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## Severe Acute Respiratory Syndrome Coronavirus 2 Seroprevalence Among HIV-Negative Participants Using Tenofovir/Emtricitabine-Based Preexposure Prophylaxis in 2020: A Substudy of the French National Agency for Research on AIDS and Viral Hepatitis PREVENIR and Inserm SAPRIS-Sero Cohorts

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### ► To cite this version:

Constance Delaugerre, Lambert Assoumou, Sarah Maylin, Marine Minier, Audrey Gabassi, et al.. Severe Acute Respiratory Syndrome Coronavirus 2 Seroprevalence Among HIV-Negative Participants Using Tenofovir/Emtricitabine-Based Preexposure Prophylaxis in 2020: A Substudy of the French National Agency for Research on AIDS and Viral Hepatitis PREVENIR and Inserm SAPRIS-Sero Cohorts. *Open Forum Infectious Diseases*, 2022, 9 (7), pp.ofac188. 10.1093/ofid/ofac188. hal-03777516

**HAL Id: hal-03777516**

**<https://hal.sorbonne-universite.fr/hal-03777516>**

Submitted on 15 Sep 2022

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**SARS CoV-2 seroprevalence among HIV-negative participants using tenofovir/emtricitabine based PrEP in 2020 – a Sub-study of ANRS PREVENIR and INSERM SAPRIS-Sero cohorts**

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**Running title:** Tenofovir/emtricitabine on SARS COV-2

**Keys words:** SARS-CoV-2;

**Text word count:** 1452/1500

**Abstract word count:** 50/50

**Number of figures and tables:** 1 table, 1 figure

**Supplementary material:** NO

**Number of references:** 12/12

## **Abstract**

The potential preventive efficacy of tenofovir/emtricitabine on SARS-CoV-2 infection was assessed in HIV pre-exposition prophylaxis (PrEP) users. Prevalence of SARS-CoV-2 IgG between May and October 2020 was similar in PrEP users and in a matched population-based cohort suggesting that tenofovir/emtricitabine has no role in reducing the risk of SARS-CoV-2 acquisition.

## **Introduction**

COVID-19 (coronavirus disease 2019), caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2), has been defined as a pandemic around the world by the World Health Organization (WHO). The SARS-CoV-2 is a coronavirus, as SARS-CoV and MERS-CoV, that is a positive-sense single-strand RNA virus with replication mechanism requiring a RNA-dependent RNA polymerase. Therefore, at the beginning of the pandemic, known drugs targeting viral RdRp of SARS-CoV or other coronaviruses were repurposed due to the urgent need for an antiviral therapy for the new member of the family, SARS-CoV-2.

Tenofovir disoproxil fumarate (TDF) one of the components of pre-exposition prophylaxis (PrEP), is transformed intracellularly in its active form, tenofovir-triphosphate which inhibits the activity of viral polymerase in HIV and HBV and has also shown an antiviral activity on SARS-CoV-2 *in vitro* and in ferret model [1–3].

Different observational studies, performed between February and September 2020, report matter of debate regarding the potential benefit of TDF to reduce the incidence of SARS-CoV-2 infection or COVID-19-related morbi-mortality in persons using TDF-based regimen as pre-exposition prophylaxis (PrEP) or treatment for HIV-infected patients [4–8].

To assess the potential preventive impact of TDF/emtricitabine (FTC) on SARS-CoV-2 acquisition, we compared during the same time period the seroprevalence of SARS-CoV-2 IgG antibodies rates in male participants of the PREVENIR cohort study of PrEP implementation in Paris area, with participants using intermittent or daily TDF/FTC to that of male participants enrolled in the SAPRIS-sero study in Paris area, France.

## **Methods**

### **Study population**

Between May 1<sup>st</sup> and October 31, 2020, male participants using either daily or on demand PrEP with TDF/FTC enrolled in the PREVENIR study conducted in Paris area, France, and who had a stored serum sample available were included in this study [9]. Participants non-exposed to TDF/FTC were male participants living in Paris area included in the SAPRIS-Sero national survey that estimate SARS-CoV-2 antibodies prevalence in the French general population [10]. Based on the factors associated with the risk of SARS-CoV-2 infection in the initial analysis of the SAPRIS cohort [11] and on available data in both studies, the matching criteria were age ( $\pm$  5 years), socio-occupational category and date of sampling ( $\pm$  1 month). Ethical approval and written or electronic informed consent were obtained from each participant before enrolment in both original cohorts. When PREVENIR participants could not be matched on the 3 criteria, they were matched on age and socio-occupational category then age and sampling date, then on age.

### **Patient Consent Statement**

Ethical approval and written or electronic informed consent were obtained from each participant before enrolment in the original cohort. The SAPRIS-SERO study was approved by

the Sud-Méditerranée III ethics committee (approval #20.04.22.74247). The PREVENIR study was approved by the CPP Paris Ile de France IV ethics committee (NCT03113123 and EudraCT 2016-A01577-44).

### **Virological tests**

A systematic serology was performed in all participants in both cohorts. In the PREVENIR cohort, the SARS-CoV-2 IgG determination was performed using the SARS-CoV-2 IgG II Quantitative antibody ELISA assay (Architect, Abbott, France) on frozen serum. It is a chemiluminescent microparticle immunoassay (CMIA) used for the qualitative and quantitative determination of IgG antibodies against the spike receptor-binding domain (RBD) of SARS-CoV-2. The analytical measurement interval is stated as 21 to 40,000 AU/ml, and positivity cutoff is  $\geq 50$  AU/ml (and low positive  $< 100$  AU/ml). In the SAPRIS-Sero cohorts, we used the Anti-SARS-CoV-2 IgG ELISA (Euroimmun, Germany) that provide semi-quantitative serology results against the S1 domain of the spike protein of SARS-CoV-2 [10]. Samples with an ELISA-S test optical density ratio of  $< 0.8$  as considered as negative,  $\geq 0.8$  to  $< 1.0$  as undetermined and  $\geq 1.0$  as positive. For both tests, the sensitivity (based on 14-day post-positive reverse transcription-PCR samples) and specificity were  $> 98\%$  and  $> 99\%$ , respectively [12].

### **Statistical methods**

Because only age, socio-professional category, and date of sampling were collected in both studies and used as matching criteria, we did not compare these factors between the two study populations.

The primary outcome was the proportion of participants with positive SARS-CoV2 IgG. The primary analysis considered low positive results as positive serology and undetermined results as negative serology. Odds-ratios (OR) of the comparison between studies was calculated using logistic regression, stratified on each matched pair without adjustment because only the matching criteria identified as the main factors associated with the risk of SARS-CoV-2 infection were available in both studies.

Two sensitivity analyses were performed: i) restricted to fully matched participants and ii) considering undetermined results as positive serology.

## **Results**

In PREVENIR, 844 participants with a median (IQR) age of 38 (31 – 45) years were matched to 844 participants of SAPRIS-Sero cohort, aged of 41 (35 – 48) years. Median month of sampling was August (July – September) for PREVENIR and August (July-August) for SAPRIS.

PrEP was on demand in 420 (49.8%) and daily in 424 (50.2%) individuals. Because the matching on 3 criteria concerned 86.5% (n=729) individuals, the results are presented for the whole and fully matched population. As shown in the table and figure, SARS-CoV-2 IgG was positive in 91 (10.8%) and 78 (9.2%) for the whole population in PREVENIR and SAPRIS-Sero cohorts, respectively (Odds-ratio: 1.17, 95% confidence interval 0.86-1.60). The seroprevalence rates were similar among daily or on-demand users (9.9% vs 11.7%, Fisher's Exact p=0.4095). Sensitivity analyses (restricted to fully matched participants or considering undetermined as positive serology) led to similar results.

## **Discussion**

We evaluated whether the use of tenofovir/emtricitabine as HIV pre-exposure prophylaxis in HIV-negative male included in the PREVENIR study could reduce the prevalence of SARS-CoV-2 seroconversion as compared to a matched to a control cohort of male from the general population not using PrEP in Paris (from SAPRIS survey). The SARS-CoV-2 IgG seroprevalence was 10.3% in the PREVENIR study and 9.2% in the SAPRIS survey among 844 male individuals between May to October 2020 in Paris region. This prevalence of 10% was those found for the Paris region corresponding to one of the most affected regions by the first wave of SARS-CoV-2 [10]. Interestingly we showed that the proportion of participants with a positive SARS-CoV-2 serology was similar whether PrEP was used daily or on demand. Because the SARS CoV-2 serology was performed in all patients in both cohorts, our results was not dependent of the presence or absence of symptoms.

Several publications have associated the use of TDF to a significantly lower risk of SARS-CoV-2 infection, COVID-19 related-hospitalization or –death among HIV –infected persons receiving TDF-based antiretroviral regimen than among those receiving other HIV therapies (as abacavir or tenofovir alafenamide (TAF)) [4–6], while the difference of effect between TAF and TDF was poorly explained. Baseline characteristic of patients as age and comorbidities were not accounted for in these studies, while each has been identified as an independent risk factor for poorer outcomes with COVID-19 [13] and can influence the choice of regimen, for instance not using TDF in patients with renal impairment. Recently, an updated of the study from del Amo demonstrated that TDF has a protective effect restricted to individuals aged 50 years and older [14]. Moreover, during the first wave, most SARS-CoV-2 PCR tests were done only in symptomatic or even hospitalized individuals that could be lead to bias.



One study from May to June 2020 in Spain assessed the effect of tenofovir-emtricitabine use as HIV PrEP in HIV-negative persons showing a higher seroprevalence to SARS-CoV-2 IgG anti nucleocapsid than in persons without PrEP (15% versus 9.2%,  $p=0.026$ ) [7]. Interestingly there were no significant differences in the sex, presence of comorbidities, occupational exposure, or exposure by households with confirmed cases. However, the population of PrEP user and those who did not take PrEP was not adjusted, in contrary to our study in which we selected factors (age, socio-occupational category and sampling date) that were found associated with the risk of SARS-CoV-2 infection in the initial analysis of the SAPRIS cohort [11].

Our study has some limitations. First, we did not collected exhaustively information about positive SARS-CoV-2 PCR and COVID-19-like symptoms to determine the effect TDF/FTC on SARS-CoV-2 infection since some individuals might become infected without seroconversion. Our study could not explore the effect of TDF on illness but only on SARS-CoV-2 infection. Second, the factors of exposition to SARS-CoV-2 were not collected. Third, we used two serological tests from different manufacturers to compare the IgG detection but the viral target is the same and sensitivity and specificity were comparable [12]. A lower sensitivity of the test used in the SAPRIS-Sero cohort compared with the test used in the PREVENIR study would not affect our conclusions as it would decrease the difference in measured seroprevalence.

To conclude, the similar seroprevalence of SARS-CoV-2 IgG found in participants using or not TDF/FTC as HIV PrEP suggested that TDF/FTC has no role in reducing SARS-CoV-2 acquisition.

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**Table 1: Proportion of participants with a positive SARS-COV-2 serology**

	Cohort	Positive rate	OR (95%CI)	P value
<b>Whole population</b>				
	SAPRIS (n =844)	78 (9.2%)	1	
	PREVENIR (n =844)	91 (10.8%)	1.2 (0.862-1.603)	0.3061
<b>Fully Matched population</b> (on 3 criteria)				
	SAPRIS (n =729)	66 (12.0%)	1	
	PREVENIR (n =729)	78 (10.7%)	1.1 (0.786-1.604)	0.5248

**Legend Figure 1** : Presence of SARS-CoV-2 immunoglobuline G (IgG) in 844 males living in Paris area, France, with the use of tenofovir/emtricitabine pre-exposure prophylaxis (PrEP) (PREVENIR cohort), matched to male without PrEP (SAPRIS cohort). In the PREVENIR cohort, PrEP was on demand in 420 (49.8%) and daily in 424 (50.2%) individuals.

#### Potential Conflict of Interest

JMM declared to participate to advisory board from Gilead, Merck and ViiV, and to receive research grants from Gilead

CD declared to participate to advisory board from ViiV, Gilead, MSD and Janssen, And to receive grant from ViiV and Gilead

Others authors declared no conflict of interest

Funding: This study was funded by a grant from ANRS-PREVENIR study

**Legend Figure 1 :** Presence of SARS-CoV-2 immunoglobuline G (IgG) in 844 males living in Paris area, France, with the use of tenofovir/emtricitabine pre-exposure prophylaxis (PrEP) (PREVENIR cohort), matched to male without PrEP (SAPRIS cohort). In the PREVENIR cohort, PrEP was on demand in 420 (49.8%) and daily in 424 (50.2%) individuals.

