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COVID-19 Clinical Trials in Alberta

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Faculty/Presenter Disclosure

- **Luanne M. Metz** MD FRCPC
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- Grants, clinical trials: MS Society of Canada
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- **I have properly cited third party material in one of the ways outlined below.**

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Disclosure of Financial Support

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- The program was developed and planned to achieve scientific integrity, objectivity and balance.

- This program has received financial support from
- Government of Alberta
- Alberta Health Services
- University of Calgary
- Calgary Health Trust
- Alberta Innovates

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Learning Objectives

After this session, participants will be able to:

- Articulate the scope of clinical therapeutic and other trials in Alberta
- Describe two key trials of therapy that will affect outpatients – ABCOV-1 trial and PEP trial
- Identify strategies for following up with and supporting your patients who are enrolled in these trials

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HOPECOVID.CA

- **A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of oral hydroxychloroquine for the treatment of SARS-CoV-2 positive patients for the prevention of severe COVID-19 disease**
- Goal is to test if early treatment with HCQ among patients with increased risk can prevent severe Covid19 disease
- HOPE = Hydroxychloroquine for Prevention
- HOPECOVID.CA

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Rationale

- HCQ has antiviral activity by reducing virus replication inside the cell
- HCQ has immunomodulatory activity
- GOAL = reduce virus replication and reduce over-exuberant immune response, leading to reduced severity of illness
- HCQ was used during the first SARS-Cov1 outbreak in Hong Kong and Toronto in 2003; however, it was only used in cohort studies
- There are no phase 2 RCTs to suggest an effect size
- We only have case series data

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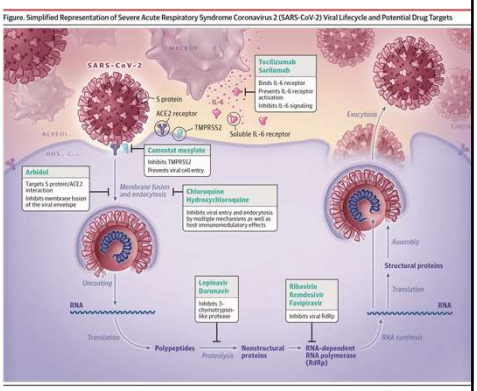
- Long half-life (~3 weeks)
- Oral medication
- BID dosing
- Generally well tolerated with few side effects
- Major concern is cardiac risk – prolong QTc with risk of ventricular arrhythmia



Sanders et al. *JAMA*. doi:10.1001/jama.2020.6019
Published online April 13, 2020.

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Rationale: Public Health Need

- public health need is GREAT
- HCQ is well-known, has a well described safety profile and we have secured a drug supply, donated from Apotex

Trial is designed to show a 35% relative risk reduction in the composite outcome of hospitalization, invasive mechanical ventilations and death.

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Alberta HOPE Covid19 Trial

- Protocol Overview

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Primary Outcome

- Trial is designed to show a 35% relative risk reduction in the composite outcome of hospitalization, invasive mechanical ventilations and death

Treatment

- Hydroxychloroquine (HCQ) or matching placebo x 5 days
  - 400 mg bid (2 tablets) x 1 day then
  - 200 mg bid (1 tablet) x 4 days
- Within 12 days of symptom onset
- Within 4 days of positive test result

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- Only telephone interaction with patients
  - Safety
  - Speed
- Telephone consent with recording
  - Replaces traditional in person consent
- Direct linkage with administrative data for outcome ascertainment
  - Blending model of telephone follow-up and electronic data from AHS
- Use of direct data entry
  - RedCAP will be the "source" documentation method
  - No paper records

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- Record time approvals by CHREB and HREB
  - Use of mock REB Exchange process which will be finalized later in the year
- A little nit-picking, but similarly amazingly fast approvals by Health Canada
- Fundraising cooperation
  - Consortium based funding for the study (UofC, Alberta Innovates, Alberta Government, SCN's, Calgary Health Trust and more pending)
- All of the team coming together so rapidly with so much expertise to share

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<u>Process</u>

- Patient is told by Public Health that they have a positive test
- AHS asks for their permission to pass along their details to us
- If yes, we get an automated list to our systems and we approach them for telephone consent

<u>Consent and Randomization</u>

- Randomize on-line
- Two drug depots in Edmonton and Calgary
- Courier drug to the patient
- Instructions to take drug for 5 days
- Telephone FU at 7 and 30 days

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Inclusion Criteria

1. **Confirmed SARS-CoV-2 infection**
2. Self-reported **symptoms** of SARS-CoV-2 infection (fever ≥37.5°C, cough, dyspnea, chest tightness, malaise, sore throat, myalgias, or coryza)
3. Treatment **within 96 hours of positive test result**
4. Treatment **within 12 days of symptom onset**
5. Adults, age 18 and over, with **any risk factor for severe disease** (as per Table below)
6. **Resident of Alberta** or if not a resident of Alberta able to provide complete follow-up data
7. Agrees to use **adequate contraception** for the duration of the study
8. Informed consent

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- **Age 40 or over**
- BMI >40 (calculated by self-report height and weight)
- Hypertension (on medical treatment)
- Current cigarette smoker
- Bone Marrow Transplant within previous 12 months
- Solid Organ Transplant
- AIDS/HIV CD4 <200 within last 6 months or CD4>200 but not on treatment
- Moderate Lymphopenia (within previous 6 months: Adults <500)
- Chronic Kidney Disease (eGFR < 60 including people on dialysis)
- Diabetes (on a hypoglycemic or insulin)
- Coronary Artery Disease (non-revascularized and as per physician diagnosis in medical chart)
- Heart Failure/Reduced LVEF (as per physician diagnosis in medical chart)
- Chronic Lung Disease (COPD, Asthma, interstitial lung disease, as per physician diagnosis)
- Any Current Cancer diagnosis (as per physician diagnosis)
- Acquired or Congenital Immune Deficiency (as per physician diagnosis in medical chart)
- Cirrhosis (normal INR and bilirubin and no history of ascites, encephalopathy, or variceal bleeding as per history and medical chart)
- Homelessness

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- **Prednisone** ≥7.5 mg daily x 3 weeks (or equivalent)
- **Methotrexate** (Greater than or equal to 7.5 -15 mg weekly suggested)
- **Azathioprine** (Imuran)
- **Cyclophosphamide** within the previous 6 months
- **Mitoxantrone** (Novantrone)
- **Cell depleting therapy** within the previous 24 months: cladribine (Mavenclad), alemtuzumab (Lemtrada, Campath)
- **Anti-TNF:** infliximab (Remicade, Inflectra, Renflexis) adalimumab (Humira), golimumab (Simponi), etanercept (Enbrel, Brenzys, Erelzi), certolizumab (Cimzia)
- **Anti-IL17**: secukinumab (Cosentyx), ixekizumab (Taltz), brodalumab (Siliq)
- **mTOR inhibitors**: sirolimus, everolimus
- Mycophenolate mofetil (**MMF)**: mycophenolic acid
- **Anti-IL12/23**: Ustekinumab (Stelara), rizankizumab (Skirizi), risankizumab (Skyrizi), guselkumab (Tremfya)
- **Anti-CD28**: abatacept (Orencia)
- **JAK2 inhibitors**: tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq)
- **Anti-CD20**: rituximab, ocrelizumab (Ocrevus) within the previous 12 months
- **S1P inhibitors**: fingolimod (Gilenya)
- **Anti-alpha4beta7**: vedolizimab (Entyvio)
- **Anti-IL4**: dupilumab (Dupixent)
- **Anti-IgE FcR**: omalizumab (Xolair)

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Exclusion Criteria

1. Currently or imminently planned admission to hospital
2. **Any contraindication to hydroxychloroquine**
3. Participation in an ongoing interventional clinical trial within the previous 30 days
4. **Use of hydroxychloroquine (Plaquenil) or chloroquine, lumefantrine, mefloquine, or quinine within the previous 30 days**.
5. **Inability to swallow pills** or any other reason that compliance with the medical regimen is not likely
6. **Pregnant or breastfeeding**
7. Severe underlying disease where treatment is **not likely to be beneficial** to the patient

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Exclusion Criteria #2

- Known diagnosis of G6PD deficiency or porphyria
- Known retinal eye disease with vision impairment, in which hydroxychloroquine is a known contraindication
- Known history of QTc prolongation
- Known significant liver disease
- Uncontrolled epilepsy
- Current use of drugs that are known to prolong the QTc. (*per list*)
- Score of 7 or more on the Tisdale scale modified

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Exclusion Criteria #2 - Drugs

Amiodarone	Droperidol	Methadone
Amitriptyline	Erythromycin	Moxifloxacin
Azithromycin	Escitalopram	Pentamidine
Chlorpromazine	Flecainide	Pimozide
Ciprofloxacin	Fluconazole	Pentamidine
Citalopram	Fluoxetine	Procainamide
Clarithromycin	Haloperidol	Propafenone
Desipramine	Ibutilide	Quinidine
Disopyramide	Imipramine	Sertraline
Dofetilide	Itraconazole	Sotalol
Doxepin	Ketoconazole	Thioridazine
Dronedarone	Levofloxacin	Venlafaxine
	Maprotiline	Voriconazole

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Exclusion Criteria #2 – Tisdale Score ≥ 7

Variable	Points	Notes
One QTc-prolonging drug (This will be hydroxychloroquine)	3	All patients score 3 points at baseline because they will be on HCQ or placebo.
Age ≥68	1	
Female	1	
Loop diuretic (furosemide/Lasix, butmetanide/Bumex, torsemide)	1	
Serum K+ (Potassium) < 3.5 mM on any blood work in the last 30 days	2	Check Netcare for recent bloodwork If there is no blood work in the last 30 days, score 0
QTc ≥450 ms on any ECG in the last 1 year.	2	Look at Netcare/SCM/CC for ECG tracing. If there is no ECG in the last year, score 0.
1 or more additional QTc-prolonging drugs from the list below	3	Score is not additive – score is 3 whether they are taking one or more than one additional drugs. These participants are ALL EXCLUDED

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<u>Randomizer / Patient Tracker</u>

- Randomization uses a balancing algorithm; on-line, dynamic
- Patient tracker provides a task list and reminders

<u>RedCAP DB</u>

- This is our Electronic Data Capture tool
- It will be considered source from the telephone conversation
- Enter data directly

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- Telephone FU at:
  - Day 7-10
  - Day 25-35 (or early end of study)
- End of study is at the primary outcome of hospitalization/IMV/death or day 30
- No simple AEs
- SERIOUS AEs only to 30 days

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On the same day you receive this:

Please take the first dose of the study medication as described on the back of this page

And

Notify the study team that you received and took your first dose of study drug by either:

Phone (answering machine) 866-990-1231

Or

Email (albertahopecovid19@ucalgary.ca)

Leave the following information when you notify us:

Your first and last name (please spell it if you phone)

Your study HOPE Study Subject ID number which is:

_____

The medication bottle number (located in the bottle label)

When you took the first dose

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Important Study Drug Information

- The study drug must be swallowed whole (not crushed or chewed).
- It is very important that you take the study drug only as directed on a regular schedule.
- If you are late taking a dose, you may still take the dose if it is within 6 hours of your scheduled dose time. Take your next dose at least 6 hours later.
- If you miss a dose (and it is more than 6 hours after your usual dose time), do not take extra medication at your next dose. Take the missed dose at the end of the treatment period.
- Take all doses of the study drug until finished.
- Do not give this study drug to anyone else.
- Take the study drug with meals to lessen the possibility of stomach upset.
- If you have any questions about the study drug, check with a health care professional at 866-990-1231
- In case of a study drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately. Tell them it may have been hydroxychloroquine.

Study Drug Storage

- Store the study drug at room temperature, between 15°C and 30°C.
- Keep the study drug out of the reach of children to avoid accidental poisoning.

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Post-exposure prophylaxis study

- This is a separate but complementary study
- Collaborating with researchers at University of Minnesota, McGill U., U. Manitoba

P: 866-990-1231 W: hopecovid.ca E: albertahopecovid19@ucalgary.ca

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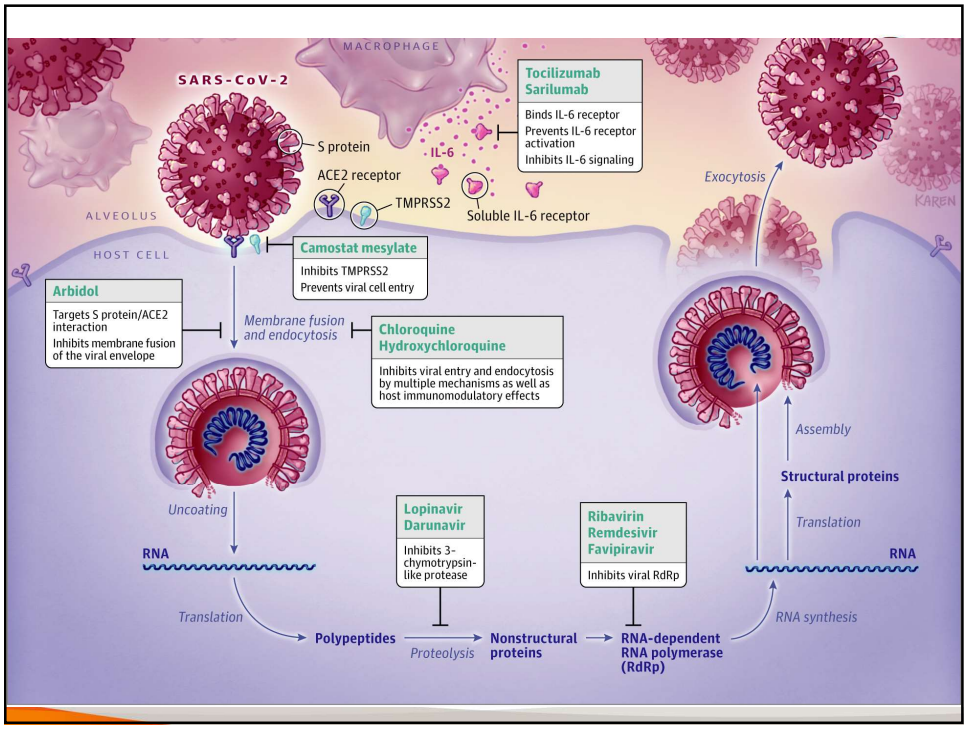
MACROPHAGE
SARS-CoV-2
S protein
ACE2 receptor
TMPRSS2
IL-6
Soluble IL-6 receptor
Tocilizumab
Sarilumab
Binds IL-6 receptor
Prevents IL-6 receptor activation
Inhibits IL-6 signaling
Exocytosis
ALVEOLUS
HOST CELL
KAREN
Camostat mesylate
Inhibits TMPRSS2
Prevents viral cell entry
Arbidol
Targets S protein/ACE2 interaction
Inhibits membrane fusion of the viral envelope
Membrane fusion and endocytosis
Chloroquine
Hydroxychloroquine
Inhibits viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects
Assembly
Structural proteins
Uncoating
Translation
RNA
Lopinavir
Darunavir
Inhibits 3-chymotrypsin-like protease
Ribavirin
Remdesivir
Favipiravir
Inhibits viral RdRp
Translation
RNA
RNA synthesis
Polypeptides
Proteolysis
Nonstructural proteins
RNA-dependent RNA polymerase (RdRp)

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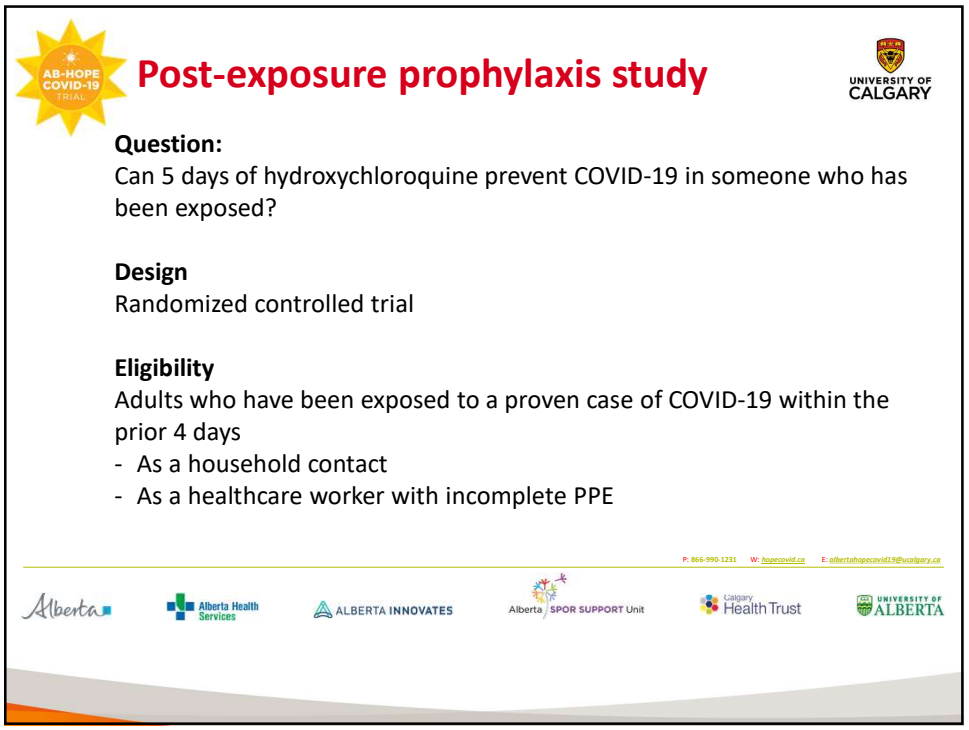
AB-HOPE COVID-19 TRIAL
Post-exposure prophylaxis study
UNIVERSITY OF CALGARY
Question:
Can 5 days of hydroxychloroquine prevent COVID-19 in someone who has been exposed?
Design
Randomized controlled trial
Eligibility
Adults who have been exposed to a proven case of COVID-19 within the prior 4 days
- As a household contact
- As a healthcare worker with incomplete PPE
P: 866-990-1231 W: hopecovid.ca E: albertahopecovid19@ucalgary.ca
Alberta
Alberta Health Services
ALBERTA INNOVATES
Alberta SPOR SUPPORT Unit
Calgary Health Trust
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Exclusions

- Current Symptoms of: Fever, Cough, or Shortness of Breath
- Positive SARS-CoV-2 test
- Current hospitalization
- Pregnancy or breastfeeding
- Current hospitalization
- Allergy to chloroquine or hydroxychloroquine
- Severe diarrhea and/or vomiting
- Significant hepatic impairment defined as known cirrhosis with history of hepatic encephalopathy or ascites.
- Prior retinal eye disease
- Concurrent malignancy requiring chemotherapy
- Known Chronic Kidney disease, Stage 4 or 5 or dialysis.
- Known glucose-6 phosphate dehydrogenase (G6PD) deficiency.
- Known ventricular arrythmia, known prolonged QTc interval, or any known episode of sudden cardiac death
- Medications that increase the QTc interval
- Known Porphyria
- Weight <40 kg

P: 866-990-1231 W: hopecovid.ca E: albertahopecovid19@ucalgary.ca

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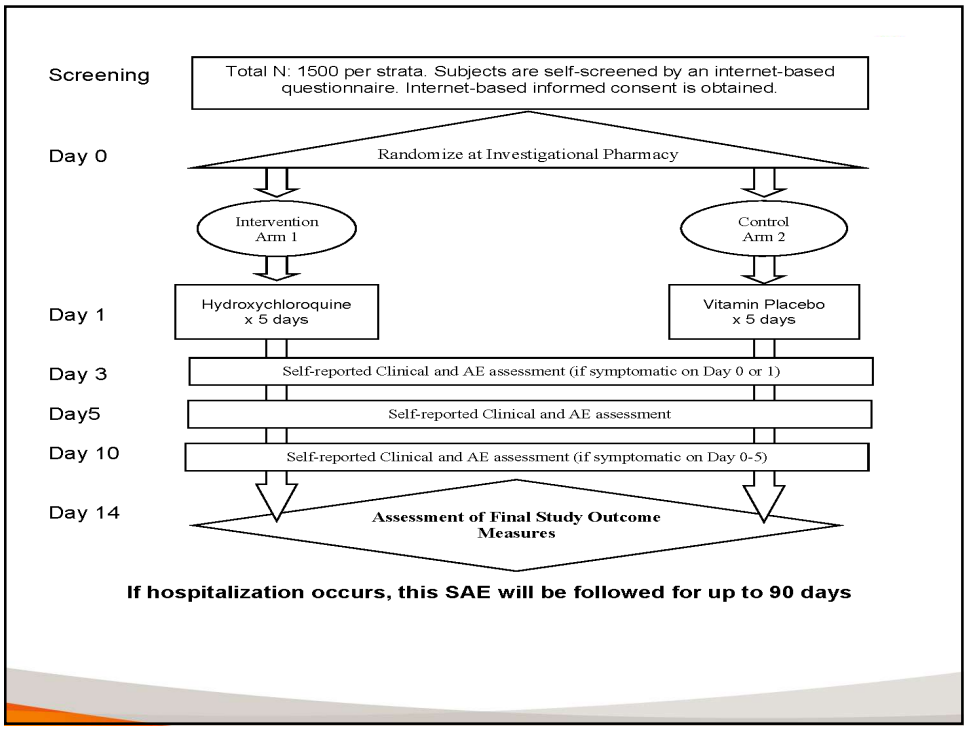

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STEP ONE: Enrollment and randomization

Email: covid19FAQ@idtrials.com	Complete online screening questionnaire	If eligible, review study documents and consent	Study medication or placebo will be shipped to your home

STEP TWO: Study period

Day 1	Day 2 to 5	Day 5	Day 10	Day 14
Online survey. Take 4 tablets by mouth. Then take 3 more tablets 6-8 hours later.	Take 3 tablets each morning. If symptomatic, a survey will be completed on Day 3.	Online survey. Study medicine is finished.	Online survey if symptomatic on enrollment or if you develop symptoms.	Online survey If you do not have symptoms this will be your last task. If you have symptoms we will contact your further.

Notes: you must take other medicines at least 4 hours apart from the study medicine.
On days 2 to 5 if you develop an upset stomach you may separate your doses (e.g. 2 at breakfast, 1 at lunch).

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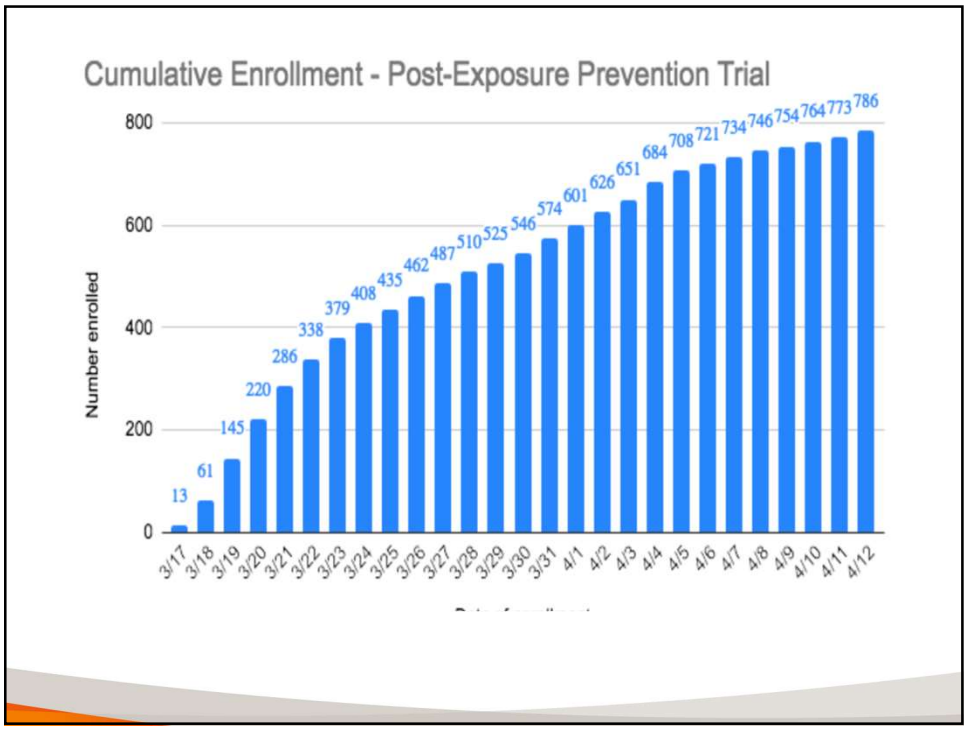

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UNIVERSITY OF CALGARY
COVID-19 PEP RCT
Home
Study Details
Study Update
Study Team
Contact
FAQs
FRANÇAIS
Enroll / S'inscrire
Post-exposure Prophylaxis (PEP) or Preemptive Therapy for COVID-19
A Pragmatic Randomized Clinical Trial
Questions: Alberta@idtrials.com

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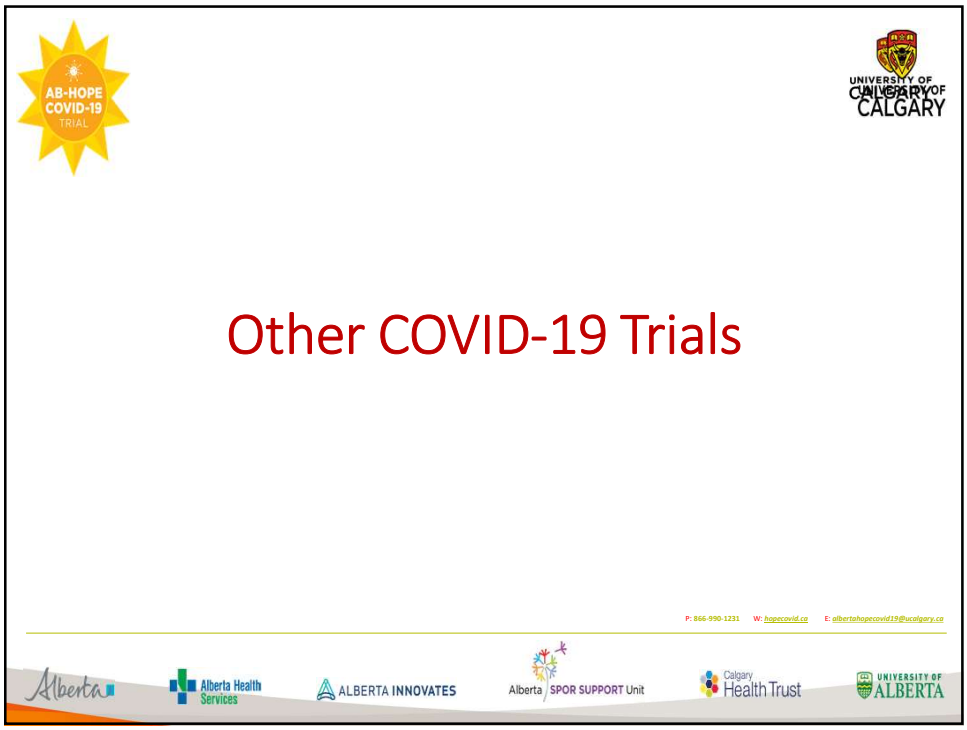
AB-HOPE COVID-19 TRIAL
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Other COVID-19 Trials
Alberta
Alberta Health Services
ALBERTA INNOVATES
Alberta SPOR SUPPORT Unit
Calgary Health Trust
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Types of Clinical Trials

- Post-exposure
- Early treatment
- Hospitalized patients
- Observational and diagnostics studies

Post-exposure

- COVID-19 PEP
  - Previously discussed by Dr. Schwartz

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Early Treatment

- Colchicine – not yet enrolling
  - Developed in Montreal
  - Dr. Bruce Ritchie is Edmonton lead
- Lopinavir/ritonavir – not yet enrolling
  - Early development stage

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Hospitalized patients

- REMAP-CAP - enrolling
  - Platform trial with multiple treatment arms
    - Macrolides
    - Corticosteroids
    - Lopinavir/ritonavir vs standard care
    - Interferon-beta-1a vs Anakinra (recombinant human interleukin-1 receptor antagonist (IL-1Ra)) vs standard care
- CATCO – not yet enrolling
  - Canadian arm of the SOLIDARITY trial
  - Lopinavir/ritonavir, HCQ, standard of care
- Medical mask vs N95 respirators

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Observational and diagnostic studies

- Approximately 50 studies
- Observation studies
  - Specific populations – e.g. healthcare workers, heart disease, immunocompromised, pregnancy, pediatrics, surgical patients
  - Emergency Departments
  - Intensive Care and ECMO
  - Immunological response
- Novel diagnostics
  - Plaque assay, rapid RNA sequencing, biosensors, serology

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Other therapeutic ideas – NO local trials

- Angiotensin converting enzyme (ACE) 2
  - Expression may be associated with susceptibility to COVID-19
  - Local proposal in development
- Remdisivir
  - Not yet licensed or approved
  - Observational study in 61 patients published NEJM

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Evaluation survey

- **Your feedback is essential; please make sure you complete the online evaluation survey.**
- https://survey.ucalgary.ca/jfe/form/SV_8HfwCBQvxZ5du1D

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