

## Commentary

# How Bioethics is Complementing Human Rights in Realizing Health Access for Clinical Trial Participants: The Case of Formative PrEP Access in South Africa

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Following the demise of apartheid, human rights in South Africa are now constitutionally enshrined.<sup>1</sup> The right to health in South Africa's Constitution has been credited with transforming the lives of millions of people by triggering programmatic reforms in HIV treatment and the prevention of mother to child transmission (MTCT) of HIV.<sup>2</sup> However, a constitutionally enshrined right to health offers no guarantee that clinical trial participants will enjoy post-trial access to beneficial interventions. Using access to HIV pre-exposure prophylaxis (PrEP) in South Africa as an example, this paper argues that adherence to bioethics norms could realize the right to health for trial participants following the end of a clinical trial.

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## South Africa's HIV policy landscape

In recent years, progressive treatment policies on the part of the South African government have resulted in more people qualifying for earlier treatment.<sup>3</sup> Generous donor funding from mechanisms such as the Global Fund for HIV, TB, and Malaria and the US President's Emergency Fund for AIDS Relief (PEPFAR) have also enabled HIV policy reforms.<sup>4</sup> Such funding and policy changes have resulted in the percentage of infected people eligible for HIV treatment climbing from 7% in 2007 to 84% in 2010.<sup>5</sup> From 400,000 people on treatment in 2004, South Africa today boasts the world's largest HIV treatment program, with an estimated 3 million individuals on HIV treatment as of May 2015, representing approximately 30% of the global total.<sup>6</sup> The government has recognized that its growing treatment program must be supplemented by a wide range of prevention modalities, including massive condom distribution, HIV counselling and testing, sexually transmitted infection management, and medical male circumcision.<sup>7</sup>

Truvada, a licensed HIV treatment drug, has been found to reduce the risk of HIV infection by up to 92%.<sup>8</sup> To date, the US Food and Drug Administration has licensed Truvada as a HIV pre-exposure prophylaxis (PrEP) agent, and the US Centers for Disease Control and the World Health Organization have published comprehensive PrEP clinical guidelines.<sup>9</sup> Notwithstanding these factors, South Africa's drug regulatory authority is yet to license Truvada as a PrEP agent and the government is yet to commit to PrEP adoption. Seen in this context, the right to health has failed to ensure that PrEP trial participants in South Africa enjoy post-trial access to PrEP.

### The right to health and its shortcomings in ensuring post-trial access to study interventions

In South Africa's landmark 2002 Constitutional Court case *Minister of Health and Others v Treatment Action Campaign and Others*, the

Treatment Action Campaign (TAC) and various other civil society organizations and individuals challenged the government's limited dispensation of nevirapine, a drug known to reduce the risk of mother-to-child transmission (MTCT) of HIV.<sup>10</sup> At issue before the Court was the constitutional right of pregnant mothers to have access to public health care services, the right of their newborn children to be afforded special protection, and the government's constitutional obligation to plan and implement an effective, comprehensive, and progressive program for the prevention of MTCT throughout the country. In handing down its judgment, the Court ordered the government, inter alia, to remove the restrictions that prevented nevirapine from being made available for the purpose of reducing the risk of MTCT of HIV at public hospitals and clinics that were not research and training sites, and to expedite the use of nevirapine for the purpose of reducing the risk of MTCT of HIV. Given that the provision of nevirapine to HIV-infected pregnant mothers is a form of PrEP for newborn infants, the Treatment Action Campaign case is significant as it established that: (a) the right to access health could trigger health policy reform in South Africa, and (b) the right to health could apply to HIV prevention. That said, States are only required to realize socio-economic rights—such as the right to health—progressively, taking into account the State's available resources. To this end, South Africa's Constitutional Court has held that "...it is impossible to give everyone access even to a 'core' service immediately."<sup>11</sup> Accordingly, if a State does not have the resources to immediately provide access to an efficacious intervention, it cannot be compelled to do so. This holds especially true if a product or drug is still awaiting licensure. The obligation to realize the right to health generally binds States, and not non-state actors, such as trial sponsors and investigators. These factors speak to the limits of human rights as a time-sensitive post-trial access mechanism for trial participants. To address this shortcoming, bioethics norms could ensure that eligible trial participants enjoy post-trial

access to beneficial trial interventions for a limited extended duration.

### Bioethics and post-trial access obligations

Controversial randomized clinical trials conducted in Africa in the mid-1990s spurred growing appreciation for the principle that a person who participates in a trial should have a chance to benefit from what is learned from the trial.<sup>12</sup> By 2000, the World Medical Association (WMA) and the Council of International Organization of Medical Sciences (CIOMS) took the lead on providing ethical guidance on the issue of post-trial access to beneficial interventions. In 2013, the WMA published the latest iteration of its guidance document, the *Declaration of Helsinki*. Paragraph 34 states:

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.<sup>13</sup>

Post-trial access to study interventions is governed by several provisions in the 2002 iteration of the *CIOMS Guidelines*. *CIOMS* Guideline 5 states:

Before requesting an individual's consent to participate in research, the investigator must provide (the research subjects) the following information (...) whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them.<sup>14</sup>

*CIOMS* Guideline 10 states:

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort

to ensure that...any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

In 2000, WHO published its *Operational Guidelines for Ethics Committees that Review Biomedical Research*.<sup>15</sup> In outlining proposed elements of review, WHO recommends that ethics committees should consider, among other factors: (i) the criteria for extended access to, the emergency use of, and/or the compassionate use of study products, and (ii) a description of the availability and affordability of any successful study product to the concerned communities following the research.<sup>16</sup> At a domestic level, South Africa's national health research ethics guidance instrument, *Ethics in Health Research: Principles, Structures, Processes*, which was revised in 2015, endorses the 2013 iteration of the *Declaration of Helsinki*.<sup>17</sup> The *CIOMS* Guidelines are currently undergoing revision.

In the years since the publication of the above guidance documents, debate in bioethics literature has largely centered on the notion of "reasonable availability" and "fair benefit" in relation to the wider host community or host country.<sup>18</sup> However, none of the above guidance documents stipulates timeframes to realize post-trial access. Such an omission recognizes that drug regulatory authorities may require the results of additional studies before they license the intervention, and before policy makers adopt the intervention for use in the public sector. Such a process typically takes years. Accordingly, realizing post-trial access must, by necessity, center on trial participants first and foremost. As a result, expanded access mechanisms such as rollover studies, open-label extensions, implementation trials, and demonstration projects are increasingly being used to meet post-trial access obligations in relation to trial participants, and occasionally, some non-trial participants too.<sup>19</sup> Such a strategy has been used to realize post-trial access in South Africa, where eligible trial participants of the CAPRISA 004 efficacy trial enjoyed continued access to Tenofovir gel as a result of their participation in the follow-up CAPRISA 008 implementation trial.<sup>20</sup> Similarly, South African trial participants of the

iPrEx efficacy trial enjoyed post-trial access to oral PrEP because of their participation in the follow-up iPrEx Open Label Extension study.<sup>21</sup>

While ethical norms have pressured sponsors and investigators to realize post-trial access of beneficial agents, access mechanisms such as implementation trials and open label extension studies only offer post-trial access to beneficial interventions for a limited duration. For example, iPrEx OLE study participants, globally, lost their access to PrEP at the conclusion of the follow-up open label extension trial.<sup>22</sup> However, as Truvada is licensed in South Africa as a treatment drug, iPrEx study participants in South Africa can access Truvada off-label through the private sector. This is not possible for participants in countries where Truvada is not licensed, even as a treatment drug.<sup>23</sup> Given the negative results of the Phase 3 FACTS 001 trial because of poor adherence on the part of trial participants, it is possible that Tenofovir gel will not be licensed in South Africa or anywhere else as a topical PrEP, despite its efficacy being demonstrated in the earlier Phase 2b CAPRISA 004 trial.<sup>24</sup> Accordingly, the participants of CAPRISA 008 may not enjoy long-term access to Tenofovir gel, and cannot gain off-label access as it is not licensed in South Africa or anywhere else. Furthermore, Tenofovir gel is not being produced commercially, as it was created by the drug sponsor exclusively for use in the CAPRISA 004, FACTS 001, and CAPRISA 008 trials. This speaks to the limits of post-trial access ethical obligations in realizing health access in the long term, and for bioethics and human rights to play a synergistic role in ensuring that post-trial access is initiated and sustained. To this end, post-trial access ethical obligations could help establish a continuum of access and care by facilitating health access to trial participants in the short-term—particularly before licensure—while the right to health could realize long-term, sustained access to the intervention in the public sector following licensure.

## Conclusion

While bioethics norms are not a panacea to the realization of health in all contexts, post-trial access ethical obligations enable trial participants to enjoy

post-trial access to beneficial interventions for an extended period when they would otherwise be unable to enjoy such access on human rights grounds alone. Such an outcome illustrates that bioethics norms can play an important contributory role in realizing a continuum of health access to beneficial trial interventions, in tandem with human rights norms.

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## References

1. Republic of South Africa, *The Constitution of the Republic of South Africa* (1996), Chapter 2. Available at <http://www.gov.za/documents/constitution/constitution-republic-south-africa-1996-1>.
2. L. Forman and J.A. Singh, “The role of rights and litigation in assuring more equitable access to health care in South Africa,” in C.M. Flood and A. Gross (eds.), *The right to health at the public/private divide. A global comparative study* (New York: Cambridge University Press, 2014), pp. 288-318; B. Honermann and M. Heywood, “A judgment that saved a million lives,” *The Star* (July 5, 2012). Available at <http://www.iol.co.za/the-star/a-judgment-that-saved-a-million-lives-1.1334636#.VUa-1Pmqkko>.
3. South African National AIDS Council, *National strategic plan on HIV, STIs, and TB 2012-2016* (Pretoria: South African National AIDS Council, 2012). Available at [http://www.sahivsoc.org/upload/documents/National\\_Strategic\\_Plan\\_2012.pdf](http://www.sahivsoc.org/upload/documents/National_Strategic_Plan_2012.pdf).
4. K. Bodibe, “Three billion for HIV and TB” (South African National AIDS Council, 2013). Available at <http://sanac.org.za/news/item/116-three-billion-for-hiv-tb>; United States’ President’s Emergency Plan for AIDS Relief (PEPFAR), *Partnership framework implementation plan in support of South Africa’s national HIV, STI and TB response. 2012/2013 to 2016/2017 between the Government of the Republic of South Africa and the Government of the United States of America*. Available at <http://www.pepfar.gov/documents/organization/196651.pdf>.
5. Y. Pillay, C. White, and N. McCormick, “How times

have changed: HIV and AIDS in South Africa in 2011,” *South African Medical Journal* 102 (2012), pp. 77-78.

6. A. Motsoaledi, Minister of Health of South Africa. Health budget speech 2015/16, May 5, 2015. Available at <http://www.gov.za/speeches/minister-aaron-motsoaledi-health-dept-budget-vote-201516-5-may-2015-0000>; L.G. Bekker, F. Venter, K. Cohen, et al., “Provision of antiretroviral therapy in South Africa: The nuts and bolts,” *Antiviral Therapy*, 19 Suppl 3 (2014), pp. 105-116.

7. A. Motsoaledi, Minister of Health of South Africa. Health budget speech 2014/2015, July 23, 2014. Available at <http://www.health-e.org.za/wp-content/uploads/2014/07/Minister-of-Health-Budget-Vote-Speech-2014-15-.pdf>.

8. R.M. Grant, J.R. Lama, P.L. Anderson, et al., “Preexposure chemoprophylaxis for HIV prevention in men who have sex with men,” *New England Journal of Medicine* 363 (2010), pp. 2587-2599.

9. United States of America Centers for Disease Control, *Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guidelines* (Atlanta: CDC, 2014). Available at <http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf>; World Health Organization, *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations* (Geneva: WHO, 2014). Available at <http://www.who.int/hiv/pub/guidelines/keypopulations/en/>.

10. *Minister of Health and Others v Treatment Action Campaign and Others*, 2002 (10) BCLR 1075.

11. *Ibid.*, Paragraph 35.

12. M. Angell, “The ethics of clinical research in the Third World,” *New England Journal of Medicine* 337 (1997), p. 847; P. Lurie and S.M. Wolfe, “Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries,” *New England Journal of Medicine* 337 (1997), p. 853; H. Varmus and D. Satcher, “Ethical complexities of conducting research in developing countries,” *New England Journal of Medicine* 337 (1997), p. 1003; C. Grady, “The challenge of assuring continued post-trial access to beneficial treatment,” *Yale Journal of Health Policy, Law, and Ethics* 5/1 (2005), p. 15. Available at <http://digitalcommons.law.yale.edu/yjhple/vol5/iss1/15>.

13. World Medical Association, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

14. Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) International Ethical Guidelines for Biomedical Research Involving Human Subject, (Geneva, CIOMS, 2002) Available at: [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf).

15. World Health Organization, *Operational Guidelines for Ethics Committees That Review Biomedical Research* (Geneva, WHO, 2000). Available at <http://www.who.int/tdr/publications/documents/ethics.pdf>.

16. *Ibid.*, paragraphs 6.2.3.6 and 6.2.6.6.

17. Paragraph 1.8.3, National Department of Health, South Africa, *Ethics in Health Research: Principles, Structures*

*Processes, Second Edition* (Pretoria: South African Department of Health, 2015). Available at [http://research.ukzn.ac.za/Libraries/Research\\_Document/Ethics\\_in\\_Health\\_Research\\_Final\\_A\\_used.sflb.ashx](http://research.ukzn.ac.za/Libraries/Research_Document/Ethics_in_Health_Research_Final_A_used.sflb.ashx).

18. Participants in the 2001 Conference on ethical aspects of research in developing countries, “Fair benefits for research in developing countries,” *Science* 298 (2002), pp. 2133-2134.; A. J. London and K.J.S. Zollman, “Research at the auction block: problems for the fair benefits approach to international research,” *Hastings Center Report*, 40/4 (2010), pp. 34-45.

19. M. Warren, “It works! Now what? Open label extensions, implementations studies, and demonstration projects,” Presentation at the TFV gel implementation follow-on studies meeting, September 18, 2013. Available at <http://www.nemus-hiv.net/resources/category/1-documents?download=17:avac-after-efficacy-2013>; R. Palacios, “Post-trial access and the new version of the Declaration of Helsinki,” *Colombia Médica*, 44/4(2013), p. 206-207. Available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4001993/>; J. Baeten, Getting to MTN-025/HOPE: The Why, How, and What of an Open Label Extension after ASPIRE. MTN-025 / HOPE Breakout Session, October 26, 2014, Cape Town, South Africa. Available at [http://www.mtnstopshiv.org/sites/default/files/attachments/1\\_HOPE%20breakout%20session%20CT%20Oct%202014%20-%20Baeten.pdf](http://www.mtnstopshiv.org/sites/default/files/attachments/1_HOPE%20breakout%20session%20CT%20Oct%202014%20-%20Baeten.pdf); L. Letvak, “Session III: Lessons Learned, Industry Case #2,” Post-Trial Responsibilities Conference, Harvard University, September 18, 2014. Available at [http://mrct.globalhealth.harvard.edu/files/mrct/files/2014-09-18\\_harvard\\_mrct\\_pta\\_conf\\_slides\\_for\\_session\\_3.pdf](http://mrct.globalhealth.harvard.edu/files/mrct/files/2014-09-18_harvard_mrct_pta_conf_slides_for_session_3.pdf).

20. Q. Abdool-Karim, S.S Abdool-Karim, J.A Frohlich, et al, “Effectiveness and safety of Tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women,” *Science* 329 (2010), pp. 1168-1174; CAPRISA, “CAPRISA 008 Executive Summary.” Available at: <http://www.caprisa.org/>.

21. R.M. Grant, J.R. Lama, P.L. Anderson, “Preexposure chemoprophylaxis for HIV prevention in men who have sex with men,” *New England Journal of Medicine* 363 (2010), pp. 2587-2599; R.M. Grant, P.L. Anderson, V. McMahan, et al, “Results of the iPrEx open-label extension (iPrEx OLE) in men and transgender women who have sex with men: PrEP uptake, sexual practices, and HIV incidence,” *AIDS* 2014, 20th International AIDS Conference. July 20-25, 2014, Melbourne, Australia. Abstract TUAC0105LB. Available at <http://pag.aids2014.org/abstracts.aspx?aid=11143>.

22. B. Ryan, “Thanks for nothing: iPrEx volunteers shut out of PrEP’s success,” (May 4, 2014). Available at [http://www.poz.com/articles/iPrEX\\_PrEP\\_401\\_25546.shtml](http://www.poz.com/articles/iPrEX_PrEP_401_25546.shtml).

23. *Ibid.*

24. H. Rees, S. Delany-Moretlwe, D. Baron, et al, “FACTS 001 Phase III trial of pericoital tenofovir 1% gel for HIV prevention in women,” CROI 2015, February 23-26, 2015, Seattle, Washington, USA. Oral late breaker abstract 26LB. Available at <http://www.croiconference.org/sessions/facts-001-phase-iii-trial-pericoital-tenofovir-1-gel-hiv-prevention-women>.