The NEW ENGLAND JOURNAL of MEDICINE

Perspective

OCTOBER 26, 2017

HIV Drug Resistance — An Emerging Threat to Epidemic Control

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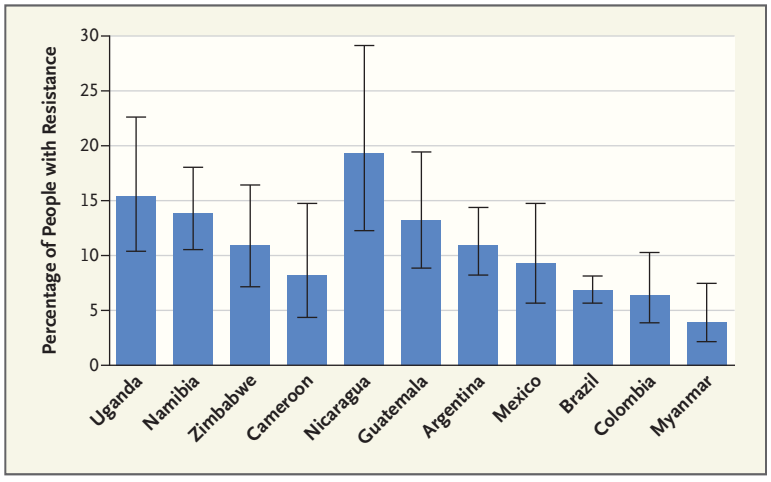
There are now an estimated 19.5 million people worldwide living with HIV and receiving antiretroviral therapy (ART). That's approximately half of all people thought to be living with the virus in 2017 — an extraordinary achievement in global health and human solidarity. The United Nations agencies, led by the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), have committed to the goals of ending the AIDS pandemic as a public health threat by 2030 and ensuring that by 2020, 90% of people with HIV infection know they have it, 90% of those infected are receiving ART, and sustained viral suppression is achieved in 90% of those receiving treatment.[1] This last goal is critically important both to individual health and survival and to epidemic control of HIV, since data continue to mount showing that viral suppression greatly reduces the risk of continued transmission — whether sexual or perinatal — of the virus.

It would arguably be enormously difficult to achieve epidemic control simply by expanding ART. Too many people and communities — from adolescents in Africa, to sexual minorities and transgender people in many countries, to injection-drug users in Eastern Europe and Central Asia — are currently excluded from care. We believe that enhanced primary prevention of infection, by means of targeted use of preexposure prophylaxis (PrEP) for people at substantial risk and probably a preventive vaccine, will be required for ultimate control. Nevertheless, treatment can have — and is having — substantial effects on the rate of new infections, including in some of the world's most HIV-burdened countries, as shown by recent data from Swaziland.[2] The emergence of HIV drug resistance is a very real threat to these gains.

A recent report from the WHO, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the Centers for Disease Control and Prevention (CDC) showed that the prevalence of HIV drug resistance has increased from 11% to 29% since the global rollout of ART in 2001.[1] The report was based on findings from 16 surveys in 14 countries that used the WHO's recommended approach to population-based sampling for HIV drug resistance among patients in public ART programs, supplemented by data from two population-based HIV impact assessments conducted through the President's Emergency Plan for AIDS Relief (PEPFAR) in Malawi and Zimbabwe.

It is worrisome that in 6 of 11 countries surveyed — Argentina, Guatemala, Namibia, Nicaragua, Uganda, and Zimbabwe — the rate of pretreatment drug resistance surpassed 10% among people receiving ART for the first time (see graph). Here HIV drug resistance was defined as resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs), core



Pretreatment HIV Drug Resistance to Nonnucleoside Reverse Transcriptase Inhibitors in 11 Countries.

Shown are the percentages of people tested who had resistance to efavirenz or nevirapine. I bars denote 95% confidence intervals. Data are from the World Health Organization.[1]

drugs in most low- and middle-income countries' first-line regimens for HIV. Among people with past exposure to ART (those restarting treatment or women with past perinatal exposure) the rate of NNRTI resistance is even higher: 21.6% (95% confidence interval [CI], 13.8 to 32.2).[1] A recent report from South Africa revealed that among children 18 months old or younger identified through early infant diagnoses, NNRTI resistance was found in 63.7% (95% CI, 59.0 to 68.4).[1]

How significant is the increase in resistance to HIV treatment? And what can be done to mitigate it?

The WHO has proposed a five-point global action plan for monitoring, combating, and preventing drug resistance using a set of interventions and resources. The plan includes roles for communities, donors, and countries in prevention, monitoring and surveillance, research, expansion of laboratory capacity, and management and governance efforts. It outlines important, though not always easily implemented, ways to support and improve current programs. These include expanding the essential rollout of viral load monitoring capacity to ensure that patients are switched early to effective ART so that much drug resistance can be prevented, and an important focus on improving engagement in care and adherence to ART. Since HIV treatment, at least for now, continues to be daily oral therapy for life, adherence remains the Achilles' heel of therapy, as it has been for PrEP. But program failures, especially drug stock-outs and long wait times at clinics and drug dispensaries, must also be addressed, since they can undermine the efforts of even the most adherent patients.

One step beyond implementation of the WHO's proposals would be the rapid rollout to all HIV-infected people who have not yet received ART of newer regimens with higher genetic barriers to resistance. The integrase inhibitor dolutegravir, for instance, has an exceptionally high resistance barrier.[3] In patients receiving first-line treatment with dolutegravir-based ART, there has been only a single reported case of resistance selection.[4] Even in patients with virologic failure and acquired resistance to nonnucleoside-based regimens, treatment with dolutegravir and one fully active nucleoside achieved virologic undetectability rates of 82% at 48 weeks, and in those who had no response there were no emergent resistance mutations to integrase or nucleosides.

These regimens will be 20 to 50% cheaper and have fewer side effects than the WHO-recommended ones, although there have been reports of increased insomnia and other neuropsychiatric side effects (but not at the level or severity seen with other drugs and classes, including the NNRTI efavirenz). Data are accumulating on the use of such regimens during pregnancy and in patients with tuberculosis–HIV coinfection. Integrase-inhibitor–based regimens including dolutegravir are being rolled out in Botswana and Brazil, and other countries, including Kenya, Uganda, and Nigeria, are starting to adopt them. Although vigilance will be required, use of dolutegravir as first-line therapy could markedly reduce the incidence of HIV drug resistance. It will also be important to know whether the new regimens will work in patients with pretreatment drug resistance, and the data to answer that question will need to be collected as soon as practicable from these early-adopter countries.

A potential challenge to the widespread use of dolutegravir is the likely use of injectable cabotegravir, a long-acting integrase inhibitor, for both treatment and PrEP and in cases in which there is concern about cross-resistance to integrase inhibitors. Even in the confines of a randomized, controlled treatment trial, resistance to cabotegravir has occurred and

could affect the activity of dolutegravir. In PrEP studies using these formulations, some participants had detectable cabotegravir levels up to a year after their last injection. This finding has raised concern that having stopped injectable PrEP, people who contract HIV after the drug has dropped below protective levels could have integrase-inhibitor–resistant virus.

What about people with HIV who have acquired drug resistance and have not had a response to an NNRTI-based regimen? Fortunately, both integrase inhibitors and boosted protease inhibitors have been shown to be effective for this population and can lead to sustained viral suppression and improved clinical outcomes. But deployment of these regimens urgently needs to be scaled up, and countries and programs will have to balance the sometimes conflicting imperatives to expand access for untreated patients and to improve quality for those already in care whose treatment is failing.

Vulnerable populations will continue to require special attention in the era of HIV drug resistance. We have to move most quickly on the WHO's recommendations for infants and children, the population with the highest resistance rates; adolescents and young adults, for whom adherence has been challenging; and stigmatized and criminalized populations, which face formidable social and structural barriers to prevention, treatment, and care.

An audio interview with Dr. Beyrer is available at NEJM.org

Drug resistance is one of the markers of failure of HIV programs. The threat it poses is both that treatment will fail clinically in individual patients and that communities will be at risk from viremic patients whose disease continues to be infectious. Our newest and most effective prevention tool, PrEP with daily oral tenofovir–emtricitabine, is also at risk from HIV drug resistance. More robust drugs with higher resistance barriers may help solve some of these problems. But we will still face the many challenges of logistics, adherence, and the funding required to sustain the massive global treatment effort launched with the 2003 creation of PEPFAR and the Global Fund. Even in 2017, half of all HIV-infected people remain untreated.

The proposed multibillion-dollar cuts to U.S. federal funding for global health, for PEPFAR, the CDC, the U.S. Agency for International Development (USAID), the State Department, and the Global Fund, would devastate this effort and undercut many of the gains we've made against the pandemic.[5] The emergence of HIV drug resistance warrants a redoubling of our efforts, not a retreat from our commitments. But if President Donald Trump's proposed 2018 budget is any indication, U.S. leadership in global health and HIV response efforts is facing unprecedented threats.

Disclosure forms provided by the authors are available at NEJM.org.

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DOI: 10.1056/NEJMp1710608

Mandating Coverage for Fertility Preservation — A Step in the Right Direction

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Connecticut and Rhode Island recently became the first U.S. states to pass legislation requiring insurance coverage of fertility-preservation services for patients about to undergo a medical treatment — surgery, radiation, or chemotherapy — that may have deleterious effects on the gonads. Although the World Health Organization considers infertility a disease, and both the American Society of Clinical Oncology and the American Society of Reproductive Medicine recommend that patients facing fertility-compromising (gonadotoxic) therapy be counseled about fertility preser-