Revised UNAIDS/WHO Ethical Guidance for HIV Prevention Trials

The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) recently released a new version of their guidance document *Ethical Considerations in HIV Prevention Trials.* A 12-month collaborative process formed the basis of the revised guidance points. Representatives of communities with an increased risk of acquiring HIV infection, regulatory authorities, manufacturers, prevention researchers, trial designers, trial sponsors, relevant funders, biostatisticians, and ethicists participated in the revision process. The participants reviewed the existing guidance points from previous versions and drafted new ones that were further developed in an iterative process between the participants, their wider networks, and a writing group for this guidance document in 2020, published by UNAIDS and WHO in January 2021. The resulting revised guidance addresses from the perspective of UNAIDS/WHO essential ethical elements for the development of safe and effective HIV prevention interventions.

Significant Changes
Virtually all guidance points (eTable in the Supplement) underwent major changes from the previous versions, some were merged, others were newly added. This Viewpoint highlights the changes that specifically relate to one or more reasons for revision.

First, the first guidance point of 2012 was reformulated to emphasize that despite the availability of PrEP, the world is still far from a target of fewer than 200,000 new infections per year by 2030. There are still more new HIV infections each year than there are deaths among all people living with HIV and so the total number of people living with HIV continues to increase. Lifelong treatment also presents challenges for individuals, clinicians, and for health budgets. Without more effective primary prevention, the HIV epidemic will not be controlled. The ethical tenets of justice and beneficence mean that research that will lead to the development of new primary HIV prevention methods remains essential. Furthermore, the first guidance point was revised to make it clearer that the development of new HIV prevention methods must be a collaborative process. Collaboration has become more important given the complexity of the development of HIV prevention methods and the need to develop prevention methods in an ethically responsible way. Moreover, the revised guidance document emphasizes that developing and funding the development pathway of HIV prevention methods starts right after early proof of concept and is essential to develop methods that also have a potential for being introduced in practice later.

Second, the guidance point on community partnership (GP2) was revised, highlighting the importance of equal partnerships among research teams, trial sponsors, and key populations, potential participants and community members who live in settings where trials are taking place. HIV prevention methods are needed that are relevant for a wide variety of populations, including adolescent girls and young women, men, pregnant women, and the key populations: men who have sex with men, sex workers, transgender and other gender diverse persons, people who use or inject drugs, and incarcerated individuals. An increasing recognition of the importance of community advisory boards and involvement of people directly affected by the challenges of HIV prevention will enhance the ethical design and implementation of trials, in line with the Greater Involvement of People Living With HIV declaration.

Third, a new guidance point was developed that considers fair and inclusive selection of study populations.

It is hoped that these revised guidance points will stimulate progress in research for novel HIV prevention methods in a scientifically and ethically responsible manner.

Reasons for Revisions
Several developments necessitated UNAIDS/WHO to revise their guidance from 2007 and 2012. First, the availability of oral preexposure prophylaxis (PrEP) and the anticipated development of other highly effective HIV prevention tools raise the standards for prevention, which has rendered the design and ethical aspects of HIV prevention trials more complex. Second, although PrEP is highly effective for preventing HIV, adherence can be challenging for some people, which highlights the need for a wider choice of preventive methods. Third, it remains a dilemma that HIV prevention trials must be carried out in populations with a high incidence of HIV infection. Individuals in such populations often live in "social or political contexts of - vulnerability," meaning social and political factors such as criminalization, systemic racism, and housing instability that may render them vulnerable. Although research into new preventive methods may be responsive to the health needs and priorities of these populations, additional guidance on more specific protections for individuals living in these contexts needed to be developed.
(GPS). Some HIV prevention products are designed and developed for particular groups or routes of transmission. Although anticipated biological interactions may lead to safety reasons for excluding individuals and groups, the guidance point emphasizes that arbitrary exclusion of individuals and populations on the basis of characteristics such as age, pregnancy, and gender identity must be avoided.

Fourth, the guidance point on vulnerability (GP6) was revised to emphasize that persons and groups should not be labeled as vulnerable but rather the emphasis should be on the social or political contexts in which people live that may render persons or groups vulnerable. Moreover, people may live in more than one context of vulnerability, including the criminalization of drug use and sex work, homophobia, and housing instability. At the same time, those who live in these contexts may also benefit most from new prevention methods. The revised document recognizes that participation in HIV prevention trials has complex implications that may exacerbate potential harms, for example, through inadvertent disclosure of activities criminalized by the state. The document emphasizes the need to mitigate harms and to balance specific protections against potential overprotection.

Fifth, the guidance point on standard of prevention was revised given the developments over the past decade and in particular the discovery of the efficacy of PrEP (GP11). The guidance point now clarifies that “researchers and trial sponsors should, at a minimum, ensure access to the package of prevention methods recommended by WHO for every participant throughout the trial and follow-up, including during any pre-enrolment or ‘run-in’ period prior to randomization, and in cohort studies set up to establish the feasibility of subsequent prevention trials.”

Ensuring access to a prevention method, such as PrEP, does not preclude participants from choosing NOT to use the method. For example, the Mosaico vaccine trial (NCT03964415) is specifically recruiting participants who, at the time of recruitment, decline the offer of PrEP. In the DISCOVER trial (NCT02842086) the existing PrEP medicines containing tenofovir disoproxil fumarate could not be offered to all participants, because the experimental product tenofovir alafenamide is metabolized to the same active product and cannot therefore be coadministered. Also in the HPTN 083 (NCT04692077) and HPTN 084 (NCT03164564) studies of long-acting cabotegravir injections for PrEP, oral PrEP has not been provided to all participants because the systemic antiretroviral mechanism of action of both parenteral cabotegravir and oral tenofovir/emtricitabine allowed for a direct comparison, without providing the proven prevention medicine to all participants.

The guidance point also recognizes that “in some circumstances, there may be a lag between WHO recommending a new product and it being manufactured commercially. In these situations, it may not be possible to include this new product in the standard of prevention until manufacturing capacity has been established and product is available.”

The document also states that departures from the WHO standard package of HIV prevention, such as outlined in the examples above, “can be justified only if relevant stakeholders, inclusive of community stakeholders, are meaningfully engaged and accept a compelling scientific, biological or manufacturing rationale for the departure from the recommended standard. Any departure from the standard should be explicitly approved by the research ethics committee.”

The guidance points should be a valuable resource for research ethics committees when reviewing HIV prevention trials. It is hoped that these revised guidance points will stimulate progress in research for novel HIV prevention methods in a scientifically and ethically responsible manner and so help to “advance the response towards the 2030 HIV prevention goal.”

ARTICLE INFORMATION
Published Online: January 27, 2021. doi:10.1001/jama.2021.0258
Conflict of Interest Disclosures: Dr van der Graaf reported she is a member of the independent Bioethics Advisory Committee to Sanofi. This committee does not advise on the ethics of HIV prevention trials. Dr Godfrey-Fausset reported grants from the Bill and Melinda Gates Foundation to support the meeting in November 2019 and UNAIDS salary outside the submitted work. No other disclosures were reported.
Disclaimer: The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.
Additional Contributions: The steering committee who organized the revision process of the 2012 UNAIDS guidance document “Ethical considerations in HIV preventive vaccine trials” and drafted the revised version of 2020 consisted of Peter Godfrey-Fausset (UNAIDS), Andreas Reis (WHO), Michelle Rodolph (WHO), Rosalind Coleman (UNAIDS) Emily Christie (UNAIDS), Rachel Baggaley (WHO), Johan Velckermans (WHO), Emer Cooke (WHO), and Rieke van der Graaf (University Medical Center Utrecht) as the scientific writer. The committee worked under the supervision of Meg Doherty (WHO), Soumya Swaminathan (WHO), and Peter Glys (UNAIDS). The 79 meeting participants provided comments and helped to shape the final version of the guidelines.
Additional Information: Dr van der Graaf is the scientific writer of the revised UNAIDS/WHO ethical guidance document on HIV prevention trials.

REFERENCES