

As part of Cambiano and colleagues⁵ future projections of the HIV epidemic among GBMSM in the UK, they predicted a decline in annual HIV infections to around 263 in 2030 if rates of testing, ART use, and PrEP use remain as they are. Unfortunately, this is five times higher than the UK government's 2030 elimination target, reflecting that current uptake is insufficient despite the UK having already exceeded the UNAIDS 95-95-95 targets among GBMSM. Despite the free availability of HIV testing, ART, and PrEP to all GBMSM at risk of HIV, there remain practical barriers to accessing these interventions. General access to the UK's National Health Service (NHS), including difficulties with booking appointments and a lack of appointment availability, is a major issue,⁶ with sexual health services facing increased demand while undergoing large cuts in funding.⁷ These barriers need to be dealt with to increase HIV testing, ART access, and PrEP use, which this analysis projects would lead to further decreases in incidence, but, worryingly, they found that the 2030 target of fewer than 50 infections is still unlikely to be reached. However, more optimistically, other research has estimated there is a 40% chance of reaching these elimination targets with current intervention levels, while long-acting PrEP, not considered in either analysis, offers new hope.⁹

In their analyses of how much should be spent on expanding testing and PrEP to ensure they are cost effective, Cambiano and colleagues⁵ estimated that an additional £1.62 million could be spent each year to increase the rate of HIV testing by around 34% and PrEP coverage by around 55%. However, this would only be achieved if there was a 16% reduction in the cost of delivering HIV testing and PrEP. The authors conclude that this cost reduction could be achieved through the expansion of self-testing and further promotion of PrEP, with poor awareness of PrEP still a potential barrier.¹⁰ So, although increased access to HIV testing, HIV treatment,

PrEP, and coverage of condom use has brought about a large decline in HIV incidence in the UK, meeting the UK government's targets for eliminating HIV transmission will be difficult without additional funding and concerted efforts to improve general NHS systems that are currently in turmoil.⁷

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INSTI era resistance: emerging concern or marginal issue?

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Ever since resistance developed against zidovudine, we have been in a race: a drug is developed and used, HIV develops resistance to it, another drug is developed and used, and so on. This largely resistance-driven process has informed HIV drug development since its inception.¹ Although this phenomenon is not unique to

HIV, the use of specific resistance data to guide regimen design is notable. Resistance-guided regimen design is unfortunately available and guideline-recommended mostly in resource-rich settings and less so elsewhere; even where it is available in lower-income settings, it is restricted to more limited circumstances.^{2,3}

The genetic barrier to antiretroviral resistance (the ease by which resistance develops) has improved with time. It is now harder for HIV to develop resistance to newer drugs. Second-generation integrase strand transfer inhibitors (INSTIs) dolutegravir, bictegravir, and cabotegravir demonstrate this concept well, with resistance being rare in clinical trials. These advances renew optimism posed by the late Mark Wainberg, an instrumental HIV drug resistance expert, who postulated a scenario in which dolutegravir resistance cannot develop or could even be beneficial.⁴

Following PEPFAR's unprecedented global impact, the price of dolutegravir-based regimens has been reduced to US\$75 per person per year,⁵ and more recently to \$45.⁶ This antiretroviral, to which resistance might not exist, is now globally accessible to almost anyone who needs it, saving people's lives in all settings, circumstances, and vulnerabilities.

Are we finally ahead of the virus, and do we have a chance to win the race? Can we give second-generation INSTI-based regimens to all people living with HIV or to those at risk of infection and not be concerned about resistance?

In *The Lancet HIV*, Tom Loosli and colleagues⁷ present data that encourage us to exercise patience and not jump to quick conclusions. In 599 people on dolutegravir-based regimens from several real-world cohorts, they report that 23 (4%) had intermediate or high dolutegravir resistance, which was (perhaps not surprisingly) more pronounced with dolutegravir monotherapy, but also in those on dual therapy, and with nucleoside reverse transcriptase inhibitor (NRTI) resistance.

Several observations emerge from this important paper. First and foremost, although not directly addressed in it, viral failure on second-generation INSTI-based regimens is uncommon, reinforcing the advantage of global access to these highly effective antiretrovirals. As we investigate resistance, we should not lose focus on this major success and its high impact on people's lives.

Second, among those in whom therapy failed, although dolutegravir resistance was rare, it existed, and in similar proportions to the highest levels from clinical trials, representing a concerning trend.⁸ Moreover, the higher frequency in people taking dual-therapy as compared with triple-therapy regimens is also worrying, as these regimens are increasingly used

for treatment initiation and optimisation. Lastly, the increased dolutegravir resistance with NRTI resistance is particularly concerning, considering that extrapolation of data from clinical trials evaluating optimal regimens after failure of first-line therapy might lead to a questionable perception that there is little necessity for or benefit from resistance testing, due to potential diminished relevance of NRTI resistance.⁹

Third, several outstanding issues exist. Most data are from people with HIV-1 subtype B, whereas non-B subtypes predominate globally. Access to individual viral load and resistance monitoring is limited in many low and middle income and high-burden settings. And global roll-out of dolutegravir-based regimens in all therapy lines is still ongoing, and the parallel use of long-acting antiretrovirals for treatment and prevention (eg, cabotegravir) is in its infancy.

Taken together, as the essential global roll-out of dolutegravir-based therapy is expanded, data presented by Loosli and colleagues suggest that now might be a good time to also notice that dolutegravir resistance can and does occur and could potentially be even higher than anticipated. We should prepare for monitoring and minimising resistance, so that we do not fall behind in the race. The WHO HIV Drug Resistance Network is appropriately planning on doing exactly that on a population level; we should also consider making plans to expand this for individual care.¹⁰

When it comes to second-generation INSTI resistance and our concern for and attention to it, the spectrum between low and high levels might be wide. Where we end up within that spectrum depends on multiple factors, such as consistent treatment access, adherence, drug formulations, viral failure thresholds, viral load and resistance monitoring, alternative resistance mechanisms, guideline implementation, and, importantly, attention to special populations, like youth, pregnant individuals, people with tuberculosis, and those unlinked to care. We must collectively ensure that all stakeholders—including people with HIV and users of pre-exposure prophylaxis—engage in optimal efforts to address these concerns. At this point in time, we should treat HIV drug resistance in the INSTI era as an emerging concern, so that with time, it becomes a marginal issue.

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