

A Randomized, Controlled Study on the Safety and Efficacy of Maraviroc and/or Favipiravir Vs Currently Used Therapy in Severe COVID-19 Adults. (COMVIVIR, clinicaltrials.gov NCT04475991)

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Abstract

Background: Multiple studies have now established that hyperinflammatory response induced by SARS CoV-2 is a main cause of complications and death in infected subjects. Such dysfunctional immune response has been described as a dysregulated and exacerbated production of cytokines and chemokines that attracts and activates inflammatory cells, which start and sustain pulmonary and systemic damage, thus causing complications that lead to multi organ failure and death. Therefore, we suggest that blocking key inflammation receptors could help to reduce migration and activation of Th17, monocytes/macrophages and neutrophils, thus mitigating the cytokine storm and averting severe complications and death. Importantly, the optimum treatment for COVID-19 severe patients could combine a modulator of the immune response with a direct antiviral drug against SARS-CoV-2, in order to address both the viral load and the hyperinflammatory effects of the immune dysregulation.

Methods: Maraviroc (MVC), a CCR5 antagonist, and Favipiravir (FPV), an antiviral, will be evaluated single and combined, added to the treatment currently used at the Hospital General de México for severe non-critical COVID-19 patients. One hundred patients will be allocated in four arms [Current treatment only (CT), CT+MVC, CT+FPV, CT+MVC+FPV]. Percentage of patients free of mechanical ventilation or death at day 28, immunophenotyping and viral load will be compared between groups

Discussion: New immune focused therapies are targeting strong inflammation mediators such as IL-6 and IL-1-B; nevertheless, to our best knowledge, controlling chemotaxis has not been explored. The use of a drug therapy that addresses both the regulation of the immune response and the inhibition of viral replication could at the same time, help to alleviate the hyperinflammatory condition and reduce the time of the viral clearance process, therefore improving treatment outcomes

Trial registration: Clinical Trials (www.clinicaltrials.gov) NCT: 04475991.

Introduction

Background and rationale {6a}

The infection by SARS-CoV2 can cause a dysregulation characterized by an exacerbated immune response that leads to a generalized hyperinflammatory condition, which in turn may cause multiple complications, and eventually death. The cells accountable for such dysregulation express receptors like CCR5, which mediate their activation and trafficking to the lungs. Therefore, CCR5 could be considered a therapeutic target. MVC is a CCR5 antagonist that could also have an antiviral effect, albeit it has not been evaluated in the context of COVID-19. Alongside, the results could be potentiated by the direct effect of an antiviral such as FPV. Currently, there is not a vaccine able to effectively prevent the disease, and the pharmacologic strategies used for treatment have not proven completely effective. Thence, more studies of different therapeutic targets are needed to search for resources that help to improve the patients' prognosis. The use of a drug therapy that addresses both the regulation of the immune response and the inhibition of viral replication could at the same time, help to alleviate the hyperinflammatory condition and reduce the time of the viral clearance process. At the present time (August 2020), there are no published studies of the use of MVC in COVID-19; the only reports are three trials registered in www.clinicaltrials.gov, one of which is this . In regard to FPV in COVID-19, an open, randomized study in 80 mild patients found that FPV reduced the time of viral clearance by 50% compared to Lopinavir/Ritonavir with less adverse effects (1), however, the study population had no risk comorbidities, and subjects with O2 saturation <93% were excluded. Another open randomized study in moderate patients reported FPV to be more effective in clinical recovery compared to Arbidol (2). An in vitro study found that FPV is capable to suppress the SARS-CoV-2 infection at high concentrations (3). Finally, a report from March 2020 (4) mentions 3 ongoing clinical trials registered in the Chinese Clinical Trials record (www.chictr.org.cn) to evaluate FPV in COVID-19 patients, all in recruiting phase.

Objectives {7}

Increase the percentage of patients free of mechanical ventilation or death by 30% at day 28 post-start of treatment.

Trial design {8}

This is a randomized, controlled study consisting of four arms. One hundred subjects will be randomized and allocated in the study arms (25/ arm; 1:1:1:1 ratio)

Methods: Participants, Interventions And Outcomes

Study setting {9}

The study will be conducted at the facilities of the Hospital General de México "Dr. Eduardo Liceaga", located near downtown Mexico City, Mexico.

Eligibility criteria {10}

Screening: criteria: Upon admission, screening criteria will be applied in the Emergency service to select the candidates

- Adult patients (18-70)
- Within 12 days of the appearance of symptoms
- Severe non-critical clinical stage at admission
- At least one of the following risk factors: DM, obesity (BMI>30), hypertension history or age >65
- Respiratory rate 25-34/min AND absence of other clinical signs of respiratory distress (nasal flaring, intercostal pulling, thoracoabdominal dissociation, hypoxic encephalopathy
- Respiratory rate 25-34/min
- Thorax USG with LUS >23
- O2 saturation 90-81% (Unassisted)

Inclusion criteria: These will confirm the selected subjects for enrollment.

- Positive for SARS-CoV-2 confirmed by PCR
- PaFi 250-100
- LDH (Lactate dehydrogenase) >350
- >50% pulmonary infiltration as determined by thoracic imaging
- FiO2 requirement >60% to maintain oxygenation goals
- Normal hepatic function, defined as a maximum of a fivefold increase of transaminases.
- Signed informed consent.
- Women in fertile capability must accept the use of a contraceptive method for 90 days after treatment completion.

Exclusion criteria

- Pregnant or lactating women
- Participating in another clinical trial
- Clinical evidence of an infectious disease different from COVID-19 at the time of admission
- Glasgow coma score <13
- Clinical signs of respiratory distress (nasal flaring, intercostal pulling, thoracoabdominal dissociation, hypoxic encephalopathy AND persisting Glasgow score \leq 13
- Glomerular filtration rate <60ml/min/1.73m² and known history of pre-existing chronic kidney disease (Chronic kidney disease stage 3,4,5)
- Coronary disease (acute or chronic)
- Previous history of allergies to MVC or FPV
- Autoimmune disorders
- History of any previous transplant
- Under treatment with psychotropic drugs of any kind.
- Cancer of any kind

Elimination criteria

- Withdrawal of the informed consent

Who will take informed consent? {26a}

All candidates must read and sign an Informed Consent Form (ICF) before enrollment. The ICF will be obtained by certified researchers, physicians and nurses of the Hospital staff participating in this study (APG, MLHM, EOMH, and MLH). A model of the ICF can be provided upon request.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable since there are no additional samples to be collected.

Interventions

Explanation for the choice of comparators {6b}

Comparison between groups was based upon treatment with MVC or FPV or both or none.

Intervention description {11a}

***ARM A: Active Comparator: Currently used therapy (CT) only.** Treatment currently used at Hospital General de México "Dr. Eduardo Liceaga" for non-critical COVID patients: Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present.

***ARM B: Experimental: Maraviroc+CT.** Maraviroc tablets. 300 mg bid, given orally for a 10 day period AND CT (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present, as per currently used at Hospital General de México "Dr. Eduardo Liceaga").

***ARM C: Experimental: Favipiravir+CT.** Favipiravir tablets 200 mg. given orally for a 7 day period. 1600 mg bid on day 1 and 600 mg tid days 2-7 AND CT (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present, as per currently used at Hospital General de México "Dr. Eduardo Liceaga").

***ARM D: Experimental: Maraviroc+Favipiravir+CT.** Maraviroc tablets. 300 mg bid, given orally for a 10 day period AND Favipiravir tablets 200 mg. given orally for the first 7 days. 1600 mg bid on day 1 and 600 mg tid days 2-7 AND CT (Enoxaparin, dexamethasone, and antibiotics if associated bacteremia is present, as per currently used at Hospital General de México "Dr. Eduardo Liceaga").

Criteria for discontinuing or modifying allocated interventions {11b}

If patients progress to critical condition, tablets will be crushed and administered using a nasogastric tube. The treatment will be discontinued in the occurrence of treatment-related adverse effects ruled so by a physician.

Strategies to improve adherence to interventions {11c}

Not applicable since all participants are inpatients.

Relevant concomitant care permitted or prohibited during the trial {11d}

Not applicable since all participants are inpatients, and such care will be provided by nursery staff if needed.

Provisions for post-trial care {30}

Not applicable since patients are discharged upon improvement

Outcomes {12}

Primary:

- Percentage of patients free of mechanically-assisted ventilation [time frame: day 28]. Clinical relevance: Evaluation of the efficacy of the treatment to prevent complications and death at day 28.

Secondary:

- Percentage of patients free of mechanically-assisted ventilation [Time frame: day 5] Clinical relevance: Evaluation of the efficacy of the treatment to prevent complications and death at day 5

- Time of improvement in at least 2 categories in the WHO 7-category ordinal scale (44) [Time frame: day 15] Clinical relevance: Evaluation of the efficacy of the treatment to improve the patients' condition and prognosis.
- Evaluation of the response to treatment of the hyperinflammatory condition by analysis of the change rate in percentage of lymphocytes, monocytes and neutrophils, as well as proinflammatory chemokine and cytokine levels [Time frame: day 10-0]

Participant timeline {13}

The following diagram depicts the arms and interventions of the study

STUDY PERIOD															
	Enrollment		Allocation		Post-allocation								Follow-up period		Close out
	Screening period		Treatment period										Follow-up period		Close out
EVENT	-D2	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	D28	D180
Informed consent	X														
Screening criteria	X														
Inclusion criteria	X														
Allocation		X													
INTERVENTION															
Arm A: Current Therapy (CT)			X	X	X	X	X	X	X	X	X	X			
Arm B: MVC + CT			X	X	X	X	X	X	X	X	X	X			
Arm C: FVP + CT			X	X	X	X	X	X	X	X	X	X			
Arm D: MVC + FVP + CT			X	X	X	X	X	X	X	X	X	X			
ASSESSMENTS															
Variables															
Hematic biometry	X														
Electrocardiogram		X											X		
Viral Load		X			X				X				X		
Chemokines		X											X		
Cytokines		X											X		X
Chest x-ray	X												X		
Disease progress							X							X	
Days free of mechanical ventilation							X						X	X	

Sample size {14}

The calculation was performed to compare survival curves using EPIDAT 4.2, based upon the current casuistry observed at the Infectology service of the Hospital General de México, with a mechanical ventilation free survival rate in severe cases of 65% and a maximum expected value of 80%, with a confidence level of 80%. For a 4-arm study, the following is obtained:

Sample size and power for survival curves comparison:

Groups: 4

Estimated losses: 15%

Confidence level: 80.0%

Survival probability (%)

Group 1: 65

Group 2: 75

Group 3: 75

Group 4: 80

Power (%)	Total
80.0	98

Therefore, 25 patients were allocated by group; 100 total.

Recruitment {15}

Participants will be recruited from the adult COVID-19 population of patients admitted to the Hospital.

Assignment of interventions: allocation

Sequence generation {16a}

The allocation order will be generated randomly by EPIDAT 4.2 to assign the subjects to the A, B, C or D arms. Each patient's medical record number will serve for identification of the assigned treatment.

Concealment mechanism {16b}

Not applicable since this is not a blinded study.

Implementation {16c}

The allocation and enrollment of patients will be performed by certified researchers and nurses from the Hospital who are members of the staff of the study. (MLHM, ARCM, APG)

Assignment of interventions: Blinding

Who will be blinded {17a}

Not applicable since this is not a blinded study

Procedure for unblinding if needed {17b}

Not applicable since this is not a blinded study

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data will be collected from the patients in printed forms by the nursery staff and then captured in a specially designed Excel data collection tool (Project EXCELEN-19 currently being conducted in the Hospital) by the study staff (LMPN), or their authorized surrogates. Double capture will be applied. Laboratory results will be uploaded to the patients database and incorporated to each participant's information.

Plans to promote participant retention and complete follow-up {18b}

After discharge, patients will be contacted by the study staff (LMPN, MMSM, MLH) or their authorized surrogates to ask them about their general health and some specific issues addressed to evaluate their pulmonary condition and the appearance of possible respiratory sequels.

Data management {19}

Data will be captured in a specially designed Excel data collection tool (Project EXCELEN-19 currently being conducted in the Hospital) by the study staff (LMPN), or their authorized surrogates. Double capture will be applied. Data will be stored in a Hospital's server with restricted access rights.

Confidentiality {27}

Participant's names will be collected only at admission, and will not be used for the study. A consecutive ID number and the patient unique file number (assigned by the Hospital database) will be used instead.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

The following diagram describes the planned collection of samples

Blood samples will be collected by certified nursery personnel. Samples will be processed in three different ways:

- Fresh samples immediately processed in laboratory.
- Serum collection and freezing at -80°C. Samples will be analyzed by flow cytometry at a later time
- Obtaining and preservation of leukocytes in DMSO at -80°C. Samples will be analyzed by flow cytometry at a later time.

Saliva and nasopharyngeal exudate samples will be collected by certified nursery personnel and frozen at -80°C. Samples will be analyzed for viral load at a later time.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary endpoint (Percentage of patients free of mechanically assisted ventilation [time frame: day 28]) will be compared between the 4 arms using a Cochran-Mantel-Haenszel test stratified in time.

The secondary endpoints will be compared between arms as follows:

- Percentage of patients free of mechanically assisted ventilation [Time frame: day 5]: Cochran-Mantel-Haenszel test stratified in time.
- Time of improvement in at least 2 categories in the WHO 7-category ordinal scale (44) [Time frame: day 15]: Kruskal-Wallis test.
- Change rate in expression of proinflammatory cytokines and chemokines in different leukocyte subpopulations [Time frame: day 10-1]: One-way ANOVA will be used to compare change rate of each cytokine/chemokine. Additionally, a Principal Component Analysis (PCA) will be performed for cluster identification and their role in the response to treatment.
- Change rate in the patterns of activation, trafficking and exhaustion in peripheral blood lymphocytes, monocytes and neutrophils [Time frame: day 10-1]: Data will be analyzed for subpopulations, percentages and mean fluorescence intensities for each molecule
 - By subsets: Gating using Flowing Software
 - By clusters: PCA using RStudio

Data will be controlled by confounding factors (BMI, sex, hypertension and diabetes). A Cox regression survival analysis adjusted by age, BMI, sex and comorbidities will be performed to estimate the relative risk of each of the following variables: Discharge by improvement or death, days of hospital stay and days free of ventilatory support.

Interim analyses {21b}

An interim analysis will be carried out when data from 50 patients had been processed. If such analysis has a minimum of 50% power, a group analysis will be performed, and the results will be published.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Not Applicable since there are no subgroups

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

We are foreseeing no issues with non-adherence, because all the subjects are inpatients. To prevent inconsistencies or biases from missing data due to interruption of treatment, the modified intention to treat (mITT) will be calculated, based on the criterion of at least one dose taken and at least one measurement after basal of the endpoints.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Access will be given on the basis of inter institutional exchanges upon request, for collaborative research purposes.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The study will be monitored by the Committees of Ethics, Research and Biosafety of the Hospital General de México "Dr. Eduardo Liceaga" The Ethics Committee has a valid registration in the National Commission of Bioethics.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Quality Manager, and a MD from the Clinical Pharmacology service, along with their authorized surrogates, will form the Data Monitoring Committee. They will review the data and will check for consistency and completeness of the records.

Adverse event reporting and harms {22}

All adverse events will be immediately recorded and reported to the MDs who serve as Officials (MLHM, EOMH). They will assess if the AE is related to the medication under study, and if the participation of the patient should be terminated for safety reasons.

Frequency and plans for auditing trial conduct {23}

Auditing will be a mixture of internal and external monitoring. Internal will be an in-house quality control, while external will assure international quality standards. Both will be performed on a regular basis during the protocol. Internal monitoring will be performed by in-house personnel, whereas external will be carried out by a third independent party

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Every relevant change to the protocol is of mandatory notification to the Committees of Ethics, Research and Biosecurity of the Hospital in the form of an amendment, which will be evaluated for approval.

Dissemination plans {31a}

The results will be available for the participants upon request. Publication in a peer-reviewed journal is being prepared. The process to register the protocol in the National Commission of National Institutes and High Specialty Hospitals (CCINSHAE for its acronym in Spanish) is already being completed.

Discussion

Despite it is known that blood samples of positive patients do not contain SARS CoV2 (5), they will be handled according to the Good Clinical Practice protocol for these samples, following the guidelines of a BSL-3 laboratory (6) and the official ruling NOM087 (7), applicable to our Normalized Operation Procedure PNO-CE-05

Trial status

The submitted version of the protocol is 5.0, September 2020. Recruitment is estimated to start on the 1 of October 2020, and estimated to end on January 2021.

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
bid	Twice a day
BSL-3	Biosafety Level 3
BMI	Body Mass Index
CCL2	Chemokine C-C motif 2
CCL3	Chemokine C-C motif 3
CCL4	Chemokine C-C motif 4
CCL5	Chemokine C-C motif 5
CCL7	Chemokine C-C motif 7
CCL8	Chemokine C-C motif 8
CCR5	Chemokine C-C motif 5 Receptor
COVID-19	Coronavirus Disease 2019
CT	Current Treatment
CXCL-10	Chemokine C-X-C motif 10
DM	Diabetes mellitus
DNA	Deoxyribonucleic Acid
FiO ₂	Fraction of Inspired Oxygen
FPV	Favipiravir
HGMEL	Hospital General de México "Dr. Eduardo Liceaga"
H1N1	Hemagglutinin Neuraminidase Influenzavirus
HIV	Human Immunodeficiency Virus
IFN- γ	Interferon- γ
IL-6	Interleukin 6
IL-12	Interleukin 12
IL-1 β	Interleukin 1 β
LDH	Lactic Dehydrogenase
LUS	Lung Ultrasonographic Score
Mpro	Main protease
MVC	Maraviroc
NET	Neutrophil Extracellular Traps
NOD2	NOD like receptor 2
NPE	Nasopharyngeal Exudate
PaFi	Quotient between PCO ₂ and FiO ₂ (Kirby Index)
PaO ₂	Partial Oxygen Pressure
PCA	Principal Component Analysis
p.o.	Oral administration
PPAR- γ	Peroxisome proliferator-activated receptor gamma
RdRP	RNA depending RNA Polymerase

RNA	Ribonucleic Acid
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2

Declarations

Acknowledgements

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Maraviroc will be donated by Glaxo Smith Kline México.

Favipiravir will be supplied by CCINSHAE.

Authors' contributions {31b}

- APG is the Chief Investigator. He co-conceived the study, searched the literature, assembled the protocol, participated in the methodologic design, submitted the protocol for approval of the Committees, coordinates inter institutional cooperation, led the proposal and protocol development.
- MLHM is the Medical Officer of the protocol. She participated in the design and contributed to outline the outcomes and the eligibility criteria. She will also monitor patient care, keep record of adverse effects and evaluates if treatment should be continued in their occurrence.
- LMPN participated in the methodological and statistical design, as well as in the outlining of the outcomes. She conducted the design of a data collection tool (Project EXCELEN, currently being developed at the Hospital).
- EOMH and DSCO will monitor patient care, keep record of adverse effects and evaluates if treatment should be continued in their occurrence.
- MMSM participated in defining quality issues and internal monitoring
- AMEG will coordinate the laboratory procedures for sample processing
- AVO participated in the design of cytometry panels and viral load tests
- HSV participated in the design of cytometry panels and viral load tests
- MLH participated in the design of the schedule for sample collection. She designed the nursery plan to accomplish the tasks within the study.
- GMLGA participated in the design of the study, assignation of resources and managed national and international exchanges
- RSL participated in the logistic design and assignation of resources.
- ARCM participated in the design of the schedule for sample collection. She will also take part in laboratory procedures for sample preparation.
- GRT participated in the design of the study, by proposing treatment schemes for different scenarios based upon drug interactions and pharmacokinetics.
- JSM participated in the design of the study, collaborated in the outlining of primary and secondary outcomes
- GSMO participated in the design of the cytometry panels. He will also conduct the cytometry tasks
- SAR participated in the design of the cytometry panels.
- JCLA outlined the statistical methodology
- JHR co-conceived the study, participated in the design of cytometry panels and the logistic design. He will act as Corresponding Author.
- All authors read and approved the final manuscript

Funding {4}

The protocol will be funded by Federal Government funds as a part of the budget that the Hospital receives. Those documents are out of access to the authors. The funding party will have no involvement in the design of the study, analysis and interpretation of data, nor in writing the manuscript.

Availability of data and materials {29}

All data generated from this protocol will be kept in official Hospital computers. Only the members of the staff who work at the Hospital will have access to them (APG, MLHM, LMPN, EOMH, AMEG, AVO, MLH, GMLGA, RSL, ARCM, MMSM, JHR). Data in government computers are protected by law under penalty of criminal liability.

Ethics approval and consent to participate {24}

The protocol was originally approved by the Institutional Ethics Committee of the Hospital General de México “Dr. Eduardo Liceaga” on the 23rd of June 2020 (Original in Spanish and English translation attached). The Ethics Committee has a valid registration in the National Commission of Bioethics (registration number CONBIOETICA-09-CEI-005-20160531). The Research Department authorized the protocol on the 24th of June 2020 and assigned the registration number DI/20/407/04/38. All participants must sign an informed consent form. A model of such form can be supplied on request.

Consent for publication {32}

Not applicable since no details, images or videos relating to an individual person will be used in the publication

Competing interests {28}

All the authors declare that they have no competing interests

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Figures

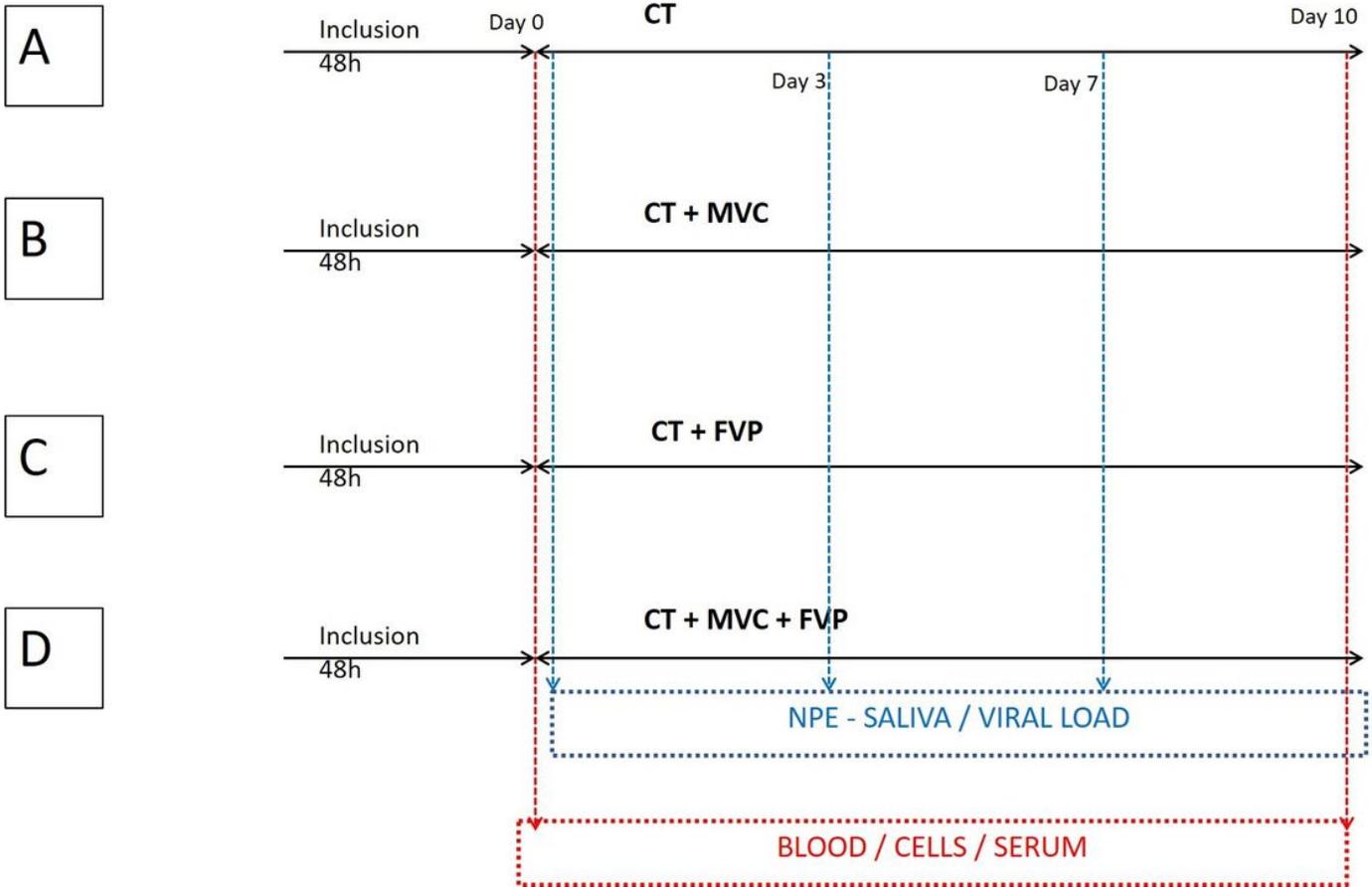


Figure 1

The diagram describes the planned collection of samples. NPE: Nasopharyngeal Exudate