Advancing Development of PrEP for COVID-19

The Current State of Research and Development + Recommendations

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The PrEP4All Collaboration
Diagnostics + Treatment Committee
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### Executive Summary

The lack of an effective vaccine or other method of pharmaceutical prophylaxis for SARS-CoV2 – the virus that causes COVID-19 – remains the single largest challenge for controlling the outbreak. While extensive efforts are currently focused on vaccine development, an effective vaccine will not be available for mass production for at least a year.

The development of a highly effective drug-based method of pre-exposure prophylaxis (PrEP) for SARS-CoV2 is likely possible in a shorter time period and could help control the outbreak until a vaccine is widely available.

Critically, development and scaling up of such technology could help abrogate the need for widespread social distancing. Drug-based PrEP has already revolutionized the fight against another deadly pandemic: HIV. Despite there being no effective vaccine, people who are vulnerable to HIV who use PrEP as directed can reduce their chance of becoming infected by over 99%. Similar progress could be possible in the fight against COVID-19.

Unfortunately, the world’s efforts to develop a method of COVID-19 PrEP are in their nascent stages and lack any coordination or direction.

While scientists have identified multiple molecules – some of which are already FDA-approved drugs – that may inhibit the replication of SARS-CoV2, no centrally coordinated processes exist to evaluate the antiviral potency of

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### Redundancies in Research

Agents being evaluated in registered clinical trials for COVID-19 PrEP or PEP

- 64% hydroxychloroquine or chloroquine
- 5% nitric oxide
- 5% allogeneic adipose-derived
- 3% mesenchymal stem cells/lopinavir/ritonavir
- 3% recombinant human interferon alpha + thymosin alpha
- 2% PUL-042
- 2% hydroxychloroquine vs. tenofovir DF/emtricitabine
- 2% hydroxychloroquine vs. lopinavir/ritonavir
- 2% hydroxychloroquine + bromhexine
- 2% nitazoxanide
- 2% hydroxychloroquine vs. azithromycin
- 2% Peginterferon lambda alfa-1a
- 2% hydroxychloroquine + azithromycin
- 2% melatonin
- 2% Autoclaved Mycobacterium w

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these compounds in vitro. As a result, a limited number of different molecules are being tested in humans for their ability to prevent COVID-19. Clinical trial evaluation of possible COVID-19 modalities is uncoordinated. As of 22 April 2020, there are forty-two clinical trials registered to evaluate a non-vaccine drug-based method of COVID-19 prevention. Nearly two-thirds (n=28) of these trials are designed to evaluate the effectiveness of just chloroquine or its prodrug, hydroxychloroquine, as a preventive. Three more trials are designed to evaluate hydroxychloroquine in combination with other drugs, and two are comparing hydroxychloroquine to other drugs. Meanwhile, only ten clinical trials are evaluating other molecules and modalities for their role in prophylaxis. Put simply, most existing clinical studies testing COVID-19 prevention modalities are redundant evaluations of the same drug (or its prodrug), while many potential candidates have not even been evaluated in vitro.

The development of an effective method of COVID-19 PrEP must be a national and international priority.

The PrEP4All Collaboration believes that three steps should be taken immediately to better coordinate the domestic and international efforts towards COVID-19 PrEP research:

Three Steps to Better Coordinate COVID-19 PrEP Research

- **Develop a coordinated process** – with the U.S. National Institutes of Health (NIH), international organizations and industry partners – to rapidly and accurately screen potential antiviral inhibitors of SARS-CoV2. This should enable increased access to biosafety level 3 facilities, as well as creation of a publicly accessible database for coordination and data-sharing for screening experiments.

- **Establish a cross-institutional committee** at NIH and World Health Organization (WHO), including extramural and industry researchers, to decide which candidate compounds should be evaluated in clinical trials.

- **Form and fund a mechanism**, such as a trial network, to coordinate clinical trial research across institutions and nations – preventing duplication and ensuring that all promising candidates are rapidly evaluated in properly designed randomized placebo-controlled clinical trials.
Why PrEP for COVID-19?

On 23 April 1984, the then Secretary of Health and Human Services (HHS) Margaret Heckler, at a press conference announcing the alleged discovery of HIV by Robert Gallo, famously proclaimed that an HIV vaccine would likely be ready for testing by 1986. Nearly four decades later, an effective HIV vaccine has still not been discovered. Despite this, a highly effective method of HIV prevention – HIV pre-exposure prophylaxis (PrEP) – is available today. HIV PrEP is the use of antiretroviral drugs by HIV negative persons to prevent HIV infection. When used properly, HIV PrEP reduces the risk of HIV acquisition by over 99% – more effective than many vaccines – and can dramatically reduce the number of new HIV cases at the population scale when made widely available. A similar approach is taken to preventing malaria – another deadly infectious disease where no effective vaccine is currently available – where people who do not have malaria take an antiprotozoal drug to prevent infection while living or traveling in areas where it is endemic. SARS-CoV2 is likely more amenable to rapid vaccine development than HIV or malaria. However, even in the most optimistic scenario, an effective vaccine will take at least a year to develop, and even longer to become widely available. While the implementation of widespread social distancing measures has proven highly effective at reducing the force of infection (i.e., the rate per unit time that a susceptible individual becomes infected) of COVID-19 outbreaks, they have a dramatic impact on the economy and individuals' lives. An analysis performed by Imperial College London found that, absent another form of epidemic control, intensive social distancing measures would need to be in place for two-thirds of the time even after the initial "peak" to avoid overwhelming the healthcare system. Alas, if no other method of epidemic control is introduced, social distancing methods may be required as late as 2022.

The necessity of developing alternative methods of epidemic control are even more important to the most vulnerable communities – like healthcare workers, other essential workers and people living in middle- or lower-income countries where widespread social distancing is unlikely to be possible. Until a vaccine is available, developing a form of epidemic control that could be rapidly brought to scale is an urgent priority. A drug or drug regimen for SARS-CoV2 that works as an effective form of PrEP could help achieve this objective. While there are no approved drugs currently for treatment or prevention of COVID-19, both expert opinion and in silico (computer modelling, lit. “within silicon”) analysis have identified a large set of compounds – both small molecules and biological macromolecules – that may inhibit SARS-CoV2 replication. Importantly, some of these possible SARS CoV2 inhibitors are already FDA-approved drugs, which if shown effective in preventing COVID-19, could be made available more quickly than an unapproved compound.

Unfortunately, the United States' – and the world's – efforts to develop a form of COVID-19 PrEP are not set up to succeed. This report identifies critical failures in every step of the research and development processes – from a lack of an organized process for high throughput screening of potential SARS-CoV2 inhibitors to redundancies and inefficiencies in current and planned clinical trials of potential PrEP modalities.

An organized, centrally coordinated process should be created by the National Institutes of Health (NIH), along with industry and international partners, using...
all resources available to the federal government, to accelerate every step of the PrEP development process. A centralized office, distinct from treatment development efforts, should be set up at the NIH to direct this process. However, certain steps, like in vitro screening, may be shared between treatment and PrEP development efforts.

While the traditional approaches to drug development are essentially a serial process – each step sequentially following the preceding step – the urgent necessity of COVID-19 PrEP development means that this process should be “parallelized.” Even before an agent or agents are selected for clinical trial evaluation, logistical preparations should be taking place for the staging of clinical trials, so that drugs can get into bodies as soon as possible for evaluation.

Pre-Clinical Development of PrEP for COVID-19

In Vitro Evaluation of Candidate COVID-19 Inhibitors

Identifying compounds that can inhibit viral replication is necessary to develop an effective method of COVID-19 PrEP. A compound’s ability to inhibit the replication of SARS-CoV2 can be evaluated by using a mammalian cell culture-based model of viral replication. A breakdown in our ability to screen a large number of compounds for antiviral activity in cell culture models impedes the identification of potential SARS-CoV2 inhibitors.

Cell culture refers to the propagation of cells in the laboratory, generally in polystyrene or glass (hence the term “in vitro,” lit. “within glass”) vessels. Many cell culture-based experiments utilize “cell lines,” a lineage of cells from a tissue of a multicellular organism, that can proliferate indefinitely, a phenomenon known as “immortalization.” Importantly, the ability of most mammalian cell lines to proliferate indefinitely is dependent on mutations that are not present in healthy cells. Results from experiments performed in cell culture do not necessarily translate to results of an experiment performed in the whole organism (generally referred to as “in vivo,” lit. “within the living”). However, the relative ease of performing cell culture-based assays, compared to experiments performed in animals or humans, make it a valuable method for initially screening compounds for their potential biological activity, like inhibition of viral replication.

Often, the first antivirals used in an emerging viral epidemic are compounds that have been previously synthesized before the outbreak was identified and are shown to inhibit viral replication in vitro. For example, the first four drugs FDA approved to treat HIV infection (zidovudine, didanosine, zalcitabine, and stavudine) were all compounds that had been synthesized before the first cases of AIDS were reported in 1981, but were then shown to inhibit replication of HIV in vitro.

Development of in vitro models of SARS-CoV2 Infection

SARS-CoV2 can be propagated in vitro. Classically, SARS-CoV2, like MERS virus (the virus that causes Middle East Respiratory Syndrome) and SARS-CoV1 (the virus that causes Severe Acute Respiratory Syndrome), is propagated in a member of the Vero family of cell lines – derived from the kidney epithelium of the African Green Monkey, Chlorocebus aethiops. Most of the initial in vitro studies evaluating the possible anti-viral effect of drugs for SARS-CoV2, like
those evaluating chloroquine and hydroxychloroquine, were done in the Vero/E6 cell line\textsuperscript{11,12}.

While the Vero cell line is noted for its ease in viral propagation studies, and is one of the most widely used mammalian cell lines in microbiology studies, it has significant downsides for its use in antiviral screening assays for SARS-CoV2 when used to evaluate drugs (like chloroquine and hydroxychloroquine) that have immunomodulatory properties. Therefore, alternative \textit{in vitro} models must be developed for antiviral screening assays.

It is well-established that Vero cell lines lack the ability to produce type I interferons (e.g., interferon-\(\alpha\), interferon-\(\beta\)) due to a nine megabase pair homozygous deletion on chromosome 12, which results in the loss of type I interferon gene cluster\textsuperscript{13,14}.

The type I interferon response may play an important role in the host response to SARS-CoV2 infection. Indeed, interferon-\(\beta\)\textsubscript{1a} has been shown to potently inhibit SARS-CoV1 (a close relative of SARS-CoV2) replication \textit{in vitro}\textsuperscript{15}. In mouse models of SARS infection, Toll-like receptor (TLR) 3 and TLR4 activation of the TIR-domain-containing adapter-inducing interferon-\(\beta\) (TRIF) dependent signal transduction pathway was highly protective\textsuperscript{16}. Activation of the TRIF dependent signal transduction circuitry canonically leads to, among other things, production of type I interferons via activation of interferon regulatory factors (IRF) 3 and 7\textsuperscript{17}.

Chloroquine and hydroxychloroquine, of course, are used not only as antimalarials, but also as immunomodulators for treatment of lupus and rheumatoid arthritis. While the mechanism of action for this indication has not been fully established, their ability to disrupt TLR signaling is thought to play a large role\textsuperscript{18}. If these drugs impact the type I interferon response to SARS-CoV2, by disrupting TLR signaling or any other mechanism, \textit{in vitro} models using Vero cell lines will not be able to detect the impact of this on viral replication. Furthermore, antiviral effects of certain compounds, including remdesivir, are less in Vero cells than in human cells, possibly due to differences in intracellular machinery in human vs. African Green Monkey cells\textsuperscript{19}.

\textbf{RECOMMENDATION 1:}

\textbf{Identification of Alternative Cells Lines for SARS-CoV2 Propagation}

The identification of other cell lines besides the Vero family of cell lines for \textit{in vitro} antiviral drug evaluation assays for SARS-CoV2 should be prioritized. This is due to the likely importance of TLRs, as well as other pattern recognition receptors (PRRs) like retinoic acid inducible gene-1 (RIG-1), and type I interferon in SARS-CoV2 pathogenesis. However, given the wide variety of cell lines that have been shown to be able to propagate SARS-CoV1, a suitable alternative cell line or cell lines may be found rapidly. Ideally, \textit{in vitro} drug evaluation assays would occur in multiple cell lines\textsuperscript{20}.

\textbf{High Throughput Screening of Potential SARS-CoV2 Inhibitors}

A centrally coordinated, high throughput screening program, orchestrated by the federal government, to identify potential SARS-CoV2 inhibitors in vitro among existing libraries of possible compounds should be undertaken urgently. This may allow for the rapid identification of multiple compounds that should be evaluated \textit{in vivo}. To our knowledge, no such coordinated programs are currently operating\textsuperscript{21}.

High throughput screening (HTS) refers to the process of evaluating the biological activity (e.g., inhibition of viral replication) of hundreds or thousands of compounds \textit{in vitro} simultaneously using automated assays. HTS has been critical to identifying potential therapies for previous emerging infectious diseases. For example, remdesivir, Gilead Sciences’ phosphoramidate prodrug of GS-441524, a cyclic monophosphate analogue of adenosine, was identified via multiple high throughput screens of a library of approximately one thousand compounds for
their activity against multiple RNA viruses, including Ebola\textsuperscript{22,23}.

Although remdesivir was initially developed for treatment of Ebola virus, it has now become a possible treatment for COVID-19\textsuperscript{24}. Critically, the identification of remdesivir as a potential treatment for Ebola virus was dependent on federal government participation. Ebola virus is a risk group four infectious agent, the most dangerous classification in WHO and NIH biosafety classification scheme. Therefore, experiments using infectious Ebola virus must be studied in highly specialized facilities that can operate at biosafety level 4 (BSL4), the highest level of biocontainment available\textsuperscript{25}. The high throughput screens of potential Ebola inhibitors took place at two federally operated BSL4 labs – the CDC’s BSL4 facility in Atlanta, GA and the United States Army Medical Research Institute of Infectious Disease (USAMRIID) BSL4 facility in Fort Detrick, MD\textsuperscript{23}.

Experiments involving propagation of infectious SARS-CoV2, like high throughput screening that uses wild type SARS-CoV2, must be performed in a biosafety level 3 (BSL3) laboratory, the second-highest level of biocontainment. While BSL3 labs are much more common than BSL4 facilities, many existing high throughput screening facilities operate at biosafety level 2 (BSL2), preventing the use of wild type SARS-CoV2. This represents a critical bottleneck in the research on SARS-CoV2 inhibitors\textsuperscript{26}.

Few high throughput screens of potential agents of anti-SARS-CoV2 agents have been performed.

\begin{itemize}
  \item NIAID’s Bill Young Center (Building 33), NIH Main Campus, Bethesda, MD (BSL3)
  \item NIAID’s Rocky Mountain Labs, Hamilton, MT (BSL3/BSL4)
  \item USAMRIID’s Fort Detrick, MD Lab (BSL3/BSL4)
  \item CDC’s Atlanta, GA Lab (BSL3/BSL4)
\end{itemize}

\textbf{RECOMMENDATION 3:}
\textit{Creation of a Centrally Coordinated, Public, High Throughput Screening Process for Evaluation of Potential SARS-CoV2 Inhibitors}

The federal government should not only perform HTS experiments, but also centrally collect data on HTS processes performed by industry and academic partners. Importantly, a publicly accessible centralized database of screened compounds with results and relevant meta-data (e.g., assay design) should be created. This could aid researchers from across sectors, prevent unnecessary duplication of experiments and make selection of compounds for further evaluation in clinical trials easier and more transparent.
Clinical Trial Evaluation of Possible COVID-19 Prevention Modalities

Following identification of compounds that show potential in inhibiting HIV in vitro, well-designed randomized, placebo-controlled clinical trials are needed to determine whether these compounds are safe and effective in treating and/or preventing SARS-CoV2 in humans. This paper is focused primarily on the potential to prevent SARS-CoV2 transmission. Testing prevention modalities in randomized placebo-controlled trials poses unique challenges – especially in a disease like COVID-19.

Current clinical research efforts lack coordination and many trials are poorly designed. To succeed in rapidly developing a form of COVID-19 PrEP, dramatic changes must take place in the way we are planning, designing and implementing clinical trials. This section begins by giving an overview and critical analysis of current or planned, registered clinical trials for COVID-19 chemoprophylaxis modalities, and concludes with recommendations for future clinical trial efforts.

![Figure 1: Agents Being Evaluated in Registered Clinical Trials for COVID-19 PrEP or PEP]

- 64% evaluate hydroxychloroquine
- 5% nitric oxide
- 5% allogeneic adipose-derived mesenchymal stem cells
- 3% lopinavir / ritonavir
- 3% recombinant human interferon alpha + thymosin alpha
- 2% Peginterferon lambda alfa-1a
- 2% hydroxychloroquine vs. tenofovir DF/emtricitabine
- 2% hydroxychloroquine vs. lopinavir/ritonavir
- 2% hydroxychloroquine + bromhexine
- 2% nitazoxanide
- 2% hydroxychloroquine vs. azithromycin
- 2% melatonin
- 2% Autoclaved Mycobacterium w
Unfortunately, the cardiac side effects – primarily QT interval prolongation, leading to an increased risk of Torsades de pointes, a type of abnormal heart rhythm (arrhythmia), that can lead to potentially fatal ventricular fibrillation – of chloroquine and hydroxychloroquine are well established. When used as a treatment for COVID-19, 11% of patients treated with hydroxychloroquine and azithromycin developed a prolonged QT interval (greater than 500 milliseconds), putting these patients at significantly increased risk for potentially fatal arrhythmias. This has led to the FDA issuing a warning against using hydroxychloroquine or chloroquine in outpatient settings. Such acute toxicity impacts the potential utility of the drug when used in the prophylactic context.

Different criteria are needed for selecting agents for prevention than for treatment. Given that people who are taking a drug for prophylactic purposes are not already sick, the criteria for what makes an acceptable drug for prevention is distinct in terms of toxicity, routes of administration and convenience compared to a drug being used for treatment. Deciding which molecules will go forward into clinical trials should be made by an impartial, centralized process, in which epidemiologists, pharmacologists, virologists, molecular biologists, and infectious disease specialists select agents that have a high potential for efficacy. This will ensure the efficient allocation of clinical trial resources, while still ensuring objective evaluation of the safety and effectiveness of potential PrEP modalities.

Remdesivir, despite being one of the most promising COVID-19 treatments, is currently administered as an injection, rather than an oral formulation. This limits its application as a prophylactic, and there are no clinical trials currently registered which evaluate it as PrEP or PEP. Whether remdesivir or another prodrug of the parent nucleotide analogue could be orally administered is not known. But the evaluation of this drug or an alternative prodrug for oral administration should be urgent priority for both Gilead Sciences and other researchers.

Current Clinical Trials Evaluating Potential COVID-19 PrEP and PEP Candidates

Currently, there are forty-two clinical trials registered on clinicaltrials.gov designed to evaluate COVID-19 PrEP or post-exposure prophylaxis (PEP) modalities. The current clinical trial landscape reflects the complete lack of coordination in the efforts to develop COVID-19 PrEP. This, coupled with the failure to identify other agents that may inhibit SARS-CoV2 replication, has led to extreme redundancies in the drugs being evaluated – with 61% of registered clinical trials (n=22) evaluating chloroquine or its prodrug, hydroxychloroquine. Promising compounds, like remdesivir, are not even being evaluated in the context of prevention.

A systematic review of the National Clinical Trial Registry was undertaken, with the latest database pull taking place at 22 April 2020. One hundred and three potential clinical trials were identified and were analyzed by the author. Trials which evaluated treatments (i.e., interventions in patients who already had or had already developed COVID-19), vaccines, or non-pharmaceutical interventions were excluded. Trials that met the inclusion criteria were centrally tracked in a Google Sheet that is publicly available. Each trial which met the inclusion criteria was analyzed for drug(s) being evaluated, clinical trial design, planned enrollment size, time frame, and current status.

Sixty-four percent of registered trials are testing the same drug (n=28), chloroquine or its prodrug, hydroxychloroquine. The mechanism by which hydroxychloroquine may inhibit viral replication remains unclear. The dominance of hydroxychloroquine and chloroquine is concerning for multiple reasons. First, this extreme redundancy in clinical trials represents a waste in resources. Second – and arguably more importantly – both chloroquine and hydroxychloroquine have significant side effects that may limit their clinical use, especially in a prophylactic context.
The NIH should convene an expert panel from across academia and industry to evaluate which candidate molecules that have demonstrated antiviral potential in vitro should proceed into clinical trials for evaluation in humans for prophylactic purposes. Such a committee should have the power to rapidly convene small, Phase I studies to generate data on pharmacology, dosing and safety, if these characteristics have not been previously characterized.

In addition to the trials evaluating just hydroxychloroquine or chloroquine, three trials compare the safety and effectiveness of hydroxychloroquine PrEP to other drugs, one trial compare hydroxychloroquine to tenofovir disoproxil/ emtricitabine (a combination of a HIV nucleotide and a nucleoside analogue reverse transcription inhibitors that may inhibit SARS-CoV2 RNA dependent RNA polymerase) one trial compares hydroxychloroquine to lopinavir/ritonavir (a combination of HIV protease inhibitors that may inhibit SARS-CoV2 main protease), and one compares hydroxychloroquine to azithromycin (a macrolide antibiotic that has no known antiviral properties).

Other agents being explored in clinical trials include:

- **Nitric oxide** (two trials) – a biological messenger molecule that, canonically, leads to bronchodilation through a guanylate cyclase-cyclic GMP-dependent protein kinase type I dependent relaxation of smooth muscle, but is also a possible inducer of the type I interferon host antiviral response.\(^\text{32,33}\)

- **Recombinant human interferon-alpha nasal drops plus subcutaneous thymosin alpha** (one trial) a type I interferon plus thymosin-alpha – a 28 amino acid peptide fragment of prothymosin alpha that has immunoregulatory properties.

- **PUL-042** (one trial) – a mixture of a synthetic diacylated lipopeptide, a TLR2 and TLR6 agonist, and ODN, a CpG-containing oligodeoxynucleotide that is an agonist of TLR9.

- **Nitazoxanide** (one trial) – a broad spectrum antiviral that has demonstrated anti-SARS CoV2 activity in vitro.\(^\text{34}\)

- **Peginterferon lambda alpha 1a** (one trial) – a type III interferon that is being evaluated for treatment of hepatitis B and hepatitis delta virus.

- **Allogeneic Adipose allogeneic adipose-derived mesenchymal stem cells** (two trials) – a form of stem cell therapy that has been hypothesized to help modulate the immune response to SARS-CoV2.\(^\text{35}\)

- **Autoclaved Mycobacterium w** – an attenuated strain of Mycobacterium that is non-pathogenic and classically used as an adjuvant, as well as an immunomodulator.

The vast majority of clinical trials currently registered are testing just chloroquine or its prodrug, hydroxychloroquine. While it is reasonable to evaluate these drugs for their possible ability to prevent COVID-19, this level of duplication is obviously unnecessary. Comparing numerous agents in a single, multi-armed, placebo-controlled clinical trial may be an efficient method of rapidly evaluating the efficacy of different possible PrEP candidates. This may be a prudent way to decrease duplication, while ensuring that numerous agents are still rigorously studied for their ability to prevent SARS-CoV2 infection. This
approach has been used in COVID-19 treatment clinical trials; for example, the “Solidarity” clinical trial coordinated by WHO evaluates four different agents (remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with interferon-ß1a, and chloroquine/hydroxychloroquine) in a randomized controlled design.

**Design of Current Clinical Trials Evaluating COVID-19 PrEP and PEP**

In order to determine whether a COVID-19 PrEP modality is, in fact, safe and effective, they must be evaluated in well-designed clinical trials. Double blinded (i.e., where both the participant and the investigator are unaware of whether the participant is on the placebo or the experimental drug), placebo-controlled clinical trials remain the gold standard for evaluating efficacy and safety. While most (n=26, 62%) registered clinical trials for COVID-19 PrEP are randomized, placebo-controlled, a significant number of trials utilize an open label (i.e., where the participant is aware whether they are on the experimental drug or the placebo, if there is even a placebo). The population in which clinical trials take place is also a critical aspect of clinical trial design. Ideally, potential COVID-19 modalities would be evaluated in population that have a high rate of underlying SARS-CoV2 infection and could easily access research staff. It is therefore not surprising that most (n=32, 76%) clinical trials evaluate PrEP modalities in healthcare workers who are treating COVID-19 cases. A minority of clinical trials take place in households with confirmed COVID-19 cases, and a single trial takes place in the general population of confirmed COVID-19 negative people.

**Power Analysis of Registered Clinical Trials**

A key component of performing successful clinical trials is that the trial is adequately powered – i.e., the probability that the trial can detect whether the intervention has an effect, if it in fact has one. Generally, power of clinical trials should be not less than 80%, that is, four out of five times the trial should be able to detect whether a treatment has the ability to prevent infection (at a previously defined efficacy) at a previously defined level of statistical significance (generally at \( p=0.05 \)). In order to analyze whether currently registered clinical trials were adequately powered, we calculated the minimum clinical trial size (of each arm) needed for a trial to detect a PrEP modality that had an effectiveness of 0.9 (i.e., it reduced the risk of infection by 90% in treated subjects vs. untreated people) at a statistical significance level of \( p=0.05 \), with a statistical power of 80%.
Through this analysis, it was found that 53% of trials with placebo arms are underpowered (i.e., power below <80%) to detect an effective PrEP regime (with a relative risk reduction of 0.9) – even assuming that the baseline incidence of COVID-19 at the trial end point in the studied population is equal to the attack rate of people who had close contacts with confirmed COVID-19 cases.

It was assumed that the incidence rate of COVID-19 would be equal to that previously reported of a cohort of close contacts of COVID-19 patients, which reported a 0.45% attack rate (i.e., cumulative incidence) at fourteen days, which is equivalent to an incidence rate of approx. 0.032 per 100 person-days. If one assumes that people cannot become re-infected and no one is infected at day zero, the portion of people (p) who are or have been infected in each arm of the clinical trial rate at day t is simply:

\[ p(t) = 1 - e^{-\eta/Jt} \]

Where \( p \) is the proportion of people infected, \( \eta \) is the efficacy of the intervention at reducing the incidence (\( \eta = 1 \) for placebos), \( J \) is the incidence-rate per person-day of COVID-19 in the baseline population, \( t \) is the number of days since enrollment, and \( e \) is Euler's number.

If we assume that the incidence of COVID-19 in a given arm of a trial is normally distributed, we can utilize a two-sided Z-test to determine the minimum size of each arm of clinical trial (n) that is powered at a given level to detect a statistically significant decrease in incidence between a placebo-controlled arm and intervention arm. Recall:

\[ n \geq \left( \frac{Z_{\alpha/2} + Z_{\beta}}{2} \right)^2 \frac{(p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2} \]

Where \( n \) is the minimum number of participants per arm, \( Z_{\alpha/2} \) is the z-score for a given confidence level for a two-tailed test (\( Z_{0.025} = 1.96 \) for \( \alpha = 0.05 \)), \( Z_{\beta} \) is the z-score for a given statistical power (\( Z_{0.84} = 0.84 \) for a power of 80%), \( p_1 \) is the proportion of people who received the drug who are not infected at the end of the trial, and \( p_2 \) is the proportion of people who received the placebo who are not infected at the end of the trial.

We found that of the 32 trials included in our analysis, 53% (n=17) were underpowered to detect even a highly effective (i.e., reduces the risk of infection by 90%) PrEP or PEP regimen.

Challenges around statistical power are likely to get worse with time, unfortunately. Outbreaks of COVID-19 are likely to experience dramatic changes in baseline incidence over time. Unless the design and implementation of clinical trials for evaluation of COVID-19 explicitly plan for this eventuality, they are unlikely to finish. Decreasing incidence decreases the statistical power of a trial. Multiple trials in China of potential COVID-19 treatments have already ended prematurely due to declining local incidence. This is not a new phenomenon – in the 2014-2015 West African Ebola Outbreak, for example, waning incidence posed significant challenges to the evaluation of both candidate vaccines and treatments.

**RECOMMENDATION 5: Creation of an International COVID-19 Prevention Trial Network**

Given the high level of redundancy in currently registered clinical trials and the lack of statistical power in many registered trials, a more coordinated approach is needed. The creation of a COVID-19 Prevention Trial Network, which can ensure that clinical trials are properly designed, identify multiple sites that are likely to have a high baseline incidence, and reduce the time needed to get trials enrolling, could help alleviate these issues. Critically, such a network could ensure that even if COVID-19 incidence is declining in a local area, potential PrEP modalities could be evaluated at other sites across the world where incidence is increasing or higher. Furthermore, it could enable the rapid design and development of properly powered multiarmed, multicentered clinical trials that could evaluate multiple candidates simultaneously.
Conclusion

The development of a safe and effective method of COVID-19 PrEP is a potential game changer for the COVID-19 pandemic. This report identifies significant failures in every step of the development process – from basic issues with in vitro screening to the lack of coordination in the development of clinical trials. Put bluntly, the current approach to research and development is unlikely to succeed as rapidly as it needs to. Yet we know from previous responses to the other pandemics, like HIV, that a coordinated process between institutions like the NIH and WHO, as well as academic and industry partners, can result in rapid advances in both basic science and clinical care.

The COVID-19 pandemic is the greatest public health challenge the world has faced in over a century. The need for an effective method of prevention is felt by nearly every person around the globe. Methods of drug-based pharmaceutical prophylaxis have proven to be highly effective in fighting previous pandemics that seemed, at first, uncontrollable. None of us today know which new method or methods of controlling this pandemic will be effective, but we owe it to the world to try to find out in the most efficient way possible.

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– James Krellenstein, Co-founder of PrEP4All
Endnotes

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6 Kissler SM et al. “Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period” Science 2020; eabb5793 DOI: 10.1126/science.eabb5793
21 Personal Communication between H. Clifford Lane (NIAID/NIH), Peter Staley (PrEP4All), and James Krellenstein (PrEP4All), 8 April 2020.


27. Search query consisted of: (“Prophylaxis” OR “Prevention” OR “preventive measures” OR “prophylactic treatment” OR “PREVENTATIVE” OR “preventive intervention” OR “Prevent procedure” OR “Preventive procedure” OR “preventive therapy” OR “preventive treatment”) AND (“COVID-19” OR “2019-nCoV” OR “severe acute respiratory syndrome coronavirus 2” OR “2019 novel coronavirus”)

28. https://docs.google.com/spreadsheets/d/1NAh1AMUUf38nAxlAuyPa_V_d4mBLflBloDzJknbfjo/edit?usp=sharing


30. Search query consisted of: (“Prophylaxis” OR “Prevention” OR “preventive measures” OR “prophylactic treatment” OR “PREVENTATIVE” OR “preventive intervention” OR “Prevent procedure” OR “Preventive procedure” OR “preventive therapy” OR “preventive treatment”) AND (“COVID-19” OR “2019-nCoV” OR “severe acute respiratory syndrome coronavirus 2” OR “2019 novel coronavirus”)