Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting

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Analytical antiretroviral treatment interruption (ATI) is an important feature of HIV research, seeking to achieve sustained viral suppression in the absence of antiretroviral therapy (ART) when the goal is to measure effects of novel therapeutic interventions on time to viral load rebound or altered viral setpoint. Trials with ATIs also intend to determine host, virological, and immunological markers that are predictive of sustained viral control off ART. Although ATI is increasingly incorporated into proof-of-concept trials, no consensus has been reached on strategies to maximise its utility and minimise its risks. In addition, differences in ATI trial designs hinder the ability to compare efficacy and safety of interventions across trials. Therefore, we held a meeting of stakeholders from many interest groups, including scientists, clinicians, ethicists, social scientists, regulators, people living with HIV, and advocacy groups, to discuss the main challenges concerning ATI studies and to formulate recommendations with an emphasis on strategies for risk mitigation and monitoring, ART resumption criteria, and ethical considerations. In this Review, we present the major points of discussion and consensus views achieved with the goal of informing the conduct of ATIs to maximise the knowledge gained and minimise the risk to participants in clinical HIV research.

Background

Despite the success of modern antiretroviral therapy (ART) in limiting HIV replication, HIV infection remains a chronic disease that long-term ART alone will probably never eliminate. Thus, efforts to eradicate HIV infection, or at least induce a state of ART-free viral suppression, are being vigorously pursued. To ultimately validate promising strategies, analytical antiretroviral therapy interruptions (ATI) appear to be necessary until a promising biomarker that robustly predicts post-treatment viral control emerges; therefore, so far, ATIs are irreplaceable. Despite the important role of ATIs in HIV research, clinical trial designs that include ATIs have been quite heterogeneous, hindering the ability to compare efficacy and safety of interventions and ATIs across trials. Therefore, on July 9, 2018, we convened a forum at the Ragon Institute of MGH, MIT and Harvard in Cambridge, Massachusetts, USA, to assess the scientific value, risks, benefits, and methods of ATIs, including the ethical and community perspectives of these approaches. Our goal was to formulate recommendations for the conduct of ATIs in a manner that maximises the knowledge gained and minimises the risk to trial participants. This Review summarises the major points of discussion (panel) and any consensus viewpoints that were achieved. It is expected that this meeting is the beginning of an ongoing discussion on how to conduct ATIs that will continue to evolve to reflect the ever-changing clinical and scientific landscape.

Methods

41 experts on HIV research (adult and paediatric clinicians; virologists and immunologists; bioethicists; patient advocates; statisticians; social scientists; and representatives of regulatory authorities and funding agencies [US Food and Drug Administration, US National Institutes of Health, and AmfAR]) and industry from Denmark, South Africa, Spain, Switzerland, Thailand, the UK and the USA, participated by invitation from the scientific committee (BJ, LD, JA, DHB, MLR, NLM, JWM, SGD, and BDW). Main challenges concerning ATI studies were identified before the meeting, including establishing strategies for risk mitigation, monitoring and ART resumption criteria, and evaluating ethical considerations. Four panels were established to prepare and present expert opinions on assigned topics and to formulate a set of questions for which opinion of the larger group was considered crucial. Panel presentations were followed by an open group discussion and concluded with an electronic, anonymous poll on selected questions. A manuscript detailing recommendations was prepared by the scientific committee and then circulated to the larger group for review and revision. The recommendations presented in this manuscript are largely based on expert opinions given the paucity of clinical evidence specific to ATIs and the limited availability of randomised controlled trials. The references used in this document were identified by literature search focusing on reported clinical studies, including observational, cohort, or interventional studies

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Panel: **Key recommendations**

Inclusion criteria
- Stable CD4 counts ≥500 cells per μL*
- HIV RNA undetectable on stable ART†
- Otherwise healthy individuals without major comorbidities

Key exclusion criteria
- Active or chronic hepatitis B virus infection, with detectable hepatitis B surface antigen, hepatitis B virus DNA, or both
- Active hepatitis C virus infection, with detectable virus RNA
- Active Mycobacterium tuberculous infection‡
- History of systemic cancers, such as Kaposi's sarcoma and lymphoma, or other virus-associated malignancies§
- History of HIV-associated dementia or progressive multifocal leukoencephalopathy
- Resistance to two or more classes of antiretroviral drugs¶
- History of cardiovascular event or at high risk of an event (eg, atherosclerotic cardiovascular disease score >15%)
- History of AIDS-defining illness according to Centers for Disease Control and Prevention criteria
- History of CD4 nadir <200 cells per μL during chronic stages of infection
- Women who are pregnant or breastfeeding
- Advanced non-alcoholic fatty liver and advanced nonalcoholic steatohepatitis, if evidence for substantial fibrosis (fibrosis score ≥F2) or evidence of cirrhosis
- HIV-related kidney disease or moderate-to-severe decrease in estimated glomerular filtration rate (<45–60 mL/min/1·73 m^2)
- Children younger than 2 years of age when the ATI is planned

Monitoring
- HIV RNA monitoring weekly for 12 weeks, then every other week
- CD4 count monitoring every two weeks
- Monitoring of clinical symptoms, in particular in people who started ART during the hyperacute HIV phase
- Monitoring of participants' psychosocial experiences

ART restart criteria
- If requested by the participant or their HIV health-care provider
- If participant becomes pregnant
- If ART is deemed medically necessary for non-HIV related causes
- Symptomatic HIV disease||
- Confirmed absolute CD4 value <350 cells per μL or CD4% <15%**
- HIV RNA ≥1000 copies per mL for 4 weeks††
- Absolute HIV RNA >100 000 copies per mL††

Reducing risk of HIV transmission to sexual partners
- Offer pre-exposure prophylaxis and HIV testing referral information that trial participants can provide to their sexual partners

Additional or more stringent criteria might be required based on known toxicities of the study drug(s) or expected risks of the study intervention(s). Inclusion and exclusion criteria, monitoring, and antiretroviral therapy (ART) restart criteria might differ in children depending on age. ART=antiretroviral therapy. *Baseline CD4 counts of ≥350 cells per μL might be considered. †Based on FDA-approved HIV RNA quantification assay.‡ Latent tuberculosis infection discussed in the text. §Other malignancies discussed in the text. ¶Defined as single key mutations or an accumulation of minor mutations that result in resistance to entire respective drug classes. ||Symptoms include, but are not limited to, unintentional weight loss (>5–10% of the pre-ATI bodyweight), otherwise unexplained persistent fever (>100·4°F/38°C), persistent night sweats, persistent diarrhoea, oral candidiasis and generalised lymphadenopathy. **Largely dependent on the CD4 entry criteria; a sufficiently large delta between the entry value versus CD4 measurement for ART resumption should be ensured. ††12–16 weeks of uncontrolled viraemia, with HIV RNA of more than 100 000 copies per mL; it might be acceptable in studies in which a stable viral set point is a primary endpoint.

in which ART was temporarily interrupted with predetermined restart criteria. We have adhered to the policies for protection of human subjects as prescribed in AR-70–25.

Results

Are ATIs appropriate and what are the risk–benefit justifications?

The group agreed that validated biomarkers predictive of virological control once ART is stopped are not yet available, which means ATIs are the only way to test the efficacy of new therapeutic interventions. Even if a promising biomarker emerges, validating its utility as a surrogate marker for an ATI read-out will prove challenging because an effective intervention that clearly affects time-to-rebound or post-treatment control does not yet exist. Although some progress in identifying candidate biomarkers that might prove to be predictive has been made,[1–4] and prospective observational studies aimed at supporting biomarker discovery are ongoing (eg, NCT03117985, NCT03225118, NCT03001128), no robust markers or assays that could replace ATIs are yet available.

Although the meeting participants acknowledged that potential risks exist for study participants undergoing ATIs, evidence thus far has not indicated a sustained effect of short-term ATIs on the HIV reservoir. Findings from a study[5] have shown that measurements of the reservoir at different timepoints following ART interruption, at least based on HIV DNA concentrations, indicate that it takes up to 60 weeks for the reservoir to significantly expand compared with pre-ATI levels (but this expansion might depend on the magnitude of viral replication during the ATI. In the same study, HIV DNA concentrations returned to pre-ATI values within 6 months following ART reinitiation with the pre-ATI regimen. Another study[6] showed that, following a long ATI of 48 weeks, total HIV-1 DNA concentrations returned to the pre-ATI amount after ART resumption, but that integrated HIV-1 DNA remained elevated at least for the duration of the study follow-up (104 weeks after resumption of ART). It has also been shown that over 4–6 weeks of ATI, viral diversity does not increase.[7–9] Although the potential effect of an ATI on the size of the reservoir was discussed as a potential risk, no consensus was reached regarding the effects of ATIs that do not last longer than several months.

The majority of meeting participants agreed that ATI studies are justifiable if the risk is adequately understood by the participant, and if the study design will answer a scientific question that could not be solved otherwise or can be solved efficiently (appendix p 1). There was strong consensus, however, that ATIs are highly context dependent, and that one single guideline for all circumstances under which ATIs are appropriate is not feasible. The group agreed that the responsibility is on investigators to show, before the ATI study, that a strong

scientific rationale exists for why the intervention might conceivably affect time-to-rebound, postinterruption setpoint, or other meaningful biological or clinical endpoints. This rationale might include previous success in preclinical animal models (eg, rhesus macaques, humanised mice), success in other diseases (such as cancer), or previous evidence that the intervention has a measurable effect on a relevant biomarker in humans, such as the size of reservoir or generation of potentially protective HIV-specific immune responses. In this context, it was suggested that investigators who want to develop a new therapeutic strategy should determine predefined go/no-go criteria (which define whether interventions should progress to the next stage of development) for incorporating ATIs in their development plans. More importantly, researchers should determine criteria for whether an intervention has achieved predefined goals (eg, stipulating that a therapeutic vaccine induces immune responses above a prespecified threshold) before subjecting participants to an ATI. In general, the group agreed that ATIs should not be used in the absence of supporting data simply to generate hypotheses.

Which participants should be included in ATI studies?

It is important to balance feasibility and risk mitigation with the likelihood of successfully conducting a trial. If a study only allows individuals with very restricted CD4 nadir and age limits, it might be difficult to enrol sufficient participants; might exclude a large proportion of the HIV infected population, thereby precluding their contribution to and participation in HIV research; and would limit generalisability of findings to the broader population of people with HIV. Although proof-of-concept studies often target populations in which a study intervention might have the highest likelihood of a detectable effect, age limits and CD4 nadir ranges that are more reflective of the overall demographics of the HIV infected population (eg, age limits of 65 or 70 years) might be considered. Nonetheless, it should be noted that the US FDA considers people with ART-controlled HIV infection who are asymptomatic and have many available treatment options to be more similar to healthy volunteers than to patients with life-threatening conditions with limited to no treatment options (eg, refractory, advanced malignancies). In line with the obvious ethical considerations, investigators must carefully consider the potential ramifications of any interventions to trial participants, because the acceptability of risk to healthy volunteers is low in clinical research.

The group agreed that no single population was best for all ATIs. There was consensus that ATI studies, which are largely experimental, should focus on otherwise healthy individuals with well controlled HIV who do not have substantial or serious comorbidities. Because experimental studies can involve relatively long ATIs, high viraemia, or both, investigators should seek participants who are expected to have a functional immune system, and who can probably tolerate a period of high viraemia or any viraemia occasioned by infrequent viral load monitoring. Therefore, an agreement that participants in ATI studies should have stable CD4 counts of equal or greater than 500 cells per µL was reached. However, support was also given for allowing CD4 counts of equal to or greater than 350 cells per µL (appendix 2). The decision regarding which CD4 count threshold to allow for enrolment will depend on the presumed overall risk of the studied intervention. As clinical studies progress, the standards of what is acceptable might also change as risks become better defined. There was strong agreement that the influence of sex, gender, race, ethnicity, and geographic location on ATI outcomes also require further investigation. For example, women in the USA have been rarely recruited for these studies,[10] although the AIDS Clinical Trial Group (ACTG) A5366 study (NCT03382834) successfully and quickly enrolled 30 postmenopausal women showing that recruitment of women is feasible (Gandhi RT, unpublished). Results from a study[11] published in 2018, suggested that post-treatment control was more common among African individuals compared with non-African individuals, suggesting that ethnicity might be associated with treatment outcomes; however, all participants in this study were women, preventing disaggregation by sex.[11] Strategies aimed at improving sex and gender balance are, therefore, clearly needed.[12,13]

Paediatric considerations are also important. The inclusion of paediatric participants in ATI studies is a complex issue. Paediatric HIV disease spans an age range from neonates to 24 years, and thus encompasses many distinct groups and development stages. Key safety concerns for younger groups include neurodevelopmental risks, uncertainty whether the immune system is sufficiently robust, and potential risks that are not yet known or understood. Timely ART in children can have very positive results (eg, improved responses to vaccination, or the absence of neurological and metabolic comorbidities). However, in contrast to adults with HIV for whom one tablet a day is feasible, continuous adherence to ART from birth is difficult to achieve, with unplanned treatment interruptions being common, especially in low-income and middle-income settings where the paediatric epidemic is concentrated. Furthermore, the long-term side-effects of continuous ART from birth are unknown and should not be dismissed. Paediatric patients might arguably benefit the most from strategies that induce ART-free viral suppression and incorporating paediatric populations into research geared towards this goal is, therefore, crucially important. Furthermore, some concerns in adults, such as HIV transmission to a sexual partner, do not exist during early childhood. There was an overall agreement that because of the unique risks and

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See Online for appendix

behaviours surrounding paediatric patients with HIV, dedicated age group-specific recommendations should be generated.

What should be considered strict exclusion criteria?

Several conditions and populations were considered to define strict exclusion criteria for ATIs: active co-infection, cancer, neurological concerns, ART resistance, cardiovascular disease, history of AIDS defining illness and CD4 nadir, pregnancy, renal and liver disease, risk of HIV transmission to sexual partners of ATI study participants, and paediatric populations.

There was a strong consensus that patients with chronic hepatitis B virus infection, detectable hepatitis B surface antigen or hepatitis B virus DNA, active hepatitis C virus infection, or detectable hepatitis C virus RNA should be strictly excluded. The group reached a consensus that individuals who have been fully treated for and cured of hepatitis C or who have cleared the virus naturally, and have documented undetectable plasma hepatitis C virus RNA, do not need to be excluded. Other co-infections, for example *Mycobacterium tuberculosis*, need to be considered, specifically given the high prevalence of *M tuberculosis* infection among people with HIV in certain geographic locations.[14] Although active *M tuberculosis* infection should be an exclusion criterion, the possibility of reactivating latent *M tuberculosis* infection should be discussed and preventive treatment might be considered.

HIV is associated with increased risk of many cancers. For certain cancers, any medical history should be generally considered strict exclusion criterion (eg, systemic cancers such as Kaposi's sarcoma and lymphoma, or other virus-associated malignancies). However, patients in Berlin, Germany,[15] and Boston, USA[16] underwent ATI following treatment for haematological malignancies and the risk–benefit ratio for participants like these needs to be assessed on a case-by-case basis. An association between HIV infection, smoking, and an elevated risk of lung cancer has been suggested,[17] and although smoking status (current or former) should not qualify for exclusion, individuals with previous history of lung cancer might be excluded. Patients should also be screened for cervical and anal cancer, and excluded if the result is positive. It is important to consider the specific type of malignancy relevant to each individual, because a history of certain in-situ cancers or a history of cancers not known to be associated with HIV (eg, prostate cancer, breast cancer, or colon cancer) might not justify as an exclusion (appendix p 3). Certain limitations—eg, remission stage for more than 10 years—could be considered.

Overall, the potential for neurological and CNS problems during acute or sustained viraemia are real, but poorly defined, risks of ATIs. Previous experience with cerebrospinal fluid monitoring during prolonged ART interruption indicated rebound of HIV RNA accompanied by elevations in biomarkers of intrathecal inflammation and neuronal injury by approximately 20 days after ATI.[18–20] However, the clinical consequences of these changes are unknown. Thus far, the risk for a neurological adverse event in the context of ATI appear low, although aseptic meningitis as a sign of acute retroviral syndrome has been reported.[16,21] In general, patients with a history of HIV-associated dementia or progressive multifocal leukoencephalopathy should be excluded. HIV-associated dementia is associated with neuroinflammation, neuronal injury, and a high burden of HIV replication in the CNS that is typically genetically compartmentalised with respect to the blood, suggesting a CNS cellular source.[22,23] These pathologies are improved by ART.[24] However, residual low-grade intrathecal immune activation and HIV RNA detection in the CNS despite suppression in the plasma suggest that the brain is a site of HIV persistence, which might be vulnerable to further injury or development of local ART resistance with CSF escape during recrudescence of viral replication and inflammation.[25,26] Progressive multifocal leukoencephalopathy is a frequently fatal disorder caused by CNS infection with the John Cunningham virus for which an effective antiviral therapy is not yet available.[27] Immune competence is essential for John Cunningham virus control and irreversible brain injury persists in individuals who survive progressive multifocal leukoencephalopathy.

The potential emergence of new drug-resistance mutations is of concern. Drug resistance might occur during the interruption phase or when ART is resumed. Specifically, stopping ART regimens containing antiretrovirals with different serum half-lives, which results, for example, in delayed wash-out of non-nucleoside reverse-transcriptase inhibitors (NNRTIs) among other drugs, poses a risk for the development of drug resistance. The treatment of study participants on such regimens should be switched to short-acting antiretrovirals (eg, switching NNRTIs to integrase inhibitors) before an ATI. Although one study[7] reported no evidence of new antiretroviral drug resistance mutations within intact sequences of HIV proviral DNA following reinitiation of ART, one patient in a different study[16] developed the K103N mutation during ART reinitiation due to adherence issues caused by an acute retroviral syndrome. Based on these observations, the consensus was that studies should only enrol individuals who have multiple alternative ART options available in case their current treatment becomes less effective. Excluding individuals who have resistance to two or more classes of drugs (defined as single key mutations or an accumulation of minor mutations that result in resistance to entire respective drug classes) was also supported (appendix p 3).

The association between cardiovascular risk and ATI is debatable. Although some investigators strictly exclude individuals with any cardiovascular risk or history, others might allow certain cases, such as individuals who have a distant history of disease and who have been treated and stable for many years. The group reached a consensus

that all potential study participants should be screened for signs and symptoms of cardiovascular disease before taking part in an ATI study. If findings on initial screening raised concern, additional testing for cardiovascular disease should be done before enrolment. Individuals with a known cardiovascular event or at high risk of an event (eg, Atherosclerotic Cardiovascular Disease Score >15%) should be excluded (appendix p 3).

Approximately two-thirds of meeting participants concluded that anyone with a history of AIDS-defining illness according to Centers for Diseases Control and Prevention criteria should be excluded (appendix p 3). In addition, the occurrence of AIDS-defining illnesses is, in most cases, linked to a CD4 nadir, which by itself is a criterion for determining eligibility. Therefore, the general consensus was that individuals with a lifetime CD4 nadir of less than 200 cells per µL should be excluded, regardless of whether they are on stable treatment with higher CD4 T-cell counts. Moreover, there was some support within the group that a lifetime CD4 nadir of less than 350 cells per µL should be considered to be an exclusion criterion while we are still in the early stages of conducting ATI studies. Overall, there was also consensus that investigators should carefully consider the context of their study when choosing a CD4 nadir cutoff. Individuals with acute infection can have a substantially decreased CD4 count, even of less than 200 cells per µL. However, this decrease is transient and might not reflect immune deficiency as observed in CD4 declines during chronic stages of infection. A hard cutoff that does not account for this transience might exclude a substantial number of potential participants and, therefore, the group suggested to consider primarily CD4 nadir limits outside of the acute infection window.

Women who are pregnant or breastfeeding should be strictly excluded, as suppression of viraemia is crucial to prevent mother-to-child transmission. Careful monitoring for pregnancy should be a component of all ATI protocols. Trial participants should also be counselled on avoiding pregnancy during the trial. This counselling includes contraception and, if necessary, referral to a health-care provider for provision of contraceptives. Because of the emphasis on recruiting more women into such trials, efforts to avoid pregnancies should also be fully incorporated into all protocols.

Patients with non-infectious liver disease (including advanced non-alcoholic fatty liver and advanced non-alcoholic steatohepatitis), should be excluded if evidence of substantial fibrosis (fibrosis score ≥F2) or cirrhosis determined by histology, imaging, or non-invasive measurements, is found. Individuals with HIV-associated kidney disease should also be excluded. Furthermore, a moderate-to-severe decrease in estimated glomerular filtration rate (<45–60 mL/min/1·73 m²) should be an exclusion criterion (appendix p 3).

Although HIV transmission is among the greatest risks during an ATI, participants undergoing ATIs might also face legal and even criminal charges should they transmit HIV while off ART.[28] Thus, HIV transmission must be vigilantly prevented for the safety of both partners and participants. Therefore, a consensus was reached that, at a minimum, participants must be clearly and comprehensively counselled on transmission risks. The majority of the meeting participants thought that having HIV-negative sexual partners who are not accessing pre-exposure or post-exposure prophylaxis should not in itself be an exclusion criterion for a potential participant of an ATI study (appendix p 3). However, counselling should be offered, as well as education about pre-exposure or post-exposure prophylaxis and HIV testing referral that trial participants can provide to their sexual partners. There was some consideration that pre-exposure prophylaxis might be made available upon request by the study to the participant's sexual partner(s). Despite this general intention, providing protection for the sexual partners of trial participants presents a great challenge due to the conflict between the ethical obligation of protecting a participant's confidentiality and warning, or otherwise protecting, known and unknown sexual partners of a participant who is undergoing an ATI and who might have a viral rebound. As an additional complicating factor, it was noted that research funding generally does not extend to providing care to sexual partners of study participants (appendix p 4).

Regarding paediatric populations, there was a consensus that all children who are younger than 2 years of age should be excluded (appendix p 5) from ART interruption because of their developing immune systems and potential elevated neurodevelopmental risks associated with unsuppressed viraemia, coupled with the feasibility for frequent viral load monitoring off ART. The group was also concerned that younger children who are not chronic survivors might have exponential increases in viraemia and disease progression, compared with older children who have reached a partial controller state in the absence of ART. Similarly to adults, any children who have resistance to two or more classes of drugs should be strictly excluded.

What is considered adequate monitoring during the ATI phase?

The consensus was that, in most circumstances, once weekly monitoring is a reasonable frequency. Although more frequent testing might be desired from a clinical and scientific perspective, it is necessary to consider the very real burden this frequency presents to participants and monitoring frequency must be balanced against participant retention, especially in studies lasting 6–12 months. It was agreed that the early weeks of ATI warrant the most thorough testing. Specifically, participants should be monitored weekly for 12 weeks, and testing frequency might be decreased to every other week thereafter, with the option of resuming weekly

monitoring if necessary (eg, when rebound of viraemia occurs; appendix p 6). The rationale for frequent monitoring in the initial 12 weeks is based on the observation that the majority of individuals rebound during this time.[29,30] Frequent early testing is thus crucial to detect rebound with precision. Nevertheless, it was noted that less frequent monitoring in later weeks could also result in undetected viraemia.

Viraemia, clinical symptoms, and CD4 counts need to be considered. There was consensus that viraemia is a crucial measurement as virological rebound might be the earliest evidence of disease activity and can precede other symptoms by days. Clinical symptoms should also be carefully monitored, and the risk of acute retroviral syndrome needs to be considered following viral rebound. Specific clinical signs and symptoms that raise concern for this condition include malaise, fever, headache, lymphadenopathy, rash, sore throat, myalgia or arthralgia, unintentional weight loss, night sweats, and diarrhoea.[31,32] Although CD4 counts should be measured every 2 weeks and included in the ART restart criteria, they are less sensitive than measuring viraemia as CD4 decline often is slower.

Home testing is another important consideration. Viral load testing at home has several key advantages. It allows increased participant monitoring without the need of frequent clinic visits and is much more convenient for participants. Although such assays are not formally licensed, they are being explored for screening of viral rebound[33] and to decide when to do formal viral load quantification in the clinic. However, home testing introduces an important caveat. The precision in estimating time to rebound depends on testing frequency; therefore, the precision of home testing depends heavily on the adherence of the participants to a testing schedule (either more or less frequent testing than scheduled would affect the study outcome). Furthermore, home testing does not allow the verification of the sample source by the clinical team because it does not occur during an observed blood draw at the study clinic and relies on the study participant's veracity.

Monitoring considerations are also important for people who started ART during the so-called 'hyperacute' HIV phase. The consensus was that unique issues are associated with ATI participants who started ART very early, generally defined as preseroconversion (Fiebig stage 1–2 or hyperacute HIV infection). Specifically, these individuals have never seroconverted and potentially will not have appreciable anti-HIV immunity but might seroconvert after an ATI and, hence, be at higher risk for acute retroviral syndrome.[34] Because becoming HIV antibody positive might pose legal risks, such as disqualification for enlisting into military service in some countries, might carry potential social harm (eg, stigma associated with HIV infection and HIV-related discrimination), and might have serious financial implications, participants should be informed of these possibilities during informed consent and carefully monitored for such issues, and appropriate support and counselling should be offered.

Monitoring of participants' psychosocial experiences during ATIs is crucial. There was consensus that the psychosocial and lived experiences of study participants should be strategically assessed during analytical treatment interruptions. The large majority of the meeting participants agreed with integrating sociobehavioural assessments and monitoring of study participants in HIV ART-free remission protocols using ATIs (appendix p 7).[35] This assessment would involve participants' motivations, needs, concerns, and perceptions throughout the study. There was a consensus on the fact that researchers should also examine participants' psychosocial tolerance for longer ATIs, particularly because the research field moves towards less restrictive ATIs and prolonged periods of viraemia. Cohort studies of people with acute HIV infection in Thailand have successfully integrated decision-making assessments in HIV remission protocols with ATIs.[36] Similar research is ongoing in the USA as part of the ACTG and HIV ART-free remission-related research at the end of life.[37] Overall, the consensus was that research protocols should include formal monitoring of both perceived health and non-health associated benefits, and also perceived risks, such as anxiety related to being off ART, stress related to becoming viraemic, and fear of transmitting HIV to sexual partners.

Regarding paediatric populations, the consensus was that they should be monitored differently (eg, adolescents who are sexually active *vs* younger paediatric patients). The challenges are different between paediatric and adult populations, including more demanding blood draws, reliance on parents for clinic visits, and disruption of school schedules. Although in an ideal scenario the duration of weekly monitoring would be at the least similar to the proposed adult schedule, or even extended beyond the 12 weeks, the specific issues with feasibility and participant burden in the paediatric populations might require every-other-week monitoring early in the ATI period.

The group agreed that drug concentrations should also be assessed in initial weeks and throughout the ATI phase to confirm that individuals have indeed stopped ART. Although this strategy would prevent the risk of misinterpretation of study outcomes, it would also add to participant safety as termination from the study would allow a participant to take ART openly rather than covertly. Further, even in the event that participants achieve post-treatment control, investigators should be mindful that it might not be clinically optimal, despite the scientific merit of the finding. ART might still be advisable for controllers to ensure their safety, and that of their partners because ART-free viral control might be associated with ongoing low viral replication and potentially increased systemic inflammation.[38,39] There was consensus that ATI studies should be done in areas

where an established infrastructure is available for contacting and monitoring patients during ATIs, and for resuming ART promptly.

When should ART be re-initiated?

The general consensus of the group was that ART should be restarted if requested by the participant or their HIV health-care provider, if a participant becomes pregnant, or if ART is deemed medically necessary for non-HIV related causes. For HIV-specific restart criteria, it was agreed that viraemia should be a major criterion; however, the choice of a virological endpoint should generally depend on the study objectives.

Time to rebound might be considered the safest endpoint in an ATI protocol. It involves frequent monitoring of plasma HIV RNA with real-time measurements. Once HIV viral load rebound is confirmed and the endpoint is achieved, ART can be resumed. The time-to-rebound can be used as a test of cure as shown in some studies.[1,40,41] It might also prove to be a useful surrogate for the overall reservoir size, which is being investigated in an ongoing ACTG trial (A5345). In contrast, many immune-based therapeutics seek to achieve control of HIV after ART is interrupted and setpoint of rebound might be, therefore, the more appropriate measure. It has been observed in elite controllers, post-treatment controllers, and several successful cure and remission studies in non-human primates, that a period of high viraemia might be necessary before control is achieved[42] (eg, in one study,[43] 33% of rhesus macaques achieved durable virological control after a year following ART interruption). Resuming ART at the time of rebound or setting restart criteria too stringently might prevent potential complications of an ATI, but will also reduce the capacity to test the effectiveness of many interventions that aim to work through an immunological mechanisms and, consequently, might prevent the identification of virological controllers.[44] Although a substantial reduction of the setpoint value following ATI compared with the natural pre-ART values (when available) might be scientifically interesting, it is generally assumed that virus control, which is comparable to that during ART, will be needed for regulatory approval of any intervention aiming to induce viral suppression in the absence of ART. Overall, the consensus was that no universal values for duration or peak of viraemia should be used as restart criteria but that, when setting limits, duration of viraemia might be more important than the amount of viraemia.

Possible viral load-based restart criteria were also discussed. There was some support for 12–16 weeks of uncontrolled viraemia as an acceptable limit in studies for which a stable viral setpoint is a primary endpoint. Another proposed limit was to tolerate a viral load of 1000 copies per mL or more for 4 weeks (appendix p 8). Data from the RV217 study[31] and from the FRESH (Females Rising through Education, Support, and Health) cohort[45] in South Africa suggest that a viral steady state might be achieved as early as 4–6 weeks following acute infection, and new viral setpoints were achieved after 8–12 weeks following ART interruption in previous ATI studies.[46,47] Early set point information might, therefore, be available if viraemia is tolerated for 4–8 weeks. However, this approach might miss a certain percentage of virological controllers who would have achieved control at a later date. It was also suggested that viraemia can be tolerated for as long as viral load concentrations are declining naturally without a predetermined time limit. There was a general consensus that anyone who reaches confirmed HIV RNA of more than 100 000 copies per mL in time-to-rebound studies should restart ART immediately, regardless of duration. If the endpoint, however, is viral setpoint, high viral peaks, even of more than 100 000 copies per mL, might need to be tolerated for several weeks. Overall, there was a consensus that each viral load measurement should be confirmed with a second test, and that no action should be taken based on a single viral load result.

There was consensus that any clinical presentation suggestive of being HIV-related would be an adequate criterion for restarting ART. Symptoms might include, but are not limited to, unintentional weight loss (>5–10% of the pre-ATI body weight), otherwise unexplained persistent fever (>38°C), persistent night sweats, persistent diarrhoea, oral candidiasis, and generalised lymphadenopathy. In general, such symptoms would need to be considered on a case by case basis.

CD4 concentrations were also considered as a criterion for re-initiating ART. Depending on the study and the participants who are enrolled, the use a confirmed absolute CD4 concentration (eg, CD4 <350 cells per µL or CD4% <15%) was proposed or, alternatively, the percentage of decline from the starting CD4 value (eg, 30–50% decline). However, the clinical relevance of such decline in participants with high starting CD4 counts is unclear. Similarly to viraemia, CD4 counts should be confirmed with a second test before taking action. For studies using an absolute CD4 concentration, there was consensus that if the entry criterion is for individuals with CD4 counts of more than 500 cells per µL, restart concentration should be of less than 350 cells per µL. However, it is important to note that this cutoff will not be applicable in all cases and will be dependent on the CD4 entry criteria. Investigators should focus on obtaining a sufficiently large difference between the entry value versus a CD4 measure to compel ART resumption. As a practical matter, ATI experience to date shows that ART is resumed for criteria associated with the duration and magnitude of viraemia in nearly all cases.

Unprotected sex was another concern discussed in the meeting. It was agreed that all participants should be counselled before, and recurrently during, the trial on how best to protect their sexual partners from HIV infection. Although expectations for transmission precautions might differ, in particular when the sexual partner is reliably on

pre-exposure prophylaxis, the group agreed that participants who engage in risky sexual behaviour, as documented by history or by the diagnosis of recurrent, multiple, or new sexually transmitted infections suggestive of unprotected vaginal or anal intercourse, should be excluded from ATI trials or restarted on ART. Some studies are now including routine monitoring for sexually transmitted infections before and during the ATI to confirm participant's adherence to barrier protection for prevention of HIV transmission during the treatment interruption. A related, but less well defined, concern is superinfection in a study participant during ATI, which could be a major bias for the study endpoints but also might pose difficulties for ART reinitiation.

Controlled data on ART pause and viral rebound in paediatric populations are scarce. Whereas for older children (eg, adolescents), similar restart criteria to that for adults might be reasonable, younger children differ substantially from adults (eg, in natural CD4 T-cell frequencies). Some investigators suggested that tolerating longer and higher viraemia in paediatric participants than adults might be considered. Overall, the group agreed that defining ART restart criteria would require specific discussions geared towards paediatric populations, which was outside of the scope of this meeting.

Should we avoid cure terminology?

There was consensus that cure should not be used in titles and the informed consent processes. Most ATI studies are early stage trials and are not designed to lead to a potential cure. Thus, the use of cure is misleading.[48] Although the group agreed that cure might be an appropriate term in some cases (eg, when raising public awareness or in a political context), there was a clear consensus that cure is not appropriate when applied to specific studies or trials and informed consent documents. Some group members considered that remission is not an acceptable substitute for cure because it carries negative connotations from the oncology field. Several alternatives were suggested, such as drug-free long-term control, undetectable off treatment, viral suppression off treatment, drug-free viral control, and durable viral load suppression. These terms should be considered for community review.

When is there sufficient justification for the ethical use of placebo-controlled study designs?

The use of a placebo-controlled group raises both scientific and ethical questions. The overall consensus was that the decision whether to use a placebo control should be driven primarily by the science, that is whether a placebo group is needed for the scientific validity of a study. If a placebo group is necessary for the findings of a study to be properly interpreted, it could be considered unethical not to include a placebo (ie, when a placebo is a scientific necessity, it is arguably an ethical imperative as well). In these scenarios, power calculations to determine sample size requirements for placebo and intervention groups should be an important consideration when formal statistical comparisons are planned. However, there was also agreement that, in early exploratory trials, placebo control groups are sometimes used more for descriptive understanding of the population studied and their underlying response rather than providing statistical power for formal hypothesis testing. Such studies might be able to forego placebo groups and, instead, use well defined historical controls for time to HIV rebound, with the caveat that such earlier cohorts might differ from current cohorts in terms of ART regimens or timing of ART initiation, and might, therefore, underestimate time to rebound compared with those diagnosed and starting ART in more recent years. It was also noted that people living with well controlled HIV might be reluctant to participate in trials in which they could be placed in a placebo group when undergoing ATI, if their main interest was to be exposed to an experimental drug; in such cases, placebo groups might make study enrolment less appealing.

How do we ensure informed consent and avoid unreasonable expectations?

Achieving and ensuring informed consent can be very challenging, and the individual engagement of the research team member(s) and the potential participant is essential for supporting informed consent in early phase clinical trials. There was consensus that trial investigators need to ensure that participants understand the risks involved with ATI studies. In addition to potential physical risks, informed consent documents should address potential social, financial, and psychological risks. This process also includes informing the participant about potential stress or worry associated with re-experiencing detectable viraemia or fear of transmitting HIV. There was some support for testing the participants' knowledge of the study after informed consent to ensure that potential participants understand the procedures and risks involved in trial participation. Evidence from a study in Thailand[36] suggests that close relationships between clinical trial teams and participants has facilitated an improved understanding of the study and required procedures. As a result of these close relationships, most participants reported feeling that they had made an active and informed choice to participate at the conclusion of the study. An important distinction was noted between participants who are misinformed (eg, those who do not understand the intent of the research) versus participants who display therapeutic optimism (eg, those who understand the intent of the research but are unrealistically optimistic about obtaining the best outcome).

Conclusion

In summary, ATIs are not yet irreplaceable for assessing the efficacy of interventions aimed at inducing HIV

Search strategy and selection criteria

References for this Review were identified through suggestions from the experts that participated in the meeting, from searches for systematic reviews on the topic, and searches in PubMed and MEDLINE up to November, 2018, using various combinations of the search terms "analytical treatment interruption", "HIV", "cure", "reservoir", "ART", "remission", "ethics", and "post-treatme nt controller". No date limitations on included studies were applied but only papers published in English were included. Studies and publications were selected if they were relevant to at least one of the topics identified to guide the Review, specifically strategies for risk mitigation, monitoring and ART resumption criteria, and ethical considerations.

suppression in the absence of ART. Guidance on how to operationalise ATI studies to maximise scientific return but minimise participant's risk is crucial. The recommendations and consensus viewpoints summarised in this Review are thought to be a step forward in building consensus about how best to implement ATIs, taking scientific, clinical, and ethical aspects, and expectations into consideration. With the field rapidly evolving and with new data emerging, the establishment of an eclectic advisory group, such as the one described in this Review, that can regularly revisit and recommend changes in the approach to ATIs in HIV research studies should accelerate the evaluation of strategies that seek ART-free viral control while minimising risk to research participants.

Contributors

BJ, LD, JA, DHB, MLR, NLM, JWM, SGD, and BDW organised the meeting. All authors wrote the manuscript and approved its final version. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of any of the affiliation institutions, the US Department of the Army or the US Department of Defense, the National Institutes of Health, the Department of Health and Human Services, or the US Government.

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