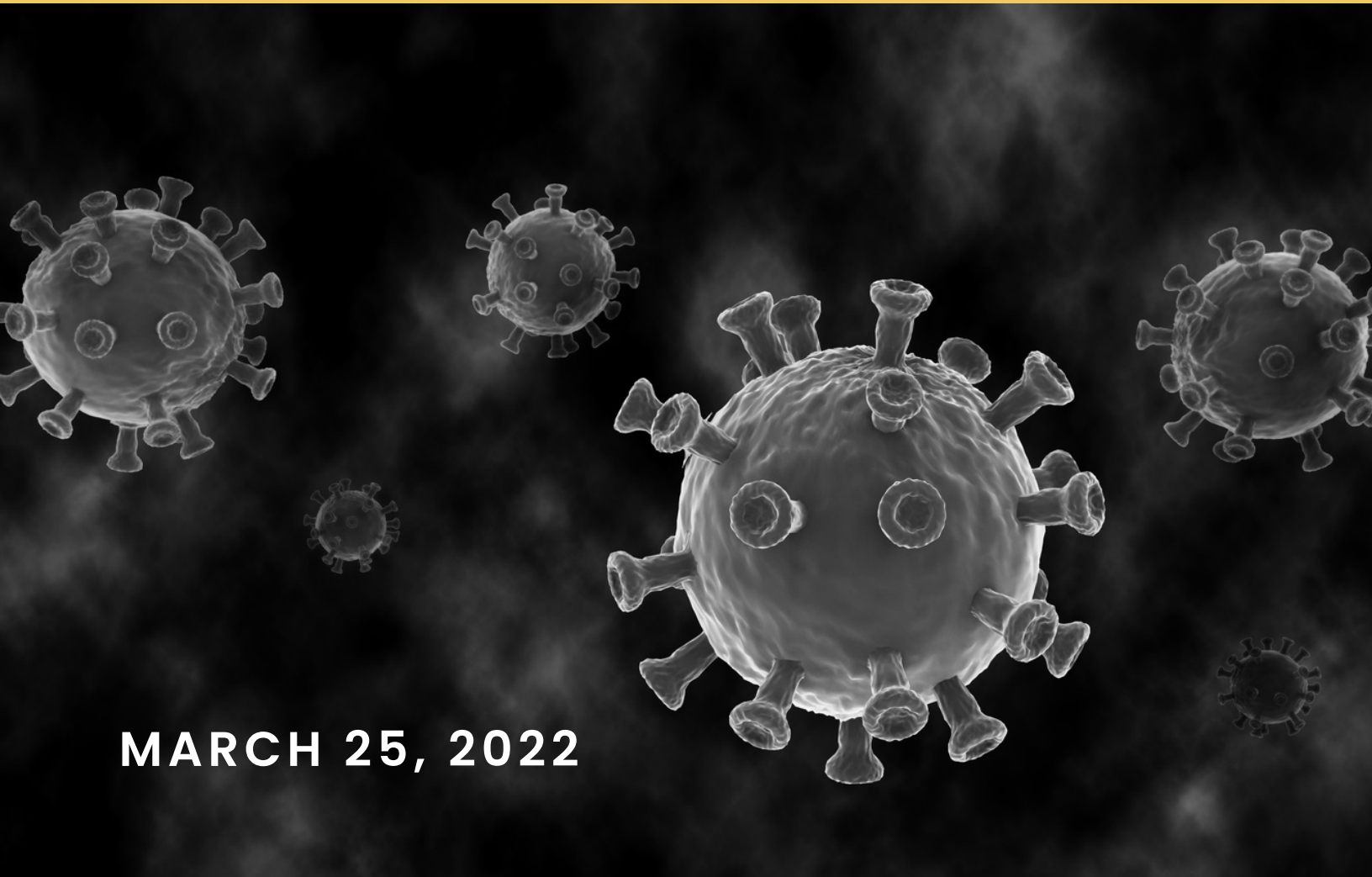
The Canadian **DONATION** and **TRANSPLANTATION** Research Program

Programme de recherche en **DON** et **TRANSPLANTATION** du Canada

NATIONAL FORUM REPORT

Emerging COVID-19 Issues in Transplantation



MARCH 25, 2022

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EXECUTIVE SUMMARY

Immunocompromised individuals such as transplant recipients are particularly impacted by COVID-19, being at higher risk of severe outcomes including mortality. Emerging research indicates that some patients do not mount an immune response upon vaccination, so preventing severe disease in these individuals will require alternate strategies. For transplant recipients recovering from COVID-19, little is known about effective rehabilitation strategies or strategies to support the long-term recovery of quality of life.

The Canadian Donation and Transplantation Research Program (CDTRP) coordinated a national Forum, **Emerging COVID-19 Issues in Transplantation**, on March 25, 2022, to evaluate COVID-19 related issues that have impacted solid organ and stem cell transplant recipients. The objective of this meeting was to develop a consensus on a national research agenda to address these urgent and emerging issues, incorporating the priorities of expert clinicians, scientists, stakeholders, patients, and families.

This Forum was the fourth CDTRP National Forum building consensus on COVID-19 research needs, each incorporating engagement with patients and families. Previous Forums developed into the PREVenT-COVID study on the safety and immunogenicity of COVID-19 vaccines, including a Knowledge Translation strategy that will engage health professionals, patients and families, and health authorities and decision-makers.

The Forum included attendees representing health professionals, biomedical and clinical researchers, industry, economists, government, and patients, to draw together perspectives from lived experience and expert knowledge collaboratively. Thirty individuals participated and identified the most urgent emerging research questions that need to be studied and discussed how to enable a more agile research response in the face of an evolving pandemic.

EXECUTIVE SUMMARY CONTINUED

In terms of the most pressing priorities, the consensus discussion prioritized the following research questions:

- **What is the optimal treatment timing in transplant recipients for antivirals and monoclonal antibodies?**
- **What are the real costs (qualitative and quantitative) of policies that impact mental health, reduce quality of health, and cause an inability to safely 'return to normal' for transplant patients?**
- **What supports are currently required to help transplant patients to return to 'normal life' – within transplant centers and in the community?**

Furthermore, participants discussed how to develop relationships between sectors and communities for a more agile research response during this evolving pandemic. There should be a framework for researchers and industry to communicate and multiple mechanisms were suggested. Including vulnerable and harder-to-engage communities was identified as a top priority for future research; inclusion requires relationships to be established and to be maintained. CDTRP could seek to establish a memorandum of understanding with Indigenous health leaders to set out a long-term model for engagement.

Using the infrastructure of the CDTRP network, the next step is to assemble specific research teams to further plan and execute the research that will answer these questions. We will continue real-time engagement at a national level with stakeholders including health professionals, researchers, government, industry, patients, and families.

WORKSHOP OBJECTIVES

The workshop's central objective was to develop consensus around the priority research questions in four key areas:

1. **What are the best uses of antiviral agents?**

2. **What are the best uses of monoclonal antibodies?**

3. **How can we develop a pathway for the research community to be quickly aware of new therapeutic agents to be able to react and plan needed studies?**

4. **What are the key questions for patient and family recovery and long-term well-being?**

LIST OF THE FORUM'S CONTRIBUTING EXPERTS AND PARTICIPANTS

(IN ALPHABETICAL ORDER)

Name	Affiliation	Expertise / Role
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BACKGROUND

COVID-19 and Vaccination in Transplant Recipients

Transplant recipients that have contracted COVID-19 are at high risk of severe outcomes. In addition to taking immunosuppressive medications, many transplant patients have other comorbidities such as chronic kidney disease, diabetes, and heart/lung disease, which are an additive risk to increased severe COVID-19 infection. Specifically, lung transplant patients seem to be at an even higher risk of severe infection (1). Although transplant recipients represent a small proportion of the Canadian population, their care is resource-intensive. Taking this population into account for the development of public health policies and clinical practices may have a significant impact on patient outcomes and health system capacity and health care costs.

While vaccines appropriate for use in transplant recipients are now widely available in Canada, emerging research suggests vaccination alone is insufficient to protect this population from severe COVID-19 outcomes. Adult transplant recipients have poor humoral responses to COVID-19 vaccination, associated with their immunosuppression regimes (2). A study of solid organ transplant patients found that only 17% developed antibodies three weeks after one dose of mRNA COVID-19 vaccines (3). A smaller cohort of kidney transplant recipients was similar: only 37.5% of transplant recipients produced anti-COVID-19 antibodies, while all non-immunosuppressed controls produced sufficient immune responses (4). Similarly, only 55% of allo-transplanted hematopoietic stem cell patients developed antibodies against COVID-19 compared to 100% of the non-immunosuppressed individuals (5). Little is known regarding pediatric transplant recipients. Overall, this leaves transplant recipients at great risk for COVID-19 infection and severe outcomes, regardless of vaccination status.

A national study coordinated by CDTRP with eight transplant centres across Canada, "Prospective Evaluation of COVID-19 Vaccine in Transplant Recipients (PREVenT-COVID)" is examining the knowledge gaps on vaccine and safety of the COVID-19 vaccines in both solid organ and stem cell recipients, in adults and children. This project is funded by the Public Health Agency of Canada, through the Vaccine Surveillance Reference group, the COVID-19 Immunity Task Force, and FRQS.

PREVenT-COVID has begun analyzing the large cohort of individuals, and early data aligns with and builds on previous studies on transplant recipient cohorts. As multiple vaccinations may not be sufficient for recipients to mount a protective immune response against COVID-19 and its potential variants, further measures and policies are needed to help protect immunocompromised transplant recipients against severe COVID-19 disease.

Current Treatment Guidelines for Transplant Recipients with COVID-19

For transplant patients, there are several authorized treatments/prophylactics that are in use to try and combat the potential for severe outcomes, and more are in development (6). Further information on these agents and their expected mode of action is in Appendix 1.

In July 2021, the monoclonal antibody **Sotrovimab** (VIR-7831) was given interim authorization by Health Canada under the COVID-19 Interim Order pending further clinical investigation. Sotrovimab is given as a treatment for mild-moderate COVID-19 infection in both children and adults (12 years or older, or above 40 kg) who are at risk of severe disease progression and or fatal infection. Sotrovimab should be administered as soon as possible after symptom onset, or positive PCR result confirmation. To see more specific guidelines regarding administration of Sotrovimab, visit (7). To note, some jurisdictions are currently reviewing the use of Sotrovimab given its reduced effectiveness for the currently dominant Omicron BA.2 variant.

Other monoclonal antibodies have been developed for pre-exposure prophylaxis which may be of value in immunocompromised individuals. Evusheld (**Tixagevimab/Cilgavimab**), a combination of two monoclonal antibodies targeted against SARs-CoV-2, is used to prevent symptomatic COVID-19. In the PROVENT Phase III clinical trial, there was a 77% reduction in the risk of developing symptomatic COVID-19 disease in high-risk immunocompromised individuals (6, 8 and 9). In the United States, Evusheld has been authorized for Emergency Use Authorization (EUA) by the FDA for pre-exposure prophylaxis treatment of COVID-19 for both children and adults (12 years or older, or above 40kg) who are moderately to severely immunocompromised and may not present with an adequate immune response against previous COVID-19 vaccinations (10). As of April 14, Evusheld has been authorized for the prevention of COVID-19 for adults and children (12 years of age and weighing at least 40 kg) who are immune compromised; unlikely to mount sufficient immune response to COVID-19 vaccination, and/or those who are not recommended to received COVID-19 vaccinations (11).

In January 2022, Health Canada authorized the use of the Paxlovid (**Nirmatrelvir/Ritonavir**) oral antiviral medication to treat mild-moderate COVID-19 infection in adults with a positive PCR test, and who are at high risk of progressing to severe and potentially fatal infection. Paxlovid is currently being administered to moderately to severely immunocompromised individuals that are unable to mount a sufficient response to COVID-19 regardless of vaccination. Treatment is administered after confirmation of positive PCR and within 5 days of symptom onset. Drug interactions are a critical issue with antiviral. To see the specific guidelines regarding administration of Paxlovid, see (12).

DISCUSSION

CONSENSUS ON A PATH FORWARD TO FILL THE GAPS IN KNOWLEDGE

1.WHAT ARE THE BEST USES FOR ANTIVIRAL AND MONOCLONAL ANTIBODY TREATMENTS?

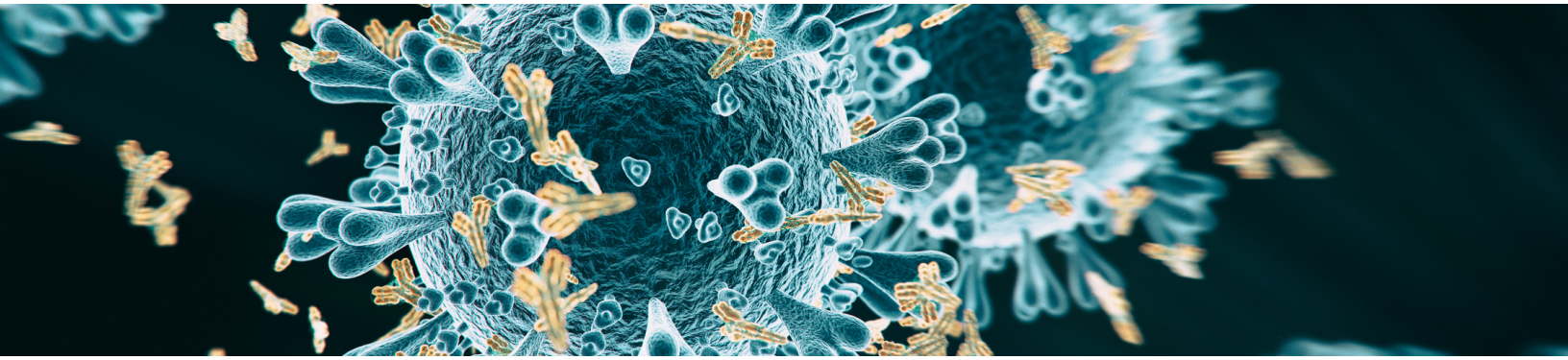
- **1.1 Highest priority study: What is the optimal treatment timing in transplant recipients for antivirals and monoclonal antibodies?**
  - There is data that shows poor efficacy of Paxlovid after 5-7 days in healthy individuals, but there is not yet evidence in immunosuppressed individuals. It is not established that a transplant patient with COVID-19 will not benefit from treatment after the 5-day (antivirals) or 7-day (monoclonal antibodies) limit. What is needed is to investigate the efficacy after the time limit with immunosuppressed individuals.
  - For allogeneic stem cell, can giving Sotrovimab after the set timeline result in more allo-immune reactivity? Does the treatment timeline vary for both antivirals and monoclonal antibodies?
  - A study should monitor long-term effects, and post-treatment effects (i.e., cases with persistent long-term symptoms, and/or delayed symptoms).
  - Who should be eligible to receive antivirals or monoclonal antibodies? This requires determining who is at high risk for severe disease progression regardless of vaccination.

- **1.2 What is the economic evaluation/burden of using antivirals and/or monoclonal antibodies for treatment?**
  - Financial implications to the health system of providing treatment (economic cost of readily available treatments for patients in need) need to be determined.
  - Micro-financial impact of dealing with COVID/long-covid for patients (missed work days, job loss, out of pocket medical expenses, repeat medical visits, etc.) are not currently understood.
  - Cost effectiveness of each treatment: what is the most cost-effective treatment per patient group?
  - There could be a comparative study across antivirals and monoclonal antibodies to understand their outcomes, then use this information to evaluate the most cost-effective treatment across certain patient groups.
  - Budget impact analysis: Is it possible to expand treatment eligibility criteria to a broader population?

- **1.3 How can antivirals and monoclonal antibodies be used safely in the context of varying immunosuppression regimens?**
  - What are the pharmo-kinetic implications of using antivirals and monoclonal antibodies with varying immunosuppression regimens? Do antivirals inhibit or stimulate the metabolism of immunosuppression? What are the appropriate immunosuppression dosages throughout the treatment for efficiency and safety (e.g., mycophenolate dosage)?
  - When is it appropriate to augment immunosuppression after COVID infection, i.e., considering Antibody Mediated Rejection (AMR) or severe Acute Cellular Rejection (ACR)? In transplant recipient COVID survivors, the approach to reintroduce immunosuppression safely is an active topic of discussion within transplant centres with no clear evidence to guide decisions.

- **1.4 How can we quickly resume transplantation or other therapies such as chemotherapy after a patient is infected and treated? Can emerging therapies speed recovery and protect patients in the period immediately following transplant?**
  - When do COVID-positive transplant patients become negative? Can antivirals and monoclonal antibodies make them negative faster? Can monoclonal antibodies speed up viral clearance?
  - How do we protect patients during the first six months post-transplant? Should Evusheld be redosed for protection?

- **1.5 How are we going to clinically evaluate Evusheld in transplant recipients?**
  - What is the studying planning behind randomization of Evusheld administration (selection of which transplant recipient receives the drug and which receives the placebo), endpoint, etc.?
  - Is there a concern for breakthrough infection? Several reports from the US from transplant patients that received Evusheld have found this to be an issue (link).



Patient perspectives on new therapies

Communication

There is currently a lack of communication and/or miscommunication in terms of guidelines. It is very important that patients/families are told what the process is and what is going to happen. Knowledge mobilization must work across the spectrum (e.g., target audience includes health care providers and patients/families). Patients emphasized the need for transplant centres to respond to patients in a timely manner. One potential mechanism could be to:

- Fast track clinic that established a pathway based on patients' symptoms
- After diagnosis, transplant coordinators would manage treatment
- This process could decrease the burden on health professionals and hospital resources

Patients and/or caregivers have different information needs. Some individuals will want more information than others, and we should meet the needs of both groups. Key information needs include:

- Short term and long-term implications to patients (e.g., side effects, reactivation of latent viruses)
- Explanation of risks and benefits for both short- and long-term effects of treatment
- Eligibility and appropriate situations for prophylaxis treatment
- Explanation of what monoclonal antibodies and antivirals are. What is the difference between prophylaxis vs. post-infection treatments?
- What is the duration of protection? How do we know this?
- What is Sotrovimab? Why do you need it?

One example of how communication around Sotrovimab is currently being done: patients from London Health Sciences Centre come directly to the hospital to receive the infusion, which gives the patients a chance to listen to risk/benefits. Patient representatives noted that they prefer receiving information directly from their transplant team, given that they know their history and current status.

Complications with drug therapies

On the question of patient/family risk assessment, the question was posed as to how willing patients would be to undergo more drug monitoring. One patient who had COVID in early 2022 shared the view that increased monitoring would not be an issue, but the information was not being provided. Patients must be informed of the risks and benefits to make an informed decision. The information being given to patients is not clear.

Operational and access issues
Operational processes need to be adapted to urban, rural, and remote locations. There are concerns about a lack of access to these medications. The "normal" system is not working now.

It should be possible to treat patients from home to limit hospital visits. A limitation to home visits is that there is no monitoring of the patient after an intervention is administered. Nevertheless, if there could be home monitoring of the patient, this would decrease the burden on the hospitals and health care providers (e.g., audio video conferencing with patients). This would also minimize patient exposure to COVID in health care settings. Alberta is one province where home visits are being done for antibody infusions from first responders to avoid hospital visits. It is worth examining how at-home PCR testing and monitoring is being utilized in different regions and how these methods could potentially be applied to treatment monitoring.

2.HOW CAN WE DEVELOP A PATHWAY FOR THE RESEARCH COMMUNITY TO BE QUICKLY AWARE OF NEW THERAPEUTIC AGENTS TO BE ABLE TO REACT AND PLAN NEEDED STUDIES?

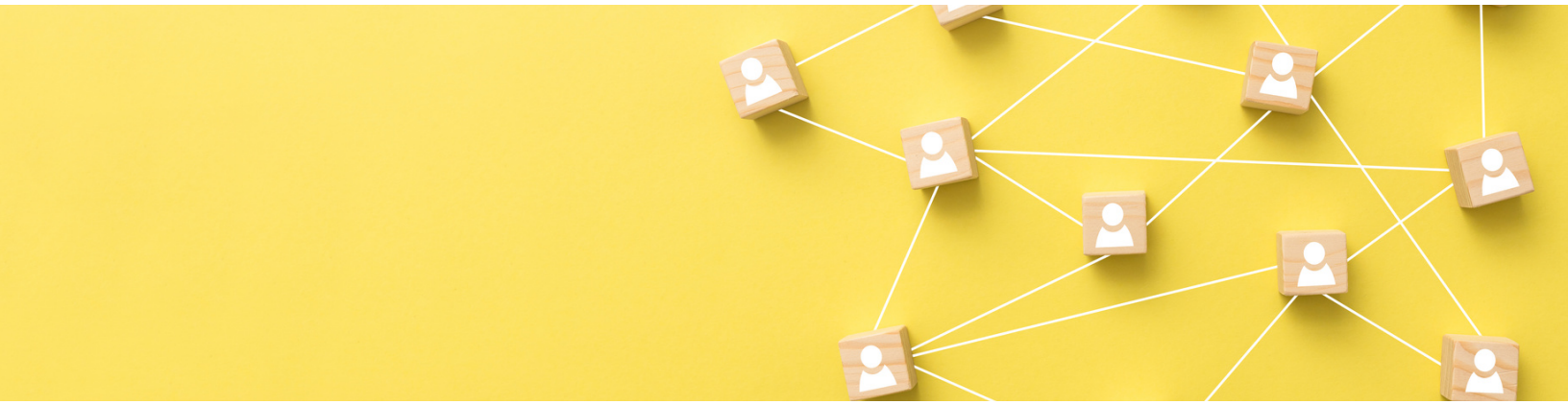
Having a pre-existing pan-Canadian group of researchers and collaborators, including patient, family, and donor partners, that can mobilize quickly and be a single point of contact is important. Projects must be able to recruit enough patients from a small population, where scientists can link to patients to help form the questions. Given CDTRP's established infrastructure, setting up a national registry and communicating the research capacity within Canada, that we are "open for business", was discussed as a priority.

- There should be an emphasis on real-life registry data collection.
- The challenge will be to recruit diverse communities (age groups, Indigenous groups, remote communities), and those voices need to be included from the beginning of the planning phase. Maintaining communication and relationships are critical but establishing long-term, meaningful partners was identified as a challenge.
- Children need to be included in research trials.

Including vulnerable and harder-to-engage communities was identified as a top priority for future research. Investigators are the gateway to prioritizing these communities and have an obligation to include them in their work, especially when interacting with partners. It was suggested that CDTRP could seek to establish a memorandum of understanding (MOU) with Indigenous health leaders tailored to each group (e.g., First Nations, Metis, Inuit). This MOU should contain elements on data sovereignty and the protection of sovereign rights. In addition, it should support building capacity among the Indigenous population to be able to participate in national discussions and projects.

There should be a central Forum where industry can share ideas with researchers. This would provide a framework for working together and to understand the latest issues. One possible model is the Health Canada – National Advisory Committee on Immunization (NACI) arrangements for sharing confidential information. There is a COVID-specific process that was put in place, but it was aimed at issuing recommendations, not research.

- Federal legislation can be a constraint as to what can be communicated when by the Public Health Agency of Canada.
- Pre-clinical trial meetings at Health Canada with industry could be a mechanism for enhancing collaboration and communication. That is, researchers could join meetings for discussion about trial development as a means of being proactive.
- Comment from a participant from industry: no barriers exist for researchers to approach industry for trials as partners. It is the job of the Medical Liaison to have such conversations. Researchers should be pro-active in engaging industry because regulations mean industry cannot be the initiators of conversations in many cases.



3.WHAT ARE THE KEY QUESTIONS FOR PATIENT AND FAMILY RECOVERY AND LONG-TERM WELL-BEING?

3.1 No long-term data on the impacts of COVID-19 on transplant patients exist. There needs to be a collection of acute and long-term data in a systematic way. National registry, and electronic health records could be used for this research (we can use the innovation made through the pandemic to our advantage).

3.2 To help understand how many transplant patients have experienced or are still experiencing long COVID, the CDTRP put out a call in February 2022 for patients or caregivers to share their experience through an online form. This was well advertised on social media by CDTRP and partners (Canadian Liver Foundation, Canadian Society of Transplantation, Can-SOLVE CKD Network, Ajmera Transplant Centre, the World Transplant Games Federation, and the Transplant Research Foundation of British Columbia) as well as Long COVID Canada, a patient-led advocacy and resource group. By April 1, 2022, there were 57 responses to the survey (13 from Canada). The survey's questions and an overview of the answers are in Appendix 2.

3.3 It is possible that patients do not identify with 'long COVID', but rather consider ongoing health concerns a part of their overall transplant health. It is also possible that immunosuppression modifies the risk of long-term impacts. Could it be more recipients are just starting now to get the virus in larger numbers? Long COVID concerns may then be coming soon. We need to know what the perspectives are from caregivers and families and need broad representation of views within the transplant community. The initial CDTRP outreach may have identified a group of patients that could be engaged through a qualitative research study.

3.4 During COVID infection, there is a lack of knowledge, evidence, and variable patterns of practice for what to do with patients' baseline immunosuppression. A recent paper in ISHLT reported on a survey of lung transplant centers and there was high variability regarding continuing CCI through the COVID-19 infection, lowering CNI targets, increasing prednisone etc. It would be highly useful to understand the associations between decisions made about baseline immunosuppression changes and consequences of graft dysfunction and needing treatment for ACR/AMR.

Patient perspectives on new therapies

Key questions: what are the long-term impacts of disease treatments related to graft survival, quality of life, reactivation of viruses, what the so-called 'cytokine storm' means for transplant recipients.

The Forum's attendees agreed that understanding the ongoing and long-term impacts of COVID-19 and public policy on the mental health of transplant patients is a priority.

Patient representatives at the Forum expressed frustration and anxiety with the continued push from governments and the public to transition back to "normal". This is despite an agreement that COVID-19 is still impacting communities, including vulnerable and immunocompromised transplant recipients, and these people are more vulnerable to experiencing severe symptoms from a COVID-19 infection than the general population. Forum participants indicated that COVID-19 public health measures have become politicized and have led to divisiveness in language and among the public. This divisiveness has been exacerbated due to unclear, mixed, and potentially misinformed government communications. In transplant recipients, this has caused ongoing stress and anxiety.

The removal of mask mandates represented one example of the ongoing stressors transplant recipients experience. Despite public health recommendations encouraging the continued use of masks, especially for immunocompromised individuals, Forum participants expressed fear, feelings of intimidation, and stigmatization when wearing masks in public settings, such as grocery stores. There may be a developing perception of how people wearing masks are being read by others in the community (i.e., are they unvaccinated or have health issues?) when the mandates are no longer in place. This impacts patients' privacy if they are pressed on why they are wearing a mask.

Coupled with pressures to adapt "back to normal" from the public, elected officials, and potentially family or friends, transplant recipients are fighting to be heard. COVID-19 is not over, and patients and families are still scared, and need support.

In one experience shared during the Forum, a pediatric transplant patient and their family felt it was best to keep their child at home once the mask mandate was dropped and continue with virtual learning. However, given the emphasis on returning to 'normal', this family was told that this was not an option. While hearing from friends and teachers that there was little masking, symptomatic students in class, and confirmed COVID-19 cases, their only options were going back to school in person or being expelled if the child missed more than 15 days of school without a doctor's note. This anecdote is an example of the real impacts COVID-19 policies are having on transplant recipients and their families.

One transplant recipient stated that research, and more specifically, the mobilization of knowledge from COVID-19 research must inform public discussions and policy decisions. The goal is to remove politics from policy.

Moreover, transplant centres need to be viewed as key stakeholders in supporting knowledge mobilization to help inform and empower transplant recipients. Patients trust their health care team and, despite 'COVID-19 and transplant recipient' information being publicly available on reputable websites (i.e., Canadian Society of Transplantation), information is better received from transplant centres. This is even more important for individuals with language barriers that are unable to access or fully understand this information.Patients who have had COVID-19 state that communication and follow up from their centers to monitor their health is not happening. A national strategy for communication and a framework on what would be appropriate in terms of follow-up is needed. This would need to be proactive in developing tools and educational resources now as these problems are developing acutely for transplant patients.

Partners (e.g., CTA, CST, CTTC) and media are critical to helping get the message out. An action item from this Forum is to write an op-ed article on these issues and stresses facing transplant patients as public health protections are being removed. Help is needed to prevent transplant patients from being ostracized from society when they need protective measures such as masking in place.

Stemming from these conversations, the priority issues surrounding COVID-19 recovery in transplant patients include:

- Assessing the mental health and quality of life impact that COVID-19 has had on transplant recipients.
- What supports and research are needed to support transplant recipients as public health measures are removed? This would involve social science research. What are the societal costs and the missed opportunity costs? How can these needs be communicated to decision-makers?
- How can CDTRP support a national framework that supports short-term and long-term knowledge mobilization needs?
- **What are the real costs (qualitative and quantitative) of policies that cause mental health issues, reduced quality of health, and an inability to safely 'return to normal' for transplant patients?**

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APPENDIX 1

LITERATURE REVIEW ON MONOCLONAL ANTIBODY AND ANTIVIRAL COVID-19 THERAPIES

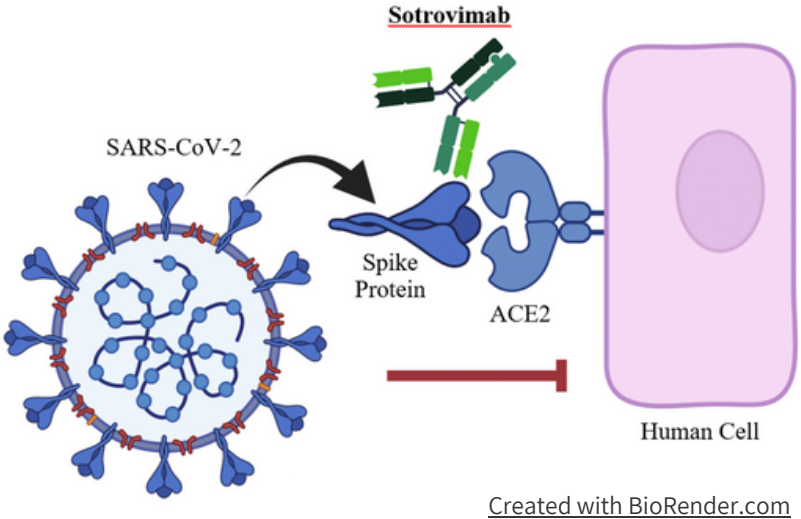
SOTROVIMAB

Introduction

Sotrovimab (VIR-7831) is a human neutralizing monoclonal antibody that is used to treat mild-moderate SARS-CoV-2 infection (1), in both adult and pediatric patients (2). Sotrovimab was initially derived from a patient infected with SARS-CoV back in 2003, and again from the same patient in 2013 (3). Sotrovimab can bind to the spike protein epitope on the surface of SARS-CoV-2 and inhibit viral infection and able to reduce disease progression (4).

Mechanism

The epitope binding site of Sotrovimab, is composed of 6 complementary determining regions which interact directly with the spike protein of SARS-CoV-2, through electrostatic and hydrophobic interactions. This interaction does not affect the binding of the spike protein to human ACE2 (3). Thus, Sotrovimab causes IgG specific neutralization mechanisms that occur after viral attachment (3), yet before fusion and entry of virus to host cells (5).



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Structure

Sotrovimab (VIR-7831) is a recombinant human monoclonal antibody, generated in a Chinese hamster (CHO) cell line, originally derived from a previously infected individual with SARS-CoV-2. Sotrovimab is classified as IgG1k, including M428L and N43S4 amino acid substitutions at the Fc region that cause the antibody to have a longer half-life (1).

- Generic Name: Sotrovimab
- Former Name: S309
- Molecular formula: C6492H10092N1744O2038S40
- Molecular Weight: ~149 kDA

Product Monograph

TIXAGEVIMAB/CILGAVIMAB (EVUSHELD)

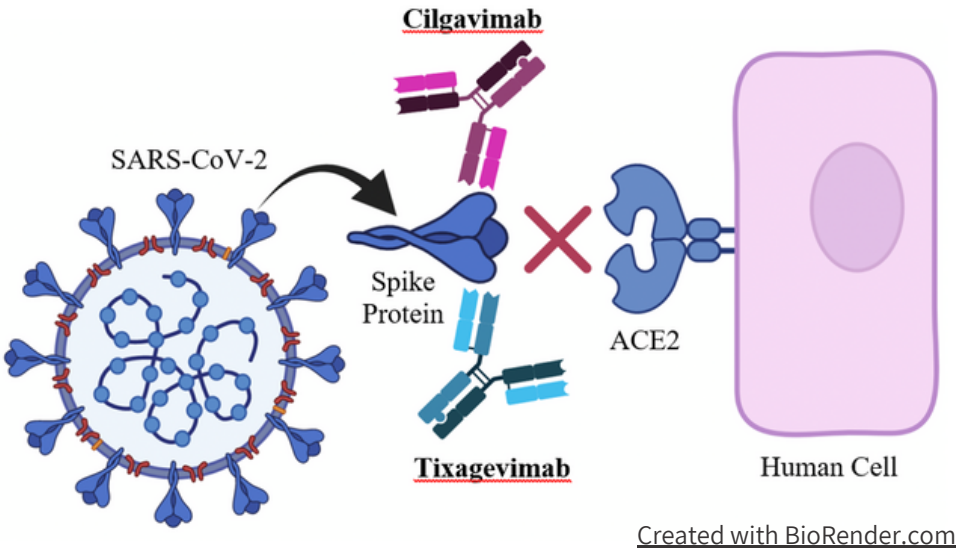
Introduction

Evusheld is a prophylactic monoclonal antibody therapy used for pre-exposure protection against SARS-CoV-2. Evusheld, also known as AZD7442, is a combination of two monoclonal antibodies designed to prevent severe COVID-19 infection in immunocompromised individuals that have reduced immune response to vaccination (6). The combination of two long-acting monoclonal antibodies Tixagevimab (AZD8895) and Cilgavimab (AZD1061), compose Evusheld (AZD7442). Like Sotrovimab, the parental antibodies were derived from B-cells from previously infected, and subsequentially recovered SARS-CoV-2 infected patients (7).

Mechanism

The two monoclonal antibodies are specific to the RBD region of the SARS-CoV-2 spike protein (8). While Tixagevimab (AZD8895) binds to the receptor binding ridge (S1 RBD), Cilgavimab (AZD1061) binds to the side of the RBD ridge (9), the “up” confirmation of the spike protein (10). This allows for the two antibodies to partially overlap the ACE2 binding site on the SARS-CoV-2 spike protein, and in turn causes competitive binding between the antibodies and the human ACE2 receptor. This competition subsequentially neutralizes the virus by inhibiting entry into host cells (9).

Along with Evusheld’s ability to inhibit ACE2 binding, amino acid substitutions in both monoclonal antibodies allow for an extended half-life. This not only allows for the potential prolonged protective benefit, but also reduces the risk of Fc receptor binding function which decreases the risk of antibody dependent enhancement of the disease itself (8).



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Structure

Tixagevimab (AZD8895) is a recombinant human monoclonal antibody, generated in vitro in a Chinese hamster ovary (CHO) cell line, originally derived from neutralizing antibodies isolated from a previously infected SARS-CoV-2 patient. Tixagevimab is classified as a IgGk1 monoclonal antibody (10), with amino acid substitutions are present within the structure of the antibody to enhance half-life (11).

- Generic Name: Tixagevimab
- Former Name: AZD8895
- Chemical Formula: C6488H10034N1746O2038S50
- Molecular Weight: ~149 kDA

Cilgavimab (AZD1061) is also a recombinant human monoclonal antibody, generated in vitro using a Chinese hamster ovary (CHO) cell line. Like Tixagevimab, Cilgavimab originally derived from neutralizing antibodies isolated from a previously infected SARS-CoV-2 patient. Cilgavimab is classified as a IgGk1 monoclonal antibody, with amino acid substitutions within the structure to enhance half-life (12).

- Generic Name: Cilgavimab
- Former Name: AZD1061
- Chemical Formula: C6626H10218N1750O2078S44
- Molecular Weight: ~152 kDA

Product Monograph

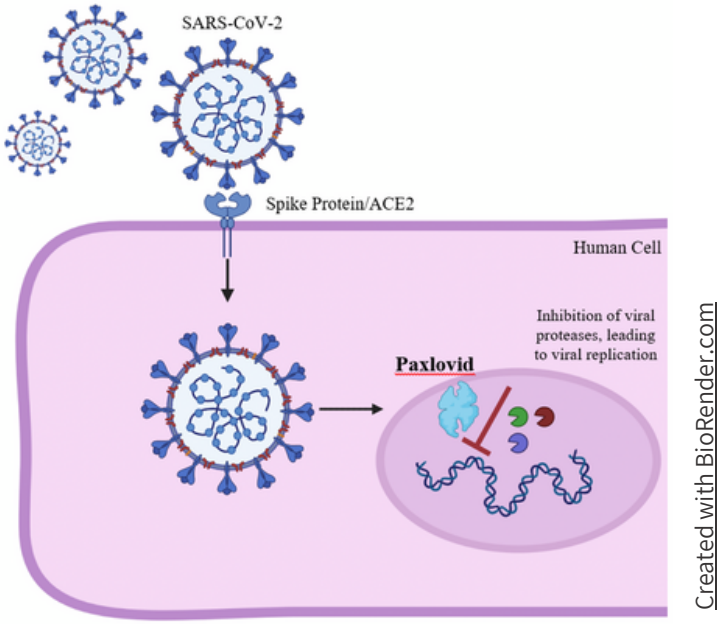
PAXLOVID

Introduction

Aside from the use of monoclonal antibodies for pre- and post-exposure therapeutics against SARS-CoV-2, antiviral medications are also being further investigated as an effort to treat COVID-19. Pfizers' Paxlovid, is an antiviral medication that can be used for the treatment of mild-moderate COVID-19 infection in both high risk pediatric and adult patients that test positive for SARS-CoV-2 (13).

Mechanism

Paxlovid is composed of two different active agents; Nirmatrelvir and Ritonavir. Nirmatrelvir is a protease inhibitor, that is active against the viral protease, MPRO. MPRO is an essential coronavirus enzyme that mediates viral replication and transcription of SARS-CoV-2 (14). Thus, Nirmatrelvir inhibits the breakdown and effector function of MPRO, and in turn stops the virus from replicating (13). The second active ingredient in Paxlovid is Ritonavir. Ritonavir is also a protease inhibitor, which when co-administered at a low dosage, reduces the breakdown of Nirmatrelvir (15), as well as increases the therapeutic range (16). Paxlovid is administered orally as three tablets, which consists of two Nirmatrelvir and two Ritonavir, taken twice daily in combination for five consecutive days after testing positive for SARS-CoV-2 (13).



Antivirals

- NIH: all emergency use approved anti-virals for COVID-19, last updated Feb 2022
- AST Statement on Oral Antiviral Therapy for COVID-19 for Organ TransplantRecipient

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APPENDIX 2

CDTRP'S CALL FOR EXPERIENCES ON LONG COVID

Survey respondents were asked the following questions:

1. Participant's full name
2. Location (country, province)
3. Are you a transplant patient or a family or caregiver to a transplant patient?
4. Please share your story on how you or your family has been impacted by long COVID.
5. Would you be willing to speak in a public setting to talk about your experience with COVID?

Survey's answers

Number of respondents	**57**
Number of countries were respondents lived	**19**
Number of caregivers who responded	**2**
Number of patients who responded	**55**
Number of respondents who would speak in public about their COVID-19 experience	**14** (out of 27 responses)

Respondents' locations

- Argentina
- Australia
- Belgium
- Canada
- Chili
- Czech Republic
- Germany
- Hong Kong
- Hungary
- India
- Ireland
- Netherlands
- Pakistan
- Peru
- Portugal
- Slovakia
- South Africa
- United Kingdom
- United States

A word cloud of **symptoms** expressed in respondents' stories.
The larger the word, the more frequently that symptom was mentioned.

Selected responses on the impact of COVID-19:

> "I got Covid in July 2021. I was down for three weeks with fever, extreme body aches, severe headache, and total loss of taste and smell. I did not experience repertory issues. I was treated in hospital for dehydration and got a morphine drip for my headache. I was there for about 6 hours. I have still not fully regained my sense of taste or smell. I have on again off again days of fatigue, depression, and mental fog. I am not in my pre-Covid health."
>
> "Nine months of exercise intolerance is the main symptom. Extreme tiredness and headaches at first with any intense work (Cross-fit), which I have been doing for the last 15 years. Through out the past 9 months also random heart rate spikes without exercise as well."
>
> "I had an extreme sore throat like I've never had before (like knives slicing my throat), high fever, headache, and body aches. I had to have fluids by IV. I was COVID free 4 weeks later. I am still very, very tired, weak and have muscle pain and some headaches. My depression has increased but I am watching it. Basically, I have good days and bad days, worse since COVID."