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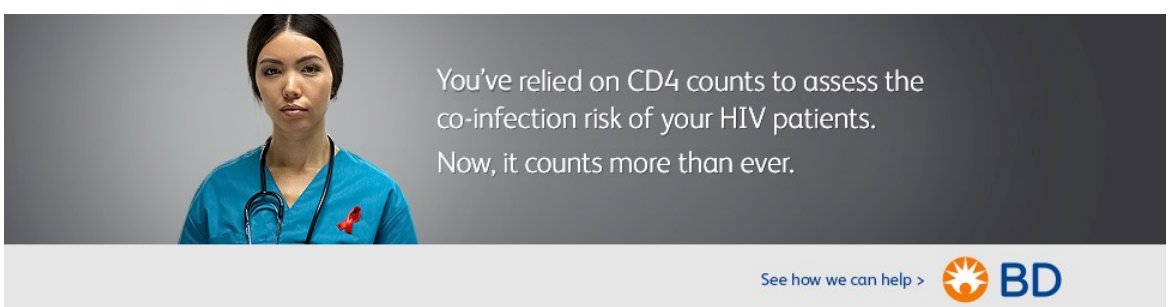
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Withholding primary PcP prophylaxis in virologically suppressed HIV patients: An emulation of a pragmatic trial in COHERE

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Summary:

Using observational data from COHERE, we emulated a randomized trial which showed that primary PcP prophylaxis can be safely withdrawn in virologically suppressed patients on ART, irrespective of the CD4 count.

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Abstract

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 with suppressed plasma HIV RNA (≤ 400c/mL) irrespective of CD4 count.

Methods

We implemented an established causal inference approach whereby observational data is used to emulate a randomised 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 two strategies for stopping prophylaxis: i.) when CD4 count was above 200 cells/µL for more than 3 months, or ii.) when the patient was virologically suppressed (two consecutive HIV RNA ≤ 400c/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 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

4'813 patients (10'324 person years) complied with eligibility conditions for the emulated trial. With primary PcP diagnosis as endpoint, the adjusted hazard ratio (aHR) indicated a slightly lower, but not statistically significant, different risk for the strategy based on viral suppression alone compared to the existing guidelines (aHR 0.8 with 95% CI [0.6, 1.1], p = 0.2).

Conclusions

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

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1. Introduction

Pneumocystis pneumonia (PcP) is an opportunistic disease contracted by individuals having 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 HIV and with low CD4 lymphocyte counts are at risk of developing PcP and should be prescribed combination antiretroviral treatment (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 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 which comprised 40 adult, paediatric, and mother/child HIV cohorts across Europe. The collaboration, which was active from 2005-2015, 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 1/100 person years 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.

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The current 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 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/mm3 to >200 cells/mm3 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 randomised 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 antiretroviral therapy with suppressed plasma HIV RNA (<400c/mL). We use the data to compare the risk of two 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 ART by applying the established causal inference approach in which observational data are used to emulate a hypothetical randomised trial comparing the two prophylaxis stopping strategies (e.g. [9, 10, 11, 12]). This approach was pursued since the incidence of PcP for patients on cART is very low, and therefore a randomised 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.

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2. Methods

2.1. 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 criteria for stopping PcP prophylaxis.

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

If eligible, patients are randomized to one of the two PcP prophylaxis strategies:

- Strategy 1 (current guidelines): Continue taking PcP prophylaxis if CD4 <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 <200 cells/μL.
- Strategy 2 (new): Continue taking PcP prophylaxis if HIV RNA ≥400 c/ml, and stop if the patient has confirmed viral suppression, defined as two consecutive HIV RNA measurements <400 c/ml in approximately a 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 c/ml). Patients re-start when they are no longer virologically suppressed, defined as having two consecutive HIV RNA measurements ≥400 c/ml.

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Patients continue taking prophylaxis on the respective strategy until the above stopping conditions for their randomised arm have been met, and then they stop taking prophylaxis. They may re-start prophylaxis also according 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 summarised graphically in Figure S1 of Appendix A in the supplementary material.

Participants continue in the trial until they are diagnosed with PcP (the endpoint), drop-out (e.g. due to protocol non-compliance, or adverse effects from treatment), die, or the administrative end of follow-up is reached (5 years).

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

2.2. Emulated trial

Study population

To emulate the target trial, we included data from the 2015 merger of the COHERE database from 23 of HIV cohorts for the period 2009 up to 1st quarter 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 drop-outs 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 <200 cells/μL and they were taking PcP prophylaxis (in line with current guidelines). Baseline patient characteristics were defined as recorded at this visit (refer to Table 2). 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 non-adherence.

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A total of 4'813 patients with 94'825 follow-up visits were eligible for the emulated trial (refer to Table 1, Appendix B, "Data set definition", and Consort-type diagram in Figure S2). We defined the point of randomisation 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.

Randomisation and artificial censoring

At the point of randomization, all patients are eligible for *both* of the stopping strategies. Therefore, we adopt 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 zero). 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 – refer to "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 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 two reasons: Firstly, if they stop taking prophylaxis before meeting the defined stopping criteria for the assigned strategy, and secondly, 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 her CD4 count >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 being on an off prophylaxis so long as they are compliant with their assigned strategy. A comparison of the target and emulated trials, and their differences is presented in Appendix A Table S1 in the supplementary material.

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Statistical methods

The longitudinal data set was expanded to have patient follow-up on a monthly basis (refer to Appendix C). We fitted a pooled logistic regression model to this expanded data set to estimate the hazard ratio comparing the risk of the two 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 non-proportional hazards, and the following baseline variables; gender, baseline age, geographical origin (Europe (reference), Africa, Asia, Latin America, North Africa and Middles East), transmission mode (Heterosexual (reference), MSM, IDU, 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 post-baseline (i.e. post-randomization) 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 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 Appendix C.

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

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Patient and Public Involvement

There was no patient or public involvement with regards 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.

3. Results

There were 4'813 patients included in the emulated trial with 52 (1.1%) PcP diagnoses (refer to Table 1). The median time between HIV RNA measurements was 2.8 months (inter-quartile range (IQR) [1.5, 3.7]). The total follow-up time was 10'324 person years (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 Strategy 1 (2.1% vs 1.3%, p=0.03). However, this difference was not mirrored in the unadjusted incidence rates (Strategy 1: 4.2 events per 1000py, 95% confidence interval (CI) [3.1, 5.3] vs Strategy 2: 4.9 [3.6, 6.3, p=0.4).

After fitting the pooled logistic regression model including all person months, adjusting for baseline factors and including the inverse probability weights, the hazard ratio (HR) for the first 5 years of follow-up was 0.8 (95% confidence interval (CI) [0.6, 1.1], p=0.2), indicating a marginal, but not statistically significant, lower risk on the stopping Strategy 2 (see Table 2). In the adjusted model, none of the covariates were significant at the 5% level, except for the variable defining the post-baseline ART adherence (p=0.02). With this latter point in mind, we performed a further analysis limited to patients with post-baseline visits exclusively on ART, censoring patients at the first visit that they were no longer on ART. Fitting the analysis model to this smaller data set of 4'089 patients, the adjusted hazard ratio attenuated slightly (HR 0.9 [0.6, 1.3], p=0.6; see Figure 1).

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Using the fitted parametric model we were able to estimate the survival probability over the course of the hypothetical trial period of 5 years (see Figure S3 in the supplementary material), and to estimate the difference in absolute risk between the two treatment strategies (i.e. Strategy 1 – Strategy 2) after 5 years (risk difference: 0.00, 95% CI [-0.01, 0.01]).

4. 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 criteria 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 two consecutive measurements over approximately a 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 or secondary prophylaxis in patients with CD4 counts above 100cells/μL, suppressed viral load on ART, and without other immunodeficiencies, is safe [16]. 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 [17, 18, 19], a randomized trial [20] and two reviews [21, 22]. In recent years, many physicians have stopped prescribing PcP prophylaxis in patients with suppressed viraemia on ART, even with low CD4 counts [23], and our results highlight an acceptable low risk associated with such an approach.

Previous studies have used the trial emulation approach [9, 10, 11], and our study highlights the generalisability of such methods. Whilst 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

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answered by RCTs" ([24] quoting from [25]). Our emulated trial aimed to mimic the design of a randomised 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 being unblinded brings with it drawbacks; we cannot rule out potential behavioural 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 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 whilst data from 23 European cohorts was included in the analysis, two of the large European countries (France, UK) were potentially under-represented 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, there were 36% of patients (N=1752) with a CD4 count of ≤100 cells/μL, and 16% of patients (N=787) with a CD4 count of ≤50 cells/μL, at baseline in the analysis. However, these patients contributed over-proportionally to the number of PcP diagnoses with 23/52 (44%) and 12/52 (23%) respectively. Notwithstanding the results presented from this study, clinicians may require further reassurance of our findings before definitely choosing to stop prophylaxis for these higher risk groups.

From a methodological standpoint, we use 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 [26], 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 non-informative

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censoring [27]. In conclusion, HIV replication measured as plasma HIV-RNA is a major contributor to the risk factor 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 to 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.

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Contributions

AA, MZ, JRC, HF were responsible for the concept and methodology. AA performed data curation, the analysis, and prepared the first draft of the manuscript. HF, JRC, MZ were responsible for supervision of the work. All authors were responsible for reviewing and editing the manuscript.

Dissemination declaration

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

Data Sharing

Data used for the analysis will generally not be publically available, but can be made available based on the approval by the chair of the executive committee of COHERE (Stéphane De Wit – refer to author list).

Role of the funding source

The funder had no role in the study de.sign, 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

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A. Atkinson is also employed by the University Children's Hospital in Basel. Diana Barger has received a speaking fee from Gilead. S. De Wit received grants from Gilead, Janssen, MSD, & ViiV, all paid to his institution. Cristina Mussini has participated in advisory boards and received study grants and/or speaker honoraria from Abbvie, Gilead Sciences, Viiv Healthcare, Janssen, Angelini, BMS and Merck Sharp & Dohme. C. Stephan received honoraria and travel support from Giliad, MSD and Janssen-Cilag, outside of the submitted work. E. Girardi received unrestricted research grants from Gilead Sciences and Mylan, a travel grant from Gilead sciences, honoraria from Gilead sciences, ViiV, Janssen, Mylan and Angelini, outside the submitted work. O. Kirk has received consulting honoraria and travel support for conferences from Gilead, Janssen, Merck and Viiv, outside the submitted work. A. Mocroft has received honoraria from Gilead, ViiV and A. Craig Eiland PC outside of the submitted work. P. Reiss reports grants from Gilead Sciences, ViiV Heakthcare, Merck & Co and Janssen Pharmaceutica, and other honoraria from Gilead Sciences, ViiV Healthcare, Merck, and Teva, outside the submitted work. Jose M. Miro received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–19, and has received consulting honoraria and/or research grants from AbbVie, Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside of the submitted work. J. R. Carpenter is supported from the UK Medical Research Council grant MC_UU_12023/21, has received a grant to his department from Astra Zeneca, and consulting honoraria from Pfizer and GSK, outside of the submitted work. H Furrer reports grants to the institution from ViiV, Gilead, MSD, Abbvie and Sandoz, outside the submitted work. P. Morlat reports personal fees from Gilead and MSD, and non-financial support from Gilead, MSD, and Viiv Health Care, outside the submitted work. All other authors report no competing interests..

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Tables and Figures

Table 1: Baseline characteristics for patient in the emulated trial

	Overall	**No PcP diagnosis**	**PcP diagnosis**	**p-value**
Number of patients	4'813	4'761	52 (1.1%)	-
Female (%)	1195 (24.8%)	1'182 (24.8%)	13 (25.5%)	0.99
Age in years (median [IQR])	40 [35, 47]	40 [25, 47]	40 [33, 46]	0.58
Geographical orgin				0.54
Europe	3'938 (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 (%)				0.44
MSM	1'606 (33.4%)	1'586 (33.3%)	20 (39.2%)	
Heterosexual	1'833 (38.1%)	1'815 (38.1%)	18 (35.3%)	
IDU	1'155 (24.0%)	1'146 (24.1%)	9 (17.6%)	
Other	219 (4.6%)	215 (4.5%)	4 (7.8%)	

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CD4 (cells/μL)	130 [77, 169]	130 [77, 169]	120 [53, 159]	0.11
HIV RNA (copies/ml)	1460 [107, 65000]	1402 [102, 63816]	46700 [540, 227600]	<0.001
Calendar year at start of emulated trial	2003 [1999, 2008]	2003 [1999, 2008]	2002 [1998, 2006]	0.18
% of follow-up on ART	84% [41%, 100%]	84% [41%, 100%]	100% [84%, 100%]	<0.001

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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; hazard ratios < 1 indicate that the new strategy using viral suppression as criteria *reduces* risk compared to the existing strategy based on CD4 count.

		Strategy 1 Existing prophylaxis guidelines	**Strategy 2 New**	**p-value**
Baseline (month 0)	Total patients	4'813	4'813	
Follow-up	Died	183 (3.8%)	158 (3.3%)	0.2
Follow-up	Dropped-out	233 (4.8%)	216 (4.5%)	0.4
Follow-up	Artificially censored	2'319 (48.2%)	1'006 (20.9%)	< 0.001
End of study (month 60)	Total patients off PcP prophylaxis on PcP prophylaxis	2'494 1'140 (45.7%) 1'354 (54.3%)	3'807 932 (24.5%) 2'875 (75.5%)	<0.001
Rate comparison (month 60)	**PcP diagnoses** off PcP prophylaxis on PcP prophylaxis	**52 (2.1%)** 17 (1.5%) 35 (2.6%)	**51 (1.3%)** 16 (1.7%) 35 (1.2%)	**0.03** 0.7 0.001
Incidence comparison	Total follow-up (py) off PcP prophylaxis on PcP prophylaxis	12'388 4'439 (35.8%) 7'749 (64.2%)	10'324 3'762 (36.4%) 6'562 (63.6%)	
	Median follow-up per patient (py) [IQR] off PcP prophylaxis on PcP prophylaxis	4.3 [1.3, 5.1] 5.0 [3.7, 5.2] 1.6 [0.7, 3.1]	2.9 [0.9, 5.1] 5.0 [2.4, 5.2] 1.4 [0.5, 4.7]	<0.001 0.01 0.02
	Incidence (per 1000 py) [95% CI]	**4.2 [3.1, 5.3]**	**4.9 [3.6, 6.3]**	**0.4**

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	off PcP prophylaxis	3.8 [2.0, 5.7]	4.3 [2.2, 6.3]	0.8
	on PcP prophylaxis	4.5 [3.0, 6.0]	5.3 [3.6, 7.1]	0.5
Hazard ratio	Primary Endpoint (hazard ratio)			
	Unadjusted analysis without IPW*	Reference	1.2 [1.0, 1.3]	0.04
	Unadjusted analysis with IPW*	Reference	0.9 [0.6, 1.1]	0.2
	Adjusted analysis without IPW**	Reference	1.1 [1.0, 1.3]	0.2
	Adjusted analysis with IPW**	Reference	**0.8 [0.6, 1.1]**	**0.2**
Absolute risk difference (60 months)	Secondary endpoint			
	Absolute risk difference	0.99 [0.97, 0.99]	0.99 [0.97, 0.99]	
			0.00 [-0.01, 0.01]	
Hazard ratio	Further Analyses			
	Adjusted and including IPW**			
	1.) 100% ART adherence	Reference	0.9 [0.6, 1.3]	0.6
	2.) No grace period^{+}	Reference	0.6 [0.3, 1.0]	0.04
	3.) Grace period 6 months^{+}	Reference	0.8 [0.7, 1.0]	0.05

IQR: Inter-quartile range, py: person years, CI: confidence interval; IPW: inverse probability weighting; * Unadjusted model has PcP diagnosis as dependent variable and as independent variables, indicator variables for the strategy along with time, time^2 and time^3. Interactions between time (and its square and cube) and the strategy were not significant at the 5% level; ** Adjusted model contains the same terms as the unadjusted model, along with the baseline covariates age, age^2, gender, mode of transmission, geographical origin, cohort, CD4, CD4^2, $\log_{10}$ HIV RNA, $\log_{10}$ HIV RNA^2, calendar year at time0 for each patient, indicator variables for death and drop-out, and the percentage post-baseline follow-up time on ART; $^{+}$ Refer to subgroup analysis at the end of Appendix C.

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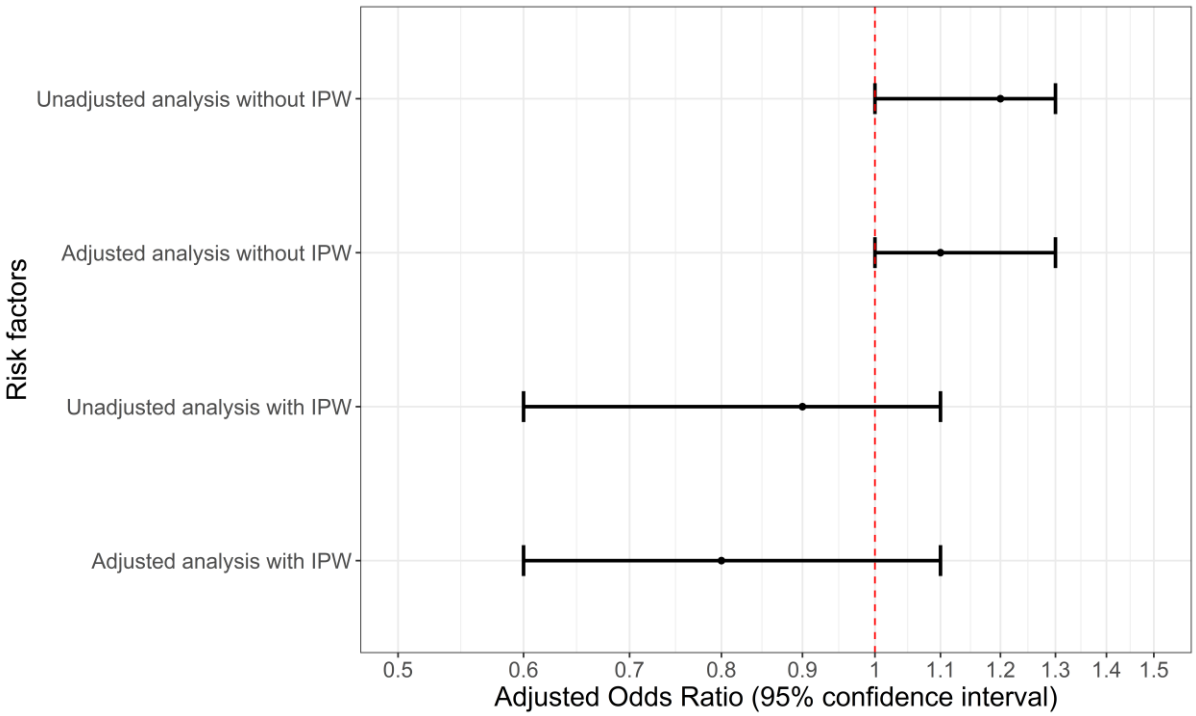
Figure 1 Legend:

Hazard ratio estimates and 95% confidence intervals from the fitted unadjusted and adjusted models with and without inverse probability weighting (IPW); hazard ratios < 1 indicate that the new strategy using viral suppression as criteria *reduces* risk compared to the existing strategy based on CD4 count.

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Figure 1



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