32–185)	30; 103 (42–165)	.17
Hospitalization	197/316 (62)	17/24 (71)	194/311 (62)	29/35 (83)	106/209 (51)	59/67 (88)	.37
Duration of hospitalization, d, No.; median (IQR)	168; 7 (4–12)	15; 7 (4–21)	166; 7 (4–12)	25; 6 (5–12)	84; 6 (4–10)	57; 10 (5–18)	.54
ICU admission	29/292 (9.9)	7/22 (32)	29/288 (10)	8/38 (25)	8/191 (4.2)	13/65 (20)	<b>&lt;.01</b>

**Table 1. Continued**

Characteristic	All Cases (N = 324)	CAP					P Value <sup>a</sup>	
		IPD (n = 24)	All CAP (n = 318)	Pneumococcal CAP (n = 36)	Undefined Pathogen CAP (n = 214)	Other Pathogen CAP (n = 68)		IPD Compared to CAP Without IPD
Disease-related mortality <sup>c</sup>	11/324 (3.4)	2/24 (8.3)	11/318 (3.5)	2/36 (5.6)	4/214 (1.9)	5/68 (7.4)	.19	.08
Comorbidities at time of diagnosis								
Any comorbidity	210/324 (65)	14/24 (58)	205/318 (65)	19/36 (53)	134/214 (63)	52/68 (77)	.49	<b>.03</b>
Cardiovascular disease <sup>d</sup>	73/324 (23)	3/24 (13)	73/318 (23)	3/36 (8.3)	50/214 (23)	20/68 (29)	.22	<b>.05</b>
COPD	85/324 (26)	1/24 (4.2)	85/318 (27)	9/36 (25)	56/214 (26)	20/68 (29)	<b>.01</b>	.84
Asthma	15/324 (4.6)	0/24 (0)	15/318 (4.7)	2/36 (5.6)	7/214 (3.3)	6/68 (8.8)	.26	.17
Diabetes	32/324 (9.9)	1/24 (4.2)	32/318 (10)	3/36 (8.3)	14/214 (6.5)	15/68 (22)	.49	<b>&lt;.01</b>
Asplenia	11/324 (3.4)	4/24 (17)	9/318 (2.8)	2/34 (5.6)	6/214 (2.8)	1/68 (1.5)	<b>.01</b>	.49
Malignancy	35/324 (11)	4/24 (17)	32/318 (10)	1/36 (2.8)	26/214 (12)	5/68 (7.4)	.55	.16
Chronic kidney disease	38/324 (12)	7/24 (30)	35/318 (11)	4/36 (11)	22/214 (10)	9/68 (13)	<b>.01</b>	.79
Liver cirrhosis	11/324 (3.4)	3/24 (13)	9/318 (2.8)	1/36 (2.8)	6/214 (2.8)	2/68 (2.9)	<b>.04</b>	1.00
Other immunodeficiency disorder <sup>e</sup>	15/324 (4.6)	4/24 (17)	12/318 (3.8)	1/36 (2.8)	10/214 (4.7)	1/68 (1.5)	<b>.02</b>	.46
Hepatitis C <sup>f</sup>	34/324 (11)	3/24 (13)	34/318 (11)	5/36 (14)	22/214 (10)	7/68 (10)	.74	.81
Hepatitis B <sup>g</sup>	18/324 (5.6)	1/24 (4.2)	18/318 (5.7)	1/36 (2.8)	11/214 (5.1)	6/68 (8.8)	.76	.38
Smoking at time of diagnosis	169/298 (57)	10/22 (46)	169/292 (58)	19/31 (61)	117/202 (58)	33/59 (56)	.27	.89
Alcohol use at time of diagnosis	189/282 (67)	16/20 (80)	185/276 (67)	23/29 (79)	125/190 (66)	37/57 (65)	.20	.33
Drug use at time of diagnosis <sup>h</sup>	88/265 (33)	6/20 (30)	88/259 (34)	13/29 (45)	60/175 (34)	15/55 (27)	.75	.27
Pneumococcal vaccination prior to diagnosis <sup>i</sup>	19/324 (5.9)	2/24 (8.3)	19/318 (6.0)	5/36 (14)	12/214 (5.6)	2/68 (2.9)	.64	.08

Data are presented as no./No. (%) unless otherwise indicated.

Abbreviations: CAP, community-acquired pneumonia; cART, combination antiretroviral therapy; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; IgG, immunoglobulin G; IPD, invasive pneumococcal disease; IQR, interquartile range; MSM, men who have sex with men.

<sup>a</sup>Bold text indicates significant difference between subgroups ( $P < .05$ ).

<sup>b</sup>Within 60 days after diagnosis.

<sup>c</sup>Within 30 days after diagnosis.

<sup>d</sup>All types of cardiovascular disease including hypertension, (ischemic) cardiomyopathy, coronary artery disease, any type of valve disease, arrhythmias, and (chronic) heart failure.

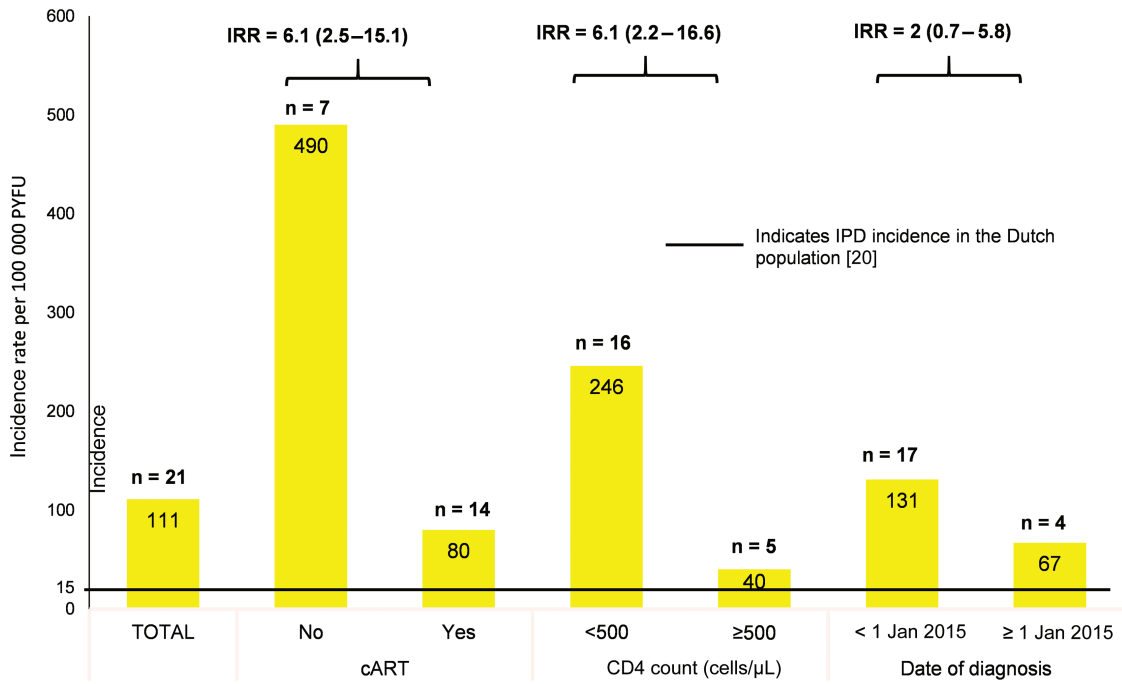
<sup>e</sup>Leukemia, lymphoma, kidney transplant, IgG subclass deficiency, use of immunosuppressive drugs for inflammatory diseases.

<sup>f</sup>Chronic hepatitis C infection.

<sup>g</sup>Active hepatitis B infection or inactive carrier.

<sup>h</sup>Any type of drug use including cannabis, cocaine, heroin, methamphetamine, amyl nitrate ("poppers"), ecstasy,  $\gamma$ -hydroxybutyrate, ketamine, and methadone.

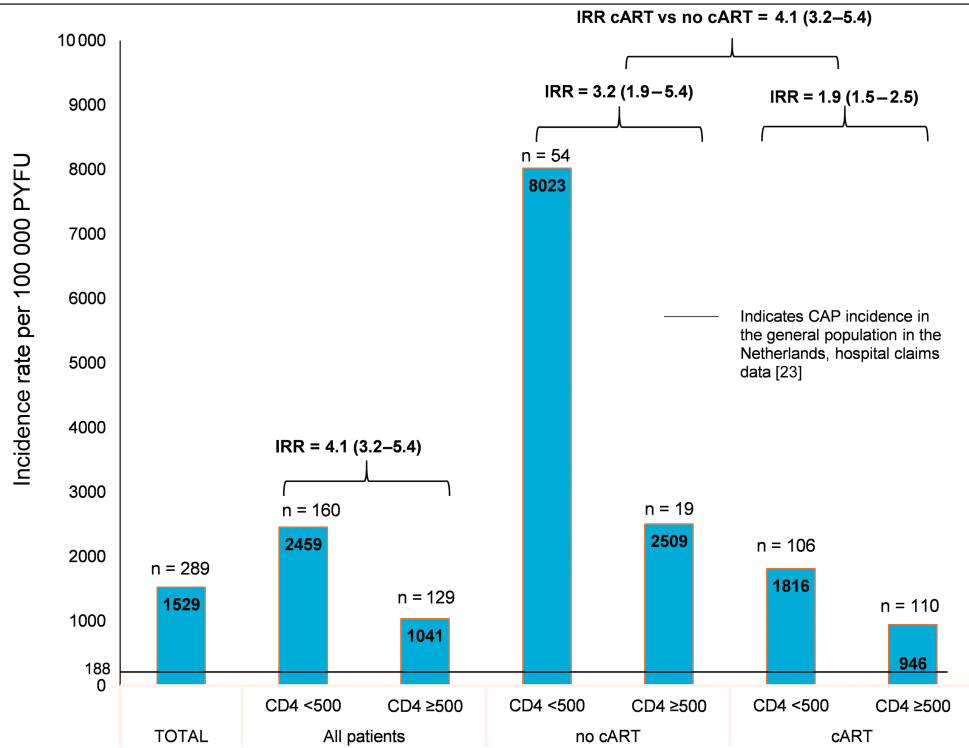
<sup>i</sup>Administration of any pneumococcal vaccine prior to diagnosis. Five of 324 cases were vaccinated with both Prevenar13 and Pneumovax23 according to international guidelines.



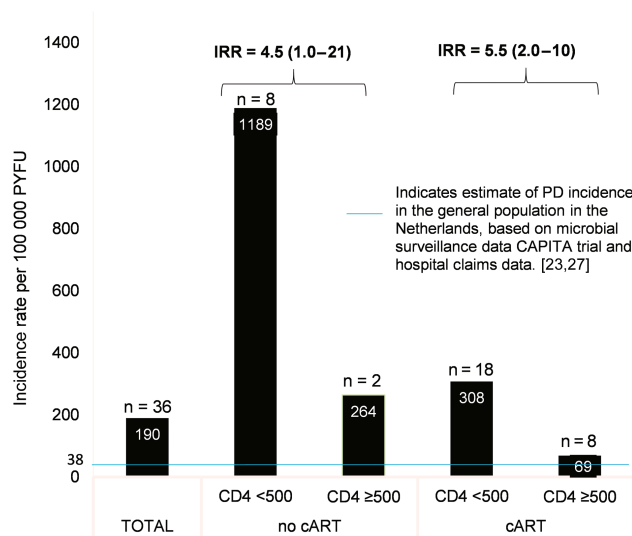
**Figure 1.** Incidence (with 95% confidence intervals) of invasive pneumococcal disease in people living with human immunodeficiency virus, stratified by CD4 cell count and treatment status. Abbreviations: cART, combination antiretroviral therapy; IPD, invasive pneumococcal disease; IRR, incidence rate ratio; PYFU, patient-years of follow-up.

Incidence rates of IPD, CAP and PD were consistently higher in the more severely immunocompromised (CD4 count <500 cells/μL) and untreated PLWH. Interestingly, also in optimally

treated PLWH (virally suppressed and CD4 >500 cells/μL), incidence rates of IPD, CAP, and PD were still 4 times, 5 times, and 2 times higher, respectively, compared with the general



**Figure 2.** Incidence (with 95% confidence intervals) of community-acquired pneumonia in people living with human immunodeficiency virus, stratified by CD4 count (cells/μL) and treatment status. Abbreviations: CAP, community-acquired pneumonia; cART, combination antiretroviral therapy; IRR, incidence rate ratio; PYFU, patient-years of follow-up.



**Figure 3.** Incidence of pneumococcal disease (with 95% confidence intervals) in people living with human immunodeficiency virus, stratified by CD4 count (cells/ $\mu$ L) and treatment status. Abbreviations: CAPITA, Community-acquired Pneumonia Immunization Trial in Adults; cART, combination antiretroviral therapy; IRR, incidence rate ratio; PD, pneumococcal disease; PYFU, patient-years of follow-up.

population [20, 23, 27]. Our results are in agreement with a large study by Yin et al, who also report a residually increased incidence of IPD in optimally treated PLWH compared with the general population [22]. An explanation for this sustained risk of IPD and CAP in PLWH after CD4 recovery could be persisting humoral immune defects, including splenic dysfunction, after cART initiation, or additional risk factors [28]. Humoral immunity and splenic function are essential in protection against capsulated bacteria. Immediate initiation of cART after HIV diagnosis could potentially reduce the impact of these B-cell defects, although it is known that they occur early after

**Table 2. Proven Pathogens of Pneumonia**

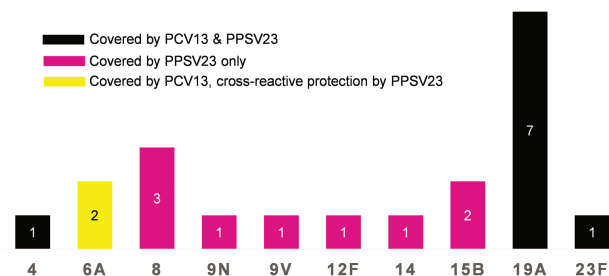
Pathogens of Pneumonia <sup>a</sup>	No. (%) (n = 119)
<i>Streptococcus pneumoniae</i>	36 (30)
<i>Haemophilus influenzae</i>	23 (19)
<i>Pneumocystis jirovecii</i>	16 (14)
Viruses <sup>b</sup>	13 (11)
<i>Staphylococcus aureus</i>	6 (5.0)
Mycobacteriaceae <sup>c</sup>	5 (4.0)
<i>Klebsiella pneumoniae</i>	4 (3.0)
<i>Pseudomonas aeruginosa</i>	4 (3.0)
<i>Aspergillus</i>	3 (3.0)
Other <sup>d</sup>	9 (8.0)

<sup>a</sup>A total of 119 pathogens were cultured in 104 patients.

<sup>b</sup>Cytomegalovirus (n = 1); respiratory syncytial virus (n = 2); influenza A and B viruses (n = 9); parainfluenza virus (n = 4).

<sup>c</sup>*Mycobacterium tuberculosis* (n = 2); *Mycobacterium avium* (n = 2); *Mycobacterium kansasii* (n = 1).

<sup>d</sup>*Legionella pneumophila* (n = 1); Enterobacteriaceae (n = 1); *Moraxella catarrhalis* (n = 2); *Entamoeba histolytica* (n = 1); *Cryptococcus* (n = 1); *Acinetobacter* (n = 1); *Escherichia coli* (n = 1); *Streptococcus mitis* (n = 1).



**Figure 4.** Number of cases per capsular serotype causing invasive pneumococcal disease. Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

HIV infection [21, 29, 30]. In patients receiving cART, a CD4 count <200 cells/ $\mu$ L, but also <500 cells/ $\mu$ L, was an independent risk factor for CAP. These findings are consistent with previous studies [1, 22, 31].

Other important risk factors for CAP in treated PLWH are similar to risk factors for CAP in the general population and include smoking, recreational drug use, and smoking [24, 28]. Cessation of smoking has been associated with a PD risk reduction in PLWH [25].

We found that all pneumococcal isolates were vaccine-covered serotypes (7 of 20 serotypes covered by PPSV23 only and 13 of 20 serotypes were covered by both 23-valent pneumococcal polysaccharide vaccine [PPSV23] and 13-valent pneumococcal conjugate vaccine [PCV13]) [8]. Our data, as well as the results of the study by Yin et al [21], indicate that in PLWH most IPD cases are still caused by vaccine serotypes. Several studies have shown that pneumococcal vaccination is safe and immunogenic in PLWH, particularly if PCV13 is followed by PPSV23, which is the current recommendation in most countries [7, 32–34]. Despite international recommendations, Dutch guidelines only recommend pneumococcal vaccination in PLWH with additional risk factors, such as asplenia and injecting drug use [35, 36]; this is reflected by a very low vaccination uptake in our study population (5.9%). However, even in the United States, vaccine uptake remains low in risk groups, including PLWH, despite longstanding recommendations for pneumococcal vaccination [5, 9, 10].

Due to the low pneumococcal vaccination rate in our study and the specific Dutch recommendations—vaccination of high-risk patients only, causing confounding by indication—our study could not provide reliable information on the effectiveness of pneumococcal vaccination.

Studies demonstrating the clinical benefit of pneumococcal vaccination in contemporary HIV cohorts are lacking. For conjugated vaccines, French et al reported a vaccine efficacy of 74% (95% confidence interval, 30%–90%) in preventing pneumococcal reinfection after 2 doses of 7-valent pneumococcal conjugate vaccine; however, this was in a low-income setting, with most patients untreated and at low CD4 cell counts [37]. Lamas

**Table 3. Community-acquired Pneumonia With Cases on Combination Antiretroviral Therapy Versus Controls: Univariable Conditional Regression Analysis<sup>a</sup>**

Characteristic	CAP Cases (n = 188) <sup>a</sup>	Controls (n = 188)	P Value, $\chi^2$ Test	Crude OR (95% CI)
	no./No. (%)	no./No. (%)		
Female sex	46/188 (25)	55/188 (29)	.295	0.80 (.52–1.24)
Median age, y (IQR)	53 (45–61)	49 (41–56)	<b>&lt;.01</b>	NA
Age group, y			<b>&lt;.01</b>	
18–40	26/188 (14)	45/188 (24)		ref
41–60	112/188 (60)	121/188 (64)		1.79 (.97–3.30)
≥61	50/188 (27)	22/188 (12)		<b>4.09 (1.94–8.60)</b>
Mode of HIV acquisition			<b>&lt;.01</b>	
Sex (heterosexual)	57/176 (32)	78/179 (44)		ref
Intravenous drug use	17/176 (9.7)	3/179 (1.7)		<b>2.01 (1.17–2.46)</b>
MSM	96/176 (55)	89/179 (50)		1.23 (.89–1.71)
Mother to child	4/176 (2.3)	2/179 (1/1)		1.58 (.57–4.35)
Blood transfusion	2/176 (1.1)	7/179 (3.9)		0.53 (.13–2.16)
Ethnic group			.063	
White European	129/184 (70)	118/188 (63)		ref
Asian	8/184 (4.3)	6/188 (3.2)		1.09 (.54–2.24)
Black African	35/184 (19)	57/188 (30)		0.73 (.50–1.06)
Hispanic	12/184 (6.5)	7/188 (3.7)		1.21 (.67–2.19)
Median CD4 count, cells/ $\mu$ L (IQR)	530 (360–760)	625 (452–839)	<b>&lt;.01</b>	NA
Median CD4 count category, cells/ $\mu$ L (IQR)			<b>&lt;.01</b>	
<200	20/188 (11)	4/188 (2.1)		
200–499	69/188 (37)	57/188 (30)		
≥500	99/188 (53)	128/188 (68)		
Median nadir CD4 count, cells/ $\mu$ L (IQR)	(n = 186) 180 (88–283)	(n = 176) 170 (80–270)	.98	NA
Detectable viral load time of episode	32/188 (17)	30/188 (16)	.78	<b>1.11 (.59–2.10)</b>
AIDS diagnosis prior to episode	25/188 (13)	6/188 (3.2)	<b>&lt;.01</b>	<b>4.80 (1.83–12.5)</b>
No cART at time of episode <sup>b</sup>	0	16/188 (8.5)	NA	NA
Median time until cART initiation, mo (IQR) <sup>c</sup>	(n = 188) 22 (3–72)	(n = 171) 16 (1–47)	.06	NA
Any comorbidity	116/188 (62)	83/118 (44)	<b>&lt;.01</b>	<b>2.07 (1.34–3.17)</b>
Cardiovascular disease	45/188 (24)	37/188 (20)	.32	1.28 (.79–2.07)
COPD	48/188 (26)	8/188 (4.3)	<b>&lt;.01</b>	<b>7.67 (3.28–18.0)</b>
Asthma	7/188 (3.7)	8/188 (4.3)	.79	0.88 (.32–2.41)
Diabetes	13/188 (6.9)	7/188 (3.7)	.16	2.00 (.77–5.33)
Asplenia	3/188 (1.6)	0	.08	65 (.01–702.391)
Malignancy	25/188 (13)	24/188 (13)	.88	1.05 (.57–1.94)
Chronic kidney disease	21/188 (11)	6/188 (3.2)	<b>&lt;.01</b>	<b>4.00 (1.50–10.7)</b>
Liver cirrhosis	7/188 (3.7)	3/188 (1.6)	.20	2.33 (.60–9.02)
Other immunodeficiency <sup>c</sup>	8/188 (4.3)	0	<b>&lt;.01</b>	65.2 (.22–19220)
Hepatitis C coinfection <sup>d</sup>	9/188 (4.8)	20/188 (11)	<b>.03</b>	
Hepatitis B coinfection <sup>e</sup>	6/188 (3.2)	12/188 (6.4)	.14	0.50 (0.19–1.33)
Smoking <sup>f</sup>	100/188 (53)	51/188 (27)	<b>&lt;.01</b>	<b>2.69 (1.76–4.12)</b>
Alcohol <sup>g</sup>	111/188 (59)	94/188 (50)	.08	1.54 (.99–2.43)
Drug use <sup>h</sup>	57/188 (30)	24/188 (13)	<b>&lt;.01</b>	<b>2.83 (1.66–4.85)</b>
Pneumococcal vaccination <sup>i</sup>	14/188 (7.4)	7/188 (3.7)	.12	<b>2.00 (.81–4.96)</b>

Boldface text indicates significant differences ( $P < .05$ ).

Abbreviations: CAP, community-acquired pneumonia; cART, combination antiretroviral therapy; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; NA, not applicable; OR, odds ratio; ref, reference.

<sup>a</sup>Of the 188 included cases of CAP, 8 were bacteremic pneumococcal CAP (also invasive pneumococcal disease).

<sup>b</sup>Only people living with HIV on cART were included in the case-control study. Controls were not selected based on cART use. Therefore, there are 16 cART-discordant case-control pairs.

<sup>c</sup>Kidney transplant, immunoglobulin G subclass deficiency, use of immunosuppressive drugs for inflammatory diseases.

<sup>d</sup>Chronic hepatitis C infection.

<sup>e</sup>Active hepatitis B infection or inactive carrier.

<sup>f</sup>Only current smokers. We assumed that patients with missing data on smoking (eg, patient file did not mention smoking) did not smoke.

<sup>g</sup>We assumed that patients with missing data on alcohol use (eg, alcohol used was not mentioned in the patient file by the HIV care provider) did not drink alcohol.

<sup>h</sup>All use of drugs mentioned in the patient files, including recreational use (eg, cannabis, cocaine, opioids, amphetamines, ketamine,  $\gamma$ -hydroxybutyrate). If data on drug use were missing, we assumed that the patient did not use drugs.

<sup>i</sup>Administration of any pneumococcal vaccine. Only 3 of 376 patients received both Prevenar13 and Pneumovax23 according to international guidelines.



**Table 4. Multivariable Conditional Logistic Regression Model With Cases and Controls Matched for Year of Human Immunodeficiency Virus Diagnosis<sup>a</sup>**

Covariates <sup>b</sup>	Adjusted OR (95% CI)
Age group, y	
18–40	ref
41–60	1.13 (.56–2.30)
≥61	2.59 (1.09–6.18)
CD4 count, cells/μL	
<200	11.1 (2.85–42.9)
200–499	1.89 (1.09–3.28)
≥500	ref
COPD	3.07 (1.98–7.87)
Smoking <sup>c</sup>	2.75 (1.56–4.85)
Drug use <sup>d</sup>	2.22 (1.12–4.37)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

<sup>a</sup>This analysis includes 16 combination antiretroviral therapy (cART)–discordant case-control pairs. We performed the same analysis excluding the 16 cART-discordant case-control pairs. This did not significantly change results (data not shown).

<sup>b</sup>Covariates in this model result from stepwise backward selection ( $P < .05$ ).

<sup>c</sup>Only current smokers. We assumed that patients with missing data on smoking (eg, patient file did not mention smoking) did not smoke.

<sup>d</sup>All current use of drugs mentioned in the patient files, including recreational use (eg, cannabis, cocaine, opioids, amphetamines, ketamine,  $\gamma$ -hydroxybutyrate). If data on drug use were missing, we assumed that the patient did not use drugs.

et al showed that vaccination with PPSV23 was associated with a lower risk of pneumonia, but cocaine use and detectable viral load were much stronger predictors [31]. Altogether, there is an urgent need for data on the value of pneumococcal vaccination in PLWH. However, given the large numbers of patients that would be required to demonstrate clinical vaccine efficacy, such data may never be available. Therefore, due to the high burden of disease and good vaccine immunogenicity, vaccination with PCV13 followed by PPSV23 is recommended in most countries [8, 9] and is likely to be cost-effective [5]. Our study provides additional argumentation in favor of this approach.

This study highlights that even in a well-managed patient population in an academic HIV treatment center in a high-income country, PD and CAP remain important causes of morbidity. Our study has several limitations, of which the most important is that our IPD IRs were calculated on the basis of a relatively small number of cases. In addition, the rates of pneumococcal CAP and PD reported in our study are most likely an underestimation of the real disease burden, as the sensitivity of sputum culture is limited and urinary antigen tests were not performed during the study period. Last, databases that we used for collection of vaccine uptake figures did cover vaccinations that were administered at the general practitioner's (GP) office. However, since Dutch guidelines do not recommend pneumococcal vaccination in PLWH, we do not expect that many patients received pneumococcal vaccines at the GP's office [38].

## CONCLUSIONS

The incidence of IPD and CAP among PLWH remains higher compared with the general population, even in those who are virally suppressed on cART and have high CD4 counts. Patients at additional increased risk are those with CD4 counts <500 cells/μL, smokers, recreational drug users, and patients with COPD. Although data on the clinical benefit of pneumococcal vaccination in PLWH are limited, our study demonstrates that the burden of pneumococcal disease remains high. With *S. pneumoniae* as the most commonly identified pathogen of CAP, and all serotyped pneumococcal isolates being covered by available pneumococcal vaccines, we provide additional argumentation against the poor current adherence to international recommendations for pneumococcal vaccination.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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