because STIs are common in the target groups included in the trial.[9]

Ngure and colleagues' study is novel and shows the potential that HIVST has to demedicalise biomedical HIV prevention and PrEP delivery. Demedicalisation could enable adaptation of the many successful differentiated HIV care models—such as pharmacies, digital health intervention, adherence clubs, community care givers, or peer support[10]—to differentiated HIV prevention, and thereby reduce both clinic and client burden while optimising prevention among participants.

We declare no competing interests.

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Integrase inhibitors hand us a new HIV clinical puzzle

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One of the remarkable recent pivots in the entire HIV field is the shift from resistance and early antiretroviral toxicity to the challenge facing the global population: growing old while staying healthy. Second-generation integrase inhibitors have bestowed an unprecedented era of robust and safe drugs for people with HIV. Dealing with the effects of weight gain, smoking, viral hepatitis, and HIV-linked low-level inflammation along with other chronic diseases seemed to be our major challenge.

However, in *The Lancet HIV*, Bastian Neesgaard and colleagues[1] report an analysis of the RESPOND cohort, in which they found a near-doubling of cardiovascular disease events in their cohort in the first 6 months after starting an integrase inhibitor, with subsequent tapering of the incidence rate back to baseline after 2 years of exposure. This finding persisted after adjusting for cardiovascular disease risk factors and other potential confounders and was consistent across a range of sensitivity analyses.[1] A large observational study reported at the 2022 Conference on Retroviruses and Opportunistic Infections from a well characterised US-based west coast and east coast cohort showed an increase in risk of myocardial infarction in 2010–17, relative to HIV-negative controls, again with speculation around the role of integrase inhibitors.[2]

The RESPOND study time-distribution of this risk, if causal, is difficult to explain by means of any reference to modification of traditional cardiovascular risk factors. The association between integrase inhibitors and weight gain is well established, but gradual and cumulative. Initial concerns about links between integrase inhibitors and increased incidence of immune reconstitution syndromes, a plausible temporal mechanism for the events seen, have not been borne out beyond initial case reports. Similarly, use of integrase inhibitors is associated with insomnia, which in turn is strongly correlated with cardiovascular events. Scientific literature also offers some clues to the findings in the current study. Although HIV itself is a well known driver of arterial inflammation, a small study by Zanni and colleagues[4] found that biomarkers of arterial inflammation and coronary plaques seemed to increase in the first 6 months after initiation on an elvitegravir–cobicistat-based regimen, despite

rapid HIV control.[3] Another study showed different inflammatory profiles within the integrase inhibitor class, which were generally worse than those seen with atazanavir.[5] Switch studies showed complex changes in inflammatory markers when changing to dolutegravir-containing regimens.[6]

Regardless of biological plausibility, we are left in a frustrating situation: what do we do with these results? These results seem to almost come too late, with almost every HIV-positive person on the planet being on either dolutegravir or bictegravir combinations in line with guideline changes, coupled with the WHO and donor push for dolutegravir introduction in low-income and middle-income countries. Large observational cohorts are liable to many biases, with the RESPOND cohort geographically representing a small fraction of the population with HIV. Similar caution should apply to industry funded studies that did not initially report weight gain in recent studies, consistently do not include sufficient women and Black people, and generally select only the healthiest people for enrolment.[7]

Many will remember the debate about the association between abacavir and myocardial infarction, with observational studies suggesting a clinically significant risk, especially in the presence of other cardiovascular risk factors, but no signal from pooled industry studies.[8] After almost 20 years of controversy, the field is none the wiser, with the issue complicating guidelines, scaring patients, perplexing clinicians, and filling conference programmes. However, the difference here is enormous if cardiovascular risk due to the integrase inhibitors being introduced proves more sustained than this study shows. We have almost no alternatives to the integrase inhibitor class, with efavirenz, darunavir, and other candidates in-class showing substantial metabolic, dosing, and drug-drug interaction issues; doravirine unavailable in most countries and with little safety data in women; and promising long-acting drugs on development pause, with little short-term toxicity data available.[9,10]

Our best hope is that subsequent studies disprove the signal identified by Neesgaard and colleagues[1] or confirm that the risk is short lived. Reliance on the new integrase inhibitors is probable for at least the next few years, and possibly decades, as with tenofovir prodrugs, the cytosine analogues, and, until recently, efavirenz. The data in this study emphasise the importance of well characterised longitudinal cohorts and the need for assembling data on cardiovascular and other events, probing plausible mechanisms, and to continue drug discovery; should we need replacements for this class, the world is in a vulnerable position, given the unprecedented reliance on dolutegravir and bictegravir.

Thankfully, data before this study suggest high levels of safety and efficacy for both drugs, so cautious watchfulness is appropriate for now. But the need to confirm or refute these data with further studies is now pressing. If confirmed, immediate attention will need to be paid to illuminate the mechanism, because its occurrence so soon after initiation suggests modifying traditional cardiovascular risk factors might not be enough to prevent adverse events.

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