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Recommendations for Analytical Antiretroviral Treatment Interruptions in HIV Research Trials – Report of a Consensus Meeting

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Summary:

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, post ART control, and/or altered set-point. Trials with ATIs also intend to determine host, virologic and immunologic markers predictive of sustained viral control off ART. Although ATI is increasingly

incorporated into proof-of-concept trials, there is no consensus on strategies to maximize its utility and minimize 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 report we present the major points of discussion and consensus views achieved with the goal of informing the conduct of ATIs to maximize the knowledge gained and minimize the risk to participants in clinical HIV research.

Background:

Despite the success of modern anti-retroviral therapy (ART) in limiting HIV replication, HIV infection remains a chronic disease that long-term ART alone will 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 treatment interruptions (ATI) appear to be necessary until a promising biomarker emerges that robustly predicts post-treatment viral control; ATIs are therefore irreplaceable at this point in time. 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 to assess the scientific value, risks, benefits and methodologies 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 maximizes the knowledge gained and minimizes the risk to trial participants. This report summarizes the major points of discussion 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:

Forty-one experts (adult and pediatric clinicians, virologists and immunologists, bioethicists, patient advocates, statisticians, social scientists, representatives of regulatory authorities and funding agencies (FDA, NIH, AmfAR) and industry from the US, Denmark, South Africa, Spain, Switzerland, Thailand and the UK participated by invitation from the scientific committee (BJ, LD, JA, DB, MR, MN, JM, SD and BDW). Main challenges concerning ATI studies were identified prior to 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 critical. 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 planning committee and then circulated to the larger group for review

and revision. The recommendations presented here are largely based on “expert opinions” given the relative absence of clinical evidence specific to ATIs and the limited availability of randomized controlled trials. The references used in this document were identified by literature search focusing on reported clinical studies including observational, cohort or interventional studies where antiretroviral therapy was temporarily interrupted with pre-determined restart criteria.

Results:

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

There was agreement that there are currently no validated biomarkers that are predictive of virological control once antiretroviral therapy is stopped, leaving ATIs as the only way to test the efficacy of newer therapeutic interventions. Even if a promising biomarker emerges, it will prove challenging to validate its utility as a surrogate marker for an ATI read out because an effective intervention that clearly affects time-to-rebound or post-treatment control does not yet exist. While some progress in identifying candidate biomarkers that may prove to be predictive has been made (1–4), and prospective observational studies aimed at supporting biomarker discovery are ongoing (, , etc.), no robust markers or assays that could replace ATIs are as yet available.

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

The majority of meeting participants thought 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 solved efficiently (Suppl Fig. 1). There was strong consensus, however, that ATIs are highly context dependent, and that there is no “one size fits all” guideline for circumstances under which ATIs are appropriate. There was agreement that the responsibility is on investigators to demonstrate, prior to the ATI study, that a strong scientific rationale exists for why the intervention might conceivably affect time-to-rebound, post-interruption set-point or other meaningful biological/clinical endpoints. This rationale might include prior success in preclinical animal models (rhesus macaques, humanized mice etc.), success in other diseases such as cancer, or prior demonstration in humans that the intervention has a measurable effect on a relevant

biomarker such as the size of reservoir or generation of potentially protective HIV-specific immune responses. In this context, it was suggested that investigators embarking on developing a new therapeutic strategy should determine predefined “go/no-go” criteria for incorporating ATIs in their development plans. More importantly, researchers should determine criteria for whether an intervention has achieved predefined goals, for example stipulating that a therapeutic vaccine induces immune responses above a prespecified threshold, before subjecting participants to an ATI. In general, there was agreement 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 (i) may be difficult to enroll sufficient participants; (ii) may exclude a large proportion of the HIV infected population, thereby precluding their contribution to and participation in HIV research; and (iii) would limit generalizability of findings to the broader HIV-infected population. While 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 more reflective of the overall demographics of the HIV infected population, e.g. age limits to 65 or 70 years, might be considered. Nonetheless it should be noted that the US Food and Drug Administration (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 (e.g., refractory, advanced malignancies). In line with the obvious ethical considerations, investigators must carefully consider the potential ramifications of any interventions to trial participants, as there is generally lower acceptability of risk to healthy volunteers in clinical research.

No single best population.—There was consensus that current 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 and/or higher viremia, investigators should seek participants who are expected to have a functional immune system, and who can be hypothesized to tolerate a period of higher viremia and/or any viremia occasioned by infrequent viral load monitoring. There was therefore agreement that participants in ATI studies should have stable CD4 counts of equal or greater than 500 cells per μL. However, there was also support for allowing CD4 counts of equal to or greater than 350 cells per μL (Suppl Fig. 2). The decision regarding which CD4 count threshold to allow for enrollment will depend on the presumed overall risk of the studied intervention. As clinical studies progress, the standards of what is “acceptable” may 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 exploration. For example, women in the US have been rarely recruited for these studies (10), although the AIDS Clinical Trial Group (ACTG) A5366 study successfully and quickly enrolled 30 post-menopausal women () demonstrating that recruitment of women is feasible. A recent study suggested that post-treatment control was more common among Africans compared to non-African individuals, suggesting an ethnic

effect, however, all participants in this study were women (11), preventing disaggregation by sex. Strategies aimed at enhancing a better sex/gender balance are therefore clearly needed (12, 13).

Pediatric considerations.—The inclusion of pediatric participants in ATI studies is a complex issue. Pediatric 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 in terms of their responses to vaccination and the absence of neurological and metabolic comorbidities. However, in contrast to infected adults where one tablet a day is feasible, continuous adherence to ART from birth is difficult to achieve, with unplanned treatment interruptions being common, especially in the less well-resourced settings where the pediatric epidemic is concentrated. Furthermore, the long-term side-effects of continuous ART from birth, are unknown and should not be dismissed. Pediatric patients might therefore arguably benefit the most from strategies that induce ART-free viral suppression and incorporating pediatric populations into research geared towards this goal is therefore critically important. Furthermore, some concerns in adults, such as HIV transmission to a sexual partner, do not exist during early childhood. There was overall agreement that because of the unique risks and behaviors surrounding pediatric HIV patients, dedicated age group-specific recommendations should be generated.

What should be considered strict exclusion criteria?

Active co-infections.—There was a strong consensus that anyone with chronic Hepatitis B virus (HBV) infection, with detectable Hepatitis B surface antigen and/or HBV DNA, or active Hepatitis C virus (HCV) infection, with detectable HCV RNA should be strictly excluded. There was consensus that individuals who have been fully treated and cured of Hepatitis C or who have cleared the virus naturally, and have documented undetectable plasma HCV RNA, need *not* to be excluded. Other co-infections, for example *Mycobacterium tuberculosis* (MTB), need to be considered, specifically given the high prevalence of MTB in the HIV infected population in certain geographical locations (14). While active MTB infection should be an exclusion criterion, the possibility of reactivating latent MTB should be discussed, and preventative MTB treatment might be considered.

Cancer.—HIV is associated with increased risk of many cancers. For certain cancers, any history should be generally considered strict exclusion criterion, for example, systemic cancers such as Kaposi's sarcoma and lymphoma or other virus-associated malignancies. This said, the Berlin and the Boston patients (15, 16) underwent ATI following treatment for hematological malignancies and the risk-benefit ratio for such participants 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 while smoking status (current or former) should not qualify for exclusion, individuals with prior history of lung cancer may be excluded. Cervical and anal cancer should also be carefully screened for and excluded. It is important to consider the specific type of malignancy relevant to each individual, as a history of certain *in situ* cancers or a history of cancers not known to be associated with HIV,

for example, prostate, breast, or colon cancer might not justify as an exclusion (Suppl Fig. 3). At least certain limitations, for example remission stage (or considered cured) for e.g. > 10 years, could be considered.

Neurological concerns.—Overall, the potential for neurological and CNS risks during acute or sustained viremia are real but poorly defined risks of ATIs. Prior 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 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, though aseptic meningitis as a manifestation of acute retroviral syndrome (ARS) has been reported (16, 21). In general, patients with a history of HIV dementia or progressive multifocal leukoencephalopathy (PML) should be excluded. HIV dementia is associated with neuroinflammation, neuronal injury, and a high burden of CNS HIV replication that is typically genetically compartmentalized 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 suggests that the brain is a site of HIV persistence that may be vulnerable to further injury or development of local ART resistance with ‘CSF escape’ during recrudescence of viral replication and inflammation (25, 26). PML is a frequently fatal disorder caused by CNS infection with the John Cunningham virus (JCV), currently lacking effective antiviral therapy (27). Immune competence is essential for JCV control, and irreversible brain injury persists in individuals who survive PML.

ART resistance.—The potential emergence of new drug-resistance mutations is of concern. This may occur during the interruption phase or when ART is resumed. Specifically, stopping ART regimens containing antiretrovirals (ARVs) with differing serum half-lives resulting in delayed wash-out, for example, of non-nucleoside reverse-transcriptase inhibitors (NNRTIs), pose a risk for the development of drug resistance. Study participants on such regimens should be switched to regimens with short-acting ARVs (e.g. switching NNRTIs to integrase inhibitors) prior to an ATI. Although one study reported no evidence of new antiretroviral drug resistance mutations within intact HIV proviral DNA sequences following reinitiation of ART (7), one of the “Boston patients” developed the K103N mutation during ART re-initiation due to adherence issues caused by an acute retroviral syndrome (16). Based on these observations, there was consensus that studies should only enroll individuals who have multiple alternative antiretroviral treatment options available in case their current treatment becomes less effective. There was also support for 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 (Suppl Fig. 3).

Cardiovascular disease.—There remains debate about cardiovascular risk and ATI. While some investigators strictly exclude individuals with any cardiovascular risk/history, others may allow certain cases, for example, an individual who has a distant history of disease and who has been treated and stable for many years. There was consensus that all

potential study participants should be screened for signs and symptoms of CVD before taking part in an ATI study. If there are concerning findings on initial screening, additional testing for CVD should be done before enrollment into such a study. Individuals with a known cardiovascular event or at high risk of an event, e.g. based on an Atherosclerotic Cardiovascular Disease Score (ASCVD) > 15%, should be excluded (Suppl Fig. 3).

History of AIDS defining illness and CD4 nadir.—Approximately two thirds of meeting participants thought that anyone with a history of AIDS-defining illness according to CDC criteria should be excluded (Suppl Fig. 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. As such, there was general consensus that individuals with a lifetime CD4 nadir <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 <350 cells per μL should be currently 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 particular study when choosing a CD4 nadir cut-off. Individuals during acute infection can have a significantly decreased CD4 count even below 200 cells per μL. However, this is transient and may not reflect immune deficiency as observed in CD4 declines during chronic stages of infection. A hard cut-off that does not account for this transience may exclude a significant number of potential participants and it was therefore suggested to primarily consider CD4 nadir limits outside of the acute infection window.

Pregnancy.—Pregnant or breastfeeding women should be strictly excluded, as suppression of viremia is crucial to preventing mother-to-child transmission. Careful monitoring for pregnancy should be a critical component of all ATI protocols. Trial participants should also be counseled on avoiding pregnancy during the trial. This includes counseling regarding contraception and if necessary, referral to a healthcare 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.

Liver and renal disease.—Non-infectious liver disease, for example, individuals with advanced nonalcoholic fatty liver (NAFL) and advanced nonalcoholic steatohepatitis (NASH), should be excluded if there is evidence for significant fibrosis (fibrosis score ≥F2), or evidence of cirrhosis as determined by histology, imaging or non-invasive measurement. Individuals with HIV-related kidney disease should be excluded. Furthermore, moderate to severely decreased estimated glomerular filtration rate (eGFR <45–60 ml/min/1.73m^2) should be an exclusion criterion (Suppl Fig. 3).

Risk of HIV transmission to sexual partners of ATI study participants.—While HIV transmission is among the greatest risks during an ATI, participants undergoing ATIs may also face legal and even criminal charges should they transmit while off ART (28). Thus, HIV transmission must be vigilantly prevented for the safety of both, partners and participants. There was therefore consensus that at a minimum, participants must be clearly and comprehensively counseled on transmission risks. The majority of meeting participants

thought that having HIV negative sexual partners who are not accessing PrEP/PEP should not be an exclusion criterion per se for a potential participant of an ATI study (Suppl Fig 3). However counseling should be offered as well as education about PrEP/PEP and HIV testing referral that trial participants can provide to their sexual partners. There was some consideration that PrEP 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 may experience 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 (Suppl Fig. 4).

Pediatric considerations.—There was consensus that all children who are younger than 2 years of age should be excluded (Suppl Fig. 5) from ART interruption because of their developing immune systems and potential elevated neurodevelopmental risks associated with unsuppressed viremia, coupled with the feasibility for frequent viral load monitoring off ART. There are also concerns that younger children who are *not* chronic survivors might experience exponential increases in viremia and disease progression, compared to older children who have reached a partial controller state in the absence of ART. As with 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?

Weekly monitoring is a realistic maximum.—There was consensus that, in most circumstances, once weekly monitoring is a reasonable frequency. While more frequent testing might be desired from a clinical and scientific perspective, it is necessary to consider the very real burden this 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 may be decreased to every other week thereafter with the option of resuming weekly monitoring if necessary, for example, when rebound of viremia occurs (Suppl Fig. 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. Frequent early testing is thus crucial to detecting rebound with precision. Nevertheless, it was noted that less frequent monitoring in later weeks could also result in undetected viremia.

Viremia, clinical symptoms and CD4 counts as measures.—There was consensus that viremia is a critical measurement as virologic 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 ARS needs to be considered following viral rebound. Specific clinical signs and symptoms that raise concern for ARS include malaise, fever, headache, lymphadenopathy, rash, sore throat, myalgia/arthralgia, unintentional weight loss, night sweats and diarrhea (29, 30). While CD4 counts should be measured every 2 weeks

and included in the ART restart criteria, they are less sensitive as CD4 decline often lags behind.

Home testing considerations.—There are key advantages to viral load testing at home. It allows increased participant monitoring without necessitating frequent clinic visits and is much more convenient for participants. Although such assays are not formally licensed they are being explored for screening for viral rebound (31) and to decide when to do formal viral load quantification in the clinic. However, this introduces an important caveat. Because precision in estimating time to rebound depends on testing frequency, 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 impact the study outcome). Furthermore, home testing prohibits 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 for people who started ART during "hyperacute" HIV.—There was consensus that there are unique issues associated with ATI participants who started ART very early, generally defined as pre-seroconversion (Fiebig stage 1–2 or "hyperacute" HIV infection). Specifically, these individuals have never seroconverted and potentially will lack appreciable anti-HIV immunity but may seroconvert after an ATI and hence be at higher risk for acute retroviral syndrome (32). As becoming HIV antibody positive (i) might pose legal risks, such as disqualification for enlisting into military service in some countries, (ii) carry potential social harm, e.g. stigma associated with HIV infection and HIV-related discrimination and (iii) have serious financial implications, participants should be informed of these possibilities during informed consent and carefully monitored for such issues and appropriate support and counseling should be offered.

Monitoring of participants' psychosocial experiences during ATIs.—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 socio-behavioral assessments and monitoring of study participants in HIV ART-free remission protocols utilizing ATIs (33) (Suppl Fig. 7). This would involve assessing participants' motivations, needs, concerns and perceptions throughout the study. There was consensus on the fact that researchers should also examine participants' psychosocial tolerance for longer ATIs, particularly as the research field moves towards less restrictive ATIs and prolonged periods of viremia. HIV acute cohorts in Thailand have successfully integrated decision-making assessments in HIV remission protocols utilizing ATIs (34). Similar research is ongoing in the United States as part of the ACTG and HIV ART-free remission-related research at the end of life (35). Overall, there was consensus that research protocols should include formal monitoring of both perceived health and non-health related benefits and also perceived risks such as anxiety related to being off ART, stresses related to becoming viremic, and fear of transmitting HIV to sexual partner(s).

Pediatric considerations.—There was consensus that there should be different monitoring considerations for pediatric populations, for example adolescents who are sexually active versus younger pediatric patients. There are different challenges in pediatric than adult populations, including more demanding blood draws, reliance on parents for clinic visits, disruption of school schedules etc. While 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 pediatric populations might require every-other-week monitoring early in the ATI period.

Additional recommendations.—It was agreed that there should also be drug level testing in initial weeks and throughout the ATI phase to confirm that individuals have indeed stopped ART. While this 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 this may not be clinically optimal, despite the scientific merit of the finding. Antiretroviral therapy may still be advisable for controllers to ensure their safety, and that of their partners as ART-free viral control might be associated with ongoing low level viral replication and potentially increased systemic inflammation (36, 37) There was consensus that ATI studies should be performed in areas where there is an established infrastructure for contacting and monitoring patients during ATIs, and for resuming ART promptly.

When should ART be re-initiated, e.g. what are safe antiretroviral restart criteria?

There was general consensus 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 viremia should be a major criterion, however, the choice of 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 levels with availability of 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 demonstrated in some recent studies (1, 38, 39). It may also prove to be a useful surrogate for the overall reservoir size, as is now 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 **set point of rebound** might be therefore the more appropriate measure. It has been observed in elite controllers, post-treatment controllers, and several successful cure/remission studies in non-human primates, that a period of high-level viremia may be necessary before control is achieved (40), e.g. in one study 33% of rhesus macaques achieved durable virologic control after a year following ART interruption (41). Resuming ART at the time of rebound and/or setting restart criteria too stringently may 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 mechanism/s and consequently may prevent the identification of virologic controllers (42). While a significant reduction of the set point value following ATI

compared to the natural pre-ART values (where available) might be scientifically interesting, it is generally assumed that virus control that 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 there was consensus that there are no universal values for duration or peak of viremia that should be used as restart criteria but that when setting limits, duration of viremia might be more important than the level of viremia.

Possible viral load-based restart criteria.—There was some support for 12–16 weeks of uncontrolled viremia as an acceptable limit in studies where a stable viral set point is a primary endpoint. Another proposed limit was to tolerate a viral load of ≥ 1,000 copies per mL for 4 weeks (Suppl Fig. 8). Recent data from RV217 (29) and from the FRESH cohort (Females Rising through Education, Support, and Health) in South Africa (43) suggest that a viral steady state might be achieved as early as 4–6 weeks following acute infection and new viral set points were achieved after 8–12 weeks following ART interruption in prior ATI studies (44, 45). Early set point information might therefore be available if viremia is tolerated for 4–8 weeks. However, this approach might miss a certain percentage of virologic controllers who would have achieved control at a later date. It was also suggested that viremia can be tolerated for as long as viral load levels are declining naturally without a predetermined time limit. There was a general consensus that anyone who reaches confirmed HIV RNA levels >100,000 copies per mL in time-to-rebound studies should restart ART immediately, regardless of duration. If the endpoint however is viral set point, higher viral peaks, even >100,000 copies per mL, might need to be tolerated for several weeks. Overall there was 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.

Symptomatic HIV disease.—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 (>100.4ºF/38ºC), persistent night sweats, persistent diarrhea, oral candidiasis and generalized lymphadenopathy. In general, such symptoms would need to be considered on a case by case basis.

CD4 levels.—There was consensus on the use of CD4 levels as restart criteria. Depending on the study and the participants who are enrolled, the use a confirmed absolute CD4 value (e.g. CD4 <350 cells per μL or CD4% <15) was proposed or alternatively, the percentage of decline, for example 30–50%, from starting CD4 value. However, the clinical relevance of such decline in participants with high starting CD4 counts is unclear. As with viremia, CD4 counts should be confirmed with a second test before acting. For studies using an absolute CD4 level, there was consensus that if the entry criterion is for individuals with CD4 counts >500 cells per μL, restart level should be <350 cells per μL. However, it is important to note that this 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 related to the duration and magnitude of viremia in nearly all cases.

Unprotected sex.—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. While expectations for transmission precautions might differ, in particular when the sexual partner is reliably taking PrEP, there was agreement that participants who engage in risky sexual behavior as documented by history or by the diagnosis of recurrent, multiple or new sexual transmitted infections (STIs), 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 STIs 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 may pose difficulties for ART reinitiation.

Pediatric considerations.—There are very limited controlled data on ART pause and viral rebound in pediatric populations. While for older children, similar restart criteria as in adults might be reasonable, younger children differ significantly from adults, for example, in regard to natural CD4 T-cell frequencies. It was suggested by some that investigators might consider tolerating longer and higher viremia in pediatric participants. Overall, it was felt that defining ART restart criteria would require specific discussions geared towards pediatric populations, which was outside of the scope of this meeting.

Should we avoid "cure" terminology? If so, what terminology should we use?

There was consensus that "cure" should *not* be used in titles and the informed consent processes. Most current ATI studies are early stage trials and are not designed to lead to a potential cure. Thus, the use of "cure" is misleading (46). While there was agreement that "cure" might be an appropriate term in some cases, for example, when raising public awareness or in a political context, there was clear consensus that "cure" is not appropriate when applied to specific studies/trials and informed consent documents. Some group members felt that "remission" is not an acceptable substitute for "cure" as it carries negative connotations from the oncology field. Several alternatives were suggested: "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? Conversely, are ATI studies valid without placebo controls?

The use of a placebo-controlled group raises both scientific and ethical questions. There was an overall consensus that the decision to use a placebo control—or not—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. In other words, 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 rate 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 may therefore underestimate time to rebound compared to 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 where they could be placed in a placebo group when undergoing ATI, if their main interest was in being exposed to an experimental agent; in such cases, placebo groups might make study enrollment less appealing.

How do we ensure informed consent and avoid unreasonable expectations?

Achieving and ensuring informed consent can be very challenging and the one-on-one engagement of the research team member(s) and the potential participant is essential for supporting informed consent (IC) 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 also includes informing the participant about potential stress or worry related to re-experiencing detectable viremia or fear of transmitting. There was some support for testing post-IC to ensure that potential participants understand the procedures and risks involved in trial participation. Evidence from Thailand suggests that close relationships between clinical trial teams and participants has facilitated a better 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 (34). It was also noted that there is an important distinction between participants who are misinformed, e.g. don’t understand the intent of the research versus participants who display “therapeutic optimism,” e.g. understand the intent of the research but are unrealistically optimistic about obtaining the best outcome.

Conclusion

In summary, ATIs are currently irreplaceable for assessing the efficacy of interventions aimed at inducing HIV suppression in the absence of ART. Guidance on how to operationalize ATI studies in order to maximize scientific return but minimize participant’s risk is vital. The recommendations and consensus viewpoints summarized here 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 here, 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 minimizing risk to research participants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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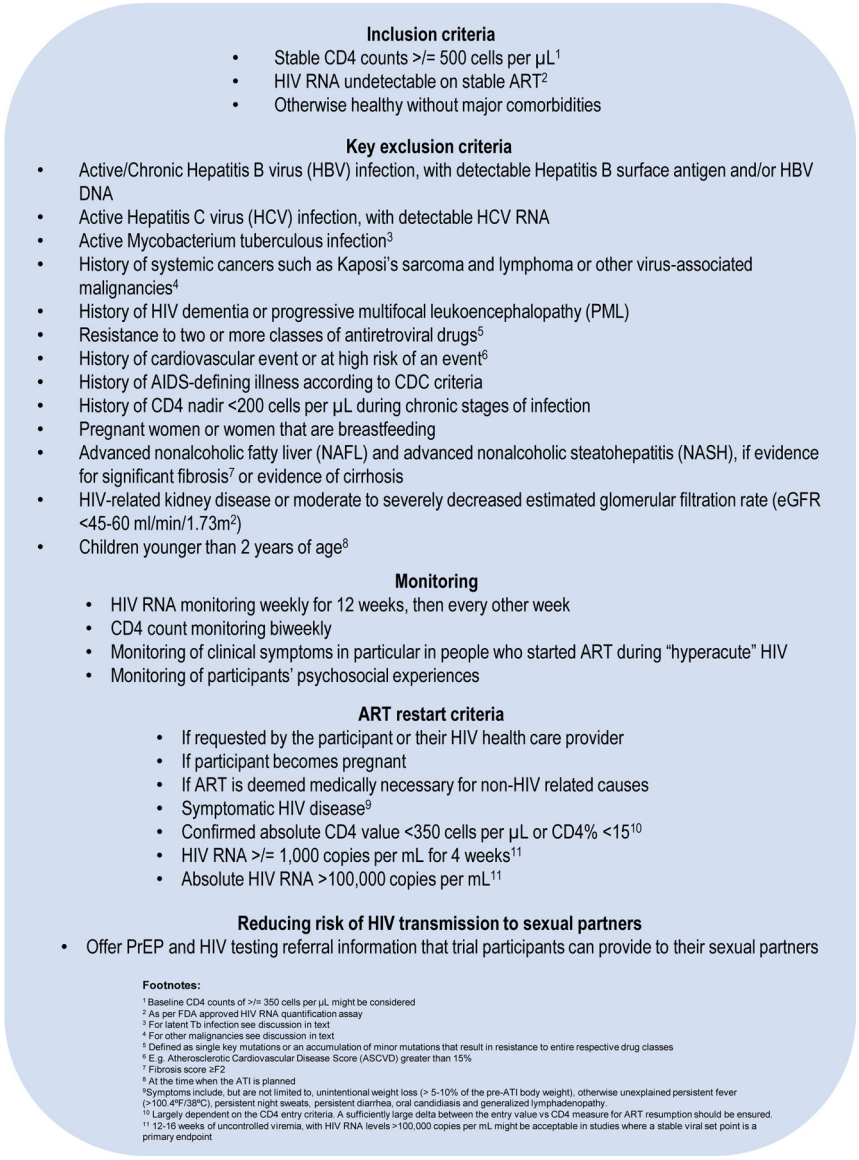

Figure 1.

Key recommendations. Additional or more stringent criteria may 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 ART restart criteria may differ in children depending on age.