The ethics of expanding access to cheaper, less effective treatments

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In 1994, the US Food and Drug Administration (FDA) approved stavudine as a treatment for HIV/AIDS at 40 mg twice a day. Stavudine quickly became standard care in high-income countries as part of highly active antiretroviral therapy (HAART).[1] In 2006, WHO recommended using a lower dose of this drug (30 mg twice a day). Although effective in reducing viral load, stavudine has serious side effects including peripheral neuropathy, lactic acidosis, and lipodystrophy. An alternative drug zidovudine, also has serious side effects such as anaemia, and is more expensive than stavudine. In 2001, the FDA approved tenofovir for treatment of HIV/AIDS. Concerned about the side effects of stavudine and zidovudine, in 2013 WHO recommended tenofovir-based antiretroviral therapy (ART) as the preferred option in low-income and middle-income countries. They recommended against using stavudine-based ART, but for decision makers to consider zidovudine if tenofovir was not available.[2]

In South Africa 6·8 million people have HIV. Of these, 3·1 million are estimated to be receiving ART. Thus, according to WHO's 2015 HIV treatment criteria, 3·7 million South Africans are eligible for ART but are not receiving it.[3] Because of the comparatively high cost of tenofovir and the millions of untreated patients, South African researchers proposed assessing low-dose stavudine (20 mg twice a day) as an alternative to tenofovir.[4] However the proposal was controversial, with some researchers and advocates arguing that stavudine should never be used[2] and others suggesting the use of cheaper stavudine early on in treatment before its side effects are likely to develop and then later switching to more expensive treatments.[1] Others have recommended continuing to use stavudine but monitoring for side effects. Finally, some have suggested shifting to zidovudine, whose cost and toxic effects are intermediate between tenofovir and stavudine.

The choice between different HIV/AIDS drugs affects millions of people. According to WHO's 2015 recommendations,[3] all 35 million people with HIV worldwide should receive ART. Unfortunately, at most only 15 million patients with HIV are receiving ART.[5] According to UNAIDS, only 41% of all adults with HIV were receiving ART at the end of 2012.[6] Current tenofovir-based treatment costs an estimated US$150 per person per year for drugs alone, whereas stavudine-based therapy costs about $60 per person per year.[7] At these prices, to transition just 15 million patients receiving stavudine-based ART to tenofovir would annually cost $1·35 billion. To cover all 20 million untreated HIV patients with tenofovir-based ART would cost an additional $3 billion. UNITAID has offered $77 million to transition patients to tenofovir, but even this would only cover fewer than a million of such transitions.[7]

Similar questions arise regarding other diseases, such as whether to treat epilepsy with phenobarbital or pricier newer drugs,[8] which antibiotics to prescribe for bacterial meningitis,[9] whether to diagnose cervical dysplasia with the human papillomavirus (HPV) test or with acetic acid, and whether to approve the re-use of medical devices.[10] WHO has taken contrasting positions in different cases. For example, WHO endorses the use of cheaper acetic acid rather than HPV tests in low-income countires, but rejects the re-use of medical devices in these same countries.

These examples raise a fundamental question of justice in global health. Is it ethically preferable to provide a larger number of people with cheaper treatments that are less effective (or more toxic), or to restrict treatments to a smaller group to provide a more expensive but more effective or less toxic alternative? As WHO's contrasting positions indicate, this debate has persisted unresolved.

This debate could be resolved by use of three foundational principles of justice: utility, equality, and priority for those worst off. These three principles favour expanding access to less effective or more toxic treatments rather than requiring the worldwide best treatment in all settings. We selected these principles because the debate is a question of population-level ethics rather than personal or professional ethics, in which bioethical principles of autonomy, beneficence, and non-maleficence are typically invoked.

Utilitarian reasoning aims for the greatest good for the greatest number. In medical contexts, this reasoning means maximising the medical benefit per unit of money spent. Utilitarianism favours expanding access to low-cost alternative drugs. Of course, in the decision between expansion of access to second-best treatments and a requirement that any treatment offered be the best available, the details matter. Sometimes more expensive, more effective interventions are more cost-effective, or expansion of access to medical treatments from 90% to 100% of people is very costly. However, if some people are receiving no treatment at all, expanding access will likely be the most cost-effective option.

The equality principle emphasises similar treatment for similar cases. Equality is typically invoked to support provision of a standard of care in low-income and middle-income countries equal to that in high-income countries. Farmer and Gastineau contend that "efficiency cannot trump equity in the field of health and human rights".[11] However, this approach reduces inequality among

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treated patients at the expense of causing far greater inequality between treated and untreated patients. When not enough funding is available to provide tenofovir-based ART to all 35 million patients with HIV, a requirement that any care provided be the best available will leave millions untreated.[9] Provision of cheaper, less effective or more toxic treatment to many who would otherwise go untreated will better decrease inequality than provision of the best care to a few patients.

Finally, patients receiving no treatment are medically worst off, and highly likely to be worse off in terms of overall justice, compared with those who receive treatment. To provide untreated patients with effective treatment, albeit with additional toxic effects, is a higher priority than to provide more effective or safer treatments to patients already receiving effective, if moderately toxic, treatments. As a previous WHO director, Gro Harlem Brundtland, stated, "if services are to be provided for all then not all services can be provided. The most cost-effective services should be provided first".[12]

Objections have been raised against the approach of providing more people with less costly but less effective or more toxic treatments. Some object that enough money is available to simultaneously expand access and improve efficacy and safety. Obtaining that money is only a matter of will, not of overcoming scarcity.

The worldwide gross-domestic product is about $78 trillion, representing more than enough money to provide adequate care for everyone. Unfortunately, global health assistance has remained relatively flat since 2010,[9] and the so-called golden age of growing global health assistance seems to have ended.[9,12] Until additional funding can plausibly be identified and allocated, the principle that any care provided be the best available means that millions of people with HIV/AIDS, especially in sub-Saharan Africa, will remain untreated.

Even if the funds needed were available, whether HIV/AIDS should be the top global health priority is unclear. Currently, global assistance is $1·4 billion for tuberculosis, $2·4 billion for malaria, and $200 million for intestinal worms, schistosomiasis, and other neglected tropical diseases.[12] The difference in cost between provision of stavudine and of tenofovir to all eligible but currently untreated individuals greatly exceeds what is spent on tuberculosis and neglected tropical diseases worldwide.

Others claim that a requirement for all care provided to be the best available will reduce the cost of the best treatments. They cite the application of such requirements to previous HIV/AIDS treatments that forced down costs, asserting that reduced prices will allow everyone—in the long term—to be treated with the world's best interventions.[2,13]

Whether requiring the expanded use of the world's best treatments will lower their market prices is an empirical question,[2,4] but there is no guarantee. The outcome depends on the treatment in question, the appeal of the patients to the public, the power of interest groups, media interest, and other factors. Furthermore, even if removal of the second-best treatment option did force down costs, because pharmaceutical companies would have to choose between reducing prices or leaving people untreated, it is manipulative to deny people treatment to pressure pharmaceutical companies to lower prices. Presumably, patients with HIV/AIDS might prefer stavudine-based ART to no ART. Even if some patients might refuse stavudine as a protest against pharmaceutical companies, this does not licence the endangerment of patients who did not consent to this strategy.

By contrast, many others object that providing less than the best available treatment wrongs patients. They contend that cheaper, less effective treatments cause patients needless suffering and deprive them of what they are entitled to receive.[2] Patients currently receiving tenofovir are entitled to continue receiving it.

This objection ignores the suffering of patients who go untreated. To require that the standard of care in high-income countries be used worldwide favours patients with HIV/AIDS and other diseases that exist in high-income countries and creates a bias against improving care for patients in low-income and middle-income countries with diseases, such as malaria and parasites, which are rare in most high-income countries.[14,15] To deny low-income and middle-income countries the opportunity to use cheaper treatments for HIV/AIDS and allocate the saved money to address health threats that are not prevalent in high-income countries makes no more sense than denying people who are ill access to a toxic but curative medicine on the basis that healthy people would refuse it. Additionally, global health actors must judge the needs of all, and not favour incumbent recipients of benefits. Other services, such as disaster response teams, can be shifted from current beneficiaries to a more pressing challenge, and so too should availability of funds for medical interventions.

In conclusion, the provision of less effective or more toxic interventions is justified by the principles of utility, equality, and priority for those worst-off. Advocates and WHO are mistaken to demand that medical care provided in low-income and middle-income countries should be the same as in high-income countries. Instead, expansion of access to treatments that are effective, even if not the most effective, should be the standard in global health.

Contributors

Both authors wrote, revised, and approved the manuscript.

Declaration of interests

EJE is represented by the speaking group Leigh Bureau who frequently book him for paid speaking engagements across the health-care spectrum. EJE is a venture partner in the venture capital firm Oak HCFT, which has no investments in global health companies. GCP declares no competing interests.

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