

# Is It Safe to Discontinue Primary *Pneumocystis jiroveci* Pneumonia Prophylaxis in Patients with Virologically Suppressed HIV Infection and a CD4 Cell Count $<200$ Cells/ $\mu$ L?

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**Background.** Current guidelines suggest that primary prophylaxis for *Pneumocystis jiroveci* pneumonia (PcP) can be safely stopped in human immunodeficiency virus (HIV)-infected patients who are receiving combined antiretroviral therapy (cART) and who have a CD4 cell count  $>200$  cells/ $\mu$ L. There are few data regarding the incidence of PcP or safety of stopping prophylaxis in virologically suppressed patients with CD4 cell counts of 101–200 cells/ $\mu$ L.

**Methods.** The Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) included data from 23,412 patients from 12 European cohorts who started taking cART after 1997. Poisson regression was used to model incidence rate ratios (IRRs) of primary PcP.

**Results.** There were 253 PcP cases during 107,016 person-years of follow-up (PYFU). Prophylaxis significantly reduced the incidence of PcP among patients with current CD4 cell counts  $\leq 100$  cells/ $\mu$ L (adjusted IRR, 0.41; 95% confidence interval [CI], 0.27–0.60) but not significantly among those with current CD4 cell counts of 101–200 cells/ $\mu$ L (adjusted IRR, 0.63; 95% CI, 0.34–1.17). The incidence of PcP among patients who had a current CD4 cell count of 100–200 cells/ $\mu$ L, who had a viral load  $<400$  copies/mL, and who were receiving prophylaxis was 2.1 cases per 1000 PYFU (95% CI, 0.8–4.3 cases per 1000 PYFU; 7 events occurred during 3363 PYFU), whereas 1.2 cases per 1000 PYFU (95% CI, 0.2–4.5 cases per 1000 PYFU; 2 events occurred during 1614 PYFU) occurred among persons who were not receiving prophylaxis (adjusted IRR, 1.65; 95% CI, 0.33–8.15). Among patients who discontinued PcP prophylaxis after starting cART, the incidence of primary PcP was 0 cases per 1000 PYFU (95% CI, 0.0–2.7 cases per 1000 PYFU; 0 events occurred during 1363 PYFU) for patients who had a current CD4 cell count of 101–200 cells/ $\mu$ L and who were receiving cART.

**Conclusions.** The incidence of primary PcP among patients who had virologically suppressed HIV infection, were receiving cART, and who had CD4 cell counts  $>100$  cells/ $\mu$ L was low irrespective of prophylaxis use. Discontinuation of prophylaxis may be safe in patients with CD4 counts of 101–200 cells/ $\mu$ L and suppressed viral load.

Before the widespread introduction of combination antiretroviral therapy (cART), *Pneumocystis jiroveci* pneumonia (PcP) was one of the most frequent AIDS-defining opportunistic infections in human immunodeficiency vi-

rus (HIV)-infected patients and occurred mainly in patients with CD4 cell counts  $<200$  cells/ $\mu$ L [1, 2]. Despite a decrease in the incidence of PcP over time, it remains one of the most common AIDS defining illnesses in Western countries [3–5]. Primary antimicrobial prophylaxis, preferably with trimethoprim-sulfamethoxazole (TMP-SMX), reduces the incidence of primary PcP, and immune reconstitution after successful cART may allow safe discontinuation of prophylaxis. Most of the studies addressing this issue found a very low risk of primary PcP among cART recipients who discontinued prophylaxis if their CD4 cell counts had increased to  $>200$  cells/ $\mu$ L for at least 3 months [6–15]. Current HIV treatment guidelines therefore suggest that primary prophylaxis

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should be discontinued in persons with such a response to cART [16]. The incidence of primary PcP when these guidelines are followed is extremely low, but to further reduce pill burden, possible toxicities, and drug resistance [16, 17], there is additional interest in whether it is possible to discontinue PcP prophylaxis in patients with lower CD4 cell counts who are receiving successful cART. To date, 1 small study of 19 patients suggested that discontinuation of primary prophylaxis may be possible in patients treated with cART who achieve undetectable viral loads but whose CD4 cell counts do not increase to >200 cells/ $\mu$ L [18].

Therefore, the primary aims of this study were to report the occurrence and risk factors for primary PcP in the era of cART and to evaluate the outcome in patients who discontinued primary PcP prophylaxis, using data from the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) group.

## METHODS

### COHERE

COHERE (<http://www.cohere.org>) is a collaboration of 33 cohorts representing 29 different European countries with a mission to conduct hypothesis-driven epidemiological research on the prognosis and outcome of HIV-infected people from across Europe, including ~240,000 adults, 6400 children, and 28,000 mother-infant pairs [19]. For the present analysis we merged data from 12 cohorts (see the Appendix for the contributing cohorts) who prospectively registered start and stop dates of specific therapeutic and prophylactic regimens against PcP. All patients included had follow-up time in their participating cohorts after 1 January 1998 and started cART on or after this date.

### Statistical Methods

In all analyses, primary PcP was diagnosed in each cohort using the presumptive or definitive criteria from the Centers for Disease Control and Prevention [20]. cART was defined as a combination of  $\geq 3$  antiretrovirals of any class. Start date of PcP prophylaxis was lagged by 1 month to ensure that we were capturing information on prophylaxis rather than PcP treatment. Baseline CD4 cell counts and viral loads (in the analysis of the incidence of and risk factors for primary PcP and the analysis of the incidence of primary PcP after stopping prophylaxis in patients having initiated cART) were the values measured closest to baseline and  $\leq 6$  months before or after baseline. Included patients had at least 1 CD4 cell count and viral load measurement obtained during the follow-up period. Incidence rates are expressed throughout per 1000 person-years of follow-up (PYFU). Ninety-five percent confidence intervals (CIs) were calculated using the exact Poisson distribution for <20 events and a normal approximation for  $\geq 20$  events. All

analyses were performed in SAS software, version 9.1 (SAS Institute). Two analyses were performed, as described below.

### *Analysis of the incidence of and risk factors for primary PcP.*

Baseline for this analysis was defined as the date of the first study visit in each participating cohort. Ninety-two patients with PcP at baseline or  $\leq 1$  month after baseline were excluded from analyses to ensure that we were capturing information on prospectively made diagnoses. Patient follow-up began at baseline and ended at the first diagnosis of PcP, last visit, or death, whichever occurred first. The extent of adherence to current treatment guidelines for primary PcP prophylaxis was assessed in patients with a current CD4 cell count  $\leq 200$  cells/ $\mu$ L by describing the number of PYFU “on” or “off” prophylaxis below this CD4 cell count level. Incidence rates of primary PcP were calculated after stratification by current use of PcP prophylaxis, current CD4 cell count, and current viral load. Poisson regression was used to model incidence rate ratios (IRRs) for progression to primary PcP. All models were adjusted for sex, HIV exposure group, region of origin, race, prior AIDS diagnosis, hepatitis B and C status, age, date of first visit, and date at which antiretroviral therapy was first started. CD4 cell count, viral load, and use of PcP prophylaxis and cART (both on-treatment) were included as time-updated variables.

### *Analysis of the incidence of primary PcP after stopping prophylaxis in patients having initiated cART.*

Baseline for this analysis was defined as the date of cessation of primary PcP prophylaxis after starting cART, or first study visit within each participating cohort if patients had discontinued PcP prophylaxis after starting cART before this first study visit. Patients who had never started primary PcP prophylaxis or stopped prior to starting cART were excluded from analyses. Patient follow-up began at baseline and ended at diagnosis of PcP, last visit, or death, whichever occurred first. The incidence of primary PcP was calculated and stratified by current use of PcP prophylaxis, current CD4 cell count, current use of cART (because some patients also discontinued cART after baseline), and current viral load.

## RESULTS

### *Analysis of the incidence of and risk factors for primary PcP.*

Characteristics of included patients at baseline are shown in Table 1. The median duration of follow-up was 4.7 years (interquartile range [IQR], 2.3–7.1 years). There were 107,016 PYFU, including 11,932 PYFU for patients with current CD4 cell counts  $\leq 200$  cells/ $\mu$ L (11%) and 20,319 PYFU for patients with a current viral load >10,000 copies/mL (19%). Adherence to primary prophylaxis guidelines was limited: 61% of the follow-up time for patients with a CD4 cell count  $\leq 200$  cells/ $\mu$ L and 68% of the follow-up time for those with a current CD4 cell count  $\leq 100$  cells/ $\mu$ L was spent on primary PcP prophylaxis. Overall, there were 253 cases of PcP (incidence, 2.4 cases per

**Table 1. Characteristics of Patients at Baseline Included in Analyses of the Incidence of and Risk Factors for Primary *Pneumocystis jirovecii* Pneumonia (PcP; Analysis A) and of the Incidence of Primary PcP after Stopping Prophylaxis in Patients Who Had Initiated Combination Antiretroviral Therapy (cART; Analysis B)**

Characteristic	Analysis A	Analysis B
All patients	23,412 (100)	4903 (100)
Sex		
Male	16,303 (69.6)	3453 (70.4)
Female	7109 (30.4)	1450 (29.6)
HIV exposure group		
Men who have sex with men	8428 (36.0)	1645 (33.5)
IDU	3030 (12.9)	455 (9.3)
Heterosexual	9271 (39.6)	2102 (42.9)
Other	1545 (6.6)	434 (8.9)
Unknown	1138 (4.9)	267 (5.4)
Race		
White	7293 (31.2)	1467 (29.9)
Other	2727 (11.6)	757 (15.4)
Unknown/unreported	13,392 (57.2)	2679 (54.6)
Origin		
Western countries	16,808 (71.8)	3139 (64.0)
Sub-Saharan Africa	4143 (17.7)	1073 (21.9)
Other	2058 (8.8)	592 (12.1)
Unknown	403 (1.7)	99 (2.0)
Prior AIDS	3014 (12.9)	1238 (25.2)
Viral load		
<400 copies/mL	4675 (22.5) <sup>a</sup>	3528 (74.3) <sup>b</sup>
400–10,000 copies/mL	9879 (47.6)	896 (18.9)
>10,000 copies/mL	6211 (29.9)	326 (6.8)
Current receipt of cART	8145 (34.8)	4903 (100)
Current receipt of PcP prophylaxis	3104 (13.3)	0 (0)
CD4 cell count, median cells/ $\mu$ L (IQR)	320 (170–500) <sup>c</sup>	264 (200–354) <sup>d</sup>
Baseline date, median (IQR)	03/02 (04/99–03/04)	06/03 (06/01–07/05)
Age, median years (IQR)	36 (30– 43)	39 (33– 46)

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. Baseline was defined as the date of the first visit in each participating cohort for analysis A or as the latest of date of cessation of primary PcP prophylaxis after commencement of cART or the first visit in analysis B. IDU, injection drug user.

<sup>a</sup> Data were available at baseline for 20,765 patients.

<sup>b</sup> Data were available at baseline for 4750 patients.

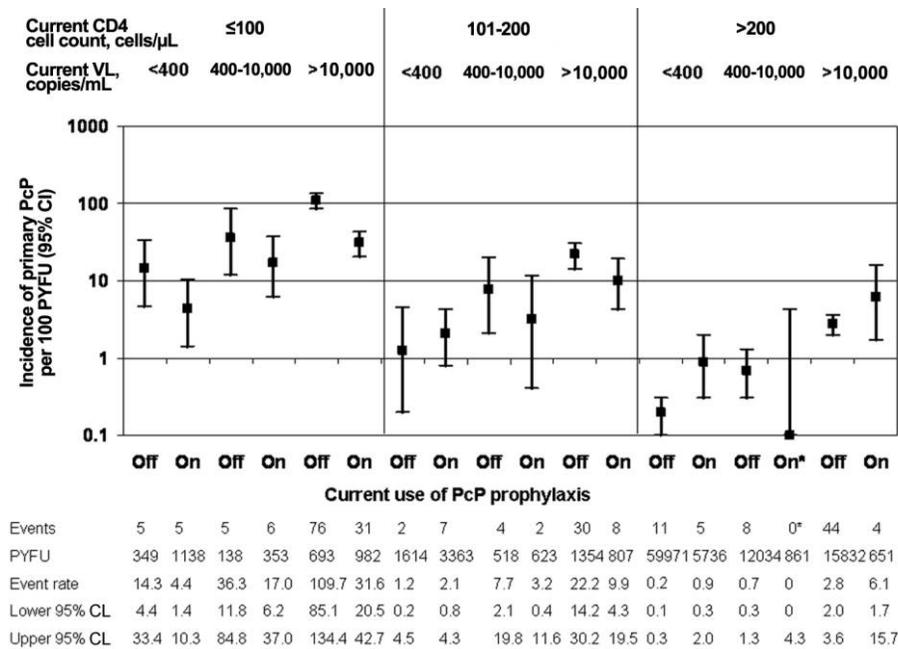
<sup>c</sup> Data were available at baseline for 21,635 patients.

<sup>d</sup> Data were available at baseline for 4791 patients.

1000 PYFU; 95% CI, 2.1–2.7 cases per 1000 PYFU). At diagnosis, the median CD4 cell count was 92 cells/ $\mu$ L (IQR, 30–220 cells/ $\mu$ L) and the median viral load was 5.0 log<sub>10</sub>copies/mL (IQR, 4.1–5.5 log<sub>10</sub>copies/mL). One hundred twenty-eight cases occurred in patients with a current CD4 cell count  $\leq$ 100 cells/ $\mu$ L (incidence, 35.1 cases per 1000 PYFU; 95% CI, 29.0–41.11 cases per 1000 PYFU), and 53 occurred in patients with a current CD4 cell count of 101–200 cells/ $\mu$ L (incidence, 6.4 cases per 1000 PYFU; 95% CI, 4.7–8.1 cases per 1000 PYFU); the incidence among patients with a current CD4 cell count >200 cells/ $\mu$ L was 0.8 cases per 1000 PYFU (95% CI, 0.6–0.9 cases per 1000 PYFU; 72 cases total). Figure 1 illustrates the inci-

dences according to current CD4 cell count, use of PcP prophylaxis, and viral load.

There was a highly statistically significant interaction between use of PcP prophylaxis and CD4 cell count ( $P<.001$ ); thus, the Poisson regression model was performed separately for patients in different CD4 cell count strata, as shown in Table 2. After adjustment, patients with a current CD4 cell count  $\leq$ 100 cells/ $\mu$ L who were receiving PcP prophylaxis had a significantly lower incidence of PcP than did those who were not taking prophylaxis (IRR, 0.41; 95% CI, 0.27–0.60;  $P<.001$ ). Patients with a current CD4 cell count of 101–200 cells/ $\mu$ L who were receiving prophylaxis had a non–statistically significant reduced inci-



**Figure 1.** Analysis of incidence of primary *Pneumocystis jiroveci* pneumonia (PcP) stratified by current CD4 cell count, current viral load (VL), and current use of PcP prophylaxis. CI, confidence interval; CL, confidence limit; PYFU, person-years of follow-up. \*No event; incidence and lower bound of 95% CI were both 0.0.

dence of PcP, compared with those who were not taking prophylaxis (IRR, 0.63; 95% CI, 0.34–1.17;  $P = .15$ ), and there was a non-statistically significant increased incidence of PcP among patients taking PcP prophylaxis with a CD4 cell count >200 cells/μL, again compared with those who were not taking prophylaxis (IRR, 1.53; 95% CI, 0.71–3.28;  $P = .28$ ). In the subset of 14,479 patients (61.8%) with CD4 cell percentage measurement data, CD4 cell percentage was added to the model but showed no significant independent association with incidence of primary PcP in any of the current CD4 cell count strata (data not shown).

Additional analysis focused on the subgroup of patients with current CD4 cell counts of 100–200 cells/μL. In total, 9600 patients contributed 8279.9 PYFU to this stratum; the median duration of follow-up in this stratum was 0.5 years (IQR, 0.2–1.1 years), and 2585 patients (26.9%) provided >1 year of follow-up. There were 7 diagnoses of PcP during 3363.0 PYFU among patients with a current viral load <400 copies/mL who were currently receiving prophylaxis (incidence, 2.1 cases per 1000 PYFU; 95% CI, 0.8–4.3 cases per 1000 PYFU); 2 of these cases occurred within 6 months after commencement of prophylaxis. The incidence was similar for patients who were currently not receiving prophylaxis, among whom 2 events occurred during 1614.3 PYFU (incidence, 1.2 cases per 1000 PYFU; 95% CI, 0.2–4.5 cases per 1000 PYFU;  $P = .53$  for comparison). These 2 events occurred in patients who had never started prophylaxis.

There was no significant difference in the incidence of primary PcP while the current viral load was <400 copies/mL among patients who were receiving versus not receiving PcP prophylaxis (adjusted IRR, 1.65; 95% CI, 0.33–8.15;  $P = .54$ ). In contrast, among patients with a current viral load of  $\geq 400$  copies/mL, patients who were taking PcP prophylaxis had a significantly reduced incidence of primary PcP, compared with those who were not taking prophylaxis (adjusted IRR, 0.47; 95% CI, 0.23–0.97;  $P = .041$ ). However, these data should be interpreted with caution. The formal test for interaction had limited power, the results did not reach statistical significance ( $P = .12$ ), and the 95% CIs were extremely wide for persons with a viral load <400 copies/mL, meaning that we exclude a benefit of PcP prophylaxis.

**Analysis of the incidence of primary PcP after stopping prophylaxis after initiation of cART.** Patients included in this analysis had responded well to cART, with a median increase in the CD4 cell count of 150 cells/μL (IQR, 56–240 cells/μL) and a median decrease in the viral load of 2.4 log<sub>10</sub> copies/mL (IQR, 1.4–2.9 log<sub>10</sub> copies/mL). Characteristics of the patients at baseline are shown in Table 1; the median duration of follow-up per patient was 3.4 years (IQR, 1.6–5.5 years). The most common prophylactic agents stopped were TMP-SMX (4263 patients [86.9%]), nebulized pentamidine (319 patients [6.5%]), and pyrimethamine-sulfadoxine (243 patients [0.5%]). All other PcP prophylaxes were used in <100 patients (<0.2%). The median time between cART initiation and cessation of prophylaxis was

**Table 2. Analysis of Incidence of and Risk Factors for Primary *Pneumocystis jiroveci* Pneumonia (PcP)**

Time updated (current value)	CD4 cell count, ≤100 cells/μL		CD4 cell count, 101–200 cells/μL		CD4 cell count, >200 cells/μL	
	IRR (95% CI)	<i>P</i>	IRR (95% CI)	<i>P</i>	IRR (95% CI)	<i>P</i>
PcP prophylaxis: yes vs no	0.41 (0.27–0.60)	<.001	0.63 (0.34–1.17)	.15	1.53 (0.71–3.28)	.28
Receipt of cART: yes vs no	0.37 (0.25–0.56)	<.001	0.48 (0.26–0.91)	.024	0.35 (0.17–0.70)	.003
CD4 cell count: per doubling	0.68 (0.62–0.76)	<.001	1.02 (0.37–2.80)	.97	0.24 (0.15–0.40)	<.001
Viral load						
<400 copies/mL	1.00		1.00		1.00	
400–10,000 copies/mL	2.45 (1.03–5.81)	.042	2.35 (0.81–6.79)	.12	1.63 (0.61–1.46)	.31
>10,000 copies/mL	3.93 (1.99–7.74)	<.001	6.09 (2.66–13.95)	<.001	4.98 (2.31–10.74)	<.0001

**NOTE.** Analysis was adjusted additionally for sex, prior AIDS, ethnic origin, human immunodeficiency virus exposure group, race, hepatitis B and C status, age, first visit, and date of commencement of antiretroviral therapy. Prophylaxis, combination antiretroviral therapy (cART), and CD4 cell count are included as time-updated (current) values. CI, confidence interval; IRR, incidence rate ratio.

0.6 years (IQR, 0.3–1.4 years), and the median duration of this episode of primary prophylaxis was 0.8 years (IQR, 0.3–1.6 years).

There were 24 diagnoses of primary PcP after cessation of prophylaxis during 18,161 PYFU (incidence, 1.3 cases per 1000 PYFU; 95% CI, 0.8–1.9 cases per 1000 PYFU). From Kaplan-Meier estimation, by 12 months after cessation of primary PcP prophylaxis, 0.17% of patients have developed primary PcP (95% CI, 0.05%–0.29%). At months 24 and 48, the corresponding proportions were 0.30% (95% CI, 0.14%–0.46%) and 0.53% (0.28%–0.78%), respectively. The incidences of primary PcP are shown in Table 3. The majority of primary PcP cases ( $n = 17$ ) occurred in patients whose current CD4 cell count was ≤100 cells/μL, where the incidence was comparatively high (with wide 95% CIs) regardless of current viral load, use of PcP prophylaxis (after initial discontinuation), or use of cART. The incidence of primary PcP among patients with a CD4 cell count of 101–200 cells/μL was 0 in all patients currently receiving cART, regardless of viral load. In the subset of 3032 patients with CD4 cell percentage measurements, there were 2 cases of PcP in patients with a current CD4 cell count of 101–200 cells/μL (Table 3); both occurred in patients who were not receiving cART and who had a current CD4 cell percentage <14%. The small number of cases overall and of cases with CD4 cell percentage data precluded more detailed multivariate analyses.

## DISCUSSION

PcP has become a rare event among patients with access to cART, and collaborative studies are essential to provide adequately powered studies. Our results suggest that the incidence of primary PcP in the cART era was low and that the incidence of PcP among patients with CD4 cell counts of 101–200 cells/μL who had virologically suppressed HIV infection was sufficiently low, both overall and among patients who had stopped primary PcP prophylaxis, to merit consideration of formally

revising current prophylaxis guidelines. The incidence of primary PcP among patients with a current CD4 cell count ≤100 cells/μL remained high, and PcP prophylaxis was beneficial for these patients.

The incidence of primary PcP was very low in our study and considerably lower than previously reported from observational studies [2, 21]. The incidence of primary PcP among patients who had a current CD4 cell count of 101–200 cells/μL, had a current viral load <400 copies/mL, were receiving cART, and were not currently taking PcP prophylaxis was 1.2 cases per 1000 PYFU, with an upper 95% confidence limit of <5 cases per 1000 PYFU, which is approximately the same level as in studies that previously investigated stopping primary PcP prophylaxis using a cutoff value of 200 cells/μL [6, 8–15]. Of note, the only 2 published randomized trials of discontinuation of primary PcP prophylaxis included <600 patients and ~600 PYFU, providing an upper estimate of the 95% confidence limit of between 80–90 cases per 1000 PYFU, yet these trials have been included in treatment guidelines as providing strong evidence [9, 10, 16].

Most studies evaluating the safety of prophylaxis discontinuation for specific opportunistic infections after commencement of cART used a CD4 cell count threshold above which discontinuation of prophylaxis was shown to be safe, irrespective of viral load. Our analysis of stratifying follow-up time according to current viral load points towards a strong negative influence of replicating HIV on immunocompetence in patients who are receiving cART and who have a given CD4 cell count. This finding confirms earlier studies showing that a reduction in viral load during cART is independent of CD4 cell count as a predictor of opportunistic infection [22–24]. In addition, it is consistent with data showing plasma HIV type 1 RNA level to be a strong predictor of vaccination response [25, 26].

Our primary analysis (ie, the incidence of and risk factors for primary PcP) was based on a population of patients who started cART after 1 January 1998 and provides useful popu-

**Table 3. Incidence of Primary *Pneumocystis jiroveci* Pneumonia (PcP) after Cessation of PcP Prophylaxis following Initiation of Combination Antiretroviral Therapy (cART)**

Variable				No. of PYFU	No. of events	Incidence rate per 1000 PYFU (95% CI)
CD4 cell count, cells/ $\mu$ L	cART	Viral load, copies/mL	PcP prophylaxis			
$\leq 100$	"On" or "off"	Any	"On" or "off"	666.9	17	25.5 (14.9–40.8)
$\leq 100$	"On"	Any	"On" or "off"	493.7	7	14.2 (5.7–29.2)
$\leq 100$	"On"	<400	"On" or "off"	282.4	4	14.2 (3.9–36.3)
$\leq 100$	"On"	<400	"Off"	104.2	4	38.4 (10.5–98.3)
101–200	"On" or "off"	Any	"On" or "off"	1578.4	2	1.3 (0.2–4.6)
101–200	"On"	Any	"On" or "off"	1362.9	0	0 (0–2.7)
101–200	"On"	<400	"On" or "off"	1070.5	0	0 (0–3.5)
101–200	"On"	<400	"Off"	570.4	0	0 (0–6.5)
>200	"On" or "off"	Any	"On" or "off"	15,915.2	5	0.3 (0.1–0.7)
>200	"On"	Any	"On" or "off"	15,182.9	1	0.1 (0.002–0.4)
>200	"On"	<400	"On" or "off"	14,604.3	1	0.1 (0.002–0.4)
>200	"On"	<400	"Off"	13,269.4	0	0 (0–0.3)

For primary PcP, a total of 24 events occurred during 18,160.5 person-years of follow-up (PYFU), for an incidence of 1.3 cases per 1000 PYFU. All strata are time updated (ie, they are current values). CI, confidence interval.

lation-based estimates of the incidence of PcP according to use of PcP prophylaxis, cART, current CD4 cell count, and current viral load. In contrast, our second analysis (ie, the incidence of primary PcP after stopping prophylaxis after initiation of cART) included a subset of patients who discontinued PcP prophylaxis after initiation of cART to address whether PcP prophylaxis can safely be discontinued. Of note, we found low rates of PcP in the second analysis among patients with a current CD4 cell count of 101–200 cells/ $\mu$ L and with virological suppression, although the rates remained high in patients with CD4 cell counts  $\leq 100$  cells/ $\mu$ L.

Our study was considerably larger and with more power than previously published research [18], although the power was still too low to permit more sophisticated statistical analyses. Although the data should be interpreted with caution, our data support discontinuation of primary PcP prophylaxis in patients with a CD4 cell count  $\geq 100$  cells/ $\mu$ L and with suppressed viral load. Reducing the need for primary PcP prophylaxis has a number of advantages, including reducing pill burden, the potential for toxicities, inconvenience, and cost [18]. Furthermore, reducing unnecessary long-term use of prophylactic TMP-SMX is likely to reduce the development of bacterial resistance observed during primary PcP prophylaxis [16, 17, 27]. Of note, patients with virologically suppressed HIV infection and CD4 cell counts of 101–200 cells/ $\mu$ L contributed 42% of follow-up data among patients with CD4 cell counts  $\leq 200$  cells/ $\mu$ L for whom prophylaxis is warranted using current guidelines [16].

There are several limitations to this study that should be noted. The data are from European observational cohort studies; patients were not randomized to continue or stop primary PcP prophylaxis in different CD4 cell count strata. Confound-

ing by indication is an important consideration and cannot be excluded. This occurs if clinicians select patients to discontinue PcP prophylaxis because they believed that they were less likely to develop primary PcP. Equally, clinicians may select patients to continue to receive PcP prophylaxis when it is no longer indicated by guidelines because of underlying concerns about PcP. Although all the contributing cohorts are well established and have their own quality assurance in place, it is possible that there were some differences regarding diagnosis of primary PcP; data regarding whether the diagnosis was definitive or presumptive were not collected. Limited power precluded a more detailed analysis of patients who stopped prophylaxis after starting cART, and we did not specifically limit the analyses to patients with a CD4 cell count greater than a threshold for >3 months, as in current treatment guidelines [16]. Because the risk of developing an opportunistic infection decreases with increasing time since commencement of cART [24], we may have overestimated the incidence of primary PcP among patients who stopped prophylaxis at a given CD4 cell count threshold. Only a subset of patients had information on CD4 cell percentage available. Our results suggested no independent association between CD4 cell percentage and risk of primary PcP in a model that included absolute CD4 cell count; these results should be interpreted with caution and should not preclude consideration of CD4 cell percentage for prescribing PcP prophylaxis in individual patients.

In conclusion, patients with virologically suppressed HIV infection who are receiving cART have a markedly decreased incidence of primary PcP, even at CD4 cell counts <200 cells/ $\mu$ L and irrespective of prophylaxis. PcP prophylaxis remained of benefit in patients with CD4 cell counts  $\leq 100$  cells/ $\mu$ L. Our

data suggest that discontinuation of primary Pcp prophylaxis may be safe in patients who are receiving cART and have virologically suppressed infection and a CD4 cell counts of 101–200 cells/ $\mu$ L. These results are based on well-described observational cohorts, but confounding by indication cannot be excluded. Analyses from other very large collaborations in resource-rich settings, such as North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), should be encouraged to strengthen the evidence for incorporating these findings in HIV treatment guidelines.

## **ANALYSIS AND WRITING COMMITTEE (OPPORTUNISTIC INFECTIONS PROJECT TEAM)**

All members of the Opportunistic Infections Project Team participated in discussions on the design of the study, the choice of statistical analyses; and interpretation of the findings and were involved in the preparation and review of the final manuscript for submission. In addition, Amanda Mocroft is responsible for performing all analyses and had full access to the dataset.

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**Potential conflicts of interest.** All authors: no conflicts.

## **APPENDIX**

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