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# Journal Pre-proof

Daily tenofovir disoproxil fumarate/emtricitabine and hydroxychloroquine for pre-exposure prophylaxis of COVID-19: a double-blind placebo controlled randomized trial in healthcare workers

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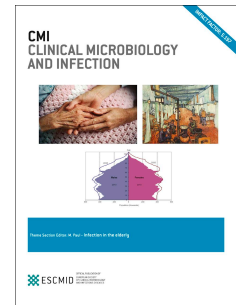
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**Daily tenofovir disoproxil fumarate/emtricitabine and hydroxychloroquine for  
pre-exposure prophylaxis of COVID-19: a double-blind placebo controlled  
randomized trial in healthcare workers**

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**Abstract**

**Objective:** To assess the effect of hydroxychloroquine (HCQ) and Tenofovir disoproxil fumarate/Emtricitabine (TDF/FTC) as pre-exposure prophylaxis on COVID-19 risk.

**Methods:** EPICOS is a double-blind, placebo-controlled randomized trial conducted in Spain, Bolivia, and Venezuela. Healthcare workers with negative SARS-CoV-2 IgM/IgG test were randomly assigned to: daily TDF/FTC plus HCQ for 12 weeks, TDF/FTC plus HCQ placebo, HCQ plus TDF/FTC placebo and TDF/FTC placebo plus HCQ placebo. Randomization was performed in groups of four. Primary outcome was laboratory-confirmed, symptomatic COVID-19. We also studied any (symptomatic or asymptomatic) COVID-19. We compared group-specific 14-week risks via differences and ratios with 95% confidence intervals (CI).

**Results:** Of 1002 individuals screened, 926 (92.4%) were eligible and there were 14 cases of symptomatic COVID-19: 220 were assigned to the TDF/FTC plus HCQ group (3 cases), 231 to the TDF/FTC placebo plus HCQ group (3 cases), 233 to the TDF/FTC plus HCQ placebo group (3 cases), and 223 to the double placebo group (5 cases). Compared with the double placebo group, 14-week risk ratios (95% CI) of symptomatic COVID-19 were 0.39 (0.00, 1.98) for TDF+HCQ, 0.34 (0.00, 2.06) for TDF, and 0.49 (0.00, 2.29) for HCQ. Corresponding risk ratios of any COVID-19 were 0.51 (0.21, 1.00) for TDF+HCQ, 0.81 (0.44, 1.49) for TDF, and 0.73 (0.41, 1.38) for HCQ.

Adverse events were generally mild.

**Conclusion:** The target sample size was not met. Our findings are compatible with both benefit and harm of pre-exposure prophylaxis with TDF/FTC and HCQ, alone or in combination, compared with placebo.

## Introduction

Drug repurposing for prophylaxis against COVID-19 started early in the pandemic (1). Based largely on in-vitro evidence, randomized trials of HCQ as pre-exposure prophylaxis were among the earliest to be launched (1-5). However, these trials were small and resulted in imprecise effect estimates (2-5). Tenofovir disoproxil fumarate (TDF) was another candidate for repurposing based on epidemiological data (6-7), in-vitro and in vivo studies (8-13), and its high bioavailability in many tissues (14-16). However, no randomized trials of TDF for pre-exposure prophylaxis have been completed.

Both hydroxychloroquine and TDF are generic drugs widely prescribed worldwide and a well-documented safety record (17-19). HCQ has been used as treatment and prophylaxis of malaria. TDF, in combination with emtricitabine (FTC), has been used for the treatment and prophylaxis of HIV infection. Despite their potential for COVID-19 prophylaxis, these safe and inexpensive drugs have not been studied in randomized trials (TDF) or the randomized trials have been relatively small (HCQ).

We carried out a double-blind placebo-controlled randomized trial to assess the effect of daily HCQ or TDF/FTC, and of their combination, during 12 weeks as pre-exposure prophylaxis against COVID-19 in healthcare workers.

## Methods

EPICOS (NCT04334928, EudraCT number 2020-001385-11) was a multicenter, double-blind, placebo-controlled randomized trial to study the effect of TDF/FTC and HCQ as pre-exposure prophylaxis for symptomatic COVID-19 among healthcare

workers in Spain, Bolivia and Venezuela. The trial was designed to recruit 4000 individuals. Assuming a 5-10% risk of symptomatic COVID-19 in the placebo group and less than half in the treatment groups, this sample size ensured that the 95% confidence intervals would only include effect values compatible with treatment benefit. However, the start of the vaccination campaign and other factors limited recruitment to 907 participants.

Recruitment into the trial was actively promoted in Spain through regional health authorities and the Ministry of Health, and in Latin America through Esther (Ensemble de Solidarité Thérapeutique Hospitalière En Réseau). Healthcare workers were approached individually and collectively through promotional in-hospital sessions, mailings and hospital-wide advertisements, and were screened for eligibility after providing informed consent. A mobile phone app was developed for electronic monitoring, weekly reminders of adherence, and side-effects reporting.

#### *Eligibility criteria*

Healthcare workers aged 18 to 70 years were eligible if they did not have a prior diagnosis of SARS-CoV-2 infection, did not have symptoms compatible with SARS-CoV-2 infection, had a negative IgM/IgG test for SARS-CoV-2, had negative HIV and (for women) pregnancy tests, a normal electrocardiogram (ECG), and no history of QT interval prolongation, maculopathy, impaired renal function, or immunosuppressive or hematologic conditions. Because women comprised the majority of healthcare workers, we ensured 40% of individuals screened for eligibility were males. Recruitment started in April 2020 in Spain, October 2020 in Bolivia, and March 2021 in Venezuela (Supplementary Figure 1). The study ended on May 30, 2021.



### *Randomization and masking*

Eligible individuals were randomly assigned to one of four treatment groups: TDF/FTC plus HCQ, TDF/FTC plus HCQ placebo, HCQ plus TDF/FTC placebo and TDF/FTC placebo plus HCQ placebo. Randomization was performed with random permuted blocks using a block size of four. The randomization list was computer-generated by a biostatistician with no clinical involvement in the study and before the study started. Medication was prepared accordingly by an external provider, labelled with a unique consecutive number and assigned in chronological order according to the date of treatment initiation in each centre. Investigators, participants, and data analysts were unaware of their treatment assignment. The allocation concealment was preserved by using identical treatment and placebo tablets. The TDF/FTC placebo was provided by the TDF/FTC manufacturing company who donated the drug and the HCQ was designed ad-hoc for the purpose of this study.

TDF/FTC was administered as a single pill with 245mg of TDF and 200 mg of FTC once daily). HCQ was administered as 200 mg once daily, the minimum dose to reach adequate tissue distribution (20). Participants received treatment for 12 weeks (or until a SARS-CoV-2 infection was diagnosed), irrespective of symptoms, or the administrative end of the study, whichever occurred first.

### *Outcomes*

The primary outcome was symptomatic COVID-19, defined as the presence of SARS-CoV-2 infection confirmed by a polymerase chain reaction (PCR) test plus any of the following symptoms: general malaise, fever, cough, joint pain, or breathing difficulty. PCR-confirmed asymptomatic SARS-CoV-2 infection was a secondary outcome. Other

secondary outcomes were duration of symptoms and severity, though the later could not be studied. We also studied the outcome “any (symptomatic or asymptomatic) COVID-19 infection”, which had not been pre-specified in the study protocol.

Adherence (number of missed pills) and adverse events were ascertained in each monthly visit and weekly through app reminders. Adverse events were classified as mild (easily tolerated), moderate (interference with normal activities), or severe (incapacitating, with inability to perform normal activities). Regardless of severity, adverse events were classified as serious if they required hospitalization, prolonged an existing hospitalization, or led to major or permanent disability.

#### *Follow-up*

Participants attended three monthly visits after randomization. In each visit, they were evaluated for the presence of adverse events, adherence, received standard laboratory tests, IgM/IgG antibody test for SARS-CoV-2, and an ECG if necessary. A PCR test was performed if the IgM/IgG antibody test was positive or if symptoms were present. A fourth monthly visit was scheduled for the evaluation of adverse events only.

The trial was stopped after recommendations to vaccinate health care workers were issued in each country. The decision was made by the trial investigators with the agreement of the Data Safety Monitoring Board.

#### *Statistical Analysis*

We used the Kaplan-Meier estimator to obtain outcome risks over 14 weeks of follow-up in each treatment group (over 95% of participants had attended their third monthly visit by 14 weeks after randomization). We compared group-specific risks via differences and ratios with the placebo-only group as the reference. Participants were

censored if/when they were lost to follow-up. In post-hoc analyses, we compared the risk between the two groups containing HCQ and the two groups not containing HCQ, and between the two groups containing TDF/FTC and the two groups not containing TDF/FTC. We calculated 95% confidence intervals using the percentile bootstrap method with 500 repetitions. In sensitivity analyses, we used a Cox model to estimate hazard ratios.

This study was approved by the institutional review boards of University Hospital de La Princesa, Madrid, Spain, Servicio Departamental de Salud de Chuquisaca in Bolivia, and Instituto Nacional de Higiene “Rafael Rangel” in Venezuela. An independent medical monitor and a data safety monitoring board provided oversight of safety and efficacy.

## Results

Of 1002 individuals screened for eligibility, 926 (92.4%) were eligible. The main reason for ineligibility was a previous COVID-19 diagnosis or compatible symptoms (Figure 1). Nineteen individuals withdrew or were lost to follow-up before treatment assignment. Of 907 randomized individuals, 220 were assigned to the TDF/FTC plus HCQ group (12 did not start treatment), 231 to the TDF/FTC placebo plus HCQ group (7 did not start treatment), 233 to the TDF/FTC plus HCQ placebo group (12 did not start treatment), and 223 to the double placebo group (12 did not start treatment). Of 696 individuals who completed the scheduled follow-up, 668 completed treatment as indicated in the protocol. Supplementary Tables 1 and 2 show the reasons for early termination of treatment and incomplete follow-up, respectively, by treatment group.

Baseline characteristics of the 907 participants are summarized in Table 1 and Supplementary Table 3. Median age was 38 years (range 18 to 68 years) and 62.5% (567/907) were female. Most participants worked at inpatient care facilities (62.3%; 565/907) and the most frequent occupation was physician (30.5%; 279/907), 64.2% (582/907) of participants were recruited in Spain, 22.3% (202/907) in Bolivia, and 13.6% (123/907) in Venezuela. Comorbidities were rare.

Figure 2A shows the cumulative risk of symptomatic COVID-19 by treatment group. There were 14 cases: 3 in each group with active treatment and 5 in the placebo-only group. All cases had mild symptoms, with variable duration, that did not require hospitalization (Supplementary Table 4). Compared with the placebo-only group, the 14-week risk ratio (95% CI) of symptomatic COVID-19 was 0.39 (0.00, 1.98) for TDF+HCQ, 0.34 (0.00, 2.06) for TDF, and 0.49 (0.00, 2.29) for HCQ (Table 2).

The 14-week risk ratio (95% CI) of symptomatic COVID-19 was 0.68 (0.10, 2.04) for the groups assigned to HCQ compared with the two groups not assigned to HCQ (Supplementary Table 5 and Supplementary Figure 2), and 0.49 (0.09, 1.70) for the groups assigned to TDF/FTC compared with the two groups not assigned to TDF/FTC (Supplementary Table 6 and Supplementary Figure 3).

Figure 2B shows the cumulative risk of asymptomatic COVID-19 by treatment group. There were 63 cases: 10 in the TDF/FTC + HC group, 17 in the TDF/FTC group, 18 in the HCQ group, and 17 in the placebo only group. Compared with the placebo only group, the 14-week risk ratio (95% CI) of symptomatic COVID-19 was 0.54 (0.21, 1.19) for TDF+HCQ, 0.83 (0.45, 1.66) for TDF, and 0.89 (0.49, 1.91) for HCQ (Table 2).

The 14-week risk ratio (95% CI) of asymptomatic COVID-19 was 0.79 (0.47, 1.33) for the groups assigned to HCQ compared with the groups not assigned to HCQ (Supplementary Table 5 and Supplementary Figure 2), and 0.74 (0.43, 1.21) for the groups assigned to TDF/FTC compared with the groups not assigned to TDF/FTC (Supplementary Table 6 and Supplementary Figure 3).

Figure 2C shows the cumulative risk of any COVID-19 diagnosis by treatment group. There were 77 cases: 13 in the TDF/FTC + HC group, 20 in the TDF/FTC group, 21 in the HCQ group, and 23 in the placebo only group. Compared with the placebo only group, the 14-week risk ratio (95% CI) of any COVID-19 diagnosis was 0.51 (0.21, 1.00) for TDF+HCQ, 0.81 (0.44, 1.49) for TDF, and 0.73 (0.41, 1.38) for HCQ (Table 2).

The 14-week risk ratio (95% CI) of any COVID-19 diagnosis was 0.78 (0.49, 1.23) for the groups assigned to HCQ compared with the groups not assigned to HCQ (Supplementary Table 5 and Supplementary Figure 2), and 0.70 (0.43, 1.10) for the groups assigned to TDF/FTC compared with the groups not assigned to TDF/FTC (Supplementary Table 6 and Supplementary Figure 3).

The corresponding hazard ratios were similar (Supplementary Table 7).

The proportion of individuals with adverse events was 45.0% (99/220) in the TDF/FTC + HCQ group, 41.2% (96/233) in the TDF/FTC group, 36.4% (84/231) in the HCQ group, and 36.8% (82/223) in the double placebo group. Most were mild and of gastrointestinal nature (Table 3). There were 5 serious adverse events: 4 in the placebo only group (hospital admission due to a bleeding uterine myoma, hospital admission due to smoke inhalation from a workplace fire, an episode of dizziness and

bradypsiquia, and an episode of jaundice and vomiting) and 1 in the TDF/FTC +HCQ group (retinal detachment).

## Discussion

EPICOS, a double-blind, placebo-controlled randomized trial, evaluated the effect of treatment with HCQ and TDF/FTC, alone or in combination, as pre-exposure prophylaxis for COVID-19 among health care workers. Because the trial recruited approximately a quarter of the intended number of participants, the effect estimates were imprecise: compared with placebo, the risk of symptomatic COVID-19 was lower in the groups assigned to HCQ or TDF/FTC, but effects between a 2-fold risk increase and perfect protection were highly compatible with the data. For any (symptomatic or asymptomatic) COVID-19, the risk in the group assigned to combined HCQ plus TDF/FTC was half the risk in the group assigned to placebo only, and effects between a 79% reduction in risk and no reduction in risk were highly compatible with the data.

HCQ and TDF/FTC were safe, with mostly mild adverse events of gastrointestinal nature, which is consistent with the well established safety record of both drugs (17-19).

Several placebo-controlled randomized trials have studied HCQ at different doses as pre-exposure prophylaxis for (mostly non-severe) COVID-19 in health care workers (2,4-5). Like EPICOS, five of these trials could not achieve their intended sample size (4,5), partly because potential participants were averse to receive HCQ after poorly conducted observational studies (later retracted) (21) suggested HCQ was not safe, and the “nonsignificant” findings of small randomized trials for prophylaxis were misinterpreted as lack of a beneficial effect. However, a meta-analysis of randomized trials found of pre-exposure prophylaxis estimated a risk ratio of COVID-19 of 0.72 (95% CI: 0.58, 0.90) for HCQ compared with no HCQ (3). The largest trial included in

the meta-analysis found similar estimates: a COVID-19 hazard ratio of 0.73 (95% CI 0.48-1.09) for HCQ vs. placebo after 12 weeks of follow-up in a trial with 1483 participants (5), a COVID-19 odds ratio of 0.75 (95% CI 0.49-1.15) for HCQ vs. placebo after 29 days follow-up in the HERO-HCQ trial with 1359 participants (4), and relative risk of 0.70 (95% CI 0.44-0.97) for HCQ vs. ascorbic acid after 42 days of follow-up in a cluster randomized trial of 1051 participants (22). When taken altogether with the findings from EPICOS, the evidence cannot rule out the possibility that prophylaxis with HCQ offers a modest protection against COVID-19 (3).

No previous randomized trials had studied TDF/FTC as pre-exposure prophylaxis for COVID-19. However, several observational studies have found a lower risk of COVID-19 diagnosis or of hospitalization among individuals who use TDF/FTC compared with those who do not (6-7,23-25). A study among people with HIV in Spain reported lower risk of COVID-19 hospitalization among individuals treated with TDF/FTC compared with those treated with other antiretrovirals (6-7). However, the estimates were not adjusted for the potentially different clinical characteristics of individuals receiving each treatment. A second study in over 50,000 persons with HIV and adequate virological control, which adjusted for comorbidities and other factors, also found a lower risk ratio of COVID-19 hospitalization for TDF/FTC compared with TAF/FTC. Adjusted and unadjusted estimates were similar (24).

A lower risk of COVID-19 hospitalization or death was also found among HIV-positive individuals who used TDF/FTC for HIV treatment in South Africa (23) and among individuals who used TDF for the treatment of hepatitis B infection (25). Also, in a study of ferrets infected with SARS-CoV-2, the group treated with TDF/FTC group had lower clinical scores and a shorter duration of symptoms (26). A phase 2 randomized trial in 60 outpatients with early COVID-19 found reductions in nasopharyngeal

shedding of SARS-CoV-2 after initiation of TDF/FTC (27). On the other hand, a recent in-vitro study report could not detect substantial activity of TDF/FTC against SARS-CoV-2 (28).

Even if HCQ and TDF/FTC were effective as pre-exposure prophylaxis for COVID-19, vaccines are a better approach to prevention when available, at least for the variants studied so far and for immunocompetent persons. The efficacy of vaccines seems to be reduced in immunocompromised patients who are in need of other prophylactic strategies (29). The predominant variants differed by country and period of study (30). The effectiveness of antivirals, unlike that of monoclonal antibodies, is not expected to vary substantially across variants that differ in surface antigens.

A timelier question is whether HCQ and TDF/FTC could be used for early treatment of COVID-19 in non-hospitalized patients. The question has already been answered for HCQ (31) but not for TDF/FTC, a generic and inexpensive drug combination with the potential for massive worldwide production, and for which the available evidence supports the need for therapeutic trials.

In summary, we conducted a randomized, double-blind, placebo-controlled clinical trial in 907 health care workers to compare the risk of COVID-19 after pre-exposure prophylaxis with HCQ and TDF/FTC. Because recruitment had to be ended prematurely, effect estimates were unstable and do not allow to draw definite conclusions. Our findings are compatible with both benefit and harm of pre-exposure prophylaxis with TDF/FTC and HCQ, alone or in combination, compared with placebo.



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The EPICOS randomized trial was sponsored by the Ministry of Health of Spain.

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**Transparency declaration**

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Table 1. Baseline characteristics of 907 participants, EPICOS randomized trial

Characteristic	TDF/FTC + HCQ (n=220)	TDF/FTC (n=233)	HCQ (n=231)	Placebo (n=223)
Sex, n (%)				
Male	85 (38.6)	93 (39.9)	82 (35.5)	80 (35.9)
Female	135 (61.4)	140 (60.1)	149 (64.5)	143 (64.1)
Age in years, median (range)	38.0 (18.0, 65.0)	39.0 (18.0, 68.0)	38.0 (18.0, 65.0)	38.0 (18.0, 65.0)
Occupation, n (%)				
Physician	71 (32.3%)	68 (29.2%)	74 (32.0%)	66 (29.6%)
Nurse	63 (28.6%)	77 (33.0%)	67 (29.0%)	72 (32.3%)
Medical student on clinical rotation	59 (26.8)	58 (24.9)	59 (25.5)	53 (23.8)
Other, with direct patient contact	13 (5.9%)	13 (5.6%)	11 (4.8%)	11 (4.9%)
Other, without direct patient contact	13 (5.9%)	10 (4.3%)	15 (6.5%)	18 (8.1%)
Unknown	1 (0.5%)	7 (3.0%)	5 (2.2%)	3 (1.3%)
Comorbidities, n (%)				
Cardiac disease	3 (1.4)	0	1 (0.4)	2 (0.9)
Hypertension	17 (7.7)	15 (6.4)	4 (1.7)	19 (8.5)
Pulmonary disease	0	0	0	0
Asthma	17 (7.7)	8 (3.4)	20 (8.7)	9 (4.0)
Neoplasia	4 (1.8)	4 (1.7)	2 (0.9)	1 (0.4)
Diabetes	4 (1.8)	3 (1.3)	1 (0.4)	3 (1.3)
Autoimmune Disease	5 (2.3)	7 (3.0)	4 (1.7)	2 (0.9)
Country, n (%)				
Spain	139 (63.2%)	151 (64.8%)	148 (64.1%)	144 (64.6%)
Venezuela	31 (14.1%)	31 (13.3%)	32 (13.9%)	29 (13.0%)
Bolivia	50 (22.7%)	51 (21.9%)	51 (22.1%)	50 (22.4%)

<sup>a</sup> This category includes, biochemists, hospital chaplains, clinical data managers, dentists, psychologists, janitors, human resources personnel, and social workers.

Table 2. Estimated 14-week risks of symptomatic, asymptomatic, and any COVID-19 diagnosis by treatment group, EPICOS randomized trial

Symptomatic COVID-19	Cases / n	14-week risk (95% CI), %	Risk difference (95% CI), %	Risk ratio (95% CI)
TDF/FTC + HCQ	3 / 220	1.10 (0.00 to 2.55)	-1.70 (-4.41 to 1.09)	0.39 (0.00 to 1.98)
TDF/FTC	3 / 233	0.94 (0.00 to 2.63)	-1.85 (-4.43 to 1.16)	0.34 (0.00 to 2.06)
HCQ	3 / 231	1.37 (0.00 to 3.12)	-1.42 (-4.48 to 1.34)	0.49 (0.00 to 2.29)
Placebo	5 / 223	2.79 (0.60 to 5.22)	Reference	Reference
Asymptomatic COVID-19				
TDF/FTC + HCQ	10 / 220	5.51 (2.25 to 9.04)	-4.61 (-10.4 to 1.30)	0.54 (0.21 to 1.19)
TDF/FTC	17 / 233	8.44 (4.70 to 12.6)	-1.68 (-7.72 to 4.26)	0.83 (0.45 to 1.66)
HCQ	18 / 231	9.01 (5.37 to 13.3)	-1.11 (-7.06 to 5.16)	0.89 (0.49 to 1.91)
Placebo	18 / 223	10.1 (5.49 to 14.5)	Reference	Reference
Any COVID-19				
TDF/FTC + HCQ	13 / 220	6.56 (2.75 to 10.27)	-6.17 (-12.32 to 0.01)	0.51 (0.21 to 1.00)
TDF/FTC	20 / 233	9.31 (5.79 to 13.69)	-3.42 (-9.61 to 3.32)	0.81 (0.44 to 1.49)
HCQ	21 / 231	10.35 (6.23 to 14.82)	-2.39 (-8.80 to 4.28)	0.73 (0.41 to 1.38)
Placebo	23 / 223	12.74 (7.92 to 17.44)	Reference	Reference

CI: confidence interval

Table 3. Frequency of adverse events\* by treatment group, EPICOS randomized trial

	TDF/FTC + HCQ (n=220)	TDF/FTC (n=233)	HCQ (n=231)	Placebo (n=223)
Severity of adverse event				
Mild	78 (35.5%)	77 (33.0%)	63 (27.3%)	63 (28.3%)
Moderate	37 (16.8%)	33 (14.2%)	36 (15.6%)	29 (13.0%)
Severe	1 (0.5%)	1 (0.4%)	1 (0.4%)	2 (0.9%)
Adverse event classified as serious	1 (0.5%)	0	0	4 (1.8%)
Adverse event classified as related to study drug	49 (22.3%)	51 (21.9%)	46 (19.9%)	37 (16.6%)
Impact of adverse event on study treatment				
Treatment was interrupted	28 (12.7%)	27 (11.6%)	14 (6.1%)	19 (8.5%)
Treatment was delayed	4 (1.8%)	4 (1.7%)	7 (3.0%)	3 (1.3%)
Concomitant treatment was prescribed	23 (10.5%)	26 (11.2%)	23 (10.0%)	21 (9.4%)
Adverse events by system organ class <sup>a</sup>				
Gastrointestinal disorders	68 (30.9%)	73 (31.3%)	56 (24.2%)	47 (21.1%)
Blood and lymphatic system disorders	1 (0.5%)	0	0	1 (0.4%)
Cardiac disorders	1 (0.5%)	2 (0.9%)	1 (0.4%)	3 (1.3%)
Ear and labyrinth disorders	1 (0.5%)	2 (0.9%)	0	3 (1.3%)
Eye disorder	3 (1.4%)	1 (0.4%)	2 (0.9%)	4 (1.8%)
General disorders	11 (5.0%)	17 (7.3%)	9 (3.9%)	10 (4.5%)
Immune system disorder	0	1 (0.4%)	0	0
Infections	4 (1.8%)	0	5 (2.2%)	3 (1.3%)
Injuries	2 (0.9%)	0	1 (0.4%)	2 (0.9%)
Investigations	2 (0.9%)	6 (2.6%)	3 (1.3%)	3 (1.3%)
Metabolism and nutrition disorders	2 (0.9%)	2 (0.9%)	1 (0.4%)	1 (0.4%)
Musculoskeletal / connective tissue disorders	9 (4.1%)	9 (3.9%)	6 (2.6%)	6 (2.7%)
Nervous system disorders	22 (10.0%)	31 (13.3%)	26 (11.3%)	19 (8.5%)
Psychiatric disorders	3 (1.4%)	3 (1.3%)	4 (1.7%)	8 (3.6%)
Renal and urinary disorders	0	1 (0.4%)	0	1 (0.4%)
Reproductive system disorder	1 (0.5%)	0	1 (0.4%)	1 (0.4%)
Respiratory disorders	1 (0.5%)	3 (1.3%)	3 (1.3%)	2 (0.9%)
Skin disorders	14 (6.4%)	6 (2.6%)	6 (2.6%)	4 (1.8%)

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Vascular disorders	0	0	1 (0.4%)	3 (1.3%)
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\* more than one adverse event per participant could occur

<sup>a</sup> See supplementary methods for a list of the observed adverse events in each system organ class

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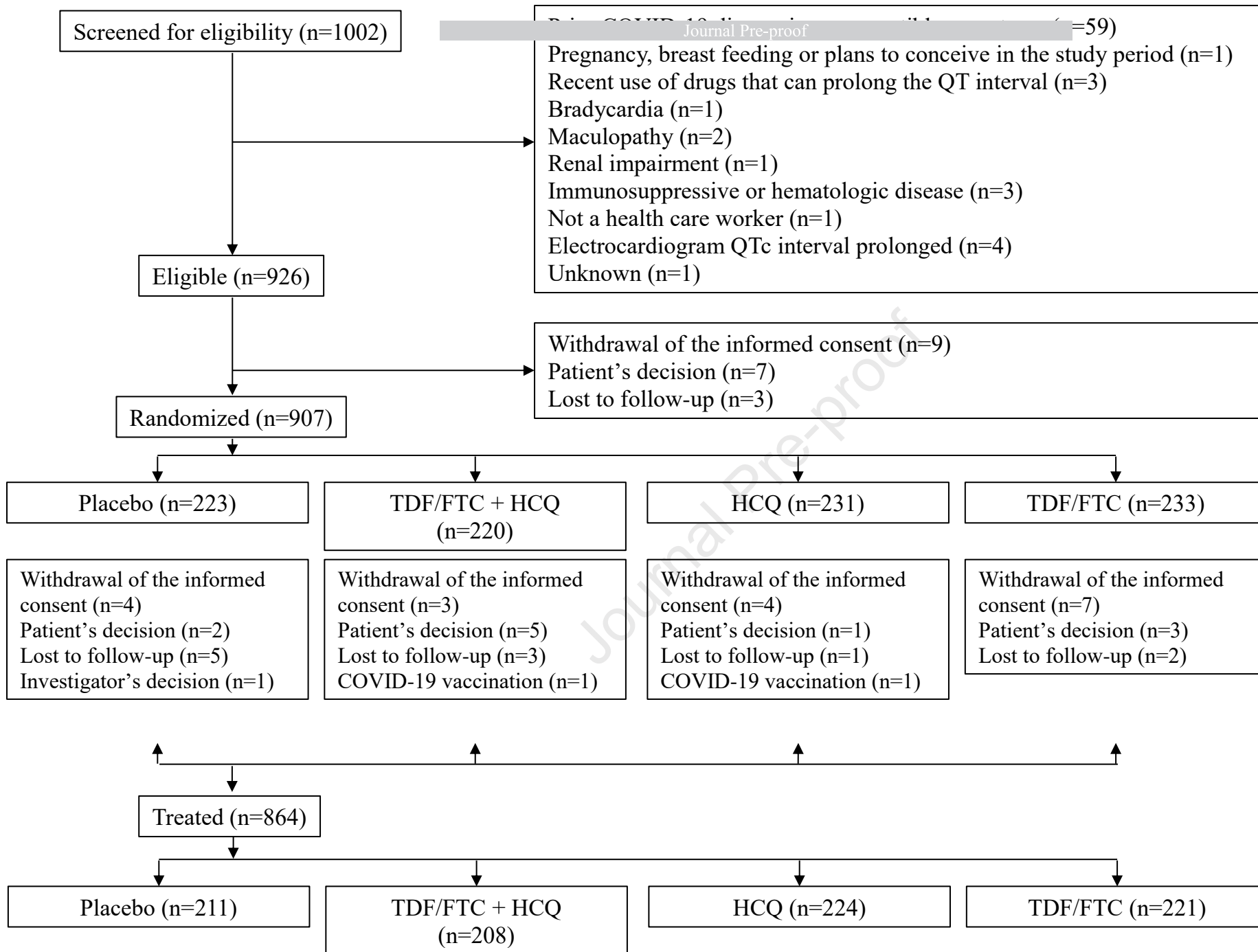


Figure 2. Cumulative risk of symptomatic and asymptomatic COVID-19 by treatment group, EPICOS randomized trial

