tolerated as tenofovir and requires twice daily dosing. The strategy of not switching NRTIs in second line would need to be tested in a randomised controlled trial before widespread implementation.

The findings from EARNEST and other studies that NRTI resistance does not affect virological outcomes in second-line ART suggest that antiretroviral resistance testing is unnecessary for patients in whom first-line ART fails. A health economic analysis of South African data found that resistance testing was cost neutral because it identified the small proportion of patients without resistance, who did not need switching to second-line ART, which is considerably more expensive than first-line ART.[8] The strategy of resistance testing at first-line failure could be cost effective if resistance tests were cheaper, and several lower cost technologies are being explored for antiretroviral resistance testing.[9]

Dolutegravir is anticipated to replace efavirenz in first-line regimens in resource limited settings in the next 5 years.[10] A dolutegravir-based first-line regimen could change the role of resistance testing at first-line failure. By contrast with the first generation non-NRTIs, dolutegravir has a high genetic barrier to resistance,[11] and treatment emergent resistance mutations in integrase or reverse transcriptase have not been observed in three clinical trials in ART-naive participants randomised to dolutegravir plus dual NRTIs.[12] Most patients with virological failure on dolutegravir-based first-line regimens will probably have treatment failure because of poor adherence rather than resistance, as is the case with patients in whom second-line ART fails.[1] Therefore empiric switches to second-line ART would be a waste of resources and expose patients to potential toxic effects from an unnecessary new regimen. We feel that antiretroviral resistance testing should be done in patients with virological failure on dolutegravir-based first-line regimens with lower cost technologies that should soon be available.

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Improved life expectancy of people living with HIV: who is left behind?

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The introduction of combination antiretroviral therapy (ART) has been one of the great public health success stories of the past 40 years. ART has led to increased survival in people living with HIV, and subsequently to individual and societal gains worldwide, because of the marked improvements in its potency, side-effect profile, and simplicity of use.[1] Results from the HIV Prevention Trials Network (HPTN) 052 study have clearly proven the efficacy of ART for prevention of transmission,[2] while the TEMPRANO and START studies have shown that early ART initiation reduces the risk of serious clinical conditions, the development of AIDS, and death.[3,4]

Despite these improvements, cohort studies show a small but persistent gap in the lifespan between HIV-positive and HIV-negative individuals, particularly within key affected populations.[5,6] Recent data from NA-ACCORD show that a 20-year-old HIV-positive adult on ART in the USA or Canada has a life expectancy approaching that of the general population,[7] but this benefit is not shared by all. Specifically, individuals who are not white, have a history of injection drug use, or began ART with low CD4 cell counts have no reduction in mortality or improvements in life expectancy.

In *The Lancet HIV*, the Antiretroviral Therapy Cohort Collaboration (ART-CC) expands these findings over a longer timeframe using retrospective data from one of the largest collaborations in Europe and North America.[8] Similar to NA-ACCORD, ART-CC found substantial improvements in mortality reduction and increased life expectancy in HIV-positive patients initiating ART. The ART-CC group surmises that these trends reflect superior antiretroviral agents, more options for patients developing resistance, fewer drug interactions, better management of opportunistic infections and chronic diseases, and the introduction of screening and prevention programmes for comorbidities in patients who benefited from treatment. However, life expectancy remains lower in people living with HIV than in the general population, and there is little evidence of a mortality reduction in people who inject drugs.

In countries in the centre of the epidemic in sub-Saharan Africa, researchers have found that mortality in people living with HIV who are receiving treatment has been declining to levels similar to those described in participating North American cohorts.[9] Furthermore, recent data support that people living with HIV in countries such as South Africa can have a near-normal life expectancy, assuming they start ART before their CD4 count drops below 200 cells per µL.[10] Although these findings suggest that results from cohorts in high-income countries can apply to low-income and middle-income countries, they might not be generalisable to countries where access to ART is limited, and challenges remain for all people living with HIV to access early treatment and stay in care.

The concern is greatest in the world's most vulnerable populations, which include people who inject drugs in Europe and North America, and individuals living in resource-constrained settings globally, where access to early ART initiation has been limited. Beyond multiple structural barriers and the persistence of HIV-related stigma,[11] the previous era of inferior drugs and poor outcomes for patients has left a legacy that will be difficult to overcome. Fear of medication-related side-effects is a leading psychosocial barrier to treatment initiation and has led to concerns that ART might actually make a patient sick.[12–14] Furthermore, restrictions in many regions on ART availability to individuals with low CD4 cells counts have created a perception that ART is reserved for individuals who are sick.[15]

These psychosocial barriers threaten to undermine the therapeutic and prevention benefits of ART in the test-and-treat era. Loss to follow-up care and treatment is typically greater in healthier individuals and, as the ART-CC study shows, health is also negatively associated with retention on ART. As efforts are scaled up to detect asymptomatic patients, the challenge will be to link these individuals to treatment and to optimise adherence. Interventions to increase awareness of the many positive benefits of early ART initiation and to allay fears of drug toxicity are needed, especially in individuals who feel healthy and might perceive ART as more of an immediate risk than a benefit.

As the ART-CC group points out, although most future patients diagnosed with HIV are likely to start ART immediately (both for their own health and to prevent transmission to others), this approach will only result in improved survival if the problems of late HIV diagnosis and access to care are addressed. Although information about improved life expectancy in people living with HIV might motivate at-risk individuals to test for HIV or convince those infected that they should start ART immediately, current data in these populations suggest that knowledge alone might not provide an adequate incentive to overcome other obstacles to ART initiation and long-term adherence.

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Collateral damage and the criminalisation of drug use

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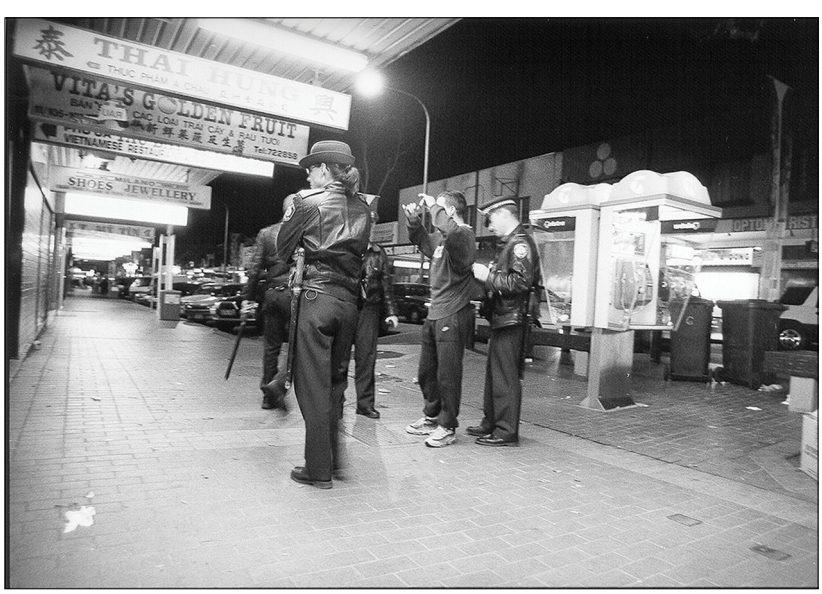
Illicit drug use is a substantial cause of mortality and morbidity globally.[1] However, current estimates of the global disease burden underestimate the contribution of illicit drugs because they fail to take into account several important adverse outcomes. One of the hypothesised drivers of these outcomes is the criminalisation of drug use—the most common drug policy globally. The systematic review by DeBeck and colleagues[2] in *The Lancet HIV* focuses on the effects of criminalisation on HIV treatment and prevention among people who inject drugs (PWID).



Tiet Ho and Lisa Maher: Walls of Silence

We already know that criminalisation increases the price of illicit drugs,[3] which in turn means that some drug users resort to crime or potentially risky activities such as sex work (also often criminalised) to support their drug use.[4] We also know that criminalisation adversely affects the health of drug users by increasing the health risks of drug use, particularly injection drug use,[5] and reducing or restricting access to interventions such as needle and syringe programmes, opioid substitution treatment, and HIV antiretroviral therapy.[6,7] By definition, criminalisation increases the risk of arrest or imprisonment, and drug use in prison has been associated with adverse health outcomes.[8] Criminalisation of drug use also increases exposure to violence[9] and fosters stigma, discrimination, and social exclusion.[10]

The study by DeBeck and colleagues is, to our knowledge, the first systematic assessment of the effect of laws criminalising drug use on HIV prevention and treatment outcomes among PWID. This systematic review focused on key criminalisation indicators, including incarceration, street-level policies, drug paraphernalia laws and practices, and prohibitions or restrictions. Results indicate that most