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Interrupting antiretroviral treatment in HIV cure research: scientific and ethical considerations

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Abstract

Over the past several years there has been intense activity directed at the possibility of achieving remission or eradication of HIV infection. Current assays for the measurement of latent HIV are insufficient to demonstrate complete clearance of replication-competent HIV. Therefore, the ultimate test for assessing whether investigational interventions have resulted in HIV remission or eradication is to interrupt standard antiretroviral therapy (ART) in a carefully controlled clinical trial setting. These procedures, known as analytic treatment interruptions (ATIs), raise important scientific and ethical questions. The lack of definitive assays for measuring viral reservoirs not only makes research on HIV remission or cure challenging, it also affects the ability to assess risks from ATIs themselves. In spite of these challenges, basic ethical criteria can be met with careful study design and close monitoring. In this brief report we outline ethical standards for HIV cure research involving ATIs. These criteria should be revisited as the science evolves.

Introduction

Over the past several years there has been intense activity directed at achieving remission or cure of HIV infection. HIV remission is the ability to maintain a very low or undetectable plasma viral load in the absence of antiretroviral therapy (ART), whereas cure implies eradication of all cells harbouring replication-competent virus. Current assays have limited ability to detect partial or complete clearance of HIV from viral reservoirs. Adequate biomarkers to assess cure do not currently exist, therefore, structured interruptions of antiretroviral therapy (ART), known as analytic treatment interruptions (ATIs), are used as part of select HIV-research protocols to assess the ability to control viraemia after discontinuation of ART.

Interruption of clinically recommended treatment of serious disease for purely scientific purposes is relatively unusual in research. Several papers have commented on the ethics of HIV cure research [1–5], but have not considered, in detail, the ethics of ATIs outside the context of bone marrow transplantation [6]. This article reviews the ethical issues surrounding the use of ATIs, which should be taken into account in any study employing this method. The discussion focuses on research with adult participants, as the ethical issues for HIV cure research with children require a separate analysis (see for example [7]).

Analytic treatment interruption: scientific utility and risks

The scientific utility of ATIs

In studies aimed at viral remission, ATIs have been used to assess control of virus replication in the absence of ART, following an intervention designed to make durable control more likely. Primary endpoints in these research studies generally include time to viral load rebound (TTR) or the proportion of participants with virological suppression at a defined point in time after ATI. Data from these research studies are also being used to identify biomarkers that are predictive of TTR [8].

At this stage of research, ATIs are essential for studies of viral control, but the usefulness of ATIs for measuring reductions in the viral reservoir is less clear-cut. The relationship between viral rebound and size of latent reservoir is neither clearly defined nor theoretically predictable. There are no interventions that can conclusively lead to a quantitative decline in the replication-competent reservoir (other than the single case example of total bone marrow transplantation with cells resistant to HIV [9]). Therefore, the relationship between reservoir size and TTR cannot be completely elucidated. Using a mathematical model, Hill *et al.* estimated that in some circumstances a 10,000-fold reduction in the reservoir is needed to prevent rebound [10]; but there are no studies yet available to validate this hypothesis. Most critically, since TTR is a multidimensional phenomenon, reflecting not only the amount of replication-competent virus but also host factors (such as size of the initial reservoir, immune response and inflammation), a similar reduction in reservoir size may not lead to the same TTR change in all patients.

Thus, questions remain about the extent to which ATIs ought to be used for assessment of the size of the viral reservoir and these scientific challenges still require further investigation [11–13].

The risks of ATIs

The same scientific challenges that complicate evaluations of the viral reservoir have implications for the utility of ATIs and for the ability to estimate risks to study participants. Because there are no precise and reproducible direct assays of the size and composition of the viral reservoir, the potential impact of an ATI for an individual patient cannot be evaluated well. Furthermore, the clinical implications of a change in size of reservoir, if it could be accurately measured, are unknown.

In the absence of data to directly inform risk assessment, concerns about the risks of ATIs are based on plausible theoretical risks and experience in somewhat analogous settings. There is concern about ATIs allowing expansion of the existing reservoir; however, currently

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little information exists about whether this happens or its possible clinical consequences. Two potential effects of an ATI are diminished responsiveness to future cure interventions, and increased chronic inflammatory processes, due to expanded viral reservoirs, even in the presence of effective ART. There are no systematic data on the risks of viral rebound in a short, closely monitored ATI, in which study participants resume ART when virus rebound is confirmed. Data from large studies involving more extensive treatment interruptions or delayed ART are difficult to extrapolate to time-limited, closely monitored scenarios such as use of ATI in current clinical trials [11]. An increased risk of transmission to sexual partners due to increased viral load may be also be an important concern [4]. A recent study of ATI in which participants underwent twice-weekly viral load monitoring and ART resumption upon viral rebound reported no clinical adverse events due to ATI [14].

Ethical considerations

Like all clinical research, studies involving ATIs must meet basic ethical criteria, including strong scientific justification, risk minimisation, and robust informed consent. Ethical assessment of ATIs is confounded in some ways by the uncertainty in risk assessment; the complicated and variable utility of ATIs in different experimental schemes; the ethics of clinical care, which is increasingly driven by multiple and diverse studies showing the benefits of immediate, continuous and lifelong ART for HIV-infected patients; and the potential for participant and members of the public to overestimate the likelihood of benefit in HIV cure studies. None of these factors make the use of ATIs *a priori* unethical, but they have the potential to cloud the discussion of risks and scientific utility, hence, careful analysis is needed.

Use of ATIs are justified only if they provide valuable data to answer an important research question where there are no, less risky alternative methods to obtain that information, and if known risks are minimised. Importantly, as a risk comparison, in many studies there are notable risks other than the ATI itself, for example, the experimental agents used to stimulate latent virus production. In summary, the stronger the scientific justification for the use of ATI, the greater the ethical acceptability of exposing participants that have already given informed consent to some level of risk. In general, the risks of the ATI itself, when closely monitored, are considered to be low. However, as described above, uncertainty about biological effects makes it difficult to make definitive statements regarding risk.

Participant selection

Some individuals who might be likely to experience greater risk in a study involving an ATI and could potentially be, at least initially, excluded are those:

- With comorbidities that might increase risks of non-AIDS adverse events during a study;
- Who would have difficulty with careful monitoring;
- Pregnant women, as maintaining viral suppression is important in preventing mother-to-child transmission of HIV.
- With low CD4 cell counts and possibly a lower pre-ART CD4 nadir (e.g. it may be prudent to include those with approximately ≥500 cells/mm^3 and ≥200 cells/mm^3, respectively), given that viral replication has been associated with a decrease in CD4 cell count and an increase in AIDS and non-AIDS events [15].
- Who have a history of virus resistant to an HIV-drug class or who have limited options for subsequent regimens (e.g. allergy or drug intolerance).

Study design and monitoring

Investigators should use the shortest ATI consistent with answering the primary scientific question(s). In some cases, a study may need some viral replication to induce immune responses for the experimental agent to work; therefore, a longer period of viraemia would be needed. However, given that this entails longer exposure to viral replication, investigators should carefully consider if this kind of design is necessary.

Most current studies require re-starting ART as soon as confirmed viral replication is detected. In general, specific feasibility, safety and futility criteria for starting and stopping an ATI and restarting ART should be clearly delineated. Frequent viral load monitoring during an ATI is essential as a risk-mitigation strategy, but the need for frequent monitoring needs to be balanced with concern about burden for study participants. A safety monitoring plan that provides independent oversight of the study may be advisable.

Although this can involve substantial blood draws, investigators may consider using the quantitative viral outgrowth assay (QVOA) before and after use of an experimental intervention(s). In studies aimed at eradication, recovery of replicative HIV from QVOA indicates a failure of the intervention and ATI would not be needed to ascertain this outcome. In contrast, for studies aimed at viral control, neither positive nor negative QVOA assays are predictive of outcomes during an ATI, based on current knowledge, and an ATI might still be needed to evaluate control.

Prior to an ATI, participants on selected antiretrovirals require transient treatment with alternative drugs, to prevent the acquisition of drug resistance. Specifically, 2–4 weeks of replacement protease inhibitors could be given when discontinuing non-nucleoside analogues. To minimise the risk of HIV transmission to sexual partners in case of viral rebound, potential participants should be counselled about the use of appropriate barrier protection and/or use of PrEP by HIV-negative partners. It should be noted that while PrEP has been highly effective in large clinical studies in populations at risk of HIV acquisition in the community, there are no systematic data indicating whether PrEP is effective against viral rebound to very high levels of viraemia that might emerge during an ATI.

Informed consent

Investigators should be aware that participants may approach studies with misconceptions about the benefits of HIV cure research, which may skew their risk assessment of a study involving ATI. The informed consent process (including the document, other informational materials, and discussions) should clearly state that there is no anticipated direct clinical benefit to the participants in early-phase HIV cure research, ATI is not recommended for clinical care, and treatment guidelines recommend lifelong treatment regardless of CD4 count. During the consent process, investigators should also make clear that individuals are being asked to participate in an *experiment* that may benefit others with HIV in the future. Use of the word 'experiment' can help emphasise the uncertain, or early nature, of the study and the anticipated lack of personal benefit [16,17]. Investigators should generally replace the term 'cure' in informational materials with more accurate terminology (e.g. long-term HIV control) [3,4]. As in any study, a full description of risks and risk minimisation procedures is required. A brief test of comprehension at the end of the consent process could also be used to ensure a potential participant's understanding of these issues [2].

Community engagement and public perception

Perceptions of risks vary widely amongst researchers, participants, and members of the public and substantial difficulties can arise

when trying to clearly communicate when experiments are in the preliminary stages and/or when there is a high degree of uncertainty. For example, as treatment guidelines have now moved towards initiation of lifelong ART for all HIV-infected individuals, conflicting messages in the HIV community can emerge: HIV-positive individuals should adhere to lifelong ART, whereas research participants coming off ART, for a defined period of time for HIV cure studies, is acceptable. In addition, stopping or withholding treatment, even with well-informed participants, may be subject to additional public scrutiny because of past controversies. For example, controversy erupted in the early 1990s regarding treatment cessation in schizophrenia studies and significant public and media attention raised tensions regarding these study designs [18]. Open and transparent dialogue with relevant stakeholders around the purpose and risks of ATIs in select research protocols is essential.

Additional recommendations

Collecting data on participants' experiences throughout the course of a study would provide valuable, real-time information, and would help the research community to better understand the decision-making process, influences on those decisions and provide satisfaction at the conclusion of a study [19]. Research sponsors should consider establishing a mechanism to follow the long-term outcomes of participants who have undergone an ATI. This would provide a crucial resource for aggregating and evaluating the risks of ATIs in HIV cure studies. And finally, because institutional review boards (IRBs) are going to play the primary role in reviewing protocols and making decisions about the appropriateness of a study, these committees should ensure they have relevant content expertise to conduct an adequate review of studies employing ATIs. If not, they should engage consultants with the relevant expertise.

Conclusion

In summary, ATIs are being used in HIV cure research, but they raise important scientific and ethical questions. The challenges of evaluating risks in a highly uncertain and rapidly moving scientific area, combined with the increasing recognition of the value of lifelong ART for the protection of patients and public health, means that ongoing efforts are needed to more precisely evaluate the risks and scientific value of HIV cure studies using ATIs. Because the science progresses rapidly, the considerations and criteria suggested here should be frequently revisited. Additional work that should be undertaken by the research community (including clinical researchers in partnership with social scientists, behavioural researchers, ethicists and the community) includes further consideration of the scientific utility of ATIs; studies of stakeholder perspectives and communication about clinical studies involving ATIs; development of more appropriate language and terminology in HIV cure research; and data collection on clinical, psychological and social consequences of ATIs.

While ATIs may continue to raise scientific and ethical concerns, their careful implementation in the context of research can be ethically appropriate.

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Declaration of interests

None declared.

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