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NOTES FROM THE FIELD

AIDS Activism and Coronavirus Vaccine Challenge Trials

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On May 6, 2020, the WHO Working Group for Guidance on Human Challenge Studies in COVID-19 released a report according to which well-designed challenge studies could accelerate COVID-19 vaccine development, and delineated 8 criteria which would suffice for them to remain ethical [1]. Rejecting this guidance the very next day, a joint statement by Global Advocacy for HIV Prevention (AVAC) and Treatment Action Group (TAG) declared:

> The WHO Working Group has articulated important criteria for assessing a challenge study, but we believe that they left out the most important one: Until there is an approved treatment, a challenge trial with a potentially fatal and as-yet untreatable pathogen is unacceptable [2].

Most SARS-CoV-2 vaccine candidates are not ready for efficacy testing yet. Challenge trials will also need to wait SARS-CoV-2 culture and viral dose confirmation. By then, therapeutics for treating COVID (beyond *Remdesivir*) might prove efficacious. But we shall argue that even now, the risk, which is real in SARS-CoV-2 challenge trials, is already tolerable, for four reasons that should especially resonate with HIV/AIDS advocates and activists. Therefore, the WHO Working Group (in which neither of us participated) was right to consider SARS-CoV-2 vaccine challenge trials permissible when conducted ethically.

The ideas that follow build upon the pioneering effort undertaken throughout the course of the AIDS epidemic, especially in the first 2 decades when few options were available for people living with HIV (PLWH), as well as in recent attempts to reach a sterilizing cure or controlled drug-free remission for HIV. Throughout the AIDS epidemic, risky scientific efforts helped transform the disease and advance the well-being of PLWH. Similar ingenuity is required in the current pandemic. Below we weigh the benefits of enacting SARS-CoV-2 vaccine challenge trials expeditiously in relation to four domains: relative risk, personal autonomy, indirect medical benefits and social value.

Relative Risk

To minimize risk to participants, live SARS-CoV-2 vaccine challenge trials would need to recruit participants who, in the—likely—event of infection, would remain at relatively low fatality risk. That means, young people without any major risk factors for severe clinical cases of COVID following SARS-Cov-2 infection [1, 3–5]. Based on concurrent evidence [6], the WHO Working Group assessed SARS-CoV-2 infection fatality rate for people in their twenties at 0.03% [1]. That equals the fatality rate following live kidney donation [5, 7], a widely-supported practice given the informed consent of the donor and the expected benefit to a single recipient. In the case of SARS-CoV-2 vaccine trials, the expected societal benefit is far greater than from a single transplantation. Indeed, since the WHO Working Group published its guidance, new data suggest a *lower* infection fatality rate for people in their twenties—0.007% [8], less than a quarter the fatality rate following kidney donation. And these figures cover both healthy and unhealthy people in their twenties, so if recruitment focuses, as it should [1, 3–5], only on those without known major risk factors for severe COVID following infection, risk of death will surely go down further. The AVAC and TAG Statement overlooks the targeted nature of recruitment to challenge trials. At one point, it warns about "a live challenge for a significant number of those at risk in a disease with a currently estimated case fatality rate (CFR) greater than 1 percent." [2] But in assessing the challenge, what matters is the risk of fatality among the low-risk subpopulation that it would

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recruit, and not the risk of fatality in the general population, or those at special risk.

Personal Autonomy

Enacted with healthy volunteers, Phase 1 studies (including studies for new vaccines) also have higher mortality rates than the latest figure we mentioned above [9], as do some of the interventions recently deployed in cure-related HIV research, enacted with participants who were stable on ART [10]. The ethical justification for all these risky studies is, in part, the free and informed consent of volunteers [11–13]. Just like these other risky studies, SARS-Cov-2 challenge trials will *not* enlist war prisoners, incarcerated people, children, or adults with compromised decisional ability. Rather, they would be preceded by thoroughgoing procedures to verify the comprehension of risks, benefits, and alternatives among non-coerced cognitively-able adults, as delineated e.g. in the Belmont Report [14], which guides all US human subjects research.

Willingness to contribute to risky experimentation has been a hallmark of the HIV-affected community for decades. Long-term survivors of HIV who were infected prior to the development and implementation of HAART have recounted how any medical approach (Chinese cucumbers included) would have been undertaken at the time in order to survive [15]. We owe treatments to thousands who were willing to engage in early trials toward them. Indeed, millions around the world continue to dose ART daily with scarce indication of its long-term effects, e.g. on older adults living with HIV [16]. Surely, volunteers' consent to participate in at least some of these trials, and patients' consent to use these relatively novel technologies, were sometimes valid, notwithstanding risks and uncertainties.

Shortly after HIV sterilizing cure trials transplanted allogenic stem cell in participants, with well over a thousand times the fatal risk of SARS-Cov-2 infection in healthy young participants [17, 18], AIDS activist David Evans interviewed the participants of these risky trials and concluded, "We should recognize their great capacity to understand the risks they may confront as research participants and, after a careful ethical and scientific review, respect the motivations of those who decide that the benefits of knowing that their contributions may help others outweighs the risks" [19].

Still, when it comes to SARS-Cov-2 challenge trials, the AVAC and TAG Statement summarily questions the possibility of informed consent:

> In recent times, live pathogen challenge trials have been conducted in diseases where a safe, effective approved treatment is available, or for which pathogenesis and risks are reasonably well characterized. That is not the case for COVID-19, which means that adequately communicating about and assessing potential risks and benefits of participating in a challenge study and ensuring appropriate informed consent may be impossible.

It is true that scientists have only limited understanding of SARS-Cov-2 and COVID-19 risks, but informed consent can be 100% valid when scientists' understanding is limited. If ample scientific understanding were required to keep consent valid, then whenever older science became obsolete, we would have to condemn earlier studies for alleged invalid consent—an absurdity. First-in-human trials, including *any* testing of new vaccines, would always be wrongful—another absurdity. What informed consent requires is that scientists communicate their best concurrent understanding of relevant features of the study to participants, who then consent [20, 21]. If anything, scientists' limited understanding may make informed consent *simpler*; instead of communicating a large body of knowledge, scientists need only communicate something like "Uncertainty runs high—take it or leave it."

Alluding to people who have declared their initial interest on a website in participating in challenge trials (nearly 27,000 so far), [22] the AVAC and TAG Statement adds, "we do not believe that individuals' expressed willingness to participate in such a trial is an adequate or appropriate measure of informed consent" [2]. As a closer look at the website and forms for volunteering would reveal, this initial and entirely revocable expression of interest is not made out to constitute the actual informed consent process, which would need to be very thorough [1, 3–5]. Some of these volunteers are highly educated [22, 23], and may comprehend complex risks after proper disclosure. The Statement paternalistically questions the agency of thousands of individuals, and assumes unlikely knowledge of their decision making processes.

Indirect Medical Benefits

Challenge trials should, with some limitations, recruit in populations where many infections are expected [3, 5]. That would reduce somewhat the incremental risk from the infection in the trial. Incremental risk of medical interventions, namely, the direct risk they introduce minus any risk that they remove, arguably matters more in their assessment than their sheer direct risk. In effect, the appropriate guaranteed access to life support and to any therapeutics proven by then for challenge participants could provide an important indirect medical benefit if those are scarce in high-transmission background communities where demand surges [3]. Some calculations of challenge studies' overall effect on participants strangely ignore the incremental risks and indirect

medical benefits and focus exclusively or myopically on the direct risks to them [5]. But the overall calculation must heed these factors [3, 24], as HIV cure-related research powerfully demonstrates. In studies of HIV sterilizing cure strategies, far riskier allogenic stem cell transplantation was justified primarily by indirect medical benefits given high background risk—specifically, the crucial benefit for patients who, in addition to HIV infection, had a far more serious terminal cancer [17].

Social Value

The level of risk that is tolerable in a study with moderate social value is nothing like the one that is tolerable in a study of immense social value [25]. In risky HIV cure-related research, another part of the justification would be the global health value of a cure [12], yet the scalability and cost-effectiveness of several cure-related strategies being investigated remains unclear [26, 27]. By contrast, the supreme global health value of rolling out earlier a proven SARS-Cov-2 vaccine is beyond doubt [24, 28].

Not only is enacting timely and potentially high-impact vaccine trials important for humanity at large. It is especially important for PLWH, who may develop more severe COVID complications [29]. Many live with additional morbidities and heightened psychosocial stressors [30, 31], primarily in countries with weakened health systems [32, 33], all of which may exacerbate risk for severe COVID outcomes. While there is speculation that ART may provide protection from COVID (or that immune dysregulation itself may help) [34], 1 in 5 PLWH are unaware of their serostatus [35]. The pandemic is everywhere disrupting HIV care, and extinguishing the hope to end HIV in this decade [36–39].

Conclusion

Statements such as those of AVAC and TAG are extremely well intentioned, but WHO Guidance is correct, and SARS-CoV-2 vaccine efficacy trials must be accelerated. As scientists we know all too well that the development of interventions cannot assure 100% safety, especially given evolving knowledge of emerging infections. Without risk, science would never advance. One of us witnessed the ravages of AIDS on his own social circle prior to 1996, and remembers all too well the desperation for identifying treatments so as to save lives. Today, we should all feel that same urgency.

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