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Invited Commentary on Dubé et al. (Perceptions of Equipoise, Risk/Benefit Ratios, and “Otherwise Healthy Volunteers” in the Context of Early-Phase HIV Cure Research in the United States—A Qualitative Inquiry): Are HIV-Infected Candidates for Participation in Risky Cure-Related Studies Otherwise Healthy?

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BACKGROUND

Much of Dubé et al.’s (2017) article is dedicated to the U.S. Food and Drug Administration (FDA) reference to people living with HIV (PLWHIV) and well-managed on antiretroviral therapy (ART) as otherwise healthy volunteers.” They focus on that reference in FDA’s response to a proposed Phase II HIV cure-related trial in 2015. The ACTIVATE study would administer a repurposed anticancer agent, panobinostat (Farydak®), along with pegylated interferon-alpha2a. The investigators hypothesized that administering the panobinostat would reactivate the latent HIV reservoir while administration of interferon-alpha2a would activate the immune system, possibly leading to the elimination of the reactivated HIV-infected cells. At the time, panobinostat had limited, provisional approval for treatment of refractory multiple myeloma in adults who have had at least two other types of cancer treatment failure. The limited approval was due to toxicities, including risks of severe diarrhea, severe or fatal cardiac toxicities, hemorrhage, hepatotoxicity, and embryo-fetal toxicity (Novartis, 2016). In the original ACTIVATE study, investigators proposed to administer the same dose of panobinostat that cancer patients receive (20 mg) to 30 PLWHIV between the ages of 18 and 65 who were stable on ART for at least 24 months and had no preexisting comorbidities (Kuritzkes, 2016). Concerned among other things about toxicity and potential adverse events, the FDA initially decided to prevent the study from proceeding, stating, “Given the known safety profile of Farydak® [panobinostat] . . . in our view, equipoise does not exist for the use of Farydak® at any dose . . . for HIV reservoir research in an *otherwise healthy HIV-infected population*” (D. Kuritzkes, personal communication, August 29, 2017,

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emphasis added). While later that year the FDA approved the study with protocol modifications and more stringent eligibility requirements, we shall focus on the FDA's initial decision to put the ACTIVATE study on clinical hold as it was originally proposed, because we believe there are general lessons to be gained from its discussion.

We shall set aside the ethical question of equipoise and focus instead on the other issue raised by the FDA, namely, that this study would be conducted in an "otherwise healthy" population. Were ACTIVATE study volunteers "otherwise healthy"? Dubé et al. seem to suggest that they were not. We concur with Dubé et al., although on very different grounds, which we shall outline below.

The question whether these volunteers were healthy is not merely semantic. It affects the appropriate design of ACTIVATE and other studies that ask PLWHIV to accept high or uncertain risk, a common feature of early-phase HIV cure-related studies, an emphasis area for the International AIDS Society and the U.S. National Institutes of Health (Deeks et al., 2016). That may include some upcoming HIV cure-related studies with checkpoint inhibitors, another toxic family of drugs used in cancer treatment. There are also general lessons for our understanding of the health state of being stable on ART in general, and our determinations of health and pathology beyond HIV.

THREE CRITERIA FOR "OTHERWISE HEALTHY"

The FDA's initial response may have rested on the following implicit criterion: *When a person is fairly asymptomatic and is medically stable on a certain regular treatment regimen (e.g., with roughly normal life expectancy if she remains adherent), then she is healthy.* In our own case, FDA might explain, for Americans stable on ART, HIV is nowadays a manageable condition with which they could live long and relatively healthy lives (Barré-Sinoussi, Ross, & Delfraissy, 2013; National Institute of Allergy and Infectious Diseases, 2017). For the sake of discussion, let us conjecture that this implicit criterion for "healthy" informed FDA's initial determination to prevent the study from proceeding.

Dubé et al.'s language suggests a reservation about FDA's criterion: "Although individuals with well-managed HIV are typically considered 'otherwise healthy,' people living with HIV may view their health differently." Dubé et al. emphasize that in interviews,

the majority of PLWHIV did not consider themselves "otherwise healthy." They felt that HIV viral suppression or undetectable status was different than being healthy, and perceived themselves as fragile individuals who often still experience great health risks, life challenges, or vulnerabilities.

As examples, Dubé et al. describe participants' worries about related comorbidities, as well as about "societal consequences of living with HIV that might affect their health, such as stigma and discrimination." Although it is not explicitly stated, Dubé et al. seem to take participants' different perceptions to count against the FDA's criterion. After all, PLWHIV are "key stakeholders" whose "perspective" matters. Dubé et al. do seem to take this fact to justify some qualification to FDA's position, for no other basis is given in support of their concluding recommendation:

Although the general FDA policy is to consider healthy PLWHIV as “otherwise healthy volunteers” for the purpose of assessing risks and benefits of HIV cure research for the field, it is important to remember that HIV cure research protocols should be evaluated on a case-by-case-basis in light of the latest scientific evidence.

We shall henceforth conjecture that Dubé et al. grant special credence on the patients’ perspective, and take it to be decisive, or nearly decisive, on the tagging of these individuals as “healthy” or as “unhealthy.” Their own implicit criterion is more subjective or culturally dependent, if you will, than FDA’s.

Both the FDA’s purportedly objective criterion for “otherwise healthy,” which emphasizes stability and lack of symptoms on ART, and Dubé et al.’s subjective or cultural criterion per interviewees’ self-description are highly problematic (and, in all fairness, their attribution to the FDA and to Dubé et al. is more our reconstruction than their explicit commitment). To illustrate why these criteria are so problematic, consider a person who has a lethal tumor but is still asymptomatic. Neither she nor her physician knows that she has the tumor, so all consider her healthy. Surely such a person is not in full health. She has developed the disease that will, most likely, kill her. Although she may look and feel healthy, define herself as healthy, and may be described by her clinician who is unaware of the tumor as healthy, in truth, her health is far from optimal. She is not healthy.

This example alone suffices to refute both the FDA’s implicit definition’s partial focus on symptoms, and Dubé et al.’s focus on self-description. Whether someone is healthy is not as superficial as being symptomatic, and not as subjective as whether she defines herself as healthy.

Of course, the FDA’s criterion had another element—stability on ART. But now consider someone who is asthmatic enough that she would have choked to death upon attack, but thankfully, whenever she has an asthma attack, she relies on her inhaler and averts a crisis. Or consider others who are stable and functioning (almost) normally, potentially with normal life expectancies and other good prognostics, but only thanks to regular or as-needed drug administration. For example, someone’s chronic pain would have expressed itself but for her regular ingestion of preventive painkillers. Someone else is stable on and responding well to insulin for treatment of diabetes. Yet, another is living with end-stage renal disease and doing extremely well on dialysis. In any of these examples, the person is not fully healthy. The reason is that she still has the condition or conditions that would probably kill or injure her *but for treatment*. She functions (almost) as well as does a healthy person who lacks her chronic condition, but she is not fully healthy. To us, this suggests that being stable thanks to ongoing regular medication intake is not being “healthy” either. This is enough to counter the other potential anchor of the FDA’s implicit criterion for “healthy” namely, being stable but only due to (antiretroviral) treatment.

Additional objections apply to Dubé et al.’s seeming reliance on participants to determine whether they are healthy. The term *health* appears in many medical contexts outside HIV. Stakeholders in the HIV arena are not authorized to change English across the board, lest the complications reverberate elsewhere. In our particular case, the stakeholders’ replies were clearly influenced by considerations beyond health. For example, some reportedly

considered themselves unhealthy in part due to “stigma”; yet, stigma is not constitutive of poor health. Stigma may causally lead to health problems, and it may bias judgments on what counts as abnormal and unhealthy, but it is not an illness.

Let us propose a third criterion for “healthy.” As we use the term, *unhealthy* denotes having a morbidity and/or being at elevated risk of developing morbidity or mortality, for reasons that reside in the present state of one’s body (not, for example, in the fact that a bullet is on its way to hit the body), except if natural healing or a cure eliminate the elevated risk, or treatment blocks its realization in full or in part. A person is unhealthy when, for example, they experience pain or ambulatory limitations, or when a tumor or a bullet or a virus is inside their body, and they generate risk of pain, ambulatory limitations, other morbidities, or death—except if the person heals, or treatment contains the risk. To illustrate this idea, a bullet inside an internal organ may be removed, but as long as it is there and poses a risk, the person cannot be in full health.

Moving back to our case of candidate volunteers for the ACTIVATE study, and considering the above examples, someone who lives with HIV—even if it is controlled and asymptomatic—is not fully healthy because that control depends on firm adherence to a medication regimen. They may be far healthier than someone whose HIV infection is uncontrollable, or who is symptomatic, or who faces high risk of death or debilitating symptoms even with medication, but the candidate volunteer is not quite as healthy as someone who has similar functioning and general health and is uninfected. An HIV-infected person would usually become unstable and symptomatic sometime after removal of ART. Perhaps one day a cure may be developed for HIV, and the infected person may be cured, potentially with no side effects. But barring that, she is objectively in less than optimal health.¹ Indeed, the quest for HIV cure or controlled remission is surely for a medical intervention. ACTIVATE is neither a study in urban design or textile improvement nor a study of “medical enhancement,” namely interventions that make people superhumanly capable. It is a study in health care—precisely because HIV, notwithstanding FDA’s implicit criterion, detracts from health; and despite Dubé et al.’s implicit criterion, it detracts from health objectively, not only because stakeholders in this area say so.

RESPONSE TO FOUR OBJECTIONS TO USING OUR CRITERION

A Small Disease Burden

One possible response to our criterion for “otherwise healthy,” and specifically to our description of ACTIVATE candidate participants as unhealthy, points to the largest project in contemporary public health, the Global Burden of Disease (GBD) study. That project assesses health losses from diseases, injuries, and risk factors using disability-adjusted life-years. Such a project requires a set of disability weights to quantify the disease burden of all health states. Using a large international survey of more than 60,000 participants from all world regions, the GBD study seeks to answer how much various health states affect health

¹The case of controlled remission for HIV is somewhat more complicated, though we would argue that optimally functional controlled remission thanks to, for example, biennial injections, is not full health either. If a perfectly “functional cure” would be roughly as choiceworthy for patients, providers, health ministries, and donors as an optimal sterilizing cure, still a “functional cure” would not constitute full health. Perhaps what this shows is that the goal of medicine is to improve function and not simply to improve health.

(Salomon et al., 2015). The health state of controlled HIV infection turns out to be designated by these participants as near to perfectly healthy. For purposes of the survey, *perfectly healthy* is set at 0, and *dead* (considered the least healthy state) is set at 1. It so happens that at 0.078 (0.052–0.111), the state *HIV/AIDS: receiving antiretroviral treatment* is close to 0, and hence near healthy (Salomon et al., 2015). This may suggest that most people around the world consider controlled HIV quite perfectly healthy.

However, this result is probably a sheer artifact of the (perhaps sensible) lay description conventions of the GBD survey. The lay description for *HIV/AIDS: receiving antiretroviral treatment* is, “has occasional fevers and infections. The person takes daily medication that sometimes causes diarrhea.” What this is not saying is that treated, well-controlled HIV remains a precarious state. Stop taking your medications, and you’re in big trouble: 0.274, which is the disability weight for *HIV: symptomatic, pre-AIDS*, or even 0.582, which is the disability weight for *AIDS: not receiving antiretroviral treatment* (Salomon et al., 2015). Part of what makes HIV a health issue is this vulnerability to deterioration upon cessation of treatment. That vulnerability and dependence on medication adherence is absent in uninfected people.

Another important element absent in the GBD’s lay description of *HIV/AIDS: receiving antiretroviral treatment* is the concern that still exists as to whether a particular treatment regimen to which a person responds well at present will continue to keep them virally suppressed and functional 5, 10, or 20 years later. PLWHIV who adhere strictly to and are doing well on their current regimen of ART are able to keep their viral loads relatively low; however, even with successful ART, the virus remains in the body. Many uncertainties remain about the long-term effects of ART and of the virus itself (Deeks et al., 2016).

Furthermore, strict adherence to a medication regimen in an effort to maintain health relies on continued access to treatment. Without this strict adherence, risk of becoming resistant to the medication that previously worked persists. A variety of factors such as homelessness, loss of insurance, loss of a job, or unstable ART supply in the community can undermine the adherence of someone who was previously adherent and stable, to make her less adherent (Kuritzkes, 2017).

Put differently, even if, counterfactually, PLWHIV fared every bit as well on a daily basis as uninfected people (pills never caused diarrhea, patients would lack infections, there would be no complications from taking ART over many years), there is an important English usage in which PLWHIV would still be suboptimally healthy—because of these vulnerabilities and dependence on medication, and the related future uncertainties. The latter do affect their health. Interestingly, Dubé et al.’s HIV-infected interviewees mention those uncertainties among the reasons why they are not healthy. We concur that these uncertainties detract from health, but what makes them do so is not simply that this is the patients’ point of view, but something more objective, which these patients identified, namely, elevated risk of developing morbidity or mortality for reasons that reside in the body’s serostatus, unless treatment (or cure) block its realization.

Another Sense in Which Candidate Participants Were “Healthy”

There is also a sense in English in which someone with a minor health problem is “healthy” although she lacks perfect or optimal health. A person who has a scratch that is being treated with a band aid is considered healthy.

But HIV is not a case in point. It is currently a permanent condition that, without treatment, would usually get out of control. And as we described, even with perfect adherence to treatment, there is some potential for complications in later life—which indeed is part of the motivation for continuing to seek cure-related solutions for HIV (Kuritzkes, 2017).

Another Sense in Which Candidate Participants Were “Otherwise Healthy”

There is also a sense in which many PLWHIV are “*otherwise healthy*,” namely that other than being unhealthy because of HIV, they lack other health issues. That certainly holds true for some ACTIVATE volunteers.

As an illustration of this usage by FDA, an FDA report that gathered patient perspectives on currently available therapies and cure research, states

Considering the growing population of patients living with HIV who must also manage other chronic conditions, one participant commented that current therapies are typically tested on *otherwise healthy* subjects, and that he believes it is important to have post-marketing studies to see how FDA- approved medications affect patients who have multiple chronic conditions. (FDA, 2014, emphasis added)

However, in our own context, FDA’s initial decision about ACTIVATE clearly did not use “otherwise healthy” in the sense given here, but, more plausibly, in the sense delineated in the implicit criterion we described. That a patient is “otherwise healthy” in the sense that she lacks comorbidities would have been a highly questionable ground for her exclusion from study participation. On the contrary, a participant’s comorbidities might have set back the study’s safety and interpretability. FDA’s point in relation to ACTIVATE was clearly not about candidate participants’ lack of unrelated comorbidities, but about the stability of their HIV.

Stigma

One might object that whatever the “truth” is on whether controlled HIV is a state of perfect health or not, there is something potentially stigmatizing about calling PLWHIV “unhealthy.” In our constant effort to reduce HIV stigma, we should instead designate them “healthy.”

But this objection assumes that there is something shameful about being unhealthy, and this assumption must be rejected.

More generally, imagine how our classifications of health states would look if whenever a state of health represented a low level of disease (treated HIV is a case in point; deafness and Down syndrome might be others), we treated them as though they constituted perfect health just to avoid the alleged stigma of “pathologizing” them. If and when these states *gradually* deteriorated just a bit to reach what we now call “very unhealthy,” the people

living with them would “jump,” in our classification, from having perfect health to having high level of disease, without ever having had a low level of disease. Such a discontinuity would be odd, given that objectively, disease progression was gradual.

CONCLUSION

In our view, FDA was wrong to call stable, asymptomatic PLWHIV who are free from related or unrelated comorbidities “otherwise healthy.” That label incorrectly implied that, barring any study borne injuries, the candidate volunteers were in perfect health despite their infection. Dubé et al. seem to assume correctly that they were unhealthy, but the seeming criterion behind their ascription is flawed. We have proposed a third criterion, on which the candidate participants turn out to have been otherwise unhealthy.

On the practical question regarding whether imposing added safety measures in ACTIVATE was justified, we tend to side with the FDA. That said, imposing added safety measures is not without cost, and there are alternative and complementary approaches to managing risky HIV cure- related studies ethically (Eyal, 2017). In some proposed and future cure-related studies that carry high or unknown medical risks to participants, added safety measures might turn out to be unjustified.

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