

and a community level. As other nations grapple with implementing other harm reduction strategies, such as opening overdose prevention centres, providing safe supplies, or liberalising methadone regulations, the results of this study underscore the urgent need to ensure access to the gold standard treatment for opioid use disorder worldwide. We strongly encourage Russian policy makers to consider a more pragmatic and patient-centred and less punitive strategy to address substance use and HIV transmission.<sup>8</sup>

The results of the LINC-II trial, and the earlier LINC trial, support the expansion of integrated care and strengths-based case management for the treatment of HIV and opioid use disorder in Russia and show a potential way forward, despite the current lack of access to opioid agonist treatment.<sup>9</sup> Although other work has shown the usefulness of online platforms and other innovative approaches for the provision of harm reduction services in this setting, these initiatives will have limited success without access to opioid agonist treatment.<sup>10</sup> We commend the authors on this compelling work and propose that the current sociopolitical instability in Russia might provide an opportunity to reconsider policies and address stigma surrounding treatment of HIV and opioid use disorder. We hope that the results of the LINC-II trial lead to policy change and the removal of structural barriers to ensure that people in Russia have access to evidence-based, life-saving care in order to stem the ongoing HIV epidemic.

JR serves on the board of directors of the Drug Policy Alliance, on the data and safety monitoring board of several studies of Jeffrey Samet (but not LINC or LINC-II), had received funding from COBRE Opioids and Overdose (grant number

P20GM125507), and is a faculty member at the Providence/Boston Center for AIDS Research (grant number P30AI042853), which facilitated this work. LH and NR declare no competing interests.

\*Leah Harvey, Natasha Rybak, Josiah Rich  
lharvey@lifespan.org

Division of Infectious Diseases, The Warren Alpert Medical School, Brown University, Providence, RI, USA (LH, NR, JR); The Center for Health and Justice Transformation, The Miriam Hospital, Providence, RI, USA (JR, LH); COBRE on Opioids and Overdose at Rhode Island Hospital, Providence, RI, USA (JR, LH)

- 1 National Academies of Sciences, Engineering, and Medicine. Medications for opioid use disorder save lives. Washington, DC: National Academies Press, 2019.
- 2 McNamara KF, Biondi BE, Hernández-Ramírez RU, Taweh N, Grimshaw AA, Springer SA. A systematic review and meta-analysis of studies evaluating the effect of medication treatment for opioid use disorder on infectious disease outcomes. *Open Forum Infect Dis* 2021; **8**: ofab289.
- 3 Samet JH, Blokhina E, Cheng DM, et al. Rapid access to antiretroviral therapy, receipt of naltrexone, and strengths-based case management versus standard of care for HIV viral load suppression in people with HIV who inject drugs in Russia (LINC-II): an open-label, randomised controlled trial. *Lancet HIV* 2023; **10**: e578–87.
- 4 Herget G. Methadone and buprenorphine added to the WHO list of essential medicines. *HIV AIDS Policy Law Rev* 2005; **10**: 23–24.
- 5 Lunze K, Lunze F, Raj A, Samet JH. Stigma and human rights abuses against people who inject drugs in Russia—a qualitative investigation to inform policy and public health strategies. *PLoS One* 2015; **10**: e0136030.
- 6 Ministry of Health and Social Development of the Russian Federation, The Federal Service of Consumer Rights Protection and Human Well-Being of the Russian Federation. Country progress report of the Russian Federation on the implementation of the declaration of commitment on HIV/AIDS. 2008. [https://data.unaids.org/pub/report/2008/russia\\_2008\\_country\\_progress\\_report\\_en.pdf](https://data.unaids.org/pub/report/2008/russia_2008_country_progress_report_en.pdf) (accessed June 30, 2023).
- 7 Vetrova MV, Cheng DM, Bendiks S, et al. HIV and substance use stigma, intersectional stigma and healthcare among HIV-positive PWID in Russia. *AIDS Behav* 2021; **25**: 2815–26.
- 8 Lunze K, Raj A, Cheng DM, et al. Punitive policing and associated substance use risks among HIV-positive people in Russia who inject drugs. *J Int AIDS Soc* 2014; **17**: 19043.
- 9 Samet JH, Blokhina E, Cheng DM, et al. A strengths-based case management intervention to link HIV-positive people who inject drugs in Russia to HIV care. *AIDS* 2019; **33**: 1467–76.
- 10 Davitadze A, Meylakh P, Lakhov A, King EJ. Harm reduction via online platforms for people who use drugs in Russia: a qualitative analysis of web outreach work. *Harm Reduct J* 2020; **17**: 98.



## Crucial need for improved pharmacovigilance in pregnancy

Despite the fact that antiretroviral therapy is essential for both maternal health and prevention of new paediatric infections, information on appropriate antiretroviral drug dosing in pregnancy is often delayed until years after drug approval for people living with HIV.<sup>1</sup> Pharmacovigilance to determine the safety of drugs used in the periconception period in women of reproductive potential or during pregnancy has been scarce and fragmented between different data sources, resulting in inadequate data to assess risk, particularly for relatively rare adverse outcomes, such as fetal demise and birth defects.<sup>2</sup>

The unexpected identification of a neural tube defect (NTD) safety signal with periconception dolutegravir exposure in the Tsepamo study on birth outcomes in Botswana in 2018 brought to attention the need for reliable data on drug safety in pregnancy and improved surveillance systems to evaluate safety of new drugs that will be widely used by women of reproductive potential.<sup>3</sup> Preliminary data reporting four cases of NTD among 494 periconception dolutegravir exposures—a prevalence significantly higher than in all comparison groups—resulted in a 2018 safety alert from WHO regarding dolutegravir use in women of reproductive

Published Online  
July 25, 2023  
[https://doi.org/10.1016/S2352-3018\(23\)00146-7](https://doi.org/10.1016/S2352-3018(23)00146-7)  
See [Articles](#) page e588

potential, recommending it be prescribed only if given with effective contraception.<sup>4</sup> Given that the alert was based on a small number of events from a single study, more data were rapidly needed to support or refute the association; however, difficulty in finding additional data in a timely manner highlighted the limitations of existing pharmacovigilance systems.<sup>5</sup> With an increased number of periconception exposures in Tsepamo accumulating over several years, the safety signal resolved;<sup>6</sup> by late 2019, WHO recommended dolutegravir-based antiretroviral therapy as a preferred regimen in all adults living with HIV.<sup>7</sup>

In *The Lancet HIV*, Athena P Kourtis and colleagues<sup>8</sup> report on innovative use of commercial and Medicaid pregnancy health-care claims data in the USA from over 18 million pregnant women delivering during 2008–20, comparing incidences of NTDs and stillbirth or pregnancy loss between women living without and with HIV, stratified in over 13500 pregnancies with HIV by periconceptional dolutegravir (n=1532) and non-dolutegravir (n=12034) exposure. No significant differences in NTD prevalence were observed between periconception dolutegravir exposure versus non-dolutegravir exposure in women with HIV, or compared with women without HIV. These data support the Tsepamo study results, which now includes 9460 periconception exposures. The incidence estimates from the study by Kourtis and colleagues provide reassurance both to pregnant women and to health-care providers that there is not an elevated risk of NTD among women using dolutegravir around the time of conception.

However, despite the apparent NTD signal resolution and revised WHO recommendations, data from sub-Saharan Africa show that even after release of new guidelines recommending dolutegravir in women regardless of reproductive potential, uptake among both pregnant and non-pregnant women has been lower than that in men, resulting in women being denied access to a potent and safe drug;<sup>9,10</sup> for example, in a large cohort from 59 South African clinics, women were less likely to receive dolutegravir than were men, with the strongest effect early during the roll-out and among younger women.<sup>9</sup> Although the data from Kourtis and colleagues is reassuring, they are being published in 2023, 5 years after the original 2018 safety signal.

As new long-acting antiretrovirals for treatment and prevention are approved and introduced, improved pharmacovigilance systems are necessary to continually evaluate birth outcomes, especially for rare outcomes that require large numbers of observations; data need to be collected in limited-resource settings where most pregnant women with HIV reside and most exposures will occur. Necessary safety evidence needs to be generated as quickly as possible as new agents enter the marketplace. Crucial to pharmacovigilance is the quality, interpretability, and comparability of data. The prevalence of each outcome has a large impact on the denominator required to understand a signal; for example, rare events such as NTDs require surveillance of several thousand exposures to gain adequate precision. Standardisation of outcome definitions within and across surveillance sites is paramount. Having an appropriate comparison group and obtaining denominator data is essential to understanding any potential signal. Surveillance must include both exposed and unexposed individuals, and normal and abnormal findings, to be interpretable. Sentinel site surveillance, such as the Tsepamo study, provides a cost-effective data collection mechanism in low-resource settings, and the analysis by Kourtis and colleagues provides an example of an innovative way to use electronic databases in higher-income settings to assist in generating safety data.

LM's employer, Elizabeth Glaser Pediatric AIDS Foundation, receives funding from ViiV for a surface birth defect outcomes surveillance pilot project in Eswatini. EJA declares no conflicts of interest.

\*Lynne M Mofenson, Elaine J Abrams  
mofensol@gmail.com

Elizabeth Glaser Pediatric AIDS Foundation, Washington, DC 20005, USA (LMM); ICAP at Columbia University, Mailman School of Public Health New York, NY, USA (EJA); Department of Paediatrics, Vagelos College of Physicians & Surgeons, Columbia University, New York, NY, USA (EJA)

- Colbers A, Mirochnick M, Schalkwijk S, Penazzato M, Townsend C, Burger D. Importance of prospective studies in pregnant and breastfeeding women living with human immunodeficiency virus. *Clin Infect Dis* 2019; **69**: 1254–58.
- Renaud F, Mofenson LM, Bakker C, et al. Surveillance of ARV safety in pregnancy and breastfeeding: towards a new framework. *J Int AIDS Soc* 2022; **25** (suppl 2): e25922.
- Zash R, Holmes L, Diseko M et al. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med* 2018; **379**: 979–81.
- WHO. Interim guidelines: updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2019. <https://apps.who.int/iris/handle/10665/277395> (accessed June 14, 2023).
- Zash RM. What will it take to refute the possible safety signal for dolutegravir and neural tube defects? *BJOG* 2019; **126**: 1346.

- 6 Zash R, Holmes LB, Diseko M, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana. International AIDS Conference; July 27–August 2, 2022 (abstr PELBB02).
- 7 WHO. Policy brief: update of recommendations on first- and second-line antiretroviral regimens. July, 2019. <https://apps.who.int/iris/handle/10665/325892> (accessed June 14, 2023).
- 8 Kourtis AP, Zhu W, Lampe MA, Huang Y-LA, Hoover KW. Dolutegravir and pregnancy outcomes including neural tube defects in the USA during 2008–20: a national cohort study. *Lancet HIV* 2023; published online July 25. [https://doi.org/10.1016/S2352-3018\(23\)00108-X](https://doi.org/10.1016/S2352-3018(23)00108-X).
- 9 Dorward J, Sookrajh Y, Khubone T, et al. Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a retrospective cohort study. *Lancet HIV* 2023; **10**: e284–94.
- 10 Romo ML, Patel RC, Edwards JK, et al. Disparities in dolutegravir uptake affecting females of reproductive age with HIV in low- and middle-income countries after initial concerns about teratogenicity: an observational study. *Ann Intern Med* 2022; **175**: 84–94.



## Malawi HIV progress: persistence and innovation are needed

Published Online  
August 13, 2023

[https://doi.org/10.1016/S2352-3018\(23\)00181-9](https://doi.org/10.1016/S2352-3018(23)00181-9)

See [Articles](#) page e597

In *The Lancet HIV*, Danielle Payne and colleagues<sup>1</sup> show that there has been remarkable progress in controlling the HIV epidemic in Malawi. HIV incidence and the proportion of adults with unsuppressed HIV fell steeply between 2015–16 and 2020–2021.<sup>1</sup> Viral suppression rates have increased to 87·0% (95% CI 85·3–88·5) among those living with HIV, reflecting gains in all steps in the treatment cascade and viral suppression levels consistent with exceeding the 95-95-95 goals.

These gains are the result of an impressive commitment by the Government of Malawi and its partners to expand access to antiretroviral therapy (ART), including through a policy shift to immediate-start ART, interventions to retain people with HIV on treatment, and proactive measures to re-engage those who have been out of care. Malawi has mounted a well managed, data-guided public health response that has been key to its success. Expanded HIV testing and the ongoing evolution of treatment options have played their part, particularly the roll out of dolutegravir, which has rapidly increased viral suppression among people on ART.<sup>2</sup> Community engagement has been a cornerstone of the response.

There are similar signs of progress across eastern and southern Africa, the region that has been the most affected by the HIV pandemic. Some authors suggested that the 90-90-90 goals were a useful aspirational target, but might not be achievable.<sup>3,4</sup> Multiple countries now reaching these goals reflects a profound success of public health implementation.<sup>5</sup> Payne and colleagues<sup>1</sup> also highlight the importance of epidemic surveillance data, particularly national surveys with HIV testing. Since the early 2000s, surveys conducted by national governments, demographic and health surveys, and the Population-based HIV Impact Assessment programmes have provided data for tracking the epidemic and maintaining global awareness.

These successes should be celebrated in Malawi and beyond. But there are important lessons for the future, too. Sustained country and global commitments are essential to end AIDS. This will require ongoing innovation in treatment, primary prevention, programme design, health system strengthening, and financing and surveillance over the coming decades.

Sustaining treatment gains is essential. Payne and colleagues<sup>1</sup> show that the cohort of those living with HIV is ageing, highlighting the changing needs among individuals accessing ART. HIV services will need to be integrated within broader health systems. Countries will need to expand options for long-term financing of treatment. The emergence of viral strains resistant to HIV treatments will remain a risk, and new therapies might be needed over time. Monitoring and preventing viral rebound and re-engaging those who drop out from treatment will be needed. Paediatric HIV remains a policy concern, with more to be done to make sure children living with HIV start and remain virally suppressed on treatment.

HIV testing programmes have focused on identifying new cases and ensuring these individuals are linked to treatment. There is an opportunity to additionally focus on identifying individuals at highest risk and linking them to HIV prevention services. Payne and colleagues acknowledge a shortfall in achieving the first 95% target. We urge caution in interpreting these data given possible reporting biases. Identifying those with HIV early and linking them to care is crucial, but so too are efforts to retain people with HIV on treatment and find and relink those who discontinue.

Strengthening prevention and treatment among key populations will remain important. While treatment expansion has driven HIV incidence declines in recent years, improving access, choices, convenience,