EFFECTIVENESS OF THE USE OF PERSONAL PROTECTIVE EQUIPMENT IN ADDITION TO TENOFOVIR/EMTRICITABINE FOR THE PREVENTION OF THE TRANSMISSION OF SARS-COV-2 TO HEALTH CARE PERSONNEL. RANDOMIZED CLINICAL TRIAL

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List of abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZT/3TC	Zidovudine/lamivudine
ABC/3TC	Abacavir/lamivudine
CDC	Centers for Disease Control and Prevention.
Cels/µl	Cells per microliter
CRF	Case Report Form
CTCAE	CTCAE, Common Terminology Criteria for Adverse Events
DAIDS	DAIDS Adverse Event Grading Tables
BD	Bone density
AE	Adverse Event
EFV	Efavirenz
ELISA	Enzyme-linked immunosorbent assay
PPE	Personal protective equipment
FDA	Food and Drug Administration
Hb	Hemoglobin
MSM	Men sex with men
HUSI	Hospital Universitario San Ignacio
INR	International standardized ratio

IPS	Health care provider institution
IRB	Institutional review board
ULN	Upper normal limit (with regards to lab testing)
mg/dl	Milligrams per deciliter
WHO	World Health Organization
PTT	Partial Thromboplastin Time
PUJ	Pontificia Universidad Javeriana
PrEP	Pre-exposure prophylaxis
RT-PCR	Real time polymerase chain reaction.
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP`s	Standard Operating Procedures
TDF/FTC	Tenofovir Disoproxil fumarate and Emtricitabine
TLR	Toll-like receptor
UAA	Universidad Autónoma de las Américas
ICU	Intensive Care Unit
UQ	Universidad del Quindío
UTP	Universidad Tecnológica de Pereira
HIV	Human Immunodeficiency virus
HBV	Hepatitis B virus

Summary of the study

Title	**Effectiveness of the use of Tenofovir/Emtricitabine in addition to personal protective equipment for the prevention of the transmission of SARS-COV-2 to health care personnel. A Randomized Clinical Trial.**
Study population	Health care professionals (Physicians, Nurses, Respiratory therapists, or nursing assistants) between older than 18 years and less than 70 years, who provide health care to confirmed or suspected cases of COVID-19 in the emergency room, COVID wards, or the intensive care units from seven hospitals in Colombia.
Study design	Randomized triple-blinded multicentric clinical trial to evaluate the effectiveness and safety of Tenofovir/Emtricitabine in addition to personal protective equipment for the prevention of infection with SARS-CoV-2 in health care personnel in Colombia.
General Objective	To evaluate the effectiveness and safety of Tenofovir/Emtricitabine in addition to the use of Personal Protective Equipment (PPE) for the prevention of SARS-CoV-2 infection in health care personnel who provide health care to confirmed or suspected cases of COVID-19 in the emergency room, COVID wards and ICU.

Specific Objectives	- To determine the effectiveness of Tenofovir Emtricitabine in addition to the use of Personal Protective Equipment (PPE) for the prevention of SARS-CoV-2 infection in health care personnel caring for patients with confirmed or suspected COVID-19 in the emergency room, general ward and ICU. - To evaluate the safety (adverse events frequency) of Tenofovir Emtricitabine in addition to the use of Personal Protective Equipment (PPE) for the prevention of SARS-CoV-2 infection in health care personnel caring for patients with confirmed or suspected COVID-19 in the emergency room, general ward and ICU. - To evaluate the adherence to Tenofovir Emtricitabine of health care personnel caring for patients with confirmed or suspected COVID-19in the emergency room, general ward, and ICU. - To determine the frequency of discontinuation for any reason of Tenofovir Emtricitabine in health care personnel caring for patients with confirmed or suspected COVID-19 in the emergency room, general ward, and ICU. - To describe and compare the clinical course and severity of participants who develop COVID-19 in the intervention and control groups.
Primary Outcome	Incidence of SARS–CoV-2 infection in health care personnel caring for patients with confirmed or suspected COVID-19
Sample size	950 healthcare workers randomized 1 to 1 to the intervention group (Tenofovir Emtricitabine + PPE), or the control group (Placebo + PPE). 475 in each group

1. Background and Problem Formulation

1.1. Approach and justification

The global impact of SARS-CoV-2/COVID-19 is unprecedented, and it is the greatest pandemic of a respiratory virus since the 1918 Influenza. With high infectiousness, important morbidity and relatively high fatality in specific groups of the population, an attack rate of approximately 80%(1), and no vaccine available yet, the pandemic will exceed the capacity of the health care systems in many settings. The health care personnel represent the most valuable resource to respond to the challenges imposed by this pandemic. As health care professionals are in the frontline of response and at a high risk of infection, it is extremely important to establish effective prevention strategies that protect them from becoming infected (2).

The main mode of transmission for SARS-CoV-2 infection is person to person through direct contact, droplets, or fomites. Moreover, aerosol-generating procedures have also been documented to transmit the infection (3,4). In countries such as Italy, where the pandemic had an accelerated behavior and high mortality rates, it has been estimated than from the total of infected people 7-9% corresponds to health care workers (5). Additionally, data from China and The USA show that between 3.8 and 19 % from the total of infected people are health care personnel, respectively (5-7). First, not only do They represent the initial barrier of response in any epidemic which increments by itself the exposition to the pathogen but by having asymptomatic infected individuals use of proper personal protective equipment may be missed.

Both hand hygiene and the use of Personal Protective Equipment (PPE) such as surgical gown, gloves, ocular protection, surgical mask, or N-95 respirator, are considered key strategies for the prevention of infection in health care professionals (8). However, there are few studies estimating the probability of infection with their use. Moreover, several pharmacological agents have been considered for a prophylactic use in SARS-CoV-2 infection.

As of today, there is preclinical evidence, principally in vitro, indicating antiviral effect of Tenofovir Disoproxil Fumarate / Emtiricitabine (TDF/FTC) on the SARS-CoV-2 RNA depended RNA polymerase (9). TDF/FTC is an approved drug for HIV treatment in combination with other antiretroviral drugs. It is widely used as HIV pre and post exposure prophylaxis, and it is the election therapy for Hepatitis B infection (10-13).

Knowing that TDF/FTC is a drug with a known security profile, has low frequency of short-term adverse events, and is capable of inhibiting SARS-CoV-2 replication in vitro, it is an interesting alternative to evaluate as prophylaxis for SARS-CoV-2 infection. On the other hand, in Spaniard HIV programs it has been noticed that in HIV positive patients under antiretroviral therapy, even those older than 50 years, a lower burden of covid-19 is observed compared to general population (14), despite of chronic inflammation and rapid immunosenescence, which is characteristic in this type of population (15). Furthermore, recently, in a clinical cohort of 77590 persons living with HIV, it was documented that those receiving TDF/FTC had a risk of COVID 19 and related hospitalization between 37 a 57% lower than those who were taking other antiretroviral medications.

Nevertheless, this observation must be evaluated rigorously, considering that it might be possible this population, knowing their risk, could have been more adherent to preventions measurements.

Consequently, we consider relevant and justified to evaluate the use of TDF/FTC for the prevention of SARS-CoV-2 infection in a high-risk population, such as health care professionals providing clinical care to confirmed or suspected cases of COVID-19 through a clinical trial. Thus, allowing to establish prevention strategies with higher scientific evidence.

1.2. Research question

What are the effectiveness and safety of Tenofovir/ Emtricitabine in addition to the use of Personal Protective Equipment (PPE) for the prevention of SARS-CoV-2 infection in health care personnel who provide clinical care to confirmed or suspected cases of COVID-19 in the emergency room, COVID wards and ICU?

1.3. Theoretical framework

In December 2019 at Wuhan, the capital city of Hubei Province in China, there was a report of a conglomerate of pneumonia cases that alarmed health authorities of this country (16). Later, it was identified that the etiology of this acute respiratory infection is a novel coronavirus (SARS-CoV2) which shares some molecular characteristics with MERS-CoV (Middle East Respiratory Syndrome) and SARS-CoV1 (acute severe respiratory syndrome) (17)

The disease caused by SARS-CoV2 known as COVID-19 has a wide range of manifestations that vary from asymptomatic individuals to patients developing acute respiratory distress syndrome (ARDS). Also, it has been reported extrapulmonary manifestations such as gastrointestinal, dermatological, and CNS involvement (16,18). Some risk factors for mortality have been described, for instance, D-dimer greater than 1ug/ml, high SOFA score, and Advanced age (19).

Outbreaks from familial clusters in which the virus has been able to be identified have been described (20). To date there is no estimative of prevalence in asymptomatic patients due to the difficulty in identification techniques. Nevertheless, it has been documented that viral load is higher at the onset of symptoms indirectly pointing that transmissibility initiates 2.5 days before the initiation of symptoms which implies that people who develop symptoms could be infective even before that happens (18).

The epidemic has extended rapidly through the globe due to its high basic reproductive number, estimated on average between 2.5 to 3.6, this obtained from mathematical modeling (2,21,22). The burden of disease is serious making health systems exceed maximum capacity (22). According to the Pan-American Health Organization (PAHO) as of July 5th, there were 5.697.954 cases alone in the Americas with 262.538 deaths (23). In Colombia, the first case was reported on March 6 with a tendency to rise. Since then, multiple public health measures were taken gradually expecting to reduce transmissibility in the upcoming weeks. According to the Colombian National Institute of Health (INS), there has been an exponential increase in reported cases with data as of June 9 of 40.719 confirmed cases and 1.308 confirmed deaths (24).

The pandemic has presented a huge economic impact globally. The economic effect of this crisis is estimated to be serious and profound. Only the closure of Wuhan, a large financial center in mainland China, meant the suspension of activities of multinationals and the collapse of multiple stock markets around the world since before the internationalization of the epidemic (25). Although the extent of the current crisis is not yet known, it could be extrapolated from previous coronavirus outbreaks such as MERS in 2015, for which losses of approximately $ 2.1 billion were estimated for tourism alone in the Republic of Korea (26). This outbreak was much smaller in terms of victims and geographic size. Meanwhile, the less conservative projections project declines in global GDP growth for the first quarter of zero and a substantial decline in growth in the world economy for the full year (25,277).

Natural history of SARS-CoV-2 / COVID 19

-Incubation period

Studies performed in confirmed cases of COVID-19 estimate an average incubation period of 5.5 days with a maximum expected of 12-14 days after the contact has occurred (28). Only between 1 to 5 % of reported cases will exceed that period of time thus making epidemiologic surveillance documents recommend a 14 day follow up after being in contact with an infected person (29-33).

-Previous period to onset of symptoms in which it is considered that persons can transmit the virus

The exact duration of the asymptomatic period in which the virus can be transmitted is unknown. It is estimated that this could be between 2 to 5 days prior to the onset of symptoms. Moreover, studies of follow up to close contacts state that an attack rate of 0.7 to 6.4% could be in this period (34,35). A mathematical model made in China establishes that infectivity is much higher in early stages of SARS-CoV-2 infection, initiating on average 2.3 days prior to the onset of symptoms with a peak at the day 0.7 after presence of symptoms and a considerable drop close to day 7 after initiation of symptoms (36).

-Calculated percentage of asymptomatic patients

There is still no clarity about the percentage of asymptomatic cases which increments the uncertainty and generates greater difficulties in order to establish infection control effective public health policies. Screening studies in confined population show frequencies of asymptomatic infected individuals between 18-46.5% (37). Nevertheless, surprisingly, up to 50% of these individuals could have radiological manifestations of COVID-19 (38,39).

-Average time of symptoms duration

The International Otorhinolaryngology Federation performed an observational study in which 1. 420 mild-moderate COVID-19 cases were assessed for describing clinical and epidemiological characteristics in Europe. The most frequent symptoms were Cephalalgia(70.3%), anosmia (70.2%) nasal congestion (67.8%), cough (63.2%), myalgias (62.5%), rhinorrhea (60.1%), dysgeusia (54.2%), odynophagia (52.9%) and fever (45.4%), respectively. Mean duration of symptoms was 11.5±5.7 days (40).

The China Medical Treatment Expert Group for COVID-19 retrospective cohort described 1.099 patients with SARS CoV 2 confirmed infection finding that up to 88.7% of hospitalized patients developed fever followed by 67.8% of patients that developed cough. Mean duration of hospital stay was 12.8 which would correspond with the symptomatic period (41).

Impact and prevention measures in health care workers

The contagion in health care workers has been a critical point in the COVID-19 pandemic. Some series report that up to 19% of contagions occur in the health care setting (42). The main basic prevention measure is the use of personal protective equipment (PPE). Both WHO and the CDC recommend the use of standard precautions of contact and droplets with complete facial protection or at least ocular protection (42,43). Aerosol Isolation measurements are required only in the case of aerosol-generating procedures, such as orotracheal intubation or extubation, bronchoscopy, non-invasive mechanical ventilation, nebulization, Cardiopulmonary resuscitation, or endoscopy (21). For its part, the CDC recommends that patients with suspected or confirmed COVID-19 be cohorted in individual rooms with a door and an exclusive bathroom (42).

Special attention is given to the placement and removal sequence of PPE in order to avoid contagion when manipulating them. The effectiveness of the adequate use of PPE has not been established by a clinical trial, however, it is known that it is a protective factor for COVID-19 (44). Nevertheless, shortage of PPE, PPE re use necessity and PPE use errors (especially when taking them out) might facilitate hand and mucous contamination, which may contribute to its ineffectiveness (45).

According to a report of the Colombian Social Protection Ministry, as of May 1st, 2020 6.5% of the total COVID-19 cases were from health care workers. A total of 459 cases from which 30.1% were nurse assistants, 23.7% were medical doctors, 15% were nurse practitioners and 2.4% were Respiratory therapists. Most of the cases were in Bogota (35.9%) followed by Risaralda (20%) and Cali (9.6%). Data on the burden and incidence of COVID-19 for health care workers is limited. Data from china reported an incidence of 38.9 per 100 exposed health care workers and 6 to 11.6 per 100 hundred health care workers in Madrid and The Netherlands respectively (7,44).

Tenofovir/Emtricitabine as prophylaxis for SARS-CoV-2 Infection

SARS-CoV-2 is a single strand positive-sense RNA virus similar to Hepatitis C Virus, West Nile Virus, Marburg, HIV, Ebola, Dengue virus, and Rhinovirus, among others. The RNA-dependent RNA polymerase (RdRp) is one of the structural proteins of SARS-CoV-2(46). The active site of RdRp is configured by two successive aspartate residues which protrude from a beta turn structure, making accessible to the surface through the nucleotide canal (47). The homology between SARS-CoV-2 RdRp and SARS-CoV-1 is higher than 97%, thus facilitating *in silico* studies (48).

Elfiky *et al.* made an RdRp SARS-CoV-2 model based on different available structures in protein banks. Using it and through simulation, they documented the theoretical effectiveness of several antiviral agents such as IDX-184, Sofosbuvir, Ribavirin y Remdisivir, and TDF/FTC for the inhibition of RdRp (47,49).

The antiretrovirals used in the treatment of HIV infection have been previously studied in vitro and in vivo for SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) (50,51). Particularly, in this pandemic some observational studies have identified a smaller number of patients with HIV acquiring COVID-19 in comparison to the general population which has brought attention to the scientific community (52).

In silico studies have identified antiretroviral drugs with potential capability of binding the catalytic center of RdRp such as Nucleoside Reverse Transcriptase Inhibitors: abacavir, emtricitabine, lamivudine, zidovudine and tenofovir, also protease inhibitors such as: lopinavir, ritonavir , saquinavir and the booster cobicistat (53-55). This information has been confirmed *in vitro* studies for TDF, which acts as analogue of a nucleotide that early finishes the replication of the RNA strand (55).

Cytotoxic and antiviral effects of some of the molecules have been evaluated in fibroblasts from human lung cells. For tenofovir and emtricitabine (TDF/FTC) the EC50 and the TC50 higher than 100 µM, however, it is inferior compared to remdesivir which might be explain for the type of assembling to the RdRp in each case (48).

Furthermore, Park, *et al.* developed an animal model of SARS-CoV-2 in ferrets in which the pathogenicity, transmissibility, and lung damage caused by the virus were demonstrated. In an experiment using this model, the virus was inoculated by the intranasal route, and a day after, numerous molecules with potential antiviral effect were administrated. These molecules were: Lopinavir/Ritonavir, Hydroxychloroquine, TDF/FTC. The duration of the intervention was 14 days and the ferret group given TDF/FTC presented lower temperature compared to the control group, and also an earlier recovery from signs including cough, rhinorrhea, and reduction of activity. Moreover, a lower load of virus was detected in the nasal samples from ferrets in the intervention group. From the drugs studied TDF/FTC showed the best results in reducing clinical signs and clearing nasal viral shedding (46).

Tenofovir/Emtricitabine is an antiviral that has been widely used for quite a long time in HIV pre exposure prophylaxis (PrEP) and treatment for hepatitis B with a known security profile and minimal incidence of adverse events (10-13). Its inhibitory effect on the RdRp of SARS CoV 2 shown in silico studies is added to some animal models which makes it a promising alternative in a high risk COVID-19 population scenario. To date there are two ongoing clinical trials, one in Spain and the other in Argentina aiming to prove the effectiveness of TDF/FTC in the prevention of SARS CoV 2 infection. (See appendix 1).

Diagnostic testing

Various diagnostic tools based on the natural history of the diseases and experience obtained from other viruses have been proposed to have rapid results on the diagnosis status of the patient. Nevertheless, the power of viral identification varies according to the dynamics of the disease (57).

Available testing alternatives are viral RNA detection by real-time polymerase chain reaction (RT-PCR), viral antigen detection in nasopharyngeal swabs, specific antibodies detection, and viral culture. Antigen viral detection has low sensitivity in previous experience with HCovs, however, there are studies ongoing with good yield according to with the reports of Diao et al. which

establish that the sensitivity is adequate in patients with 3-day fever, still at publishing stage (57). For its cost time and biosecurity required the viral culture has a research application but not a clinical one (57). Thus, basing the clinical diagnoses in the method RT-PCR and antibody detection.

During the COVID-19 outbreak, the RT-PCR has been one of the most used testing tools. Corman et al at Charité Hospital in Germany developed an RT-PCR identifying E and RdRP viral genes with a sensitivity greater than 95% and a specificity of 100% (58). It is important to clarify that detection varies from the site of the testing sample being positive in 32% of oropharyngeal swabs, 62% in nasopharyngeal swabs, and 80% from bronchoalveolar lavage. Only 15% of patients with pneumonia had positive serum RNA (59,60).

In symptomatic patient the viral load has its peak at the first week of symptoms (60% sensitivity before day 11), usually, around day 4 with a gradual decline starting on the second week, still being detectable in up to 33% of patients. The median of negativization is 24 days (IQR: 18-31 days) being lower in COVID-19 mild to moderate (13 days) and higher in critical patients (31 days) with detectable viral loads between 42 to 48 days after the onset of symptoms (36,61-64). Nevertheless, despite of the longtime of detectable viral load, there are studies suggesting that the viral culture negativize at day 8 from the onset of symptoms independently of initial viral load (65).

With regards to antibody detection, it is important to know that according to a Cochrane Systematic review, the yield of the different test available depends on the onset of symptoms and sample taking. IgG and IgM sensitivity at day 15 from the onset of symptoms is 75.4% and 88.2% respectively, whereas, at day 21 from the onset of symptoms is 99.1% and 98.7% (66). Although, a recent published study found a seroconversion rate of 10% in asymptomatic contacts evaluated after 14 days from the onset of symptoms, there is not certain data of sensitivity and specificity of this tests in asymptomatic people (67).

The detection of antibodies has been described even at the onset of symptoms; however, the general total antibody seroconversion starts at day 4 from the onset of symptoms. When evaluating IgM seroconversion, a 5-day median of positivization (IQR:3-6 days) with a sensitivity around 50% at day 7, higher than 70% after day 8 and highest after day 10 with a progressive decline over the next month (68) . For IgG the positivization increases after day 9 with a median of 14 days (IQR:10.18 days) with a sensitivity between 80 to 95% at day 15 and 98 to 100% between the third and fourth week after the onset of symptoms with an IgG duration yet unspecified (68-73). Serologic testing may present crossed reactions with SARS-CoV explained by a 90.5% coincidence in the genomic sequence (74).

Data available on diagnostic testing is based on symptomatic patient. It has been described on several occasions since the beginning of the pandemic asymptomatic people with positive RT-PCR in respiratory secretions (69,70). However, the RT-PCR sensitivity and the ideal moment to perform it remains unclear with report as low as 24.3% (75).

Taking into consideration everything that has been discussed previously, we establish a research proposal in which it is planned to evaluate the efficacy and safety of Tenofovir/Emtricitabine and adequate use of PPE as a preventive measurement for COVID-19 in health care personnel.

2. Objectives

2.1. General Objective

To evaluate the effectiveness and safety of Tenofovir/ Emtricitabine in addition to the use of Personal Protective Equipment (PPE) for the prevention of SARS-CoV-2 infection in health care personnel who provide clinical care to confirmed or suspected cases of COVID-19 in the emergency room, COVID wards and ICU.

2.2. Specific Objectives

- To determine the effectiveness of Tenofovir Emtricitabine in addition to the use of Personal Protective Equipment (PPE) for the prevention of SARS-CoV-2 infection in health care personnel caring for patients with confirmed or suspected COVID-19 in the emergency room, general ward and ICU.

- To evaluate the safety (adverse events frequency) of Tenofovir Emtricitabine in addition to the use of Personal Protective Equipment (PPE) for the prevention of SARS-CoV-2 infection in health care personnel caring for patients with confirmed or suspected COVID-19 in the emergency room, general ward and ICU.
- To evaluate the adherence to Tenofovir Emtricitabine of health care personnel caring for patients with confirmed or suspected COVID-19in the emergency room, general ward, and ICU.
- To determine the frequency of discontinuation for any reason of Tenofovir Emtricitabine in health care personnel caring for patients with confirmed or suspected COVID-19 in the emergency room, general ward, and ICU.
- To describe and compare the clinical course and severity of participants who develop COVID-19 in the intervention and control groups.

3. Methodology

3.1. Study design

Randomized triple-blinded multicentric clinical trial, conducted in parallel, with to arms:

The trial Will be performed with health care workers (Physicians, Nurses, Respiratory therapists, or nurse assistants) free of SARS-CoV-2 infection prior, recent or at the time of the inclusion and who directly care for confirmed or suspected cases of COVID-19 in the emergency room, general COVID wards or intensive care units. A screening at baseline will de carried out in order to evaluate for eligibility by performing: SARS-CoV-2 RT-PCR, SARS-CoV-2 IgG antibodies, as well as, hemogram, creatinine, serum phosphorus, AST, ALT, ELISA for HIV, surface Hepatitis B antigen antibodies, qualitative pregnancy test (b-HCG). Once

eligibility is verified participants will be randomly assigned to either an intervention or a control group.

The interventions consists in the administration of Tenofovir/ Emtricitabine (300 mg / 200 mg daily during 60 days) + Personal Protective Equipment (PPE) and the control consists in the administration of placebo (1 tablet daily during 60 days) + Personal Protective Equipment (PPE)

All participants will have PPE recommended for the preventions of COVID-19 by the WHO which include mayo dress, nonfluid long sleeve gown, ocular protection with googles, face shield or visor and surgical mask in procedures that do not aerosolize. N-95 respirators are required for procedure that generate aerosols. For detailed description see Table 2.

The re-use of N-95 respirators will be allowed according to CDC and WHO guidelines. This taking into consideration the shortage of supplies for the actual situation. The N-95 continuous use will be for 8 hours and the N-95 intermittent use will be allowed up to 5 times with the precaution of storage in a paper and plastic bag label them with the participant name and placed them in a plastic recipient at the end of shifts(48).

After baseline evaluation and confirming eligibility an initial visit and 4 follow up visits at day 20, 40, 60, 75 days will be carried out. See Table 1 and Graph 1.

In the case of presenting COVID-19 related symptoms at any time after enrolling a SARS-CoV2 RT-PCR will be performed between day 1 to 5 of the onset of symptoms and will be repeated it after 72 hours in case that the first one is negative. In the case of having any positive SARS-CoV2 RT-PCR or SARS-CoV2 IgG SARS-CoV2 infection will be confirmed and the intervention will be suspended.

On the other hand, the participant who develop symptoms and has one or two negative SARS-CoV2 RT-PCR the intervention will not be suspended with an exception if the participant requires hospitalization with a high clinical suspicion. For his group of participants, a SARS-CoV2 IgM and IgG antibodies will be performed at day 14 from the onset of symptoms. If they are positive, the participant Will be considered as a positive case of COVID-19.

3.2. Study population

-Reference population: Health care professionals (Physicians, Nurses, Respiratory therapists, or nurse assistants) between the ages of 18 and 70 years, who directly care for confirmed or suspected cases of COVID-19 in the emergency room, general COVID wards or intensive care units.

-Eligible population:

Inclusion criteria

- Medical doctor, Nurse, Respiratory therapist, or nurse assistant who work in the emergency room, general COVID-19 ward, or intensive care unit
- Age: between 18-70 years
- RT-PCR and serology tests for SARS-CoV-2 negative at baseline evaluation

- Direct care of patients in the emergency room, general COVID-19 ward, or intensive care unit
- Informed consent signed

Exclusion criteria

- Two or more of the following
  - ✓ Body temperature higher than 38 Celsius
  - ✓ Cough of recent onset (in the previous 10 days)
  - ✓ Dyspnea
  - ✓ Odynophagia
  - ✓ Malaise, fatigue
  - ✓ Acute diarrheal disease
- History of COVID-19 confirmed by RT-PCR or IgG antibodies
- Family member with suspected or confirmed COVID 19
- cohabitating with a suspected or confirmed case of COVID-19
- Hepatitis B anti-surface antigen antibodies lower than 10mU/ml at baseline evaluation
- Acute or chronic Hepatitis B
- Confirmed diagnosis of HIV infection either by clinical history or ELISA immunoassay at baseline evaluation
- Use of TDF/FTC in the last three months for other clinical conditions
- ALT or AST higher than 2 times the upper reference limit
- Serum hemoglobin <11g/dl or neutropenia<1.000cell/mm3
- Renal dysfunction defined as eGFR lower than 60ml/min (using the CKDEPI formula) or history of Chronic kidney disease
- Known hypersensitivity to TDF/FTC
- Serum phosphorus level <2.5mg/dl
- Use of the following medications (for detailed description see appendix 2):
- Uso de los siguientes medicamentos (See appendix 2 for detailed description): Cidofovir, Celecoxib, Diclofenac, Ibuprofen, Methadone, Naproxen, Nimesulide, Piroxicam, Amiodarone, Quinine, Amikacin, Cephalexin, Clarithromycin, Gentamicin, Piperacillin / Tazobazorcin, Flucomycin, Sulfadiazine, Vancomycin , Ganciclovir, Ledipasvir / Sofosbuvir, Sofosbuvir / Velpatasvir, Furosemide, Hydralazine, Sacubitril, Verapamil, Interferon, Hydroxyurea, Dolutegravir / Lamivudine Abacavir, Didanosine, Lamivudine, Atazanavir / cobicistat, Atazanavir / ritonavir, Darunavir / ritonavir, Darunavir / cobicistat, Indinavir, Interferon, Hydroxyurea, Cyclosporine, Mycophenolate, Sirolimus, Tacrolimus, Acetazolamide Orlistat, Probenecid, Pyridostigmine, Sevelamer, Zoledronic acid.
- Diagnosed osteopenia or osteoporosis
- History of pathological fractures
- Pregnancy, lactation, or pregnancy desire during the period of the study
- Being a participant in another Clinical trial of prevention for COVID-19

-Source population: Health care professionals (Physicians, Nurses, Respiratory therapists, or nurse assistants) between the ages of 18 and 70 years, who directly care for confirmed or suspected cases of COVID-19 in the emergency room, general COVID wards or intensive care units from seven health care institutions in Colombia (Hospital Universitario San Ignacio, Clínica Reina Sofía, Clínica Universitaria Colombia, Clínica Santa María de Lago, Hospital Universitario Nacional, Hospital Universitario de la Samaritana. Sede Bogotá y Hospital Universitario de la Samaritana. Sede Zipaquira, Hospital Universitario San Jorge de Pereira).

3.3. Result and primary Outcome

Primary Outcome

✓ SARS–CoV-2 infection defined as:

- Detection of SARS–CoV-2 nucleic acid using RT-PCR in any of the specimens collected during the study-follow-up including the asymptomatic participant

-Positive IgG antibodies against SARS–CoV-2 in any of the specimens collected during the study-follow-up

Secondary outcomes

- Serious and non-serious adverse events

- Discontinuation of using the intervention (TDF/FTC or placebo) for any reason

- Adherence to TDF/FTC defined as: number of tablets taken/total number of dispensed tablets

- Severity of SARS-CoV-2 infections according to the following categories:

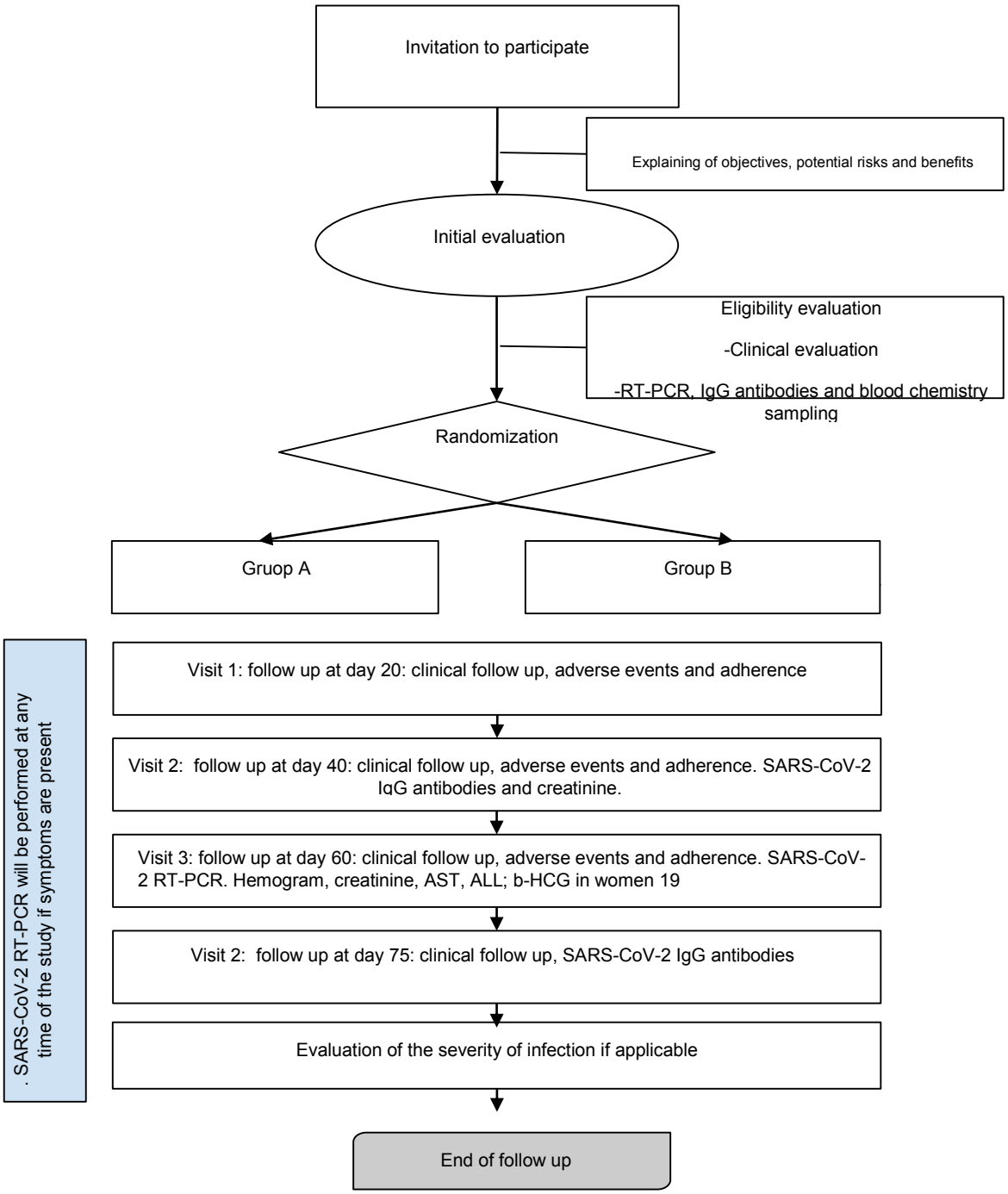
  - Asymptomatic infection.

  - Mild symptomatic SARS-CoV-2 infection with no need for hospitalization.

  - Moderate symptomatic SARS-CoV-2 infection that requires hospitalization, but no ICU.

  - Severe SARS-CoV-2 infection: dyspnea with other SARS-CoV-2 symptoms requiring ICU hospitalization.

Graph 1. Flowchart of assignations and follow up of the clinical trial.



3.4. Sample size

An estimative of the number of required participants was done according to the following parameters:

- Risk of SARS-CoV-2 infection reported in the world: despite of the little data available on incidence reports from China, The Netherlands and Madrid vary from 6 to 38.9 per 100 exposed health care workers. The high variability on the incidence is related to the develop of institutional outbreaks, thus establishing a latent risk in all hospital institutions in a pandemic scenario (7,44,76). To assess the sampling size calculation for this study, besides what has been reported internationally, an approximate calculation of the incidence of SARS-CoV-2 infection in the health care institutions in which the study will be held was performed. It is important to know the infection and epidemic control variates from one institution to another. While some actively screen asymptomatic health care personnel others only screen symptomatic health care personnel. The incidence observed in a 2-month period of time variates between 3.3% and 13.7% with a mean of 11.2 cases per 100 health care workers.

  Based on that preliminary information, an expected risk for SARS-CoV-2 infection in the control group (Placebo + PPE) of 0.10 was used for the calculation. With the objective of estimating precisely a 50% relative risk reduction an assumption of an expected risk of 0.05 was done in the intervention group (Tenofovir/Emtricitabine + PPE) in order for a difference of 0.05 to detec between both groups.

- Power: 0,80. Alfa level: 0.05
- Assignation ratio n1/n2= 1: 1 (randomization1: 1).
- Sample size: 858 (429 per group).

Considering possible loses up to 10% it is risen to 950 in total (with randomization 475 participants to each group).

As a limitation of the study, if the incidence or the effect of the interventions are considerably lower than expected, the power to detect significant differences between both groups will be reduce. However, due to the progression of the pandemic in our country, with a tendency to increase, it is probable that the incidence observed in health care professionals will remain stable or even increase not only for the intrahospital risk, but for the risk in the community,

3.5. Duration of the study and time of termination

- Duration of the interventions: 60 days
- Total duration of the Project: 8 months
  - ✓ 2 months planning, 5 months collecting data, 2.5 months recruiting and a month for data analysis and publication.

3.6. Procedures

In table 1. Detailed follow up evaluations are described.

Table 1. Description of the evaluations to be done during the trial.

Follow up table				
Day	**General activity**	**Specific activity**	**Responsible**	**Result**
0	Base line diagnoses	Initial Clinical evaluation	Medical doctor of the study	Evaluating inclusion and exclusion criteria. Signing informed consent form
		Blood samples	Nurse Lab tech	Laboratory report: hemogram, creatinine, phosphorus, AST, ALT HIV ELISA, HB Surface antigen antibodies
		SARS-CoV-2 RT-PCR sampling	Respiratory therapist or nurse	Result of SARS-CoV-2 RT-PCR
		SARS-CoV-2 IgM and IgG antibodies	Nurse Lab tech	Result of IgM and IgG antibodies
		b-HCG sampling in women	Nurse Lab tech	Report of b-HCG
20	Visit 1	Clinical evaluation	Medical doctor of the study	Clinical record and eCRF for clinical evaluation, adherence, and adverse events

40	Visit 2	Blood sample for: SARS-CoV2 IgM, IgG antibodies and blood chemistry	Nurse Lab tech	Laboratory report of SARS-CoV2 IgM, IgG antibodies and creatinine
		Clinical evaluation	Medical doctor of the study	Clinical record and eCRF for clinical evaluation, adherence, and adverse events
60	Visit 3	Blood samples	Nurse Lab tech	hemogram, creatinine, phosphorus, AST, ALT HIV ELISA, HB Surface antigen antibodies b-HCG in women
		SARS-CoV-2 RT-PCR sampling	Respiratory therapist	Result of SARS-CoV-2 RT-PCR
		Clinical evaluation	Medical doctor of the study	Clinical record and eCRF for clinical evaluation, adherence, and adverse events
75	Visit 4	Blood samples	Nurse Lab tech	Laboratory report of SARS-CoV2 IgG
		Clinical evaluation	Medical doctor of the study	Clinical record and eCRF for clinical evaluation,
		End of follow up and communication to study subject	Clinical coordinator	Minutes

During follow up to any participant who develop COVID-19 related symptoms at any time after randomization given by two or more of the following: Body temperature higher than 38 Celsius, cough of recent onset (in the previous 10 days), dyspnea, odynophagia, malaise, fatigue, acute diarrheal disease, ageusia, dysgeusia, anosmia or hyposmia, an RT-PCR will be performed within the next 5 days and will be repeat it if the result is negative and the symptoms persist. This RT-PCR will be performed at every of the centers of the study and will request the patient the immediate report of the symptoms through an app or via phone call. In case of a positive RT-PCR the infection

will be confirmed. While confirmation RT-PCR arrives, the participant will not quit taking the intervention. In that scenario, the intervention will only be suspended in the case of a highly suspected case or severe case requiring hospitalization.

In case the infection is ruled out in the follow up, the participant will continue the interventions and follow up scheduled, according to graph 1.

With regards to diagnostic testing during follow up as shown in table 1. IgG antibodies will be done at visit 2 and 4 (40 days from initially taking the intervention and 15 day after finalizing it). This considering volunteer that might acquire the infection in the last days of the pharmacological intervention. Moreover, at day 60, last of the intervention, an RT-PCR will be performed to all participants. This in order to detect participants who develop asymptomatic infection. The research group is aware that this follow up will not identify a 100% of the asymptomatic infection for the low sensitivity of testing in this scenario, approximately 30 to 40% (46,47), yet it will be done in both arms.
Importantly, for the covid-19 emergency, clinical follow up, adverse event reporting and adherence reporting could be done online.

Personal Protective Equipment

All volunteers will be using the following personal protective equipment. This based on the guidelines of the WHO (23). See table 2.

Table 2. Use of PPE by study volunteers.

Area	Health care personnel or patients	Activity	Type of PPE or activity
Emergency room, general COVID wards or intensive care units	Health care workers	Direct contact with the patient of non-aerosol generating procedures.	Surgical mask Visor or glasses. Long sleeve gown Nonsterile gloves.
		Direct contact with the patient and aerosol generating procedures.	N95 respirator Visor or glasses. Long sleeve gown Nonsterile gloves. May dress

			under the robe that is removed at the end of the shift
Other areas of transit (hallways or waiting rooms)	All personnel including health care workers	Any activity that does not involve contact shorter than 2 meters in distance between people	Surgical mask

Adapted from: Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19). Interim guidance 27 February 2020. World Health Organization. (23)

*Health care worker: person in whose activity directly care a contact, suspected, or confirmed case of COVID-19.

3.6.1. Informed consent and enrolling

Volunteers Will be recruited at High complexity Health institutions that are part of the study. Through direct invitation either personal or by email. An information sheet for the participant Will be done (appendix 5. According to good clinical practice and considering eligibility criteria one of the investigators will perform the informed consent process explaining study objectives, potential benefit, and risks. After verifying understanding by the potential participant, the informed consent format will be signed according to current regulation.

3.6.2. Baseline evaluation

The doctor assigned to the study takes a medical history that includes a review of systems, past medical history, and a complete physical examination. In addition, he or she will order laboratory exams described in Table 1. In case of clinical or laboratory alteration defined in the exclusion criteria, the volunteer will be excluded and will not continue in the following phases. Additionally, a RT-PCR will be carried out with a nasopharyngeal swab sample and a serological test of IgG antibody titers against SARS-CoV-2. In case of having any of the previously mentioned tests positive, the volunteer will be excluded. Female volunteers will undergo qualitative β-HCG and, if positive, they will be excluded or if they report the desire to become pregnant in the next two months. At 24 to 48 hours with the results of the examinations and a new anamnesis the eligibility of the volunteer will be confirmed. If so, the randomization process will be carried out and the intervention will be delivered according to the process defined in the concealment section of allocation (3.6.4) and administration of the intervention product or placebo (3.6.5).

3.6.3. Randomization

A simple randomization will be carried out, considering that it is not deemed necessary to stratify by any characteristics of the individuals, or by center. Additionally, due to the size of the sample there is little possibility of presenting a significant imbalance between the groups regarding characteristics that affect the outcome.

The randomization will be carried out with a 1:1 relationship between the active intervention and the placebo, a randomization system generated by the REDCap software will be used, with random numbers that will meet the following requirements: each volunteer will have a known probability, and equal to be assigned to any of the interventions, future assignments will not be predictable based on previous assignments, the order of assignment will be reproducible.

The randomization will be carried out centrally, by a trained member of the HUSI research office, who is not part of the research group, or the study staff, after generating the randomization, this will be communicated exclusively to the chemist central pharmacist of the research team.

3.6.4. Allocation concealment

Mechanisms will be applied to ensure concealment of randomization. The decision to include a volunteer in the study will be made without knowing the intervention that said individual will receive if they participate, that is, neither the investigators nor the study personnel will know the assignment before the start of the intervention. The following strategies will be used in the study to ensure this:

- The randomization will be carried out centrally, the center that sends the volunteer to randomize at the central level, ensures that he meets all the eligibility criteria and registers the volunteer in the REDCap system, in such a way that it is impossible to subsequently change the allocation generated.

- Prior to the start of recruitment, the central pharmaceutical chemist will mark 1000 bottles with labels with randomly assigned numerical codes, to the 500 bottles corresponding to TDF/FTC 300/200mg and the other 500 bottles containing placebo. The only one who will know the information on the specific contents of the vials is the central pharmaceutical chemist of the study.

- The person who will carry out the randomization process is not part of the research group or the research team, he will receive a notification by telephone and by REDCap, that there is a volunteer who is eligible to participate in the study. Through REDCap the random assignment will be generated, and the system will give you the code of the bottle that the volunteer should receive. This person will only inform the central pharmaceutical chemist, the code of the bottle that the subject must receive.

- The central pharmaceutical chemist will communicate with the local pharmaceutical chemist, by means of a telephone call, and will inform him of the code of the bottle that must be given to each volunteer. The local pharmaceutical chemist will be blind to the intervention.

- In REDCap a record will be kept of the selection of the study patient, as well as the fulfillment of the delivery of the bottle assigned by the program.

3.6.5. Administration of the intervention product and placebo

Volunteers assigned to the intervention group will receive one tablet of TDF/FTC 300/200mg each day. Each volunteer will be given 60 tablets of the medicine at the beginning of the treatment and its administration will be verified daily by sending a virtual survey, in which the subject answers if he took the intervention, plus a follow-up diary that will be given to the patient of Virtual or manual way for people without access, to write adverse events, as well as the hours of daily exposure to patients with suspected or diagnosed COVID 19 and adherence to personal protection elements. These data will be stored in an eCRF for clinical follow-up, adverse events, and adherence.

Patients assigned to the control group will receive a placebo that will have the same appearance and size and will not have any active ingredients. Similarly, 60 placebos will be delivered from the start of treatment.

The medicine must be stored at a temperature not exceeding 30 ° C and in an environment without excessive humidity in its authorized container and packaging.

3.6.6. Blind or masked evaluation

To control for biases related to the measurement or evaluation of the study subjects, during the study, it will be ensured that the investigators and the volunteers are blind to the assigned intervention.

To ensure that the volunteer is blind to the intervention, they will not be informed which intervention they are receiving (tenofovir / emtricitabine or placebo) and additionally a placebo with a taste and presentation similar to tenofovir / emtricitabine will be used, on the other hand, the vials In which both the active drug and the placebo will be packed, they will be the same and will only be differentiated by the numbers on the labels.

The researcher will be blind throughout the volunteer's follow-up, and this will be ensured because a central randomization will be carried out, only the central pharmaceutical chemist will know the assignment and the researcher will only know the code of the drug that the patient receives, which is not decodable.

Finally, the person in charge of data analysis will receive a database that will be downloaded from REDCap, in which there will be a code that will identify which of two different interventions a volunteer has received, but which will not allow identifying whether they correspond to tenofovir/emtricitabine or placebo. This coding will only be revealed when the analysis is complete. There is only one person independent of the analysts and the researchers, who knows the code.

3.6.7. Study variables

The study variables are in Annex 3 with their respective conceptual and operational definitions.

3.6.8. Sample processing and interpretation of laboratory tests.

● RT-PCR: it will be processed in the HUSI clinical laboratory for the volunteers of the HUSI, the National University Hospital and the Samaritana Hospitals; The centers of the Colsanitas Group will perform the PCR in the Colsanitas group laboratory and the PCR of the San Jorge Hospital at the

Technological University of Pereira according to the protocols used in each of these institutions, with internal and external quality controls, as well as technical endorsed by the National Institute of Health. The results will be sent within 24 hours after taking the sample to the doctors assigned to the study, who will inform the patient and carry out the pertinent follow-up. (See Annex 6. Diagnostic tests)

● Serological tests for IgG antibodies will be processed in the HUSI clinical laboratory and the Colsanitas Group centers. The qualitative detection of IgG antibodies against SARS-CoV-2 will be carried out in human serum or whole blood obtained from the volunteers, using the immunochromatography test: Standard Q, SD Biosensor®. The antibodies present in the sample form a complex with the antigen labeled with colloidal gold (SARS-CoV-2 recombinant antigen), the complex progresses under the action of chromatography and combines with the coated antibody (mouse monoclonal antibody IgM / IgG anti-human) in the IgG line to form a complex and develop color, which is a positive result. When the sample does not contain the SARS-CoV-2 IgG antibody, the complex cannot form and a red band does not appear on the IgG line, which is a negative result. Regardless of whether either SARS-CoV-2 IgG or IgM antibodies are present in the sample, the gold-labeled quality control antibody will bind to the coated antibody on line C to form a complex and develop color (line C) to validate the test. For the study, only IgG antibody results will be considered, contemplating the high rate of false positives of IgM tests, especially in asymptomatic patients (66).

● Blood samples will be taken by nurses or bacteriologists assigned to the study, who will store, label, and manage them following the SOPs (standard operating procedures) established in each participating center. Complete blood count, liver, kidney function, phosphorus, HIV- ELISA, HBsAg Ab tests will be processed following the SOPs of the clinical laboratories hired for this purpose. The results will be sent via institutional email to the physicians assigned to the study and in charge of monitoring each volunteer. Their interpretation will be carried out in accordance with the values established as normal by said laboratory, in conjunction with the criteria described in this protocol to graduate the severity of AE (See table 4). The results of the paraclinical tests will be interpreted by a doctor assigned to the study who decide on the volunteer's continuity in the study.

3.6.9. Procedure in case of presenting the primary outcome

If the volunteer, after the start of the study, has a positive result of RT-PCR or IgG for SARS CoV2, which confirms the infection by COVID 19, they will be contacted virtually or in person. During this intervention, the following actions will be carried out:

- You will be given information about your result, and you will be instructed to contact your occupational risk and health insurer.

- The presence of alarm signs (drowsiness, dyspnea, cyanosis) will be evaluated. In case of any of these symptoms are present, the patient will be instructed to attend the emergency service, to receive treatment in accordance with current national and institutional guidelines.

- The volunteer will be instructed to suspend the intervention product, and the masking will be released.

- National Public Health Surveillance System mandatory notification form will be filled out, the institution where the volunteer works will be informed, and the completed form will be sent.

- The volunteer will be informed that telephone follow-up will be carried out every 5 days until the symptoms are resolved or a maximum of six weeks after the diagnosis of COVID 19. In case of presenting any alarm sign during the follow-up, the patient will be recommended to attend the emergency department.

During the telephone follow-up, the volunteer's primary outcome (COVID 19 infection) will be classified as follows: asymptomatic, mild, moderate, or severe COVID. If the patient does not answer due to physical impossibility (e.g. intubation), communication with a companion or family member previously authorized by the patient will be sought.

3.6.9 Study withdrawal criteria

The following criteria should determine the immediate withdrawal of the volunteer from the study:

● Grade 2 or greater kidney abnormalities at any time of follow-up.

● Clinical indication to start a drug with significant interactions with TDF/FTC during the development of the study.

● Presentation of any serious adverse event related to the intervention, defined by the physicians assigned to the study.

● Any Adverse Event (AE) that determines that the volunteer wishes to interrupt the intervention.

● That the volunteer voluntarily and for any reason decide to withdraw from the study.

If any of the previously mentioned criteria are met, the doctor assigned to the study in charge of the follow-up will immediately inform the coordinator of their respective center. The report of all AE will be made by the principal investigator of each center, in accordance with the INVIMA regulations and taking into account the Standardized Operating Procedures (SOP) established by the study.

In the event that the patient withdraws their consent, no additional monitoring will be possible. This situation will be reported immediately to the clinical monitor and monthly to the Institutional Research and Ethics Committee (CIEI).

3.6.10. Follow-up of volunteers with a positive pregnancy test at the end of follow-up

Despite the fact that TDF/FTC is a classification B drug in pregnancy, and its use is recommended as one of the antiretrovirals of choice in pregnant women with HIV (76), within this study it was defined to exclude pregnant women, or with the desire to become pregnant, to avoid exposure to this drug given its high placental transfer to the fetus.

There is no evidence in humans of teratogenicity with TDF/FTC, however there is evidence in monkeys, at doses twice as high as the therapeutic doses in humans, of decreased fetal growth and reduced fetal bone porosity within two months of initiation of maternal therapy; Regarding human studies, there is no demonstrated relationship with low birth weight, but there are conflicting results on the outcome of growth in childhood (77).

In a randomized, double-blind, placebo-controlled trial of PrEP in African women, Mugo NR, and colleagues (78) evaluated the effect of TDF/FTC on pregnancy for HIV-uninfected women. Differences in the incidence of pregnancy, delivery outcomes, and infant growth were not statistically different for women who received PrEP with TDF alone, or combination of FTC + TDF compared to placebo at conception. Considering that PrEP was discontinued when pregnancy was detected and that the confidence intervals for delivery outcomes were wide, the authors did not commit to making definitive statements about the safety of PrEP in the period of periconception (78) .

For the above reasons, if any volunteer presents a pregnancy at the end of the intervention period, a specific Informed Consent Form will be filled out to carry out a follow-up during the pregnancy.

4. Statistical analysis plan

Initially, a descriptive analysis of the information will be made, and measures of central tendency and dispersion will be reported according to the type of variables. In this phase, the similarity between the groups of the experiment will be evaluated and it will be calculated if there are differences in the groups due to chance.

Primary outcome

Taking into account that this study is a pragmatic clinical experiment, which will evaluate effectiveness, an intention-to-treat analysis will be carried out, to solve the main objective, the proportion of incidence of SARS-CoV-2 infection in each group will be determined at the day 75 post-randomization, estimated as the cumulative incidence of infection using the Kaplan Meier method.

Exposure of interest: Prophylaxis with TDF/FTC plus EPP vs placebo plus EPP.

Primary outcome: SARS CoV2 infection

Zero follow-up time (registration time in the registry): the time that the volunteer is randomized to the study interventions.

Follow-up time**:** All individuals have a follow-up until they present the primary outcome, or meet any of the withdrawal criteria, or up to 75 days after the zero follow-up time, if they do not present the outcome.

Event**:** SARS-CoV-2 infection.

Censorship: censorship occurs when the outcome is not presented, the two types of censorship will be: administrative censorship 75 days after randomization, or censorship for compliance with any of the criteria for withdrawal from the study, or loss of follow-up.

The hazard ratio will be estimated by comparing the risk of infection in the intervention group (TDF/FTC + EPP), with the risk in the control group (placebo + EPP), with a confidence interval of 95 %, using a univariate Cox regression model.

If necessary, adjustment will be made for variables that may affect the occurrence of the primary outcome and that are not balanced between the intervention group and the placebo group; The need for adjustment with an OR greater than 1.5 will be considered for dichotomous categorical

variables, such as sex; or if there are differences between the groups greater than 0.25 of the standard deviation for continuous variables such as age, adherence to pharmacological intervention or EPP, and hours of exposure to the COVID area. For the calculation of the adjusted hazard ratio, a multivariate Cox proportional hazards model will be used, if the proportionality assumption is met, or an extended Cox model if this assumption is not met.

For secondary outcomes

-The proportion of incidence of total adverse effects in each group will be determined at day 60 after randomization, estimated as the cumulative incidence using the Kaplan Meier method.

The hazard ratio ("Hazard Ratio") will be estimated by comparing the risk of adverse events in the intervention group (TDF/FTC + EPP), with the risk in the control group (placebo + EPP), with a confidence interval of 95%, using a univariate Cox regression model.

Additionally, the same analysis will be performed for serious adverse events.

- The proportion of incidence of discontinuation of the intervention in each group, for any reason, will be determined at day 60 after randomization, estimated as the cumulative incidence using the Kaplan Meier method.

The hazard ratio will be estimated by comparing the discontinuation of the intervention in the intervention group (TDF/FTC + EPP), with the risk in the control group (placebo + EPP), with a confidence interval of 95 %, using a univariate Cox regression model.

- It will be determined as the difference in the mean or median (according to the distribution of the data) of the percentage in which the individuals were adherent

-For the severity of the clinical course of the patients who develop the infection in both groups, a descriptive analysis will be carried out, the quantitative variables will be summarized by measures of central tendency and dispersion, according to the most appropriate measures for their distribution. The qualitative variables will be summarized by using absolute and relative frequencies (proportions) represented by percentages.

4.1 Data and Security Surveillance Committee:

A data and safety surveillance committee (DSSC) is defined as a group of experts, independent of the sponsor and investigators, who monitor the safety and validity of clinical trials. The committee carries out surveillance activities during established time intervals, in which, in addition to the safety data, the adequate recruitment of volunteers, compliance with the protocol, and the quality of the data obtained are evaluated (79).

A review of the literature by Sydes and colleagues (80) found that a DSSC is recommended when trials have any of the following characteristics: trials on high-profile topics that are a focus of community concern, to be used to search regulatory approval, or likely to profoundly affect clinical practice; trials with serious safety problems, unknown risks or that are implemented in vulnerable populations; and trials where independent monitoring is needed due to double-blind treatment allocation or long-term follow-up or because the sponsoring company does not have standard operating procedures. These authors also consider that DSSC may not be needed for trials of short

duration (where it is not feasible to convene a DSSC in a timely manner to review the data), for trials with known risks that are minimal, for trials where the objective is to demonstrate biological principles (as in early phase clinical trials) or for trials on behavioral or administrative problems.

In the case of this study, in favor of having a data and security monitoring committee, it is found that the issue addressed in the research is of high concern to society, given the importance of health workers for the management of people with COVID-19 infection, but also the implications that demonstrating the effectiveness of this intervention in this population may have, to later be able to demonstrate it in other populations such as the elderly or the general population. However, the difficulty of conducting a data monitoring committee in this experiment lies in its short duration, with a collection of information in only four months, which makes it impossible, a timely review of it, which allows making decisions before Upon completion of recruitment, on the other hand, TDF/FTC is not a new drug and there is extensive knowledge about its safety and tolerance, and based on this information, a large part of the inclusion and exclusion criteria of the present study have been included , therefore, frequent and serious safety problems are not expected (10-13)

For this reason, it has been decided that this clinical experiment does not have a data monitoring committee, for the reasons previously stated. To avoid deviations in the protocol, there will be an investigator's manual, in which the management of serious and non-serious adverse events is explicit, as well as their causality analysis, and a set of standard operating procedures (SOPs). that will be delivered, disseminated and knowledge will be guaranteed by each of the participating centers during the enlistment process, strict monitoring by each of the monitors of the centers will also be guaranteed during recruitment, with internal audits and with minus one external audit before the third month of recruitment for each center, which will evaluate the conduct of the study, adequate recruitment of volunteers, compliance with the protocol, investigator's manual, SOPs, good clinical practice, and data quality.

5. Risks and benefits for volunteers

5.1 Risks for volunteers

The risks for volunteers will be divided into those related to the pharmacological intervention.

5.1.1 Risks potentially associated with pharmacological intervention

TDF/FTC is considered a safe drug in the short term, and in periods of up to 2 to 3 years of use (81). In the studies of PrEP in HIV in which this drug is used as monotherapy, the systematic review by Fonner et al. (82) found no differences in the proportion of adverse events comparing TDF/FTC with placebo, in 10 randomized clinical trials (RCTs) controlled (OR 1.01, 95% CI 0.99 to 1.03, p = 0.27); It also found no differences in the subgroup analysis, according to adherence, gender, dose or age; nor in grade 3 or 4 adverse events when comparing the PrEP and placebo groups in 11 placebo-controlled RCTs (risk ratio = 1.02, 95% CI 0.92-1.13, p = 0.76).

The most common adverse effects reported with the drug are nausea, gastrointestinal (abdominal pain, bloating), and headache (77, 81). The use of TDF-FTC as PrEP has been associated with a mild non-progressive decrease in creatinine clearance (83), which is reversible on discontinuation of the drug (84).

An association has also been described between a decrease in bone mineral density (BMD) and the use of FTC-TDF for 24 weeks (84-87), but no evidence of an increased risk of fractures has been found, on the other hand, change in BMD did not progress after 24 weeks of use and recovered to levels seen in the placebo arm after stopping TDF/FTC (88-89).

Finally, there is a risk of severe acute exacerbations of hepatitis B in patients with hepatitis B virus (HBV) infection who discontinue TDF/FTC. Liver function should be closely monitored with clinical and laboratory follow-up for several months in HBV-infected patients who interrupt TDF/FTC, however, this phenomenon is rare, and the only evidence available is case reports. (90-92). In the present study, this risk will be avoided, because people with acute or chronic hepatitis B infection will be excluded and all volunteers will have immunity to hepatitis B, with anti-HBs greater than 10 IU/ml.

The following information presents, in more detail, the safety of TDF/FTC based on clinical, laboratory abnormalities, as well as alterations in bone mineralization and kidney function.

- Experience based on clinical experiments

Due to the control conditions of clinical trials, it is possible that the rates of adverse reactions that have been described do not necessarily reflect those observed in clinical practice and may be overestimated.

Gallant JE et al. In a randomized clinical trial comparing efavirenz (EFV) plus TDF/FTC (N = 257) vs EFV plus zidovudine (AZT) / lamivudine (3TC) (N = 254) for the management of HIV infection in 511 Subjects over 18 years of age, for 144 weeks, reported the following adverse reactions: dizziness (8%), diarrhea (7%), nausea (8%), fatigue (7%), headache (5%), depression (4%), insomnia (4%), skin rash (5%) (93).

Reported laboratory abnormalities included: amylase greater than or equal to 132 (17%), triglycerides greater than 400 mg / dL (13%), neutrophils less than 1000 (7%), hematuria (9%), AST greater than 109 in men or 86 in women (8%), ALT greater than 91IU / L in men or 86 IU / mL in women (7%) (93). However, in this study TDF/FTC was accompanied by EFV, which explains several of the adverse effects, especially psychiatric ones, and skin rash.

More recently, the safety and risk profile of TDF/FTC adverse reactions has been studied in clinical studies of HIV pre-exposure prophylaxis (PrEP) in monotherapy. Grohskopf A. et al. Conducted a clinical experiment to evaluate the safety of a daily dose of TDF in HIV-uninfected subjects for 24 months. The study drug was initiated by 373 (93%) volunteers (186 TDF and 187 placebo), of whom 325 (87%) completed the final study visit. Of 2428 adverse effects (AE) reported among 334 (90%) volunteers, 2366 (97%) were of mild or moderate severity. The frequencies of commonly reported AE did not differ significantly between the TDF and placebo arms. In multivariate analyzes, back pain was more likely among TDF recipients (P = 0.04), these reports were not associated with documented fractures or other objective findings. There was no grade ≥3 creatinine elevations, and grade 1 and 2 creatinine elevation were not associated with TDF reception. The estimated percentage of adherence was 92% per pill count. (94).

The Partners PrEP study recruited 4,758 couples, of which 4,747 were followed, 1,584 randomly assigned to TDF, 1,579 to TDF-FTC, and 1,584 to placebo. The rate of serious adverse events at 36

months of follow-up was similar in all study groups. There were no statistically significant differences in the frequency of deaths, serious adverse events, or serum creatinine and phosphorus abnormalities in the study arms. Neutropenia was seen more frequently in the TDF/FTC arm (15% with a grade 1 or 2 event, 4% with a grade 3 or 4 event), but not in the TDF arm (12% with a grade 1/2 , 2% grade 3/4), compared to placebo (12% grade 1/2, 2% grade 3/4). The study medication was well tolerated, with a moderate increase in reports of gastrointestinal side effects and fatigue in the two active arms compared to the placebo arm, mainly during the first month of administration (77,95)

Retention was 96% or greater during the study period. Study medication interruptions for safety-related reasons accounted for less than 1% of the total follow-up time: 0.6% in the TDF group, 0.7% in the TDF-FTC group, and 0.6% in the placebo group. (77.95)

The iPrEX study enrolled 1603 volunteers, of whom 1,225 chose to take PrEP. Reported symptoms peaked in the first month, with 39% potentially related to PrEP compared to 22% at baseline. Symptoms largely resolved within 3 months. Symptoms related to the digestive tract in the first 4 weeks were inversely associated with adherence at 4 weeks (OR = 0.47, 95% CI 0.23 to 0.96). Reports of gastrointestinal symptoms were associated with 7% (95% CI, 4% -11%) of suboptimal adherence in this cohort (96).

In this study, PrEP delivery was discontinued during the study in 56 (5%) volunteers due to "adverse effects." The study volunteer or medical staff could initiate interruptions. The interruption was temporary for 22 volunteers, the combined duration of these temporary interruptions totaled 10 person-years, a reduction of 0.6% (10 person-years from a possible 1784 person-years) in the total possible person-years. The discontinuation was permanent for 34 volunteers and decreased the total possible use of PrEP in 35 person years, 2.9% of the possible use in the cohort. The most common adverse effects cited for non-dispensing were nausea, abdominal pain (0.9% possible use), diarrhea (0.4%), and skin problems / itching, pain in head and flatulence (0.3% each (96).

- Laboratory abnormalities

Grade 2 to 4 laboratory abnormalities seen in the iPrEx and Partners PrEP assays are rare, generally less than 5% (80-82). Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued the trial due to an increase in serum creatinine, compared with no discontinuation in the placebo group. One subject in the TDF/FTC arm of the iPrEx trial discontinued due to an increase in serum creatinine and another subject discontinued due to low serum phosphorus. Grades 2-3 proteinuria (2-4 +) and / or glycosuria (3+) occurred in less than 1% of TDF/FTC-treated subjects in the iPrEx trial and the Partners PrEP trial.

- Alterations in bone mineralization.

In some clinical trials evaluating TDF/FTC in pre-exposure prophylaxis for HIV for 18 months, decreases in bone mineral density (BMD) have been observed and described in uninfected individuals. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD

ranging from –0.4% to –1.0% in total hip, spine, femoral neck, and trochanter in the TDF/FTC group compared to the placebo group, who returned to their baseline values after PrEP was discontinued. 13% of TDF/FTC treated subjects, in contrast to 6% of placebo treated subjects, lost at least 5% of BMD in the spine during treatment. Bone fractures were reported in 1.7% of the TDF/FTC group compared to 1.4% in the placebo group, however, no correlation was observed between BMD and fractures. (96)

The Partners PrEP trial found similar fracture rates between the treatment and placebo groups (0.8% and 0.6%, respectively); BMD was not assessed in this trial (81). Liu AY, et al. In 2011 evaluated the prevalence of low BMD using dual energy X-ray absorptiometry (DEXA), in a baseline cohort of 210 HIV-uninfected men who have sex with men (MSM) who underwent a randomized clinical trial of daily TDF versus placebo. At baseline, 20 volunteers (10%) had low BMD (Z score ≤ 2.0 at L2-L4 spine, total hip, or femoral neck). Low BMD was associated with the use of amphetamines (OR = 5.86, 95% CI 1.70-20.20) and inhalants (OR = 4.57, 95% CI 1.32-15.81); there was a 1.1% net decrease in mean BMD in the TDF group versus the pretreatment / placebo group in the femoral neck (95% CI 0.4-1.9%), 0.8% net decrease in the total hip (95% CI 0.3-1.3%) and 0.7% in column L2-L4 (95% CI -0.1-1.5%). At 24 months, 13% vs. 6% of volunteers experienced more than 5% loss of BMD at the femoral neck in the TDF versus placebo groups, however these associations were not statistically significant (p = 0.13) (87)

Kasonde M, et al. Evaluated the effect on bone mineral density of daily TDF/FTC use compared to placebo among heterosexual men and women aged 18 to 29 years enrolled in the Botswana TDF2 PrEP study. Volunteers had BMD measurements at baseline and then every 6 months with dual-energy X-ray absorptiometry (DEXA) performed on the hip, spine, and forearm. A total of 220 volunteers (108 TDF-FTC, 112 placebo) had baseline BMD measurements at all three anatomical sites; 15 (6.8%) of the volunteers had a low BMD level at baseline (z-score <-2.0 at each anatomical site) including 3/114 women (2.6%) and 12/106 men (11.3%) (p = 0.02) (97).

Low baseline BMD was associated with low weight (p = 0.02), high blood urea nitrogen content (p = 0.02) or high alkaline phosphatase (p = 0.03), and low creatinine clearance (p = 0.04). BMD losses> 3.0% at any anatomical site at any time after study initiation were significantly greater for the TDF-FTC treatment group [34/68 (50.0%) versus 26/79 (32.9%) placebo (p = 0.04). There was a small but significant difference in mean percentage change in BMD from baseline for TDF/FTC versus placebo at all three sites at month 30 [forearm -0.84% (p = 0.01), column -1.62% (p = 0.0002), hip -1.51% (p = 0.003). In conclusion, the use of TDF-FTC was associated with a small but statistically significant decrease in BMD in the forearm, hip and lumbar spine. A high percentage (6.8%) of healthy young adults in Botswana had an abnormal baseline BMD. This association is in relation to the time of exposure to TDF/FTC. (97).

- TDF/FTC and kidney function

Tenofovir-associated nephrotoxicity encompasses a spectrum of manifestations including proximal tubular dysfunction, acute kidney injury, CKD, and nephrogenic diabetes insipidus. Proximal tubular dysfunction is the main one among them, it has to do with the depletion of mitochondrial DNA mediated by the accumulation of drugs within the proximal renal tubules. Proximal tubular dysfunction can rarely progress to Fanconi syndrome, a complete tubulopathy that includes

metabolic acidosis and bone disorders and occurs in 0.3 to 2% of people who take this drug chronically (98,99)

In patients with human immunodeficiency virus infection, it has been recommended to avoid the use of tenofovir when the glomerular filtration rate (GFR) is less than 60 mL / minute / 1.73 m2, this is a strong recommendation in favor made by IDSA (Infectious Diseases Society of America). Likewise, in patients in whom a decrease in GFR greater than 25% from baseline or when it is less than 60 mL / minute / 1.73 m2 has been confirmed, it is recommended to replace tenofovir, especially when there is evidence of proximal tubular dysfunction. (100)

Tenofovir has been infrequently associated with renal dysfunction due to tubular necrosis. Herlitz LC, et al., described 13 cases of tenofovir-associated nephrotoxicity: 6 women and 7 men with a mean age of 51.1 ± 9.6 years. Patients were treated with tenofovir for a mean of 19.6 months. Nine patients had acute kidney injury and 4 had mild kidney failure with sub nephrotic proteinuria. The mean serum creatinine was 1.3 ± 0.3 mg/dl, increasing to 5.7 ± 4.0 mg/dl at the time of the biopsy. Renal biopsy revealed acute toxic tubular necrosis. Clinical follow-up after tenofovir discontinuation averaged 13.6 months in 11 of the 13 patients. Recovery of kidney function occurred in all patients, including 4 who required temporary hemodialysis. The study showed that tenofovir disoproxil can lead to a form of reversible acute tubular necrosis. (101)

This effect in the reduction of GFR with the use of tenofovir seems to be related to the time of exposure to the drug and behaves as a reversible toxic damage, for which the timely withdrawal of the drug is indicated (102). During the clinical experiment, the intervention with tenofovir disoproxil is planned to be administered for 60 days, for which we estimate that this nephrotoxic effect will be very infrequent.

Cooper RD et al., In a systematic review and meta-analysis of 17 studies that included 9 randomized clinical trials and 7 prospective observational cohorts found that tenofovir was associated with lower creatinine clearance (averaging -3.9 ml / minute) compared to regimens without tenofovir (103). The studies included in the meta-analysis had a median follow-up of 48 weeks, and subjects with a GFR <50 or <60 ml/min/1.73 m2 were excluded in 11 of them (102, 103).

Post marketing experience

Multiple adverse reactions have been described during post-approval use of TDF. No additional adverse reactions have been identified during use after FTC approval. These reactions are voluntarily reported by a population of uncertain size; Therefore, it is not always possible to establish causal relationships with drug exposure.

Among the adverse reactions that have been reported for TDF during surveillance are:

o Immune system disorders: allergic reaction, including angioedema.

o Metabolism and nutrition disorders: lactic acidosis, hypokalemia, hypophosphatemia.

o Respiratory, thoracic, and mediastinal disorders: dyspnea

o Gastrointestinal disorders: pancreatitis, increased amylase, abdominal pain.

o Hepatobiliary disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT)

o Skin and subcutaneous tissue disorders: rash

o Musculoskeletal and connective tissue disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and may contribute to fractures), muscle weakness, myopathy.

o Renal and urinary disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal failure, increased creatinine, proteinuria, polyuria.

Most of the adverse events as described are mild and infrequent. Severe events are much rarer and most of them are dose dependent and occur with prolonged use of the drug. During the present study, the intervention time is short, which minimizes the risk of adverse events dependent on the prolonged use of TDF.

5.1.2 Potential risks not associated with pharmacological intervention

Volunteers are potentially exposed to the risks inherent in taking any blood sample such as:

● Pain at the puncture site.

● Extravasation or bruising.

● Peripheral nerve injury (Very rare).

● Infection (Very rare).

● Anxiety.

All these risks will be mitigated by using established and validated protocols in each of the participating institutions, taking timely paraclinical tests, and constant supervision of the study by qualified personnel trained in the study procedures.

5.2 Benefit for volunteers

The study is based on previously reported findings in the scientific literature regarding the potential ability of tenofovir disoproxil/emtricitabine to inhibit SARS-CoV-2 replication (13, 47–50). Therefore, volunteers could benefit from the reduced risk of developing COVID-19 which could mean a decreased risk of developing symptoms, temporary disability, hospitalization, transmission to family members and close contacts, and to other members of the community. Among the possible complications associated with COVID-19, it could reduce the severity or risk of mortality during the follow-up period. Additionally, the continuous and accessible use of EPP for the study volunteers reduces the risk of contagion by COVID-19. The findings of the present study could lead to a change in public policies that in the future will reduce the risk of acquiring COVID-19 by health personnel. In accordance with current Colombian regulations, volunteers will not receive any type of financial compensation for their participation in the study.

6. Report of adverse events

6.1. Definitions

● Adverse event (AE)

Any adverse medical occurrence in a patient or subject of a clinical investigation to whom a pharmaceutical product was administered and that does not necessarily have a causal relationship with this treatment. Therefore, an adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or illness temporarily associated with the use of a medicinal (research) product, whether it is related. (104).

Considering the above, the United States National Institute of Health in conjunction with the National Cancer Institute of the same country published standardized definitions of adverse events known as Common Terminology Criteria for Adverse Events (CTCAE). Events, for its acronym in English), to describe the severity of the organic damage caused to patients by the various medications (104,105). According to them, the following events are considered:

● Serious adverse event (SAE)

Any unfavorable occurrence than at any dose that:

- Results in death.
- Is life threatening, requires hospitalization of the patient or prolongation of existing hospitalization.
- Results in persistent or significant disability / disability.
- Generates a congenital anomaly / birth defect.

● Fatal Serious Adverse Event.

EAS that end in the death of the subject or threaten the life of the same.

● Expected / Listed Serious Adverse Event.

EAS whose specificity or severity is consistent with that described in the Research Protocol, Investigator's Manual / basic prescription information or product label.

● Unexpected / Unlisted Serious Adverse Event.

EAS whose specificity or severity is not consistent with that described in the Research Protocol, Investigator's Manual / basic prescription information or product label.

● Non-Serious adverse event

All other events that do not meet any of the EAS seriousness criteria

● Adverse event requested

They are the AE that will be searched for in each assessment of the subjects participating in the study.

● Unsolicited adverse events

They are the AEs that are voluntarily manifested by the patient that may or may not be related to the study drug.

6.2. Assessment and documentation of adverse events.

The researcher assigned to follow up the study subjects will be responsible for recording all adverse events in each participating institution, regardless of the group evaluated, with the following exceptions:

A case report form will be created which must have the following information:

- Description of the adverse event
- Date of presentation, duration, and day of resolution.
- Severity according to degrees mentioned
- Conduct taken (need for treatment, suspension of medication, hospitalization)
- The probability of relationship with the drug under study.

All the follow-up of adverse events will be determined according to the Standardized Operational Plan for adverse events of the study.

6.3. Degree of severity

If the definition is met, the degree of severity of adverse events will be categorized. The categorization is found in Table 4 and is based on the (CTCAE) (104,105). According to them and the medicine used, the following events are considered:

Table 4. Adverse event's degree of severity

CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nervous system disorders					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Gastrointestinal disorders					

Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Flatulence	Mild symptoms: intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Skin and subcutaneous tissue disorders					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL	-	-
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g.,	Skin sloughing covering 10 - 30% BSA with	Death

			erythema, purpura, epidermal detachment, and mucous membrane detachment)	associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm: hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences: urgent intervention indicated	Death

Table 5. Tables for Laboratory Abnormalities

Laboratory abnormality	**Mild (Grade 1) ****	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**	**Death (Grade 5)**
Laboratory					
ALT and AST	>3 x ULN if baseline was normal. 1.5-3 x ULN of baseline if it was not normal.	>3-5 x ULN ULN if baseline was normal. >3-5 x ULN of baseline if it was not normal.	>5-20 x ULN if baseline was normal. >5-20 x ULN of baseline if it was not normal.	>20 x LSN ULN if baseline was normal. >20 x ULN of baseline if it was not normal.	
Hemoconcentration	Rise of 0-2 g/dl from baseline.	Rise of 2-4 g/dl from baseline.	Rise of > 4 g/dl from baseline.		
Anemia	Hb<ULN-10g/dl	Hb<10-8g/dl	Hb<8g/dl	Life Threatening; Medical	Death

				intervention is required.	
Lymphocytes Decrease - cell/mm³	< 800/mm3; < ULN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Neutrophils Decrease - cell/mm³	<LLN - 1500/mm3; <LIN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	
Platelets Decreased - cell/mm³	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9	
Creatinine – mg/dL	Rise of 1.5x ULN	Rise of 1.5 – 3x from baseline; 1.5 – 3 x ULN	Rise of 3x ULN from baseline.; 3 – 6 x ULN	Rise of 6x ULN	

ULN: Upper limit of normal range. LLN: Lower limit of the normal range.

Table 5. Causation of adverse events. Taken from the Common Terminology Criteria for Adverse Events (104,105).

Imputed causation	Definition
Definitive	A clinical event, or alterations in laboratory tests, that manifests with a plausible temporal sequence in relation to the administration of the drug, and that cannot be explained by the concurrent disease, or by other drugs or substances. The response to drug withdrawal (withdrawal; dechallenge) must be clinically plausible. The event must be definitive from a pharmacological or phenomenological point of view, with a conclusive re-exposure (rechallenge).
Probable	A clinical event, or alterations in laboratory tests, that manifests with a reasonable time sequence in relation to the administration of the drug, that is unlikely to be attributed to the concurrent disease, or to other drugs or substances, and that when withdrawing the drug presents a clinically reasonable response. Information on re-exposure is not required to assign this definition.

Possible	A clinical event, or alterations in laboratory tests, that manifests with a reasonable time sequence in relation to the administration of the drug, but that can also be explained by the concurrent disease, or by other drugs or substances. Information regarding the withdrawal of the drug may be missing or unclear.
Improbable	A clinical event, or alterations in laboratory tests, that manifests with an unlikely time sequence in relation to the administration of the drug, and that can be more plausibly explained by the concurrent disease, or by other drugs or substances.
Conditional / Not classifiable	A clinical event, or laboratory test abnormalities, reported as an adverse reaction, for which more data is required to make a proper evaluation, or additional data is under review.
Not assessable / Unclassifiable	A notification that suggests an adverse reaction but cannot be judged because the information is insufficient or contradictory, and that cannot be verified or completed in your data.

7. Ethical considerations

This research is considered to have a risk greater than the minimum, since it is a clinical experiment in which a pharmacological intervention will be carried out, according to Resolution 8430 of 1993. Therefore, there may be modifications in the biological variables, and adverse effects from the intervention could occur.

This research will be presented to the Research and Ethics Committee of the Hospital Universitario San Ignacio and the Pontificia Universidad Javeriana, and to the ethics committees of the participating institutions for approval. Attached to this document, the informed consent forms (Annex 4), as well as the corresponding annexes, will be presented. These documents will be thoroughly evaluated and approved when the committee considers that they meet the necessary quality and ethical standards.

To obtain the data, an in-depth explanation of the informed consent will be made to the volunteers in individual sessions. Additionally, the volunteer will be explained the days of clinical follow-up, the possible adverse effects of the intervention, any doubts that may arise will be resolved and it will be made clear to them that they are free to participate or not in the study and that they can be withdrawn at any time. moment.

● Privacy and confidentiality

It will seek to respect privacy, confidentiality and promote the rights and well-being of all the subjects involved in this research defined in article 5 of this same resolution. Additionally, under the support of statutory law 1581 of 2012 "Habeas data", approval will be requested for the handling of personal data in the informed consent. It will be guaranteed that their identification is not taken within the variables to be analyzed in the study, and that, at the time of information analysis, the database is anonymized (each volunteer will have an assignment code that will not be decipherable),

respecting the this way the confidentiality and privacy of the data of each volunteer who is part of the study.

All the data of the study volunteers will be kept in a password-protected database and stored according to the information management protocols for research purposes of the Hospital Universitario San Ignacio and the other participating centers. Volunteers will not be able to access their personal information related to the study.

The database will be known to the principal investigators and will be stored during the study on their computer (s). Researchers will have access for data analysis through a storage platform called "RedCap". This platform complies with the transfer law. Upon completion of the study, a copy of the information will be made, and it will be stored on magnetic media and deleted from the work computer (s). The study information will be stored for up to 5 years after this.

● Conflicts of interest

The researchers declare that they have no conflicts of interest. However, if this changes, conflicts of interest will be declared for each researcher. In Annex 7. The conflicts of interest of each of the researchers are presented during the development of the research protocol.

● Policy of publication and dissemination of results

No personal information that can identify the study subjects will be disclosed when the research results are published. A report will be prepared with the conclusions of the study to present in the academic-scientific spaces of the San Ignacio University Hospital, the participating centers and in national and international scientific academic events. Additionally, two manuscripts will be prepared for publication in a journal of national or international biomedical interest. The first manuscript about the main results of the study and the second about the description of the kinetics of diagnostic tests in the clinical experiment.

The decision about the order of the authors will be determined by the scientific committee of the experiment, which will be made up of one person from each of the participating institutions.

● Completion of the study

The Research and Ethics Committee of the Hospital Universitario San Ignacio and the Pontificia Universidad Javeriana, may decide to terminate the study at any time with prior notice to the researchers and co-investigators.

● Insurance policy for clinical trials

This study will have an insurance policy for volunteers in clinical trials that complies with article 13 of Resolution 8430 of 1993 of the Ministry of Health of Colombia. This policy will be taken for a value of COP $ 70,000,000 MCTE and will cover the probable adverse events caused by the intervention that the volunteers may present.

The policyholder is the Pontificia Universidad Javeriana, and this has been preliminarily contracted with the Previsora, Insurance company. Headquarters Address: Calle 57 # 9 -07. PBX: +571 348 5757 / Postal Code 52946.

Table 6. Study schedule

WORK PLAN AND SCHEDULE											
Timetable											
	Preparation and logistics	Recruitment	**Follow up**				**Results**	**Data analysis**	**Communication and publication**		
Months	**1-2**	**3-5**	**Visits**				**5-7**	**8**	**8**		
Activities			**1**	**2**	**3**	**4**				**Product**	**Deliverable result**
Documentary enlistment of procedures	X									Standard Operating Procedures and Investigator Manual	SOP protocol documents and Investigator Manual
Acquisition of supplies and equipment	X									Diagnostic test kits, PPEs, computers, tablets	Inventories, purchase orders, invoices
CRF design	X									Data extraction form	CRF registration number - Certificate

Training and opening of centers	X									GCP courses carried out in centers, Visits to study centers	Minutes - GCP course approval certificates
Telephone contact potential volunteers		X								Registration with participants interested in being included	Record of execution of the procedure and database in Excel.
Informed consent		X								Signed informed consents	Database of study subjects recruited
Clinical CRF history		X	X	X	X	X				Clinical History of the study subject	Clinical CRF Registry
Clinical Assessment		X	X	X	X	X				Clinical History of the study subject	Clinical CRF Registry
Supervised first dose of drug administration		x								Confirmation of taking at least 1 dose of TDF/FTC or placebo	Drug dispensing registration document
Taking of RT-PCR for SARS-CoV-2		X			X					Positive or negative diagnostic test result	Laboratory report
Antibody IgG - IgM SARS - CoV-2 testing		X		x		x				Positive or negative diagnostic test result	Laboratory report
Sampling for CBC, Creatinine, AST, ALT, P, HIV ELISA, Acs anti HBsAg and		X		X		X				Results of liver, kidney, hematological, electrolyte function tests and pregnancy status in the	Laboratory report

Beta HCG in women										case of participating women.	
Verification of eligibility criteria		X								Determination of the inclusion or not of the participant	Check list
Randomization		X								Random Assignments to Intervention or Placebo	Database
CRF Adverse Events Registry			X	X	X	X				History of adverse events	CRF registration document Adverse event
Finish follow-up and communication to the study subject							X			Formal follow-up completion record	Completion certificate document
Systematization and organization of data							X			Office registry refined with data extracted from the clinical trial	Systematized database
Results analysis								X		Outcome estimates, statistical associations, causality inferences and risks of bias and limitations	Document with results, tables, graphs and data of the study
Communication and publication of results and conclusions.									X	National and international communication of the results and	Two articles of scientific publication, report of results and recommendatio

									conclusions of the study	ns of the researchers

9. Budget

9.1 Technical services

No.	Item	Site	Justification	Quantity		Unit value (cop)		Subtotal (cop)
1	Civil liability policy for volunteers and clinical trial personnel	Pontificia Universidad Javeriana	Regulatory agency requires a liability protection for both, volunteers and clinical trial personnel regarding risks during COVID-19 pandemic.	1	$	96,101,872.44	$	96,101,872.44
2	Clinical laboratory tests (Creatinine; CBC; ALT; AST; BHCG in women, antiHBS; HIV, IgG Antibodies; Serum phosphorus, CRP)	Pontificia Universidad Javeriana	Laboratory exams required at baseline and follow-up	1	$	535,959,372.00	$	535,959,372.00
3	rtPCR for symptomatic volunteers (7,5%)	Pontificia Universidad Javeriana	rtPCR for follow-up 1, for volunteers who develop respiratory symptoms (estimated of 7.5%)	71	$	250,000.00	$	17,750,000.00
4	Laboratories for follow-up 2 (creatinine and antibodies)	Pontificia Universidad Javeriana	Laboratory tests for 950 volunteers	1	$	50,071,650.00	$	50,071,650.00
5	RtPCR including transport media for follow-up 2.	Pontificia Universidad Javeriana	Laboratory tests. It is estimated that 7.5% of volunteers will develop symptoms that require rtPCR. Services will be provided by recruitment sites	71	$	250,000.00	$	17,750,000.00
6	Laboratory tests (Creatinine, CBC, ALT, AST, BHCG for women (80% of volunteers) and rtPCR for all subjects.	Pontificia Universidad Javeriana	Laboratory tests for each participant (80% women; 20% men)	1	$	285,512,810.00	$	285,512,810.00
7	IgG antibody tests for follow up 4	Pontificia Universidad Javeriana	IgG antibody tests for follow up 4	1	$	43,320,000.00	$	43,320,000.00
8	Recruitment services	Pontificia Universidad Javeriana	Recruitment costs per volunteer including PPE + workhours of pharmaceutical chemist, respiratory therapist, assistant nurse, and laboratory assistant	950	$	105,699	$	100,414,240
								$1,146,879,944

9.2 Materials and supplies

No.	Item	Site	Justification	Quantity	Unit value (cop)	Subtotal (cop)

1	IgG antibody tests box (20 kits)	Pontificia Universidad Javeriana	Antibody test for 342 subjects at baseline; 950 for follow-up 1, 475 for follow-up 3 (Brand: Biosensor)	55	$ 780,000	$ 42,666,000
2	Placebo; 60 units X 475 volunteers	Pontificia Universidad Javeriana	475 volunteers X 60 days	30000	$ 200	$ 6,000,000
3	Investigational drug TDF/FTC	Pontificia Universidad Javeriana	475 volunteers X 60 days	30000	$ 800	$ 24,000,000
						$ 72,666,000

9.3 Total budget

Item	Funded by grant	Pontificia Universidad Javeriana offsetting		Hospital Universitario San Ignacio offsetting		Total
		Cash	**In kind**	**Cash**	**In kind**	
Registry and certification costs	$0.00	$0	$0	$0	$0	$0
Equipment	$0.00	$0	$0	$0	$0	$0
Materials and supplies	$67,876,084	$4,789,916	$0	$0	$0	$ 72,666,000
Scientific staff	$0.00	$0	$18,322,123	$0	$172,708,003	$ 191,030,126
Support staff	$284,472,000	$0	$0	$0	$0	$ 284,472,000
Publications	$28,000,000	$0	$0	$0	$0	$ 28,000,000
Technical support and assistance services	$23,690,536	$0	$0	$0	$0	$ 23,690,536
Technical services	$1,131,535,948.00	$15,343,996	$0	$0	$0	$1,146,879,944
Management (7%)	$107,490,220	$0	$0	$0	$0	$ 107,490,220
CTEI instrument management (5%)	$82,153,239	$0	$0	$0	$0	$ 82,153,239
TOTAL	**$1,725,218,040**	**$20,133,912**	**$18,322,123**	**$0**	**$172,708,003**	**$1,936,382,066**

Appendix 1.
Clinical trials on prophylaxis for COVID-19 with TF/FTC currently registered in ClinicalTrials.gov

Study	**Recruitment**	**Study site**	**Description and objectives**	**Outcomes**	**Design**
Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel (EPICOS)	Recruiting	Plan Nacional sobre el Sida (PNS), Spain	To evaluate the efficacy of a daily single dose of TDF/FTC (245/200 mg) or a daily single dose of hydroxychloroquine or combination of both vs placebo for prevention of COVID-19. 4000 volunteers will be included assigned to treatment arm in proportion of 1:1:1:1. The length of treatment will be 12 weeks. Follow-up will go on for 4 weeks after completion of treatment. Interim analyses will be performed monthly.	Number of symptomatic serology confirmed SARS-CoV-2 infections. Number of asymptomatic serology confirmed SARS-CoV-2 infections. Severity of COVID-19, determined as follows: - Duration of symptoms. - Relationship between treatment duration and development of symptoms. - Relationship between treatment duration and duration of symptoms. - Seroconversion of IgM/IgG since development of symptoms.	Study type: Clinical trial. Number of participants: 4000. Allocation: randomized. Trial design: parallel. Masking: double. Primary outcome: protection. Estimated recruitment start date: April 1, 2020. Estimated recruitment end date: June 30, 2020. Estimated completion date: July 31, 2020.

TAF/FTC for Pre-exposure Prophylaxis of COVID-19 in Healthcare Workers (CoviPrep Study)- ARGENTINA	Not yet recruiting	Hospital Italiano, Buenos Aires, Argentina	To evaluate the efficacy of TAF/FTC for 12 weeks vs placebo for the prevention of COVID-19 in health care workers.	Number of symptomatic or asymptomatic COVID-19 cases assessed by antibodies and confirmed by rtPCR. Number of asymptomatic serology confirmed COVID-19. Severity of symptoms defined as follows: - Mild: malaise, fever, cough, myalgia, arthralgia. - Moderate: shortness of breath. - Severe: requirement of intensive care. Duration of symptoms. Relationship between treatment and duration of symptoms. Time to seroconversion.	Study type: Clinical trial. Number of participants: 1378 Allocation: randomized. Trial design: parallel Masking: triple. Primary outcome: protection. Estimated recruitment start date: June 15, 2020. Estimated recruitment end date: non specified. Estimated completion date: November 11, 2020
A real-world study for lopinavir/ritonavir (LPV/r) and emtritabine (FTC) / Tenofovir alafenamide Fumarate tablets (TAF) regimen in the treatment of novel coronavirus pneumonia (COVID-19)- CHINA	Not yet recruiting	Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital	Real-life stydy. Non-randomized non-blinded study of treatment of health care professionals with TAF/FTC plus LPV/r vs LPV/r alone. Duration not specified.	Primary outcome: survival rate. Secondary outcomes: -Time to negative rtPCR. -Time to ARDS development. - Hospitalization length.	Study type: real life interventional study. Number of participants: 120. Allocation: non-specified. Masking: no masking. Primary outcome: protection. Estimated recruitment start date: February 2, 2020. Estimated recruitment end date: not specified. Estimated completion date: June 30, 2020.

Appendix 2. Drug interactions of TDF/FTC

Drugs not allowed in the trial.

Analgesics
Chronic use (two or more weeks) of any of the following: Celecoxib, Diclofenac, Ibuprofen Methadone Naproxen Nimesulide Piroxicam
Antiarrhythmics
Amiodarone Quinidine
Antibiotics

Amikacin Cefalexin Clarithromycin Gentamicin Piperacillin/ Tazobactam Rifampicin Sulfadiazine Vancomycin
Contraceptives
Ethinyl estradiol and norgestimate
Anticonvulsants
Topiramate
Antidepressants
Lithium
Antidiabetics
Canagliflozin Empagliflozin
Antifungal
Amphotericin B Fluconazole Itraconazole Flucytosine Ketoconazole
Antiretrovirals
Dolutegravir/Lamivudine Abacavir Didanosine Lamivudine Atazanavir/cobicistat Atazanavir/ritonavir Darunavir/ritonavir Darunavir/cobicistat Indinavir
Antivirals
Acyclovir Ganciclovir Ledipasvir/Sofosbuvir Sofosbuvir/Velpatasvir
Calcium channel blockers
Verapamil
Antihypertensives / Heart failure
Furosemide Hydralazine Sacubitril
Immunomodulators
Interferon Hydroxyurea
Immunosuppressors

Ciclosporin Mycophenolate Sirolimus Tacrolimus
Others
Acetazolamide Orlistat Probenecid Pyridostigmine Sevelamer Zoledronic Acid

Low interaction drugs allowed in the trial:

References

- HIV Drug interactions. University of Liverpool. https://www.hiv-druginteractions.org/view_all_interactions/445855

- Ficha técnica TDF/FTC TRUVADA Gilead Sciences Ireland UC https://www.ema.europa.eu/en/documents/product-information/truvada-epar-product-information_es.pdf

Appendix 3. Variables

Inclusion-exclusion criteria

Variable	Variable type	Conceptual definition	Operative definition
Informed consent signature date	Quantitative	Informed consent signature date	Day/Month/Year
Age	Qualitative/dichotomous	Age 18 to 70 years according to legal ID	0- No 1- Yes
Profession	Qualitative/nominal	Profession	1- Physician 2- Nurse 3- Nursing assistant 4- Respiratory therapist
Caring for COVID-19 patients	Qualitative/dichotomous	Subject has direct contact with confirmed or suspected COVID-19 patients	0- No 1- Yes
Serology IgG for SARS-CoV-2	Qualitative/dichotomous	Result of serology IgG test for COVID-19 before randomization and administration of drug/placebo	0- Negative 1- Positive
Baseline RT-PCR for SARS-CoV-2	Qualitative/dichotomous	Result of RT-PCR for SARS-CoV-2 of nasopharyngeal swab before randomization and administration of drug/placebo	0- Negative 1- Positive
Exclusion criteria			
COVID-19 related symptoms	Qualitative/dichotomous	Presence of two or more of the following at initial screening: - Body temperature ≥ 38 °C - Acute cough (onset less than 10 days) - Shortness of breath - Sore throat - Malaise. - Acute diarrhea	0- No 1- Yes

History of COVID-19	Qualitative/dichotomous	History of serology or rtPCR confirmed COVID-19	0- No 1- Yes
Cohabitation with people with COVID-19 infection or COVID-19 symptoms	Qualitative/dichotomous	Cohabitation with people with COVID-19 infection or COVID-19 symptoms	0- No 1- Yes
Treatment during last month with medications that have significant interactions with TDF/FTC	Qualitative/dichotomous	Treatment during last month with medications that have significant interactions with TDF/FTC (see Appendix 2)	0- No 1- Yes
HIV infection	Qualitative/dichotomous	Confirmed HIV infection	0- No 1- Yes
B hepatitis immunity	Qualitative/dichotomous	Volunteer with anti-HBsAg less than 10 UI/ml	0- No 1- Yes
Hepatitis B infection	Qualitative/dichotomous	History of hepatitis B virus infection	0- No 1- Yes
Recent use of TDF/FTC	Qualitative/dichotomous	Use of TDF/FTC within the last month for any other indication	0- No 1- Yes
Hypophosphatemia	Qualitative/dichotomous	Phosphorus serum concentration less than lower reference laboratory value	0- No 1- Yes
Liver disfunction	Qualitative/dichotomous	Liver disfunction as defined by ALT or AST levels ≥ 2 times upper limit of normal (x ULN) (66)	0- No 1- Yes
Hematologic disfunction	Qualitative/dichotomous	Hemoglobin concentration less than 11 mg/dl or neutrophil count less than 1000 cel/mm3	0- No 1- Yes
Chronic kidney disease	Qualitative/dichotomous	eTFG ≤ 60 mL/min/1.73 m2, calculated by CKD-EPI formula with baseline creatinine or past history of chronic kidney disease as disclosed by volunteer	0- No 1- Yes
Hypersensitivity to TDF/FTC	Qualitative/dichotomous	History of hypersensitivity to TDF/FTC	0- No 1- Yes
Metabolic bone disease	Qualitative/dichotomous	History of osteopenia, osteoporosis or pathologic fractures	0- No 1- Yes
Pregnancy, breastfeeding or plans to seek pregnancy during the study	Qualitative/dichotomous	Pregnancy, breastfeeding or plans to seek pregnancy during the foreseen duration of participation in the study	0- No 1- Yes 2- Not applicable
Pregnancy test	Qualitative/dichotomous	Result of quantitative serum Beta-HCG above the limit of detection of laboratory for non-pregnant women	0- No 1- Yes 2- Not applicable
Participation in another study	Qualitative/dichotomous	Participation in any other study of prevention of COVID-19	0- No 1- Yes
Withdrawal criteria			
Kidney disfunction	Qualitative/dichotomous	Any grade 2 kidney function adverse evento during the study	0- No 1- Yes
Related Serious adverse evento	Qualitative/dichotomous	Any serous adverse event deemed to be related to study intervention as assessed by investigators	0- No 1- Yes
Voluntary withdrawal	Qualitative/dichotomous	The volunteer decides to withdraw from study for any reason	0- No 1- Yes
Requirement of any medication with significant interactions	Qualitative/dichotomous	Requirement of any medication that has significant interactions with TDF/FTC during participation in study	0- No 1- Yes
Demographic variables			
Age	Quantitative/continuous	Age of volunteer at the beginning of the study	Number of years
Randomization date	Quantitative/continuous	Randomization date	Day/Month/Year
Date drug/placebo start	Quantitative/continuous	Date of drug/placebo start	Day/Month/Year
Sex	Cualitativa/ nominal	Birth sex of patient	1- Feminine 2- Masculine
Site	Cualitativa/ nominal	Research site where volunteer works	1-Hospital Universitario San Ignacio 2-Clínica Colombia 3-Clínica Reina Sofia

			4-Clinica Santa María del Lago 5-Hospital Universitario Nacional 6-Clínica Samaritana-Bogotá 7-Clínica Samaritana-Zipaquira 8-Hospital San Jorge
Profession	Qualitative/nominal	Profession	1- Physician 2- Nurse 3- Nursing assistant 4- Respiratory therapist
Department	Qualitative/nominal	Hospital department in which volunteer works. Multiple answers possible	1- Emergency department 2- Hospitalization floors 3- ICU
Time of daily exposure to COVID-19 patients	Quantitative/continuous	Declared average time of daily exposure per volunteer to COVID-19 patients	Number of hours
Shift	Qualitative/nonomino	Volunteer's work shifts	1- Morning 2- Afternoon 3- Night 4- Whole day 5- Whole day and night shifts
Number of institutions in which volunteer works	Quantitative/ discrete	Number of institutions in which volunteer works	Number of institutions
Physician role in institution	Qualitative/nonomino	Role of physician in the institution	1. Intern 2. General practitioner 3. Resident 4. Specialist 5. Not applicable
Specialty	Qualitative/nonomino	Physician's specialty (or residency)	1. Emergency medicine 2. Internal medicine 3. Adult intensive care 4. Pediatric intensive care 5. Geriatrics 6. Anesthesiology 7. Pediatrics 8. Neonatology 9. Surgery 10. Surgical specialties 11. Pulmonology 12. Infectious diseases 13. Other 14. Not applicable
Weight	Quantitative/continuous	Weight at enrollment measured with a calibrated clinical scale	Weight in kilograms with one decimal
Height	Quantitative/continuous	Height at enrollment measured with a clinical stadiometer	Height in centimeters without decimals
Number of cohabitating people	Quantitative/discrete	Number of people that cohabit with volunteer	Number of people
Comorbidities			
Chronic obstructive pulmonary disease (COPD)	Qualitative/dichotomous	History of confirmed COPD as disclosed by the patient	0- No 1- Yes
Cardiovascular disease	Cualitative/nominal	History of hypertension, stroke, peripheral artery disease, heart failure	1- No 2- HTA 3- Stroke 4- PAD 5- HF
Diabetes mellitus	Qualitative/nominal	Classification of diabetes mellitus	0- No 1-Diabetes tipo I 2-Diabetes tipo II

Diabetes control	Qualitative/nonomino	Controlled diabetes: defined as glycated A1C hemoglobin (HbA1C) equal or less than 7% within the last 3 months. Uncontrolled diabetes: defined as HbA1C higher than 7%.	1-Uncontrolled diabetes 2-Controlled diabetes 3-No HbA1C data
Data to be collected in Follow-up 1, Follow-up 2 y Follow-up 3			
Follow-up date	Quantitative/continuous	Date	Day/Month/Year
COVID-19 related symptoms	Qualitative/dichotomous	Development of any of the following symptoms: - Fever: body temperature higher than 38°C - Acute cough (start within the last 10 days) - Shortness of breath - Rhinorrhea - Sore throat - Malaise - Acute diarrhea - Anosmia or hyposmia - Dysgeusia - Headache	0- No symptoms 1- Fever 2- Acute cough 3- Shortness of breath 4- Rhinorrhea 5- Sore throat 6- Malaise 7- Acute diarrhea 8- Anosmia or hyposmia 9- Dysgeusia 10- Headache 11- Other, Specify
Date of symptom start	Quantitative/continuous	Date of start of first COVID-19 related symptom. If no symptoms register 00/00/00.	Day/Month/Year
Adverse event (AE)	Quantitative/nominal	Any untoward adverse event during administration of investigational product that may or may not have a causal relationship with it.	0-No 1-Yes
Serious adverse event (SAE)	Qualitative/nonomino	Any adverse event that: - Results in death. - Threatens life and requires hospitalization or prolongation of hospitalization. - Results in permanent or prolonged inability or disability. - Causes congenital defects or malformations.	0-No 1-Yes
Serious adverse event classification	Qualitative/nonomino	Expected SAE: An AE whose nature and severity is consistent with what is described in investigator's brochure or drug insert. Unexpected SAE: An AE whose natura and severity are not consistent with what is described in investigator's brochure or drug insert.	1- Expected serious adverse event 2- Unexpected serious adverse event
Fatal SAE	Qualitative/nonomino	SAE that results in death	0- No 1- Yes
Type of SAE	Qualitative/nonomino	Type of SAE the volunteer developed	1- Acute kidney injury 2- Proximal tubulopathy 3- Emesis 4- Abdominal pain 5- Headache 6- Insomnia 7- Diarrhea 8- Hypersensitivity skin reaction 9- Steven-Johnson's syndrome 10- Maculopapular rash 11- Appendicitis 12- Pancreatitis 13- Other, specify
Date of SAE start	Quantitative/continuous	Date when SAE started	Day/Month/Year
Date of SAE end	Quantitative/continuous	Date when SAE ended	Day/Month/Year

Non serious AE	Qualitative/nonomino	Whether volunteer developed non serious AE	0- No 1- Yes
Type of non-serious AR	Qualitative/nominal	Type of non serious AE that volunteer developed	1- Nausea 2- Headache 3- Abdominal pain 4- Flatulence 5- Weakness or tiredness 6- Insomnia 7- Fatigue 8- Vomiting 9- Maculopapular rash 10- Steven-Johnson's syndrome 11- Allergic skin reaction 12- Other, specify
Nausea	Qualitative/nonomino	A feeling of sickness featured by an urge to vomit.	1-Grade 1 2-Grade 2 3-Grade 3
Headache	Qualitative/nominal	Headache	1-Grade 1 2-Grade 2 3-Grade 3
Abdominal pain	Cualitativa/ Nominal	A feeling of distress or pain in abdominal area.	1-Grade 1 2-Grade 2 3-Grade 3
Flatulence	Qualitative/nonomino	A disorder highlighted by abnormally increased gas discharge by lower gastrointestinal tract.	1-Grade 1 2-Grade 2
Insomnia	Qualitative/nominal	A disorder characterized by difficulty to start or maintain sleep.	1-Grade 1 2-Grade 2 3-Grade 3
Vomit	Qualitative/nonomino	A disorder featured by a reflex act or actively regurgitating stomach contents through mouth	1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4 5-Grade 5
Maculopapular skin rash	Qualitative/nominal	A disorder featured by the appearance of macules and papules. Also known as morbilliform eruption. Often associated with pruritus.	1-Grade 1 2-Grade 2 3-Grade 3
Steven-Johnson's syndrome	Qualitative/nominal	A disease in which at least 10% of body surface area develops a severe sphacelating lesions and bullae, also compromising mucosal membranes.	3-Grade 3 4-Grade 4 5-Grade 5
Allergic reaction	Qualitative/nominal	A disorder featured by a local or diffuse skin reaction upon exposure to an allergenic.	1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4 5-Grade 5
Other allergic reaction	Qualitative/nominal	Se coloca la clasificación de la reacción alérgica reportada según la	1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4 5-Grade 5
Adherence by tablet count	Qualitative/discrete	Number of drug/placebo tablets taken to follow-up date	Number of tablets
Drug/placebo interruption	Qualitative/dichotomous	Any interruption of investigational product	0- No 1- Yes
Days of product interruption	Quantitative/discrete	Days of drug interruption	Number of days
Cause of drug interruption	Qualitative/nominal	Reason of drug interruption	1- Omission 2- AE 3- Accidental los of drug/placebo 4- Non-availability of drug/placebo
Additional data to be collected in Follow-up 2 and 3			

Temperature	Quantitative/continuous	Body temperature in Celsius degrees	Temperature in Celsius degrees
Heart rate	Quantitative/discrete	Heart rate	Heart rate in beats per minute
Respiratory rate	Quantitative/discrete	Respiratory rate	Respiratory rate in respirations per minute
Systolic blood pressure	Quantitative/discrete	Systolic blood presure	Systolic blood pressure in mmHg
Diastolic blood pressure	Quantitative/discrete	Diastolic blood presure	Diastolic blood pressure in mmHg
Creatinine	Quantitative/continuous	Serum creatinine concentration (mg/dl).	Serum creatinine concentration (mg/dl).
Creatinine rise	Qualitative/nominal	Severity of creatinine rise	0-Normal0 1-Grado 1 2-Grado 2 3-Grado 3 4-Grado 4
IgG forSARS-CoV-2	Qualitative/dichotomous	Result of serology test for SARS-CoV-2 (only for follow-up 2)	0- Negative 1- Positive
Data to be collected in follow-up 3			
Platelets	Quantitative/discrete	Number of platelets in complete blood count (CBC)	Number of platelets per microliter (Cels/µl).
Thrombocytopenia	Qualitative/nominal	Severity of thromocytopenia	0-Normal 1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4
Hemoglobin (Hb)	Qualitative/continuous	Hemoglobin concentration in CBC	Hb (g/dl).
Anemia	Qualitative/nominal	Classification of severity of anemia	0-Normal 1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4
Lymphocytes	Quantitative/discrete	Number of lymphocytes in complete blood count (CBC)	Number of lymphocytes per microliter (Cels/µl).
Lymphopenia	Qualitative/nominal	Classification of severity of lymphopenia	0-Normal 1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4
Neutrophils	Quantitative/discrete	Number of neutrophils in complete blood count (CBC)	Number of neutrophils per microliter (Cels/µl).
Neutropenia	Qualitative/nominal	Classification of severity of neutropenia	0-Normal 1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4
Aspartate aminotransferase (AST)	Quantitative/continuous	AST concentration in international units per litter (UI/l)	AST (UI/l).
Aspartate aminotransferase elevation	Qualitative/nominal	Severity of elevation of AST	0-Normal 1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4
Alanine aminotransferase (ALT)	Quantitative/continuous	ALT concentration in international units per litter (UI/l)	ALT (UI/l).
Alanine aminotransferase elevation	Qualitative/nominal	Severity of elevation of ALT	0-Normal 1-Grade 1 2-Grade 2 3-Grade 3 4-Grade 4

Pregnancy test	Qualitative/dichotomous	Applicable only to women. Result of quantitative serum Beta-HCG test regarding upper reference value for non-pregnant women.	0- Negative 1- Positive
RT-PCR SARS-CoV-2	Qualitative/dichotomous	Detection of SARS-CoV-2 by RT-PCR de	0- Undetectable 1- Detectable
Data to be collected only in Follow-up 4			
Follow-up date	Quantitative/continuous	Follow-up date	Day/month/year
COVID-19 related symptoms	Qualitative/dichotomous	Development of any of the following symptoms: - Fever: body temperature higher than 38°C - Acute cough (start within the last 10 days) - Shortness of breath - Rhinorrhea - Sore throat - Malaise - Acute diarrhea - Anosmia or hyposmia - Dysgeusia - Headache	0- No symptoms 1- Fever 2- Acute cough 3- Shortness of breath 4- Rhinorrhea 5- Sore throat 6- Malaise 7- Acute diarrhea 8- Anosmia or hyposmia 9- Dysgeusia 10- Headache 11- Other, Specify
Date of symptom start	Quantitative/continuous	Date of start of first COVID-19 related symptom. If no symptoms register 00/00/00.	Day/Month/Year
Temperature	Quantitative/continuous	Body temperature in Celsius degrees	Temperature in Celsius degrees
Heart rate	Quantitative/discrete	Heart rate	Heart rate in beats per minute
Respiratory rate	Quantitative/discrete	Respiratory rate	Respiratory rate in respirations per minute
Systolic blood pressure	Quantitative/discrete	Systolic blood presure	Systolic blood pressure in mmHg
Diastolic blood pressure	Quantitative/discrete	Diastolic blood presure	Diastolic blood pressure in mmHg
Serology IgG for SARS-CoV-2	Qualitative/dichotomous	Result of serology IgG test for COVID-19 before randomization and administration of drug/placebo	0- Negative 1- Positive
Dependent variables/primary outcomes			
Development of COVID-19	Qualitative/dichotomous	Positive RT-PCR for SARS-Cov-2 at any time during follow-up	0- No 1- Si
Date of positive RT-PCR for SARS-CoV-2	Quantitative/continuous	Date of positive result	Day/Month/Year
Time to positive result positive RT-PCR for SARS-CoV-2	Quantitative/discrete	Time between start of administration of drug/placebo to a positive RT-PCR result.	Number in days
Symptoms probably related to COVID-19	Qualitative/nominal	Recording of presence or absence of solicited symptoms probably related to COVID-19 during each of 4 follow-up visits.	0-None 1-Fever 2-Acute cough 3-Shortness of breath 4-Rinorrhea 5-Sore throat 6-Malaise 7-Acute diarrhea 8-Anosmia hyposmia 9-Dysgeusia 10-Mialgya 11-Other, specify
Date of symptom start	Quantitative/continuous	Date of start of first COVID-19 related symptom. If no symptoms register 00/00/00.	Day/Month/Year
Time to development of first COVID-19 related symptom	Quantitative/discrete	Number of days between start of administration of drug/placebo and appearance of first COVID-19 related symptom	Number of days
Dependent variables/secondary outcomes			

Withdrawal of investigational product	Qualitative/nominal	Decision by investigator or patient to withdraw investigational product before planned.	0-Not aplicable 1- Withdrawal due to kidney disfunction. 2- Withdrawal due to need for new interacting medicatio ns. 3- Withdrawal due to development of any SAE deemed to be related to intervention. 4- Withdrawal due to any AE that makes the volunteer decide to interrupt investigational product. 5-Voluntary withdrawal.
Date of investigational product withdrawal	Quantitative/contin uous	Date of discontinuation of investigational product, only if previous answer was other than 0	Day/month/year
Time to discontinuation of investigational product	Quantitative/discret e	Time between initiation of investigation product to discontinuation	Number of days
Severity of COVID-19	Qualitative/nominal	Classification of severity as follows: - Asymptomatic infection - Mild disease: defined as not requiring hospitalization. - Moderate disease: defined as requiring hospitalization outside of the ICU. - Severe disease: defined as requiring hospitalization in ICU.	1-Asymptomatic 2-Mild 3-Moderate 4-Severe
Date of hospitalization start	Quantitative/contin uous	Date of hospitalization start	Day/month/year
Date of hospital discharge	Quantitative/contin uous	Date of hospital discharge	Day/month/year
Date of ICU admission	Quantitative/contin uous	Date of ICU admission	Day/month/year
Fecha de egreso del UCI	Quantitative/contin uous	Date of ICU discharge or date of death	Day/month/year
Date of recovery from COVID-19	Quantitative/contin uous	Recovery from COVID-19 defined as a minimum of 10 days after symptom start plus at least 72 hours of symptom improvement. If the patient died, record 00/00/00	Day/month/year
Final status	Quantitative/contin uous	Record of volunteer status at the end of follow-up	0- Death 1- Alive
Date of end of follow-up	Quantitative/contin uous	Date of end of follow-up	Day/month/year

Appendix 4. Informed consent format

	MANAGEMENT OF CLINICAL RESEARCH	

INFORMED CONSENT IN CLINICAL RESEARCH PROJECTS

INTRODUCTION

Volunteer's code: _____

This informed consent format is intended for use in a project with subjects that can consent participation. In this document "you" refers to the research volunteer or participant.

You are being invited to participate in the research project "**effectiveness of personal protective elements plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for prevention of transmission of SARS-CoV-2 in previously healthy adult health care workers younger than 60 years."** This document will give you the necessary information to participate willingly and freely. This project is conducted by Pontificia Universidad Javeriana, Hospital Universitario San Ignacio, Clínica Colsanitas (Clínica Universitaria Colombia see, Clínica Reina Sofía see, Clínica Santa María del Lago see), Fundación Universitaria Sanitas, Hospital Universitario Nacional de Colombia, Hospital Universitario de la Samaritana E.S.E, Hospital Universitario de la Samaritana Unidad Funcional Zipaquirá, Universidad del Quindío, Fundación Universitaria Autónoma de Las Américas, Hospital Universitario San Jorge and La Universidad Tecnológica de Pereira. Before consenting, you need to fully understand the purpose of your decision. This process is called informed consent. Once you have read this document and solved with the investigator any doubt, you will be asked whether you want to participate in this study.

GENERAL INFORMATION

- Why is this study carried out?

The pandemic of COVID-19 caused by SARS-CoV-2 is an event of interest in public health that directly affects health care workers. Social distancing and temporary isolation of infected people and their contacts are the main strategies to contain the spread of disease. However, health care workers are at increased risk of infection.

Personal protective equipment (PPE) is required for assisting suspected or confirmed COVID-19 and other preventive strategies have been proposed. That is why this research will evaluate the use of TDF/FTC as prevention of SARS-CoV-2 transmission in health professionals.

TDF/FTC is a drug routinely used for treatment of HIV and Hepatitis B infection. It has an established safety profile and has been evaluated for prophylaxis of HIV infection in at risk populations. Additionally, its inhibitory activity on ARN dependent ARN polymerase of SARS-CoV-2 has been confirmed in biologic models.

- What is the aim of this study?

To evaluate the efficacy and safety of TDF/FTC (300/200 mg/day) in addition to the use of personal protective equipment for the prevention of SARS-CoV-2 infection in health professionals that care for COVID-19 patients in the emergency department, hospital ward and intensive care unit.

- How will the study be carried out?

It is a randomized clinical trial with triple masking (which means neither you nor the investigators that directly take care of you or the personnel performing statistical analyses, will know whether you are receiving TDF/FTC or placebo) that involves health professionals (physicians, nurses, nurse assistants, respiratory therapists) in the emergency department, hospitalization ward and ICU.

During initial screening, we will perform a clinical assessment, laboratory blood tests, and molecular (nasal swab) and antibody tests to rule out the presence of SARS-CoV-2 before starting your participation. Women will also receive a pregnancy tests and will be excluded in case of a positive result.

Eligible participants will be randomly assigned to one of two groups: TDF/FTC (300/200 mg) once daily for 60 days plus PPE or placebo plus PPE. The participant will attend a baseline visit and 4 follow-up visits at days 20, 40 and 60 after starting the investigational product, and 15 days after ending-up investigational product administration (75 days after baseline visit). During these visits, we will perform clinical assessment, look for adverse events, confirm adherence to treatment, and take samples for the aforementioned tests, including tests for detection of COVID-19.

We may also perform an additional virtual or telephonic follow up in between visits, and require you to keep a diary of adherence, symptoms and adverse events and use of PPE.

In case of developing COVID-19, treatment will be withheld and we will give you recommendations to consult with your EPS or ARL, while keeping a telephonic follow up. This will be reported to the institutional review board (IRB) and also to SIVIGILA, as required by the authorities.

- What are the risks involved in your participation?

There are risks involved with the participation of this study. The most frequently reported risk in clinical trials (25-32%) independently of receiving the investigational intervention or placebo are:

- Nausea
- Headache
- Abdominal pain, bloating

Less frequently

- Malaise, fatigue
- Sleep disturbances
- Diarrhea
- Skin rash
- Kidney disfunction associated to the use of TDF/FTC, which comprises a variaty of manifestations, including proximal tubular disfunction, acute kidney injury, diabetes insipidus. However, it is infrequent, and it presents in less than 1% of patients that use it for less than six months. For that reason, people with baseline kidney disfunction defined as estimated glomerular filtration rate less than 60 ml/min/1,72 m^2 will be excluded, as will people taking other potentially nephrotoxic medications.
- Acute severe exacerbation of B hepatitis. To avoid this possibility, all people without immunity to B hepatitis, defined as Anti-HBs less than 10 UI/ml will be excluded.
- Loss of bone mineral density. This effect has been described after six months of use and are reversible after drug withdrawal.

Most of adverse events are mild. Serious adverse events are much more infrequent and depend of a prolonged use of the medicines. In previous studies involving TDF/FTC for prophylaxis, less than 2% of participants suspended the medication due to adverse events.

The length of treatment in this study will be short, thus minimizing the risk of serious adverse events.

Additionally, you may present discomfort associated with sample drawing. A total of 4 samples are scheduled (one prior to starting the drug and again on days 40, 60 and 75 after initiation of treatment), during which you may feel:

- Pain and bruises in puncture sites.

- You may also feel discomfort (cough, irritation and pain of nasal or nasopharyngeal mucosa, nausea, vomiting) associated with nasopharyngeal swab, of which you will receive at least two, one prior to starting the medication and one at day 60.

- What are the potential benefits of my participation in the study?

- In case of intervention being effective, you may have your risk of developing COVID-19 reduced.
- You may also contribute to acquire information that will help other health care workers.
- You may also benefit to access to early diagnosis of infection.

- Will there be confidentiality with management of my data?

This Project is subjected to law 1581 of 2012 (Habeas data) that applies for the treatment of personal data. When signing this document you agree to the use of your personal data by the investigators.

Only the members of the research team will know that you are participating in the study. Your records will be stored granting confidentiality by using a ciphered database in the software REDCap, which is held by Hospital Universitario San Ignacio. The database has controlled access using individual passcodes and it is restricted to the data analysis personnel.

All the study forms will be assigned a unique code that differs from your legal identification number. None of your personal data, such as name, address, telephone number or ID, will be used in any of the study forms, except for this informed consent form.

You will have the possibility of knowing and requiring rectification of all your personal data, and to withdraw your consent for personal data use.

- Is there any financial obligation for me?

You will incur in no financial obligation or expenditure while participating in this trial.

- How long will be my participation in the study?

Your expected participation time will be approximately 65 days (between 65 and 80 days), taking into account that if you develop COVID-19 at the end of the study, we will perform a telephone follow up to define the duration of infection and we may take some additional tests.

- What happens if I chose not to participate?

You may choose not to participate or withdraw at any moment along the course of the study without this carrying any consequence for you at work.

The investigators commit to update you with any new information that arises along the course of the study, even if this may affect your decision to continue your participation.

- What happens if this research directly affects my health?

While it is very unlikely that the intervention results in significant lesion, Pontificia Universidad Javeriana will cover all the medical expenditure resulting from a direct injury to your health related with the medication or study procedures. The study site will deliver any required treatment without any cost to you or to the health system. To cover all these potential costs, Pontificia Universidad Javeriana has purchased an insurance policy with La Previsora, Compañía de Seguros. Address of headquarters: Calle 57 # 9 -07, Bogotá, DC. PBX: +571 348 5757 / Código Postal 52946.

- What liability does my ARL (professional risks insurance company) have regarding any adverse events of damages resulting from my participation in the study?

Since this is a study for which you are completely free to participate, neither you employer not your ARL are responsible for the coverage of any risks directly associated with your participation in the study. These risks are covered by the terms and mechanism described above. However, should you develop COVID-19, your participation does not limit or exclude your ARL from the coverage of all disease associated expenditures.

In case you need information or in case of emergency, you may contact the principal investigator, Dr. Sandra Valderrama to the number 3103322297. The principal investigator will contact the Director of Clinical Research office of Hospital Universitario San Ignacio, Dr. Margarita Manrique to the phone number 31534656992 or to the email mmmanrique@husi.org.co.

If you have any doubt regarding the ethical issues of this research, which apply to all the study sites, you may contact the Institutional Review Board of the Pontificia Universidad Javeriana, Dr. Carlos Gómez-Restrepo (President) to the number 3208320 ext. 2770.

By signing this from you **DO NOT** give up any legal right to receive medical care or accept payment for medical expenditures.

AUTHORIZATION

I have understood all explanations that have been given to me in a clear and simple language. The investigator has allowed me to put forward all my doubts and concerns regarding aims, methods, benefits, inconveniences, and prognosis associated with my participation in the study and they have been clarified. I received a copy of this document.

By signing this document, I voluntarily consent to participating in the study "**effectiveness of personal protective elements plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for**

prevention of transmission of SARS-CoV-2 in previously healthy adult health care workers younger than 60 years.".

If you have any doubts regarding your participation in this study, you may contact the principal investigator, Dr. Sandra Valderrama to the number 3103322297, 5946161 ext. 6932 or the president of the Institucional Review Board of Pontificia Universidad Javeriana, Carlos Gómez-Restrepo, 3208320 ext. 2770, Carrera 7 No 40-62 Piso 8 Facultad de Medicina.

Volunteer's name	
Volunteer's signature	
Type and number of identification	
Telephone	
Date	

Name of impartial witness 1	
Signature	
Type and number of identification	
Telephone	
Relationship with volunteer	
Date	

Name of impartial witness 2	
Signature	
Type and number of identification	
Telephone	
Relationship with volunteer	
Date	

Name of the research team member that carries-out the informed consent process	
Signature	
Type and number of identification	
Date	
Role in the study	

Aappendix 5. Informed consent form in pregnancy

	MANAGEMENT OF CLINICAL RESEARCH	

INFORMED CONSENT IN CLINICAL RESEARCH PROJECTS

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INTRODUCTION
Volunteer's code: _____ Since you became pregnant during your participation in the study **effectiveness of personal protective elements plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for**

prevention of transmission of SARS-CoV-2 in previously healthy adult health care workers younger than 60 years." This document seeks to obtain your authorization to gather information regarding de development and outcome of you pregnancy and the health of your newborn.

INFORMACIÓN GENERAL

1. Why is this follow-up carried out?

TDF/FTC is a medication classified as B in pregnancy, which means it belongs to a group of medicines for which there is no evidence fetal risk. The use of this medication is generally accepted during pregnancy. For instance, it is a drug of choice as part of the antiretroviral regimen for pregnant women infected with HIV, to avoid transmission of infection to the newborn.

There is no evidence of teratogenicity in humans, which means it does not induce or increase the risk of malformations while administered during pregnancy. Nevertheless, there is evidence that it may cause fetal growth delay and reduction of fetal bone porosity while administered to monkeys at doses twice the dose used in humans during the first two months of pregnancy. In human studies, there is no proven association with these outcomes.

In spite of being a drug with well established safety in pregnancy, we chose to carry out this follow up because at the beginning of the study you had a negative pregnancy test and now you have a positive pregnancy test, which means you pregnant and were exposed to TDF/FTC.

2. How will be this follow-up done?

After confirming your pregnancy we will gather information at the following moments:

- We will make phone calls every trimester and keep a record of the status of your pregnancy, maternofetal ultrasound and gestational age.
- We will contact you after birth to record the newborn's sex, weight, length, cephalic perimeter, gestational age, delivery route and clinical status.
- By signing this document, you voluntarily accept telephone follow-up and review of your clinical records.

3. What are the benefits of this follow-up?

The only Benefit is to grant that you will have a follow up under the conditions described in question 2, due to your exposure to TDF/FTC during pregnancy.

- Will there be confidentiality with management of my data?

As described in the main informed consent form for the participation in the study, information contained in this follow-up will be protected according to law 1581 of 2012 (Habeas data) that applies for the treatment of personal data.

All information gathered regarding your pregnancy and the health of you newborn will be kept confidential and will not be shared with any person or institution apart from investigators or the Institucional Review Board, without you prior authorization.

Information obtained in this follow-up will be kept in the same manner as described in the main Informed Consent Format of the study, which was previously signed by you.

- Is there any financial obligation for me?

You will incur in no financial obligation or expenditure while participating in this additional follow-up regarding your pregnancy.

- How long will be my participation in the study?

Information will be collected along all your pregnancy up to birth.

- What happens if I chose not to participate?

You may choose not to accept this follow-up or to withdraw your consent for follow-up at any time without this having any consequence for you or your newborn.

4. What happens if this follow-up results in any direct injury or damage to my health?

There is no potential medical risk associated with gathering this information by telephone.

While it is very unlikely that you or your child suffer any damage derived from you taking TDF/FTC during pregnancy, Pontificia Universidad Javeriana will cover for any medical expenditures resulting from direct damage related with the investigational drug. The study site with deliver any necessary treatment to you or your newborn without you or the health system incurring in any expenditure. To cover for all these potential costs, Pontificia Universidad Javeriana has purchased an insurance policy with La Previsora, Compañía de Seguros, address: Calle 57 # 9-07, Bogotá, Colombia.

Likewise, the policy will cover the costs of medical care and treatments in the case your newborn suffers any damage or disability resulting from participation in the study. The causality of the drug over these injuries or disabilities must be effectively established and demonstrated.

In case you need information or in case of emergency, you may contact the principal investigator, Dr. Sandra Valderrama to the number 3103322297. The principal investigator will contact the Director of Clinical Research office of Hospital Universitario San Ignacio, Dr. Margarita Manrique to the phone number 31534656992 or to the email mmmanrique@husi.org.co.

By signing this from you **DO NOT** give up any legal right to receive medical care or accept payment for medical expenditures.

AUTHORIZATION

I have understood all explanations that have been given to me in a clear and simple language. The investigator has allowed me to put forward all my doubts and concerns regarding aims, methods, benefits, inconveniences, and prognosis associated with my participation in this pregnancy follow up and they have been clarified.

By signing this document, I voluntarily consent to be contacted with the purpose of gathering information about my pregnancy and its outcome, during pregnancy and after childbirth. Likewise, I authorize access to my personal information and that of my child.

I received a copy of this document.

If you have any doubts regarding your participation in this study, you may contact the principal investigator, Dr. Sandra Valderrama to the number 3103322297, 5946161 ext. 6932 or the president of the Institutional Review Board of Pontificia Universidad Javeriana, Carlos Gómez-Restrepo, 3208320 ext. 2770, Carrera 7 No 40-62 Piso 8 Facultad de Medicina.

Volunteer's name	
Volunteer's signature	
Type and number of identification	
Telephone	
Date	

Name of couple/other parent of the minor	
Signature of couple/other parent of the minor	
Type and number of identification	
Telephone	
Date	

Name of impartial witness 1	
Signature	
Type and number of identification	

Telephone	
Relationship with volunteer	
Date	
Name of impartial witness 2	
Signature	
Type and number of identification	
Telephone	
Relationship with volunteer	
Date	
Name of the research team member that carries-out the informed consent process	
Signature	
Type and number of identification	
Date	
Role in the study	

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