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Viewpoint

HIV cure research in the time of COVID-19 - Antiretroviral therapy treatment interruption trials: A discussion paper

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ABSTRACT

This discussion paper addresses the safety of HIV cure studies, particularly those involving stopping antiretroviral therapy, known as an analytic treatment interruption (ATI) in the context of the SARS-CoV-2 pandemic. More than 30 studies listed on ClinicalTrials.gov include an ATI and many others were planned to begin over the next 12 months but most were halted due to the COVID-19 pandemic. We consider the ethics, risks and practical considerations to be taken into account before re-opening HIV cure clinical trials, noting the specific risks of ATI in the context of circulating SARS-CoV-2.

Introduction

Control of HIV replication using antiretroviral therapy (ART) has transformed survival for people living with HIV.[1,2] Viral suppression enables immune recovery[3] and limits the risk of onward viral transmission[4,5] but requires lifelong adherence to ART,[6] which presents a challenge to some and a major constraint to healthcare systems, particularly in resource-limited settings.[7] Potential HIV remission or cure is a recognised goal of both researchers and the community of people living with HIV.[8]

Interruption of ART usually leads to a rapid return of viraemia within 2–6 weeks of stopping medication.[9,10] Long-lived cells that harbour replication-competent HIV (the "HIV reservoir")[11] are the source of this rebounding virus. Whilst there are many laboratory-based assays that measure the size, location and characteristics of the HIV reservoir,[12] to date none have been shown to accurately predict the risk of viral rebound upon stopping ART. It is for this reason that clinical trials exploring the ability of novel strategies to maintain viral control off ART usually require a carefully monitored analytical treatment interruption (ATI). The ATI protocols require a rigorous clinical, ethical and practical evaluation to determine risk mitigation for participants and their sexual partners, as well as the evaluation of the commitment to regular HIV viral load measurements. Conducting an ATI, even in the absence of a dynamic global pandemic, is challenging,[13] but there are now standard approaches and a general consensus on how these studies should be performed.[14] Conducting an ATI during the COVID-19 pandemic raises many additional issues that will need to be addressed by clinicians, the community, funders and regulators.

Since December 2019 the global SARS-CoV-2 pandemic has dramatically altered daily lives,[14] medical care and research.[15] Limitation of travel and physical distancing were universally adopted, leading to a new clinical environment designed to minimize people's exposure to the health care system. The manner in which care has been provided for people living with HIV has also had to change. To help define policies, many countries drew up guidelines to inform management and care for people living with HIV, whilst SARS-CoV-2 continued to circulate at significant levels.[16] At the same time, all non-COVID-19-related clinical research was paused, diverting resources to the COVID-19 response. As the pandemic continues, we need to carefully re-evaluate the risks and benefits of resuming HIV clinical trials, even those including an ATI.

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Importance of continuing HIV cure research: an open question

As the impact of SARS-CoV-2 declines, it will be possible to restart answering important research questions for the 39 million people globally living with HIV. Generally, most people still hope for an HIV cure. Cure studies need to optimise safety for participants, but also maintain maximal scientific rigor through continued engagement among all stakeholders to ensure that any risk to participants i can also be justified by the potential benefit to the larger community.[17]

The ethical debate about the pros and cons of an indefinite deferral versus careful resumption of ATI HIV cure studies is important. One option is to indefinitely stop all HIV trials including an ATI until there is a widely available SARS-CoV-2 prophylactic vaccine[18] or effective treatment for COVID-19 disease.[19] Whilst there is a global commitment to both of these goals, the potential for delay with this option is high and many ground-breaking novel HIV remission therapies and approaches currently in trial would remain paused. In the meantime, challenges continue for people living with HIV globally to receive and adhere to reliable, sustainable and programmatic delivery of daily ART,[20] further threatened by ongoing COVID-related clinical burden and limitation of movement of people, drugs and reagents.

If HIV cure and ATI trials are to continue, each individual study will need to be reviewed and evaluated on a case-by-case basis, once background COVID-19 incidence drops to low levels, as yet undefined. Common mitigation approaches to reduce risk within the field of HIV cure and remission trials might provide a framework to safely reinstitute ATI studies. This will require changes to patient information and informed consent so that study participants are aware of the implications from COVID-19.

Preservation of trial scientific integrity to retain the capacity to generate meaningful data is critical. Exclusion of participants or alteration of study outcomes (eg viral control off ART), to mitigate COVID-19 risk that might compromise trial rigor, could undermine the value of continuing such research in the current climate. Besides being able to ensure adequate HIV viral load monitoring to generate sufficient data points for analysis, a reality that cure studies may have to face is to consider alternative primary endpoints to HIV viral load, (e.g. if participants need to re-initiate ART because of acquiring SARS-CoV-2 infection, exposure, inability to travel). Studies may need to be re-designed around the "imperfect" other measurements of immune responses and HIV reservoir, as back up.

Risk of SARS-CoV-2 acquisition amongst people living with HIV

The overall risk of SARS-CoV-2 acquisition is largely related to exposure. This will vary based on: (i) local incidence, (ii) physical circumstances (proximity to people with SARS-CoV-2), (iii) behavioural factors (distancing, masks and hand washing, etc), and (iv) individual susceptibility to SARS-CoV-2 acquisition, including level of immune suppression. There is no evidence to date showing that people living with HIV on ART are at significantly increased risk of SARS-Cov-2 acquisition compared to HIV negative people[21] or to determine whether HIV viraemia increases the risk of SARS-CoV-2 acquisition. Therefore, there are theoretical concerns that uncontrolled HIV might increase the risk of SARS-CoV-2 infection, predominantly weighted around the concern of decreased immunity due to a low CD4 T cell count rather than evidence for increased risk specifically caused by HIV viraemia. The current recommendation is, therefore, that all people living with HIV should be on ART.[22]

Risk of more severe COVID-19 disease amongst people living with HIV

Severe COVID-19 disease has been associated with many risk factors. These include: older age (>60 years), male gender and comorbidities (including cardiovascular and renal disease, hypertension, diabetes, obesity, ongoing cancer and recent organ recipients).[23] Poverty, poor housing, minority ethnic populations and other linked socioeconomic factors are important risk factors for more severe disease.[24] Many of the socioeconomic, ethnicity and comorbidity risks are over-represented amongst the population of PLWH.

To date there is limited but increasing data on the absolute risk of severe COVID-19 for people living with HIV.[25–30] Most studies have found no evidence of an increased risk of COVID-19-related death in people living with HIV, once co-morbidities are taken into account.[29] One large study of HIV/COVID-19 coinfections in South Africa reported a 2-fold increase in mortality associated with HIV, but acknowledged that the data could be largely explained by confounding factors in this population.[30] However, again the quality of evidence for those who were viremic or not on ART is less good, and, although no clear risks have been identified, this caveat needs to be considered.

Specific considerations associated with ATI in SARS-CoV-2 pandemic:

1. **Risks associated with taking part into a clinical trial which** usually require additional hospital visits and procedures that could be associated with higher risk of SARS-CoV-2 acquisition.
2. **Risk of increased susceptibility to SARS-CoV-2 associated with the ATI** due to HIV-associated inflammation and immunodeficiency, which may hypothetically increase the risk of acquisition after exposure.
3. **Risk of a worse clinical outcome from COVID-19 disease**: acute SARS-CoV-2 infection causes lymphopenia and this in turn is associated with a poor outcome.[23] There is a hypothetical increased risk of severe COVID-19 disease for people living with HIV undertaking an ATI due to a possible increased susceptibility to immune activation and a 'cytokine storm'[31] during an ATI-induced viral rebound. Because of ATI trial closures, there is no data at present showing that this is the case, but this cannot infer safety. This potential risk may be further accentuated in cure ATI studies involving immune-enhancing interventions (e.g. broadly neutralizing antibodies, therapeutic HIV vaccines, toll-like receptor agonists), although at this stage this remains a theoretical risk in the absence of data.
4. **Risk of a worse outcome of the ATI:** the ATI itself has been associated with increased levels of inflammation related to adverse events. Acquisition of SARS-CoV-2 infection during an ATI might be an additional trigger for inflammation[32] and increase the risk of ATI-related cardiovascular events.[33] ATI studies may exclude participants at higher risk of inflammation-related complications.
5. **Risk of disruption to ART availability** could severely impact ATI studies if drugs are not available for ART resumption, which may influence some settings more than others. The challenges in resource-limited and high HIV burden settings are driven by limited global manufacturer production capacities and global supply chain disruptions, coupled with limited access to health services within countries as a result of the COVID-19 pandemic.[34]

Suggested risk mitigation strategies for recommencing studies with an ATI in the setting of COVID-19 (Table 1)

Assuming that there will remain consensus that HIV ATI studies are ethical and should continue we would like to explore how they might be safely implemented. Should an effective SARS-CoV-2 vaccine become available during the implementation of an HIV cure trial, vaccination should be recommended for all study participants and ideally prior to an ATI.

We propose the following mitigation considerations prior to enrolment into ATI studies in the absence of a SARS-CoV-2 prophylactic vaccine or effective treatment:

Modification of study eligibility criteria

Inclusion only of individuals who do not have known risk factors for

Table 1
Risk assessment.

Risk	Suggested mitigation approach	Challenges to trial integrity
Increased risk of severe COVID-19 disease	Evaluation of severe COVID-19 risk groups to exclude enrolment during high levels of COVID-19 transmission.	Reduce access to trials, limit recruitment. Some non-medical risk factors raise ethical issues – i.e. limiting research by ethnicity or employment.
Risk of severe COVID-19 if acquired at time of any high-risk curative intervention	SARS-CoV-2 PCR test prior to administration of any therapy that might alter the risk of COVID-19 disease.	Ensure rapid access to PCR and results – ideally POCT testing on same day.
Risk of severe COVID-19 if acquired at time of an ATI	SARS-CoV-2 PCR test on day of enrolment into ATI protocol.	Ensure rapid access to PCR and results – ideally if available POCT testing on same day.
Risk of severe COVID-19 if acquired during an ATI	Offer rapid SARS-Cov-2 PCR throughout ATI period, screen all symptomatic participants and rapid re-start of ART if PCR+ Restart ART if high risk SARS-CoV-2 exposure during an ATI: e.g. if household contact becomes COVID+.	Ensure rapid access to PCR and results – ideally POCT testing on same day. Challenge to study power if many have to re-start ART prior to viral endpoint.
Risk of SARS-CoV-2 acquisition due to frequent hospital visits for blood draws	Limit number of visits for VL measurement. Evaluate novel point of care or self-sampling blood for VL (DBS) and possible role of community blood draw teams for household research staff visits.	Often an HIV VL is the study primary endpoint. It is important to ensure capture of sufficient and high quality data to power study and avoid non-validated VL measurements.
Increases in local/ regional incidence of COVID-19: potential lockdown for second and subsequent waves of COVID-19.	All the above strategies might need to be intensified and distancing recommendations change during the study.	This duration of risk might vary for different study arms and length of expected duration of ATI. Individual responses to an ATI are likely to vary, even within arms.
Participants not being aware of additional risk associated with COVID-19.	Include COVID-19 risk in participant information and informed consent, including how an ATI might increase risk and increased importance of avoiding infection with behavioural approaches.	Ensure participants understand how risk might change during the study and understand medical, behavioural and other risks.

severe COVID-19 disease. This would require clear definition of these risk factors (e.g. age, diabetes mellitus, hypertension, and obesity) based on data from large population studies.[23] Flu vaccination is recommended prior to enrolment dependent on season availability.

SARS-CoV-2 testing at study entry

Enrolment should be limited to those without symptoms who test negative on SARS-CoV-2 PCR prior to study implementation.

For anyone testing SARS-CoV-2 PCR positive and excluded from enrolment, once repeat testing is negative, they may then be eligible to join the study.

At present, there is not enough data in terms of SARS-CoV-2 serological assays to be useful decision-making tools for trial eligibility,[35] although further validation could direct eligibility in the future.

SARS-Cov-2 testing through the ATI period

Vigilance will be recommended for all study participants in terms of symptoms associated with COVID-19 throughout the ATI period.

SARS-CoV-2 testing will be offered to all study participants who report any symptoms suggestive of infection.[36]

SARS-Cov-2 PCR testing will also be offered to all study participants in close contact with a confirmed COVID-19 case identified through contact tracing procedures or direct household contacts.

Despite a participant testing negative for SARS-CoV-2 PCR, if a household member or close contact is diagnosed SARS-CoV-2 positive, isolation is required for a 14 day-quarantine period after exposure. Repeat testing will be offered as needed and attendance for hospital visits will be deferred during this time.

Modification of HIV viral load testing strategies during ATI

During periods of increased SARS-CoV-2 incidence in the immediate communities, relaxation of frequency of hospital attendances for HIV viral load testing could be made or household blood draws for those study participants who prefer this option. For example, in protocols with an initial weekly plasma viral load test following commencement of ATI, this could be relaxed to a fortnightly one.

Exploration of alternative types of viral load measurements such as using self-taken finger prick blood samples that might be sent directly to a laboratory for assessment.[37]

Exclusion of acute SARS-CoV-2 infection at commencement of a curative interventions (e.g., chemotherapy in transplant protocols, most immunotherapies) and prior to the ATI

Swab for PCR within 48 h or ideally a point of care SARS-CoV-2 PCR assay prior to any experimental therapy that might alter the risk of COVID-19 and on the day of ATI start, to exclude acute infection.

Screening for symptoms (anosmia, cough, fever, myalgia, and headache) to occur at all ATI visits and by telephone consultation for missed or deferred visits.

Any individual testing SARS-CoV-2 positive can defer enrolment until the infection has cleared and rejoin study enrolment at a later date.

Review of ART re-start criteria if SARS-CoV-2 PCR positivity

Re-start of ART will be recommended in the presence of symptoms ***and*** a SARS-Cov-2 PCR positive test result. Symptoms alone would not trigger ART re-start, unless severe.This will be an important decision to be made on an individual participant basis in discussion with the trial physician. Depending on the individual and the trial protocol, ATI might recommence once symptoms resolve and the PCR result has become negative.

Sensitivity to changes in local SARS-CoV-2 risk

As exposure is the main factor driving risk of infection, the background incidence of SARS-CoV-2 will need to be low enough for local lockdown measures to have been lifted. While this might be clear at enrolment, it is not possible to predict during the course of the study how this might change. Strategies will need to adapt to changes in local and regional resurgences of COVID-19. An independent committee might be assembled to provide investigators with advice on when local conditions might result in a study being paused or terminated.

Informed consent. Ensuring consistent and thorough participant information should include recent COVID-19 data and concerns relating to COVID-19 as well as the ways that the research has been modified to reduce risks. We propose that a COVID-19 risk assessment tool should be recommended as part of the informed consent procedure.

Community perspective and interest in ATI participation in the time of COVID

There will be different community and also researchers views on the safest way to continue with studies that involve an ATI.

Early news of effective vaccines

As this paper was in press, the first reports of high levels of vaccine protection (both at >90%) were reported from the Pfizer/BioNTech[39] and Moderna/NIH[40] phase 3 studies and the Oxford/Astrozeneca trial[41] (>70%). The data is yet to be published in peer reviewed journals and data on vaccine safety and efficacy in PLWH remains unknown. However, provided the SARS-CoV-2 protection and immune responses are durable and confirmed with longer-term follow-up, then access to these or subsequent vaccines will dramatically change the risk:benefit of both running and participating in research that involves an ATI. The choice to access a vaccine might therefore be added to research protocols and/or having received a vaccine prior to study enrolment and ideally prior to ATI might be added to inclusion criteria.

Conclusion

The HIV global epidemic continues to be present during the COVID-19 pandemic, and whilst focus must clearly shift to ensure above all else the preservation of health and safety of people living with HIV, there remains a commitment and drive from the communities and researchers to pursue novel and optimal long-term therapies.[37] This discussion document summarises potential risks and suggests pragmatic mitigation strategies to allow the safe re-opening of HIV intervention trials that include an ATI once the absolute risk of COVID-19 is manageable. The approaches suggested here will be impacted by circumstantial SARS-CoV-2 prevalence and incidence as well as the availability of treatments and a prophylactic vaccine.

Declaration of competing interest

The co-authors of this manuscript have no conflicts of interest to declare.

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