

# Pre-Exposure Prophylaxis During COVID-19 Pandemic: Can PrEP Prevent Flu-Like Symptoms?

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## Research article

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# Abstract

**Background:** Considering speculations on an eventual contribution of antiretroviral drugs to treat novel coronavirus, PrEP regular use may provide useful information and clarify its role in preventing flu-like symptoms.

**Objective:** To identify risk and/or protective factors against flu-like symptoms during COVID-19 pandemic among PrEP regular users.

**Methods:** Phone call interview or digital investigation (through WhatsApp® or e-mail) about PrEP regular use during the novel coronavirus pandemic, social distancing, exposure to suspected or confirmed cases of COVID-19 and recent flu-like symptoms.

**Findings:** Among 108 individuals, the majority were cisgender, white, and gay men. Although most of the individuals were in social distancing (68,52%), they did not stop taking PrEP (75,93%). Fewer people had had contact with suspected or confirmed cases of COVID-19 (12,04%), but some did have flu-like symptoms the month before the interview (27,78%) including rhinorrhea (56,67%), cough (53,33%), asthenia (50,00%) and headache (43,33%). Also, PrEP regular use was a protective factor against flu-like symptoms (OR = 0.26, 95% CI 0.07-0.96, p = 0.04) and was associated with social distancing adherence (OR = 7.2, 95% CI 2.74-19.02, p < 0.001).

**Conclusion:** In our sample, regular use of PrEP was a protective factor against flu-like symptoms and was related to the accomplishment of social distancing during the COVID-19 pandemic in São Paulo, Brazil.

## Introduction

In March 2020, the World Health Organization (WHO) declared a pandemic situation of COVID-19, a virus whose epicenter was China, recording on December 31st, 2019 several cases of pneumonia caused by an unknown virus [1]. On January 7th, 2020 the virus was discovered and temporarily named 2019-nCoV [1].

In Brazil, by the end of February, close to carnival celebrations, the first suspected cases of COVID-19 started to appear [2] and were further confirmed by the RT-PCR test. Despite the country's president statements, governors of Brazilian states and the previous Ministry of Health instituted social distancing, following the worldwide campaign proposed by WHO to flatten de curve of COVID-19 incidence, also avoiding the health system collapse. Like many others around the world, São Paulo - the most populous city in Brazil - changed its routine to obey worldwide "stay home" recommendations, preventing the virus from spreading.

Since PrEP has been distributed in Brazil, in 2018, it is aimed to be a combined strategy of prevention against HIV infection according to the global burden of this virus [3,4]. It is constituted by 300 mg de tenofovir disoproxil fumarate (TDF) and 200 mg de emtricitabine (FTC) and it is prescribed as a daily oral

medication, especially, for men who have sex with men (MSM), transgender women, serodiscordant couples and sex workers [5] who are oriented to come back to the clinic every other three or four months.

To investigate the effects of PrEP, social distancing, and change in sexual behavior during the COVID-19 pandemic, we conducted this research whose objective was to identify risk and/or protective factors for flu-like and other COVID19 infection common symptoms among PrEP regular users.

## Material And Methods

This is a unique center study developed at Universidade Federal de São Paulo (UNIFESP), Brazil. This protocol was approved by the Ethical Committee on Research of the UNIFESP (CAAE 96087918.9.0000.5505) and was developed according to the principles expressed in the Declaration of Helsinki. All participants provided written informed consent.

Inclusion criteria were regular use of PrEP along at least 6 months or discontinuation due only to social distancing (from March 2020 on). All individuals who did not use PrEP regularly for other reasons were excluded.

### *Procedures*

Individuals were contacted through phone calls, WhatsApp®, or e-mail as shown in figure 1, and invited to respond to a few questions about PrEP use during the COVID-19 pandemic in Brazil. The questions were:

- Have you been taking PrEP regularly?
- Have you been in social distancing during the last two weeks?
- Have you had contact with someone with suspected or confirmed COVID-19?
- Have you had respiratory symptoms last month? If yes, which ones (rhinorrhea, cough, asthenia, headache, sore throat, fever, decreased taste, dyspnea, loss of smell, diarrhea)?

They should answer “yes” or “no” to each of them.

### *Statistical analysis*

Data were typed and organized in Microsoft Excel for Mac®, version 16.35, and analyzed in SPSS statistics®, version 26. The normal distribution of data was verified using the Kolmogorov-Smirnov test with  $p > 0.05$ . The descriptive analysis presents nominal (absolute and relative frequencies) and numerical (mean and standard deviation) variables. We used the Pearson Chi-square test to identify the most relevant variables related to PrEP regular use that should be tested in univariate logistic regression. We set  $\alpha = 0.05$  and a confidence interval of 95% for all tests.

## Results

After excluding 9 individuals who did not return our attempts and 2 individuals who interrupted PrEP use before COVID-19 pandemic, we evaluated information of 108 subjects.

The majority of them were cisgender (95,37%), white (86,11%), eutrophic (62,04%), and gay men (90,74%). They were, on average, 33,9 ( $\pm$  8,36) years-old and highly educated (96,30%). Some of them were sex workers (11,11%) and they have had, on average, 44,5 ( $\pm$  72,83) sexual partners within the last 6 months. Most of them did not show other diseases (71,30%) and have not been taking other medications (56,48%) (Table 1).

**Table 1.** Sociodemographic characteristics of the PrEP users.

Gender, n (%)		
Cis man	103	(95,37%)
Cis woman	4	(3,70%)
Trans Woman	1	(0,93%)
Ethnicity, n (%)		
White	93	(86,11%)
Mixed	13	(12,04%)
Black	2	(1,85%)
Age, mean (SD), y	33,9	(8,36)
Sexual orientation, n (%)		
Homossexual	98	(90,74%)
Bissexual	5	(4,63%)
Heterossexual	5	(4,63%)
Education, n (%), y		
< 12	4	(3,70%)
≥ 12	104	(96,30%)
Weight, mean (SD), kg	75,9	(11,58)
Height, mean (SD), cm	175,9	(6,88)
BMI category, n (%), kg/m <sup>2</sup>		
< 18.5	0	(0,00%)
18.5 - 24.9	67	(62,04%)
25 - 29.9	31	(28,70%)
≥ 30	9	(8,33%)
Drug or tobacco use, n (%)		
Alcohol	93	(86,11%)
Marijuana	40	(37,04%)
Tobacco	37	(34,26%)
Sex workers, n (%)	12	(11,11%)
Sexual partners in the last 6 months, mean (SD)	44,5	(72,83)

Other diseases, n (%)	31	(28,70%)
Other medications, n (%)	47	(43,52%)
Abbreviations: n, sample; BMI, body mass index; SD, standard deviation; COVID-19, coronavirus disease 2019; PrEP, Pre-Exposure Prophylaxis.		

Although most of the individuals were in social distancing (68,52%), they did not stop taking PrEP and 75,93% kept on taking it. Fewer people had had contact with suspected or confirmed cases of COVID-19 (12,04%), but some did have flu-like symptoms the month before the interview (27,78%). The most frequent symptoms were rhinorrhea (56,67%), cough (53,33%), asthenia (50,00%), and headache (43,33%) (Table 2) and one of the subjects took oseltamivir without medical prescription.

**Table 2. Answers to the survey and the most frequent flu-like symptoms.**

Questions	n	
Have you been taking PrEP regularly?	82	(75,93%)
Have you been in social distancing during the last two weeks?	74	(68,52%)
Have you had contact with someone suspect of confirmed COVID-19?	13	(12,04%)
Have you had flu-like symptoms last month? *	30	(27,78%)
Rhinorrhea	17	(56,67%)
Cough	16	(53,33%)
Asthenia	15	(50,00%)
Headache	13	(43,33%)
Sore throat	11	(36,67%)
Fever	8	(26,67%)
Ageusia	4	(13,33%)
Dyspnea	4	(13,33%)
Anosmia	4	(13,33%)
Diarrhea	3	(10,00%)
Abbreviations: n, sample; COVID-19, coronavirus disease 2019; PrEP, Pre-Exposure Prophylaxis.		
* and/or additional symptoms described in COVID19 infection		

The Pearson Chi-square test showed statistical significance for less flu-like symptoms ( $p = 0.03$ ) and social distancing adherence ( $p < 0.001$ ) associated with PrEP regular use. Then, we performed an univariate logistic regression for PrEP regular use as an independent variable for “flu-like symptoms

within last month” (OR = 0.26, 95% CI 0.07-0.96, p = 0.04) and after for “social distancing within last two weeks” (OR = 7.2, 95% CI 2.74-19.02, p < 0.001). It was shown that PrEP regular use had an impact on both variables (Table 3).

**Table 3.** Univariate logistic regression for flu-like symptoms and social distancing related to the current use of PrEP.

	Current use of PrEP	p-value	OR	(95% CI)
Are flu-like symptoms associated with PrEP use?	No (reference)		-	-
	Yes	0,04	0,27	(0,07 - 0,96)
Is PrEP use associated with social distancing?	No (reference)		-	-
	Yes	< 0,001	7,20	(2,74 - 19,02)

Abbreviations: OR, odds ratio.

## Discussion

As the global targets for controlling HIV spreading, PrEP is an important combined prevention strategy [3,6] against both individual and populational HIV infection [7]. It is estimated that most of the PrEP users are healthy and their main goal is to stay healthy, free of diseases [8]. Based on the findings of this research, we think PrEP may be considered as a protective factor against COVID-19 symptoms. There are lots of aspects that should have contributed to the observed results such as general health conditions, high education, and general health care, but they were not as significant as PrEP regular use. Also, most evaluated subjects were not obese, which has been identified as a potential risk factor for COVID-19 infection severity [9].

In general, people who use PrEP are young adults, highly educated, and healthy[3,10]. As shown in international studies [3,6] and a previous Brazilian one [10], we observed the same already described patterns of PrEP user’s profile. Furthermore, most of these individuals are people who have no comorbidities and who do not chronically use other medications which supports they are mostly a healthy group.

Although recent studies [11,12] showed promising results regarding antiretroviral drug effects against *in vitro* COVID-19 infection, recent clinical research does not confirm their potential in *in vivo* infection [13]. The molecular basis relies on the ability that some of these drugs have to inhibit viral RNA polymerase, a vital enzyme for the COVID-19 cycle [11]. Clinically, antiretroviral drugs did not change the course of SARS-CoV-2 or mortality [13]. To date, it remains a disease with no well-established therapeutic options and several research approaches may help to suggest targets in epidemiological, experimental, and clinical investigations.

In March 2020, around 50-60% of the São Paulo population has adhered to social distancing. Although, this attitude was also observed among those who are PrEP users reaching nearly 70% most of them were highly exposed to social contact during carnival celebrations which was the exact moment of COVID-19 outbreak in Brazil.

Even though social distancing minimized sexual and social risky exposure, most of them kept on taking PrEP regularly. Only fewer isolated individuals stopped using PrEP. It upholds that they highly adhere to this preventive strategy against HIV [10].

Albeit just a small number of subjects admitted to being exposed to suspected or confirmed COVID-19 cases, some had symptoms compatible with the flu (rhinorrhea, cough, asthenia, headache) [14,15]. Some individuals described they had a fever, ageusia, and/or anosmia which have been described as highly suggestive symptoms of COVID-19 infection. In our sample, there was no demand for medical care during the symptoms. It made us believe that, even when occurring, symptoms were mild enough to avoid hospital assistance. Further, a low incidence of dyspnea and the absence of hospitalization support non-severe symptoms.

Seven people of our sample are physicians who kept on working in COVID-19 frontline with higher exposure rates to SARS-CoV-2 infection. Despite their daily exposition to the virus, they did not stop taking PrEP and had only mild symptoms such as rhinorrhea, cough, anosmia, and/or ageusia. If tenofovir plus emtricitabine were a good strategy for preventing SARS-CoV-2 infection, it may be safer to use PrEP rather than hydroxychloroquine which has a huge potential for cardiotoxicity.

It is also interesting to observe that people who kept on taking PrEP showed higher adherence to social distancing, possibly because they are concerned about their general health status. Also, those people motivated to adhere to daily PreP were more likely to be more motivated to adhere to social distancing which has been shown to reduce exposure to respiratory pathogens and thus symptoms. Even though risky exposure is low, those people still go to the supermarkets and drug stores and are continuously exposed to risky situations.

## Limitations

Whereas our analysis has shown a protective effect of PrEP against flu-like symptoms, it is not the most adequate design of the study to state PrEP reduces the risk for respiratory viral infections in general or COVID-19 in particular. Also, we could not confirm SARS-CoV-2 infection by RT-PCR or serology due to the economic status of our country, so we were limited by the clinical presentation of COVID-19 symptoms. Despite the statistical validity of the results, we suggest that researches with larger and more heterogeneous samples can contribute to elucidate associations we observed and described in this study. Besides, considering the impossibility of carrying out laboratory tests to confirm COVID-19 infection so far, it is not possible to restrict our findings to novel coronavirus infection.

## Conclusion

In our sample, regular use of PrEP was a protective factor against flu-like symptoms and was related to the accomplishment of social distancing during the COVID-19 pandemic in São Paulo, Brazil.

## Declaration

**Conflict of Interest Statement:** The authors declare no conflict of interest related to this paper subject.

### Author's Contributions

Danilo Euclides Fernandes: Data curation, analysis, and interpretation, manuscript writing and final approval of the version to be published.

Paulo Roberto Abrão Ferreira: Data interpretation, revising the article, final approval of the version to be published.

Gianna Mastroianni Kirsztajn: Conception and design of the study, analysis, and interpretation of data, drafting the article, final approval of the version to be published.

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## Figures

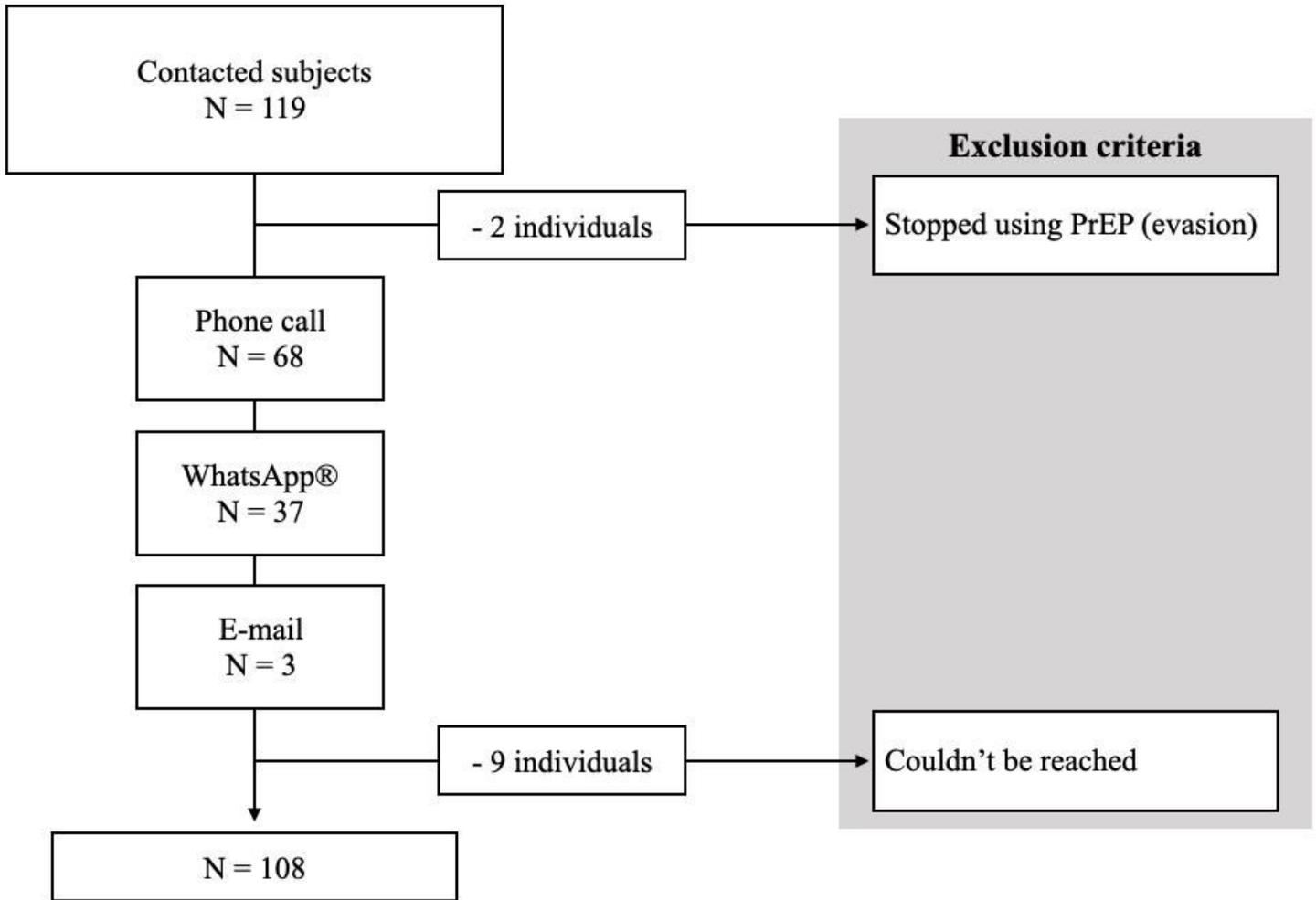


Figure 1

Enrolment flowchart.