



Original research

The ethical case for placebo control in HIV-cure-related studies with ART interruption

Monica Magalhaes^{a,*}, Daniel R. Kuritzkes^{b,c}, Nir Eyal^{a,d,e}

^a Center for Population-Level Bioethics, Rutgers University, New Brunswick, NJ, USA

^b Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA, USA

^c Harvard Medical School, Boston, MA, USA

^d Department of Philosophy, Rutgers University, New Brunswick, NJ, USA

^e Department of Health Behavior, Society, and Policy, Rutgers School of Public Health, Piscataway, NJ, USA

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ABSTRACT

Many studies that seek to cure HIV must ask participants to interrupt their antiretroviral treatment. In such circumstances, is it permissible to include a placebo group in the study? We explain why doing so is a scientific and an ethical necessity, and more benign than imagined.

“One has only to review the graveyard of discarded therapies to discover how many patients might have benefited from being randomly assigned to a control group.” T. C. Chalmers

1. Introduction¹

There is consensus about the continuing need for an analytical treatment interruption (ATI), a period following the investigative intervention in which the participant does not take ART, in many HIV cure-related studies.¹ By “HIV cure” we mean either sterilization—expunging the virus from the body; or remission—a period without detectable virus and without symptoms, absent antiretroviral treatment (ART), although HIV remains in the body.² It is only thanks to the ATI that researchers can see whether sterilization or remission has taken place.

Some completed, ongoing, or planned HIV cure-related studies, typically early-phase, include control arms where participants receive either a placebo substance or simply no intervention. For brevity, we refer to either form of control as “placebo”. In a cure-related study without an ATI, the participants on “placebo” would remain on standard of care, namely, ART. Obviously, in studies with an ATI, during that ATI, participants on “placebo” would not receive standard of care.

While there also seems to be a consensus about the scientific value of placebo control in cure-related studies, on grounds relayed below, in HIV cure conferences some investigators expressed doubt that it can ever be ethical to include a placebo arm in cure studies that involve an ATI. In other words, while both placebos and an ATI are individually acceptable, the combination of placebo and an ATI is sometimes said to be beyond the pale, ethically.

What concerns these investigators may be the following: participants in placebo arms would be exposed to some study risks, including the risks of ATI, as well as the study burdens and somewhat invasive diagnostics. Active arm participants face risks and burdens, but also some prospect of curative benefit. In placebo arms, such an offsetting prospect of benefit is impossible. So it may initially seem like participants assigned to the placebo arm can only lose from participation, unfairly. We aim to show why that thought is misguided.

Scientific consensus favoring inclusion of placebo control in cure-related studies with an ATI may also be emerging.¹ This perspective provides the ethical rationale for this consensus. It shows that including placebo controls in HIV cure-related clinical trials with an ATI is, when necessary to achieve study aims in a scientifically valid and interpretable way, not only permissible but obligatory from an ethical standpoint. Finally, this perspective preemptively addresses ethical questions about including placebo control in these studies. It assesses alternative ways to

* Corresponding author.

E-mail addresses: monica.magalhaes@rutgers.edu (M. Magalhaes), dkuritzkes@bwh.harvard.edu (D.R. Kuritzkes), nir.eyal@rutgers.edu (N. Eyal).

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serve the scientific goal of placebo control; gauges the possibility of skipping placebo control in late-phase cure-related studies; adumbrates our duties to protect participants' sex partners in these special studies, and describes the normative upshot of the fact that many participants of cure-related studies hope to be on the active arm.

We start by relaying the scientific case for using placebo arms in many cure-related studies that include an ATI. We then make the full case for ethical permissibility of relying on placebos: first, we recall the consensus that reliance on placebos is compatible with our duties toward participants of cure studies that do not include an ATI. We then show why this compatibility implies that reliance on placebos is also compatible with those duties in cure trials with an ATI. Our duties toward sexual partners of participants of cure-related studies with an ATI are weaker, if they exist—their very existence is more debatable—but the case for placebo can be made successfully even here. We conclude that reliance on placebo control in many cure-related studies with an ATI is permissible—and obligatory.

2. The basic scientific rationale for including a placebo arm in cure-related studies

There have been a number of pilot cure-related studies in which just one or two participants appeared to have shown a response to the intervention. That outcome could be explained as showing merely that these participants were post-treatment controllers (PTCs), and not necessarily as indicative of the curative potential of the intervention. Examples include the BCN02 study³, another therapeutic vaccine study⁴, and a dendritic cell-based therapeutic vaccine study.⁵ In general, in the absence of a placebo arm, false positives might motivate unwarranted reliance on the curative strategy being tested.

As an alternative to placebo control, it may be tempting to rely on comparison to what is generally known about “natural” rates of PTC in the wider HIV-infected population. However, the latter numbers have changed over the years,¹ and our assessments of them are probably inaccurate. Comparison to the rates of PTC in a cohort of carefully studied patients on placebo, such as the Control of HIV After Antiretroviral Medication Pause (CHAMP) study, is a better alternative, which would work for some early-phase studies (see below), but not for all studies. (Obviously, when reliance on credible placebo is simply impossible,⁶ a placebo arm does not add scientific value.)

3. Why including a placebo arm in cure-related studies without treatment interruption can respect participants' moral rights

Agreement already exists about including placebo controls in cure-related studies without an ATI, for example, in early phase therapeutic vaccine studies. Controls are essential to determine if the vaccine increases immune responses; in this case placebo participants are at lower risk than participants assigned to the active drug. The reason is that the main risk to participants of cure-related studies without ATI comes from the toxicities of the substances under study (other burdens and risks are much smaller), and participants in the placebo arm are spared that risk. Because these placebo participants provide informed consent, help to advance socially valuable cure science, and remain on their regular drug regimen, their treatment is easy to justify.

Table 1 below describes the main factors that affect, positively or negatively, the medical prospects for the most affected parties: participants and their sexual partners in cure-related studies with or without ATI (unless otherwise specified).

Consider first the effect of factors a-d on the medical prospects of participants in active and placebo arms. While participants in the placebo arm are denied the potential curative effects of active participation (factor a), they are spared the main risk, the toxicity of the active intervention (factor b). In early-phase curative studies that tend to be far more risky than likely to cure, the risk-benefit balance is clearly easier to justify in placebo arms than in active arms. Placebo participants are

Table 1

Key factors affecting medical risks and benefits to study participants and their sexual partners in cure-related studies. A plus sign designates better prospects than nonparticipation and a minus sign, worse ones. The greater the number of minus signs, the worse the risk.

Factor	Prospective medical value of this factor for ...			
	... active arm participants	... placebo arm participants	... partners of active participants	... partners of placebo participants
a. Potential curative effect	+ to ++ ^a	0	0 to + ^b	0
b. Potential toxicity	-- to --- ^c	0	0	0
c. Burdens and risky diagnostics	-	-	0	0
d. Close medical attention	+	+	0	0
e. In studies with ATI, risks from the ATI ^d	- to --	- to --	- to ---	- to ---
f. In studies with ATI, potential discovery of PTC status	0 to +	0 to +	0	0

^a The prospect of being cured or reaching remission is greater in late-phase studies.

^b Partners cannot be “cured”, but a curative effect for the participant would slightly enhance partners' safety, which should rest primarily on safe sex practices.

^c Depending on the trial type.

^d Risks in this row tend to be higher in remission studies than in eradication studies, both for participants and for their sexual partners.

denied a very small chance to obtain the exhilarating but, for someone who is stable on ART (as participants of these studies tend to be, for scientific reasons), non-crucial curative benefits; and they are spared a somewhat greater likelihood of major injuries. The small burdens and risks that come from the fact that they participate in the study (factor c) remain small enough in these studies as to leave this basic balance as is, and in any case are counterbalanced by the minor improvement in medical prospects from the close medical attention typically provided (factor d). Placebo-arm participants are, therefore, made no worse off by participating in the trial than active-arm participants. If researchers in these kinds of studies can permissibly assign participants to the active arm, then surely they can also permissibly assign participants to the placebo arm.

In later-phase (but pre-approval) studies, then, the use of placebo is both scientifically more essential,¹ and harder to justify ethically. Active study interventions that reach late-phase trials tend to have a greater prospect of curative benefit than of toxicity, thus potentially reversing the balance of risks and benefits, which, we argued above, made placebo arms easy to justify in early-phase studies.¹ Even for later-phase studies, however, the interventions being tested are experimental and unapproved. So participants assigned to placebo arms are not asked to forego a curative intervention available to them outside the trial.

Some might respond that all participants are entitled to any promising and safety-tested curative intervention under study, and giving them a mere chance at being randomized to receiving it, conditioned on their participating in the trial, is exploitative. However, after the completion a trial of a curative intervention that turns out to be safe and effective, placebo participants should, and almost certainly would per today's norms, be offered the curative intervention. Therefore, in a scenario where the curative intervention confers benefits that outweigh its risks, the disadvantage suffered by placebo-arm participants in

relation to active-arm participants would be merely a delay in receiving the effective curative intervention. In this scenario, placebo-arm participants are arguably better off than active-arm participants, as they avoid the risks of receiving an experimental treatment but are guaranteed early access if it proves to work. While for some drugs and vaccines delayed access can come too late, these participants are stable on ART. Therefore, mortality or permanent morbidity is unlikely to preclude later access.

Even in the absence of such a guarantee, there are several problems with the exploitation objection. For one, it is not the case that participants in either arm have a just entitlement to the promising curative intervention when it is unapproved, and hence unavailable to other patients or to themselves outside the study. Unapproved interventions may still prove inefficacious or unsafe in efficacy studies. So-called compassionate use (offering investigational treatment pre-approval, e.g. to terminal cancer patients in whom all approved treatments have failed) tends to undermine trial recruitment and is reserved to truly desperate cases. Patients who are stable on ART, as recruits of cure studies usually are, are not desperate cases.

4. Why including a placebo arm in cure-related studies with treatment interruption can respect participants' moral rights

So far, we reviewed why it is permissible to use placebos in cure studies that do not include an ATI. The case may seem much harder to make when an ATI is involved. Here, placebo participants are being asked to stop taking their antiretroviral drugs with no prospect of a dramatic curative benefit that might make this "worthwhile" for their health. Yet, in the aggregate, the prospects for an ATI trial participant assigned to the placebo arm can be better than the prospects for an ATI trial participant assigned to the active arm.

The minor burdens and risks of study participation and diagnostics (factor c), as well as the benefits of close medical attention typical of centers in which cure studies are pursued (factor d), do not move the needle much one way or the other. In addition, both placebo and active arm participants may discover, as a result of their participation in the trial, that they are post-treatment controllers (PTC), which may one day have beneficial implications for their healthcare (factor f in Table 1). The CHAMP study analyzed a large pool of ART study participants and found that 4% of those treated with ART during chronic infection and 13% of those treated during early infection were PTC (defined as "individuals who remained off ART for ≥ 24 weeks posttreatment interruption and maintained viral loads ≤ 400 copies/mL for at least two-thirds of the time points").⁷ So this benefit is also the same, or similar enough, for active and control-arm participants.

So it may still seem as though placebo arm participants have overall worse medical prospects than active arm participants. However, placebo participants also avoid the main risk for active arm participants: the risk of toxicity (factor b). In early-phase cure-related studies, the absence of that risk affects placebo participants' net risk portfolios much more than the other factors mentioned above, because toxicity—and even, depending on the trial, severe toxicity—is much more likely in early-phase trials than a cure.

We concede that the net negative impact on prospects from trial participation compared to non-participation is more obvious in advance in placebo arms than it is in active arms. Presumably, that explains investigators' reluctance to include placebo arms in their studies. However, compare the columns referring to active arm participants and placebo arm participants in Table 1 above: in four out of six factors (c, d, e and f), there is no difference in prospect between the arms. Out of the remaining three factors, one is safer for active arm participants (a) and one is safer for placebo arm participants (b). The greatest safety differential, the risk of toxicity (b), favors the placebo arm. So, if anything, the active arm is the riskier arm: the net negative impact of trial participation on medical prospects is *smaller* in placebo arms than in active arms, and will remain so as long as cure-related interventions remain highly

experimental and by no means guarantee viral suppression.

When the scientific validity of a trial would be greatly strengthened by the use of placebo control (as it often would) then, *if* the trial is important enough to justify exposing active arm participants to certain net risks, *then* including a placebo arm should usually be even easier to justify. The reason is not that placebo arm participation in such a trial is somehow good for the participant's health; it often will carry a negative medical risk-benefit ratio for that individual. But the same could be said, to an even greater extent, about active arm participation. The point is, rather, comparative. If asking participants to accept the risks of being in the active arm of a study with an ATI is ethically permissible (e.g. because participants autonomously authorized it; because they gain enough psycho-socially; because the study has high value for society),⁸ then surely asking participants to accept the smaller medical net risks of being assigned to placebo in such a study is also justified.

In early-phase studies, then, the use of placebo remains, in our view, easily justifiable even with an ATI. It may, however, be avoidable in some cases, as existing data about viremia control after ART interruption may be good enough to serve the purposes of a control arm, much like population fertility data is used as a comparator to assess the effectiveness of contraceptives. Data for such artificial control arms could come from studies such as the CHAMP study, described above.¹ A strategy like this would not work, however, for late-phase studies where effect sizes need to be estimated as precisely as possible. Therefore, just as in the case of trials without an ATI, in late-phase trials with an ATI placebo control is both scientifically more essential and somewhat harder to justify ethically. If and when cure-related research advances to the point where promising curative interventions are being tested, the balance will become more favorable to the active arm. Still, in our view, placebo control remains justifiable on balance. Even in late-phase studies, the intervention, however promising, is unproven. New safety risks may be uncovered, and control group participants are likely to benefit from early access to the intervention, if it proves effective. So, on balance, participants assigned to placebo arms are not treated so as to make placebo use ethically unjustifiable. The need for placebo controls to make the results of the efficacy trial interpretable and acceptable to the medical community, to regulators, and payers will often justify the inclusion of placebo arms. Rigorous placebo-controlled randomized trials could help an effective curative intervention to be adopted faster and more widely than would happen in the absence of placebo control.

Faster approvals would respect not only societal interests in curing HIV, but also participants' rights. Both active arm and placebo arm participants accept risks for little or no expected benefit, partly in order to help the development and wide adoption of a curative intervention. If trials with no placebo control delay availability of a therapy, then even knowingly being assigned to a placebo group would be entirely consistent with participants' motivation to participate. Moreover, if refraining from using placebo controls weakens the credibility of the study as evidence so that more studies are needed before an effective therapy is widely adopted, then the number of study participants who will have to undertake study risks must increase. More patients will be put at risk in order to spare fewer participants from the much smaller incremental risks of taking a placebo in addition to undergoing ATI—ethically an undesirable outcome.

5. Why including a placebo arm in cure-related studies with treatment interruption can respect participants' sexual partners' moral rights

For all the worry about placebo participants' rights in studies with ATIs, the hardest ethical questions about these studies surround the rights of participants' sexual partners, in both stable and casual partnerships. For placebo arm participants themselves, the background of intensive medical follow-up required in studies somewhat limits any risks (for example, when an increase in viral load is caught early on and measures are taken to contain any clinical deterioration). The same is

not true for the sexual partners of participants, certainly not for those in casual sexual partnerships. Specifically, during long ATIs, participants may become highly infectious and infect some sexual partners or transmit new strains to infected partners, giving rise to new risks (including, for some casual partners, the risk of an infection they are not aware of), and a host of ethical questions.⁹

In Table 1 above, consider the two columns on the right. Because toxicity that may harm participants is irrelevant for sexual partners' health, the overall medical benefit for sexual partners in active arms is clearly somewhat greater than in placebo arms. They may benefit medically from the participant's cure, if it happens, but are not at greater risk than the partners of participants in placebo arms.

Moreover, unlike participants in either arm, sexual partners of participants in either arm will rarely if ever have provided informed consent to taking on risks. Nor do the partners of participants in either arm have any prospect of gaining social recognition from the study. How can the risk of infection to them during long ATIs be justified?¹⁰

The answer, again, is conditional. If it is permissible to expose sexual partners of participants in active arms to risk, then usually it would be permissible to do that also to sexual partners of participants in placebo arms. The inclusion of a placebo arm doesn't pose an ethical problem in its own right. It is true that partners of any cured participants would usually benefit somewhat from their partners' cure (less worry about getting infected and, potentially, psychological benefits). But the prospect of a cure is small in early-phase studies.

In possible future studies that investigate promising curative interventions, the chance at a cure might be large. In these possible future studies, therefore, the difference between placebo arms' and active arms' impacts on partners may need to be revisited, and additional protections against (re)infection of partners may be warranted. Again, guaranteeing access to the curative intervention for all placebo-arm participants after the end of the trial, if the intervention proves safe and effective, would significantly mitigate this difference.

6. Why the matter of participants' aspirations and psychosocial benefits from participation does not fundamentally alter this

There is another difference between placebo and active arms that could ground concerns about using placebo controls in cure-related studies, with or without an ATI. Unlike active-arm participants, placebo-arm participants have no prospect of gaining psychosocially, say, in self-worth and international fame, following a cure. Active participants' chance at this psychosocial gain may be thought to make active arm participation objectively a far better prospect to many than placebo arm participation. However, during the trial, blinding thwarts psychosocial rewards to any given participant as allegedly a member of the active group. After the trial, a big difference in social recognition and self-worth may ensue between anyone cured and placebo participants (or active-arm participants who were not cured). But recall the exceedingly low chance of getting cured in early-phase studies. Even if that psychosocial gain is enormous, the *expected* gain from active arm participation remains negligibly small.

Two complications remain. One is that many participants may feel more excited to discover, once the blind is removed, that they had served in the active arm as compared to the placebo arm—if you will, as the equivalents of the glorified attacker of enemy barracks not the “mere” decoy operation—even if they are not cured. An opponent may argue that discovering that one was a “mere” placebo participant would be so disappointing to many and inimical to the hopes that brought them to the study that it is unfair to put any participants in that position.

As noted, both arms of a trial contribute crucially to cure science. Therefore, a candidate participant motivated by the very best altruistic reasons and a full understanding of the value of a study and what is necessary to keep it valid will want to participate even in a placebo arm. We concede that some sense of disappointment is possible. But we also speculate that, by far, the greatest hope for most participants (besides

helping science and staying safe) is to be cured, not simply to have served in the active arm. And the chances of *that* happening are so low in these early-phase studies that all these studies are likely to bring some disappointment to many participants, regardless of the arm to which they are assigned. On that, we already have consensus that cure studies remain justified (thanks to their social value and the participants' informed consent) even if they rarely fulfil participants' very highest hopes.

If anything, the existence of a placebo arm may make the trial more ethical. The possibility of being assigned to placebo may put off candidate participants who simply cannot tolerate any outcome except having been cured—an unlikely prospect even in the active arm. Such false hopes should not drive study participation.

Some might worry that only few real-world candidates would want to take on risk for the less glorified role of control-arm participant. As far as we know, this question has not thus far been tested. But so far, cure-related studies with or without placebo arms have had little if any problem recruiting.

7. Conclusion

In cure-related studies with or without an ATI, a placebo control has clear scientific value. Contrary to some investigators' worries, the medical risks for study participants who serve on a placebo arm of an early-phase cure study that includes an ATI are smaller and easier to justify than the risks for study participants who serve on an active arm. While that picture is reversed for the sexual partners of study participants, especially for seronegative ones, the difference in medical prospects of participants and the partners of participants in active vs. in placebo arms is very small. If the study's treatment of active-arm participants and their partners is defensible, then its treatment of placebo-arm participants and their sexual partners is likely to be defensible as well. As HIV-curative research advances and potential cures being trialed become more promising, the balance of risks and benefits will become more favorable to active-arm participants. As a mitigation strategy for such risk differentials, we suggest a guarantee of access to any curative interventions that prove safe and effective to placebo-arm study participants.

Thus, if there is ethical warrant for the medical risks for participants and their partners in cure-related studies with an ATI, then a placebo arm is also warranted. Without a placebo arm, the findings might not be interpretable or persuasive to regulators and payers. So placebo is clearly justified.

Lastly, consideration of the subjective aspirations of study candidates and the psychosocial benefits they stand to gain from participation, in the event of a scientific breakthrough, does not fundamentally undermine this conclusion.

If we are right about all this, it is arguably not only permissible to include a placebo arm in most cure studies (with or without an ATI) where placebo control has scientific value, but researchers have a duty to do so. Participants agree to take part in research not simply in order to be in a study, but in order to participate in a study whose design permits it to be fully valid, and hence truly helpful towards discovering a cure for HIV. That's why placebo control that is scientifically necessary is also ethically necessary if any study is to take place.

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