Clinical Infectious Diseases

MAJOR ARTICLE

Withholding Primary Pneumocystis Pneumonia Prophylaxis in Virologically Suppressed Patients With Human Immunodeficiency Virus: An Emulation of a Pragmatic Trial in COHERE

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Background. Using data from the COHERE collaboration, we investigated whether primary prophylaxis for pneumocystis pneumonia (PcP) might be withheld in all patients on antiretroviral therapy (ART) with suppressed plasma human immunodeficiency virus (HIV) RNA (≤400 copies/mL), irrespective of CD4 count.

Methods. We implemented an established causal inference approach whereby observational data are used to emulate a randomized trial. Patients taking PcP prophylaxis were eligible for the emulated trial if their CD4 count was ≤200 cells/μL in line with existing recommendations. We compared the following 2 strategies for stopping prophylaxis: (1) when CD4 count was >200 cells/μL for >3 months or (2) when the patient was virologically suppressed (2 consecutive HIV RNA ≤400 copies/mL). Patients were artificially censored if they did not comply with these stopping rules. We estimated the risk of primary PcP in patients on ART, using the hazard ratio (HR) to compare the stopping strategies by fitting a pooled logistic model, including inverse probability weights to adjust for the selection bias introduced by the artificial censoring.

Results. A total of 4813 patients (10 324 person-years) complied with eligibility conditions for the emulated trial. With primary PcP diagnosis as an endpoint, the adjusted HR (aHR) indicated a slightly lower, but not statistically significant, different risk for the strategy based on viral suppression alone compared with the existing guidelines (aHR, .8; 95% confidence interval, .6–1.1; $P = .2$).

Conclusions. This study suggests that primary PcP prophylaxis might be safely withheld in confirmed virologically suppressed patients on ART, regardless of their CD4 count.

Keywords. human immunodeficiency virus; pneumocystis pneumonia; prophylaxis; HIV-RNA.

Pneumocystis pneumonia (PcP) is an opportunistic disease contracted by individuals with a weakened immune system, and it remains one of the most frequent AIDS-defining diagnoses in resource-rich countries in late presenters [1, 2].

People diagnosed with human immunodeficiency virus (HIV) and with low CD4 lymphocyte counts are at risk of developing PcP and should be prescribed combination antiretroviral therapy (ART) in order to suppress plasma viral load and prophylactic treatments [3, 4]. Adding prophylactic treatment, apart from increasing pill burden, could cause adverse events

Received 9 March 2020; editorial decision 24 April 2020; accepted 19 May 2020; published online May 25, 2020.

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Clinical Infectious Diseases® 2021;73(2):195–202

DOI: 10.1093/cid/ciaa615

and potentially increase the risk of antibacterial resistance due to prolonged usage.

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord was a project-based collaboration that comprised 40 adult, pediatric, and mother–child HIV cohorts across Europe. The collaboration, which was active from 2005 to 2015, allowed for annual coordinated data collection via a centrally developed standardized operating procedure. The COHERE collaboration addressed novel research questions that could not be studied adequately in individual cohorts (http://www.cohere.org).

Previous analyses conducted on COHERE suggested that primary PcP prophylaxis can be safely withdrawn in patients with CD4 counts of 100–200 cells/μL if HIV RNA is suppressed [5]. A more recent study added new findings, indicating that PcP incidence off prophylaxis was below 1 per 100 person-years (py) for virologically suppressed individuals with a CD4 count above 100 cells/μL, concluding that primary (and secondary) prophylaxis might not be needed in such cases [6]. However, it remains to be determined if PcP prophylaxis might be fully withdrawn for patients with consistently suppressed HIV viral load (VL), irrespective of CD4 count.

The current European AIDS Clinical Society (EACS) guidelines that are, at least partially, based on the results from these studies recommend the following rules for stopping primary PcP prophylaxis (page 105 of [7]): "Stop: if CD4 count >100 cells/μL and HIV-VL undetectable for over 3 months," whereas the US National Institutes of Health (NIH) guidelines state [8]: "Primary pneumocystis prophylaxis should be discontinued in adult and adolescent patients who have responded to ART with an increase in CD4 counts from <200 cells/mm^3 to >200 cells/mm^3 for >3 months."

The gold standard for estimating the risk of PcP would be to conduct a randomized trial. However, due to the low levels of PcP diagnoses for patients on ART, a randomized trial would be prohibitive both in terms of time and cost. Given the wealth of new data available in COHERE since initial studies focusing on PcP were carried out, the goal of our study was to investigate whether PcP prophylaxis might be withheld in all patients on ART with suppressed plasma HIV RNA (<400 copies/mL). We use the data to compare the risk of 2 PcP prophylaxis stopping strategies: (1) the existing guidelines with a CD4 count of 200 as threshold versus (2) a new strategy based solely on confirmed viral suppression. We estimate the risk of primary PcP in patients on combined antiretroviral therapy (cART) by applying the established causal inference approach in which observational data are used to emulate a hypothetical randomized trial comparing the 2 prophylaxis stopping strategies (eg, [9–12]). This approach was pursued since the incidence of PcP for patients on cART is very low, and therefore a randomized trial would be prohibitive both in terms of time and cost. An "emulated trial" using observational data offers a viable alternative to estimate the risk of a proposed new treatment strategy.

METHODS

Hypothetical Target Trial

We emulated a pragmatic randomized controlled trial using observational data, and the natural starting point for this approach is to first define the hypothetical target trial to investigate the hypothesis. Since there is some degree of inconsistency between the current guidelines, in the interests of greater applicability for our study results we chose a least common denominator of both the EACS and NIH guidelines with just the CD4 threshold of 200 cells/μL as a criterion for stopping PcP prophylaxis.

The target trial is defined as a 2-arm, open-label study comparing the risk of 2 different strategies for taking and stopping PcP prophylaxis. Individuals with HIV are eligible to enter the hypothetical target trial if (1) they began follow-up in their cohort after 1998, (2) they started ART on or after this date (defined as any combination of 3 or more antiretrovirals of any type), (3) are 16 years or older, (4) have no history of previous PcP, and finally, (5) they are taking PcP prophylaxis in line with existing recommendations (ie, they have a CD4 count <200 cells/μL).

If eligible, patients are randomized to 1 of the 2 PcP prophylaxis strategies:

1. Strategy 1 (current guidelines): Continue taking PcP prophylaxis if CD4 count is <200 cells/μL and stop if CD4 increases from <200 cells/μL to >200 cells/μL for >3 months. Patients re-start prophylaxis if CD4 count is <200 cells/μL.
2. Strategy 2 (new): Continue taking PcP prophylaxis if HIV RNA ≥400 copies/mL and stop if the patient has confirmed viral suppression, defined as 2 consecutive HIV RNA measurements <400 copies/mL in an approximately 3-month period. (This lower limit of quantification was implemented to account for earlier follow-up visits in which detection thresholds were higher than the current 20 copies/mL.) Patients re-start when they are no longer virologically suppressed, defined as having 2 consecutive HIV RNA measurements ≥400 copies/mL.

Patients continue taking prophylaxis on the respective strategy until the above stopping conditions for their randomized arm have been met, and then they stop taking prophylaxis. They may re-start prophylaxis also according to the rules for the respective strategy. Individuals not complying with the stopping and re-starting rules of their randomized arm are considered to be deviating from the trial protocol. This process is summarized graphically in Supplementary Figure 1 in Supplementary Appendix A.

Participants continue in the trial until they are diagnosed with PcP (the endpoint), drop out (eg, due to protocol

noncompliance or adverse effects from treatment), die, or the administrative end of follow-up is reached (5 years).

The next section summarizes the steps taken to emulate the hypothetical target trial using observational data.

Emulated Trial

Study Population

To emulate the target trial, we included data from the 2015 merger of the COHERE database from 23 HIV cohorts for the period 2009 up to the first quarter of 2015. All patients were therefore treated when the guidelines for PcP prophylaxis were based only on the CD4 count threshold of 200 cells/μL. Information on patient characteristics (age, gender, geographical origin, and transmission category), use of ART (type of regimes and dates of start and discontinuation), CD4 cell counts and plasma HIV RNA over time and their dates of measurement, AIDS-defining conditions, and recorded dropouts and deaths was recorded. We selected patients in COHERE compliant with the same eligibility criteria as in the target trial defined in the previous section. Specifically, a patient was deemed eligible at the first visit at which the CD4 count was less than 200 cells/μL and he or she was taking PcP prophylaxis (in line with current guidelines). Baseline patient characteristics were defined as recorded at this visit (Table 1). All subsequent visits for such patients were included as the follow-up for that specific patient. It is assumed that patients continue ART treatment once started, irrespective of any intermittent periods of nonadherence.

A total of 4813 patients with 94 825 follow-up visits were eligible for the emulated trial (Table 1; Supplementary Appendix B "Data set definition" and Supplementary Figure 2). We defined the point of randomization for the emulated trial to be the first time point at which the eligibility criteria were met, defining this as "time 0" for the particular patient, and measuring the time in months from this starting point.

Randomization and Artificial Censoring

At the point of randomization, all patients are eligible for both of the stopping strategies. Therefore, we adopted the approach set out, for example, in Cain et al [10], and replicate all patients, so that each patient is on both arms at the point of randomization (time 0). This cloning process means that at time 0 there are no differences between the patients assigned to the strategies. (However, this does mean that we have to compensate in the analysis for cloning the patients in this way; see "Statistical Methods".)

As in the target trial, follow-up visits from patients are included in the emulated trial until they are diagnosed with PcP or the administrative end of follow-up is reached (5 years). Visits are included for patients up to the point they drop out (for any reason) or die, after which they are censored as usual in a time-to-event analysis.

In addition, a patient can be "artificially censored" for 2 reasons: first, if they stop taking prophylaxis before meeting the defined stopping criteria for the assigned strategy, and second, if they keep taking prophylaxis when they should have stopped according to their strategy. So, for example, a patient on strategy 1 who does not stop prophylaxis when his/her CD4 count is more than 200 cells/μL is artificially censored. Analogously, a patient on the new strategy 2 is artificially censored if he/she is virologically suppressed and does not stop taking prophylaxis. As in the target trial, patients can have multiple periods of

Table 1. Baseline Characteristics of Patients in the Emulated Trial

	Overall	No PcP Diagnosis	PcP Diagnosis	*P*
Number of patients	4813	4761	52 (1.1%)	
Female, n (%)	1195 (24.8)	1182 (24.8)	13 (25.5)	.99
Age, median [IQR], years	40 [35, 47]	40 [25, 47]	40 [33, 46]	.58
Geographical orgin, n (%)				.54
Europe	3938 (81.8)	3'895 (81.8)	43 (84.3)	
Africa	482 (10.0)	478 (10.0)	4 (7.8)	
Asia	83 (1.7)	82 (1.7)	1 (2.0)	
Latin America	236 (4.9)	235 (4.9)	1 (2.0)	
North Africa and Middle East	74 (1.5)	72 (1.5)	2 (3.9)	
HIV transmission mode, n (%)				.44
MSM	1606 (33.4)	1586 (33.3)	20 (39.2)	
Heterosexual	1833 (38.1)	1815 (38.1)	18 (35.3)	
IDU	1155 (24.0)	1146 (24.1)	9 (17.6)	
Other	219 (4.6)	215 (4.5)	4 (7.8)	
CD4, median [IQR], cells/μL	130 [77, 169]	130 [77, 169]	120 [53, 159]	.11
HIV RNA, median [IQR], copies/mL	1460 [107, 65 000]	1402 [102, 63 816]	46 700 [540, 227 600]	<.001
Calendar year at start of emulated trial, median (IQR)	2003 [1999, 2008]	2003 [1999, 2008]	2002 [1998, 2006]	.18
Follow-up on ART, median [IQR], %	84 [41, 100]	84 [41, 100]	100 [84, 100]	<.001

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; MSM, men who have sex with men; PcP, pneumocystis pneumonia.

being on and off prophylaxis as long as they are compliant with their assigned strategy. A comparison of the target and emulated trials, and their differences, is presented in Supplementary Table S1 in Supplementary Appendix A.

Statistical Methods

The longitudinal dataset was expanded to have patient follow-up on a monthly basis (Supplementary Appendix B). We fitted a pooled logistic regression model to this expanded dataset to estimate the hazard ratio (HR) comparing the risk of the 2 treatment strategies. This approach provides a reasonable approximation to the Cox proportional hazards model when the risk of an event is small in any particular time window [13, 14].

To model the baseline hazard, we included "time" (measured in months from time 0 for each patient), along with its square and cubic terms. The model included an indicator variable for the strategy, along with an interaction term between stopping strategy and time to allow for nonproportional hazards, and the following baseline variables; gender, baseline age, geographical origin (Europe [reference], Africa, Asia, Latin America, North Africa, and Middle East), transmission mode (heterosexual [reference], men who have sex with men, injection drug user, other), baseline CD4 (and its square), cohort, baseline HIV RNA (and its square), calendar year at time 0 for this patient (to take into account changes in guidelines), indicator variable for censoring due to death or drop-out, and a variable defining the percentage of postbaseline (ie, postrandomization) follow-up time on ART. Where CD4 counts, HIV RNA measurements, and details of prophylaxis were not available for a patient in a particular month, we used the last observation carried forward (LOCF) method to impute the missing values. Due to the relatively low (<5%) number of missing records for baseline covariates, only the complete records were analyzed. Furthermore, we included inverse probability weights in the model to compensate for potential selection bias from artificial censoring. Details of the modelling approach, along with a subgroup analysis investigating "grace periods" for stopping prophylaxis, are defined in Supplementary Appendix C.

All analyses were carried out in R version 3.2.4 [15], using the function *svyglm* in the package "survey" to calculate robust sandwich errors from logistic models. Throughout, we used a level of 0.05 as statistically significant.

Patient and Public Involvement

There was no patient or public involvement with regard to the design, conduct, reporting, or dissemination of the research.

Ethical Approval

Ethical approval was applied for and granted for the research from the appropriate body in the host country of the cohort contributing the data to COHERE.

RESULTS

There were 4813 patients included in the emulated trial, with 52 (1.1%) PcP diagnoses (Table 1). The median time between HIV RNA measurements was 2.8 months (interquartile range [IQR], 1.5, 3.7). The total follow-up time was 10 324 py on strategy 1 (existing prophylaxis guidelines; median, 4.3 py per patient; IQR, 1.3, 5.1) and 10 324 py on strategy 2 (based on viral suppression only; 2.9 py; IQR, 0.9, 5.1).

A crude rate comparison considering those patients still in follow-up after 60 months implied treatment strategy 2 had a lower rate of PcP diagnosis than did strategy 1 (2.1% vs 1.3%; $P = .03$). However, this difference was not mirrored in the unadjusted incidence rates (strategy 1: 4.2 events per 1000 py; 95% confidence interval [CI], 3.1, 5.3] vs strategy 2: 4.9 events per 1000 py; 95% CI, 3.6, 6.3; $P = .4$).

After fitting the pooled logistic regression model including all person-months, adjusting for baseline factors and including the inverse probability weights, the HR for the first 5 years of follow-up was .8 (95% CI, .6, 1.1; $P = .2$), indicating a marginal, but not statistically significant, lower risk on the stopping strategy 2 (Table 2). In the adjusted model, none of the covariates were significant at the 5% level, except for the variable defining the postbaseline ART adherence ($P = .02$). With this latter point in mind, we performed a further analysis limited to patients with postbaseline visits exclusively on ART, censoring patients at the first visit that they were no longer on ART. Fitting the analysis model to this smaller dataset of 4089 patients, the adjusted HR was attenuated slightly (HR, .9; 95% CI, [.6, 1.3], $P = .6$) (Figure 1).

Using the fitted parametric model we were able to estimate the survival probability over the course of the hypothetical trial period of 5 years (Supplementary Figure 3) and to estimate the difference in absolute risk between the 2 treatment strategies (ie, strategy 1—strategy 2) after 5 years (risk difference, 0.00; 95% CI, –.01, .01).

DISCUSSION

Comparison of the PcP prophylaxis–stopping strategies using a suitably adjusted model indicated that the risk using only confirmed and maintained plasma HIV RNA viral suppression on ART as the criterion for stopping PcP prophylaxis is the same as that for the current NIH guidelines using a CD4 count threshold of 200 cells/μL. We defined viral suppression to be at least 2 consecutive measurements over an approximately 3-month period. The newest EACS guidelines are less conservative than the prophylaxis-stopping rules we used as the comparator in our study, and therefore the study results presented here would tend to underestimate the potential benefit of a stopping strategy based solely on viral suppression.

A previous study using the COHERE data indicated that discontinuing or withholding primary prophylaxis in patients

Table 2. Patient Numbers at Baseline and at the End of Follow-up (60 months) Along With Crude Rate and Incidence Comparisons of Strategies and Hazard Ratio Estimates From the Pooled Logistic Model

	Strategy 1: Existing Prophylaxis Guidelines	Strategy 2: New	*P*
Baseline (month 0)			
Total patients, n	4813	4813	
Follow-up, n (%)			
Died	183 (3.8)	158 (3.3)	.2
Dropped out	233 (4.8)	216 (4.5)	.4
Artificially censored	2319 (48.2)	1006 (20.9)	<.001
End of study (month 60)			
Total patients, n	2494	3807	
Off PcP prophylaxis, n (%)	1140 (45.7)	932 (24.5)	<.001
On PcP prophylaxis, n (%)	1354 (54.3)	2875 (75.5)	
Rate comparison (month 60)			
PcP diagnoses, n (%)	52 (2.1)	51 (1.3)	.03
Off PcP prophylaxis	17 (1.5)	16 (1.7)	.7
On PcP prophylaxis	35 (2.6)	35 (1.2)	.001
Incidence comparison			
Total follow-up, py	12 388	10 324	
Off PcP prophylaxis, n (%)	4439 (35.8)	3762 (36.4)	
On PcP prophylaxis, n (%)	7749 (64.2)	6562 (63.6)	
Median follow-up per patient [IQR], py	4.3 [1.3, 5.1]	2.9 [0.9, 5.1]	<.001
Off PcP prophylaxis	5.0 [3.7, 5.2]	5.0 [2.4, 5.2]	.01
On PcP prophylaxis	1.6 [0.7, 3.1]	1.4 [0.5, 4.7]	.02
Incidence (per 1000 py) [95% CI]	4.2 [3.1, 5.3]	4.9 [3.6, 6.3]	.4
Off PcP prophylaxis	3.8 [2.0, 5.7]	4.3 [2.2, 6.3]	.8
On PcP prophylaxis	4.5 [3.0, 6.0]	5.3 [3.6, 7.1]	.5
Hazard ratio [95% CI]			
Primary endpoint			
Unadjusted analysis without IPW[a]	Reference	1.2 [1.0, 1.3]	.04
Unadjusted analysis with IPW[a]	Reference	.9 [.6, 1.1]	.2
Adjusted analysis without IPW[b]	Reference	1.1 [1.0, 1.3]	.2
Adjusted analysis with IPW[b]	Reference	.8 [.6, 1.1]	.2
Absolute risk difference (60 months)			
Secondary endpoint			
Absolute risk	.99 [.97, .99]	.99 [.97, .99] 0.00 [−.01, .01]	
Hazard ratio [95% CI]			
Further analyses			
Adjusted and including IPW[b]			
(1) 100% ART adherence	Reference	.9 [.6, 1.3]	.6
(2) No grace period[c]	Reference	.6 [.3, 1.0]	.04
(3) Grace period, 6 months[c]	Reference	.8 [.7, 1.0]	.05

Hazard ratios <1 indicate that the new strategy using viral suppression as criteria reduces risk compared with the existing strategy based on CD4 count.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IPW, inverse probability weighting; IQR, interquartile range; PcP, pneumocystis pneumonia; py, person-years.

[a]Unadjusted model has PcP diagnosis as a dependent variable and as independent variables, indicator variables for the strategy along with time, time-squared, and time-cubed. Interactions between time (and its square and cube) and the strategy were not significant at the 5% level.

[b]Adjusted model contains the same terms as the unadjusted model, along with the baseline covariates age, age-squared, gender, mode of transmission, geographical origin, cohort, CD4, CD4-squared, $\log_{10}$ HIV RNA, $\log_{10}$ HIV RNA-squared, calendar year at time 0 for each patient, indicator variables for death and dropout, and the percentage postbaseline follow-up time on ART.

[c]Refer to subgroup analysis at the end of Supplementary Appendix C.

with CD4 counts above 100 cells/μL, suppressed viral load on ART, and without other immunodeficiencies is safe [5]. To our knowledge, the present study involves the largest cohort of patients comparing the effects of stopping primary PCP prophylaxis in virologically suppressed patients irrespective of CD4 counts.

Our study extends results from smaller cohorts [16–18], a randomized trial [19], and 2 reviews [20, 21]. In recent years, many physicians have stopped prescribing PcP prophylaxis in patients with suppressed viremia on ART, even with low CD4 counts [22], and our results highlight an acceptably low risk associated with such an approach.

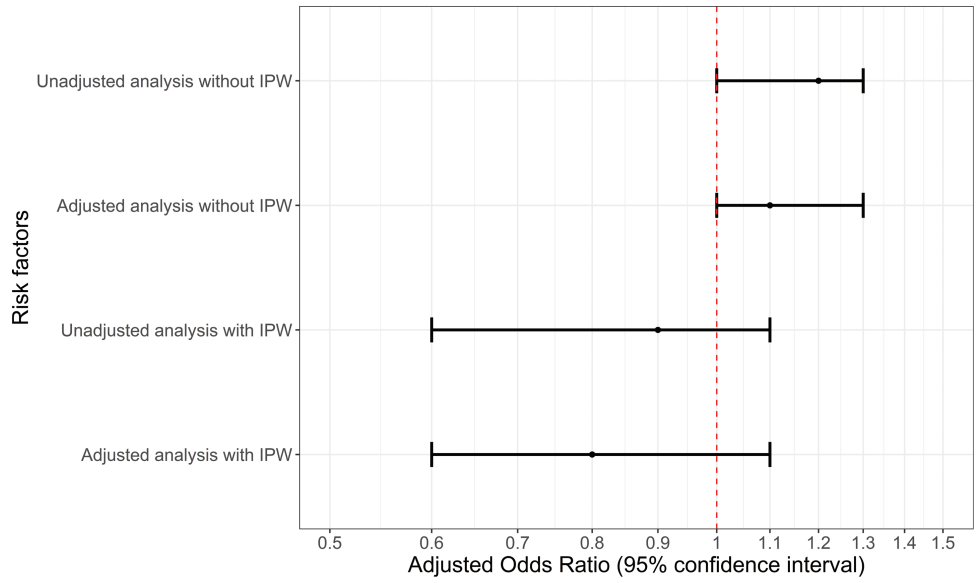

Figure 1. Hazard ratio estimates and 95% confidence intervals from the fitted unadjusted and adjusted models with and without IPW; hazard ratios <1 indicate that the new strategy using viral suppression as a criterion reduces risk compared with the existing strategy based on CD4 count. Abbreviation: IPW, inverse probability weighting.

Previous studies have used the trial emulation approach [9–11], and our study highlights the generalizability of such methods. While using observational data in this way remains rather novel, the American Society of Clinical Oncology recently provided a cautious endorsement explaining "observational studies can also answer or inform questions that either have not been or cannot be answered by RCTs" ([23]; quoting from [24]). Our emulated trial aimed to mimic the design of a randomized trial as closely as possible, and thereafter to be precise and open about the limitations of the adopted approach. We make the assumption of no unmeasured confounding throughout—unfortunately, there is no definitive way of determining if this assumption is justified.

Our study has a number of other limitations. We emulate a target trial and it being unblinded has drawbacks; we cannot rule out potential behavioral changes associated with a patient knowing that he/she is on prophylaxis. The presence of undiagnosed PcP at the time the trial is started is a potential risk in both a hypothetical target and an emulated trial. In our observational data, certain physicians may be more, or less, cautious about prescribing prophylaxis, perhaps depending on unrecorded characteristics that may influence the outcome. We restricted follow-up to 5 years to mirror a realistic trial, but this means our risk analysis is accordingly limited to this time period. In terms of the general application of our results, it is important to note that, although data from 23 European cohorts were included in the analysis, 2 of the large European countries (France, United Kingdom) were potentially underrepresented in the analysis. In addition, our study does not include participants under 16 years of age, and therefore the conclusions are not generalizable to children living with HIV. Finally, and perhaps most importantly, 36% of patients (n = 1752) had a CD4 count of 100 cells/μL or less and 16% of patients (n = 787) had a CD4 count of 50 cells/μL or less at baseline in the analysis. However, these patients contributed overproportionally to the number of PcP diagnoses with 23 of 52 (44%) and 12 of 52 (23%), respectively. Notwithstanding the results presented from this study, clinicians may require further reassurance of our findings before choosing to stop prophylaxis for these higher-risk groups.

From a methodological standpoint, we used a single imputation method (LOCF) to estimate the trajectory of the CD4 and RNA measurements over time. This has the same potential drawbacks of other single imputation methods in terms of variance estimation and potential bias. An alternative would be to multiply impute the time-varying covariates [25], and this is an area for potential further study. Furthermore, since inverse probability weighting inherently assumes patients are censored at random, a sensitivity analysis might be considered to investigate potentially noninformative censoring. In conclusion, HIV replication measured as plasma HIV RNA is a major contributor to the risk of developing primary PcP. In virologically suppressed patients on ART, irrespective of CD4 levels, the risk of PcP is marginally lower using viral suppression alone, compared with when prophylaxis is taken based on the CD4 count threshold according to current guidelines. The study suggests that primary PcP prophylaxis might be safely withheld in patients on ART with confirmed plasma viral suppression, regardless of their CD4 count.

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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Author contributions. A. A., M. Z., J. R. C., and H. F. were responsible for the concept and methodology. A. A. performed data curation and analysis and prepared the first draft of the manuscript. H. F., J. R. C., and M. Z. were responsible for supervision of the work. All authors were responsible for reviewing and editing the manuscript.

Acknowledgments. The authors thank Professor Miguel Hernan of Harvard University for numerous discussions and advice during the course of the project and preparation of the manuscript.

Dissemination declaration. We do not intend to disseminate the results to study participants and/or patient organizations. The results from the study may filter into the appropriate international guidelines.

Data sharing. Data used for the analysis will generally not be publicly available but can be made available based on the approval by the chair of the executive committee of COHERE (Stephane De Wit; refer to author list).

Disclaimer. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Financial support. The COHERE study group has received unrestricted funding from Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, The Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results received funding from the European Union Seventh Framework Program (FP7/2007–2013) under EuroCoord grant agreement number 260694. A list of the funders of the participating cohorts can be found at www.COHERE.org. Research reported in this publication was supported by the Swiss National Science Foundation (grant number 324730_149792, principal investigator: H. F.), specifically for H. F. and A. A.

Potential conflicts of interest. A. A. is also employed by the University Children's Hospital in Basel. D. B. has been part of an advisory board and received speaking fees from Gilead. S. D. W. received grants from Gilead Sciences, Janssen, Merck, Sharp & Dohme (MSD), and ViiV Healthcare, all paid to his institution. A. N.- J. was supported by "Subvencions per a la Intensificacio de Facultatius Especialistes" (Departament de Salut de la Generalitat de Catalunya, Programa PERIS 2016-2020) (SLT008/18/00193). C. M. has participated on advisory boards and received study grants and/or speaker honoraria from AbbVie, Gilead Sciences, ViiV Healthcare, Janssen, Angelini, BMS, and MSD. C. S. received honoraria and travel support from Gilead Sciences, MSD, and Janssen-Cilag, outside of the submitted work. E. G. received unrestricted research grants from Gilead Sciences and Mylan, a travel grant from Gilead Sciences, and honoraria from Gilead Sciences, ViiV Healthcare, Janssen, Mylan, and Angelini, outside the submitted work. O. K. has received consulting honoraria and travel support for conferences from Gilead Sciences, Janssen, MSD, and ViiV Healthcare, outside the submitted work. A. M. has received honoraria from Gilead Sciences, ViiV Healthcare, and A. Craig Eiland PC, outside of the submitted work. P. R. reports grants from Gilead Sciences, ViiV Healthcare, MSD, and Janssen, and other honoraria from Gilead Sciences, ViiV Healthcare, MSD, and Teva, outside the submitted work. J. M. M. received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–2021, and has received consulting honoraria and/or research grants from AbbVie, Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Janssen, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside of the submitted work. J. R. C. is supported by the UK Medical Research Council grant MC_UU_12023/21 and has received a grant to his department from Astra Zeneca and consulting honoraria from Pfizer and GSK, outside of the submitted work. H. F. reports grants to the institution from ViiV Healthcare, Gilead Sciences, MSD, AbbVie, and Sandoz, outside the submitted work. P. M. reports personal fees from Gilead Sciences and MSD and nonfinancial support from Gilead Sciences, MSD, and ViiV Healthcare, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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