Early HIV treatment to forestall drug resistance

In this issue, Ravindra Gupta and colleagues[1] present compelling findings of the epidemiology of HIV drug resistance. Based on the results of a collaborative study termed TenoRes, the researchers clearly document that the prevalence of HIV drug resistance against the commonly used antiretroviral drug tenofovir is far higher than expected, especially in sub-Saharan Africa. This result is disconcerting because it had previously been thought that tenofovir might be less prone to development of drug resistance than other compounds. The investigators went on to show that a strong predictor of tenofovir resistance was a CD4 cell count of less than 100 cells per μL, suggesting an HIV-damaged immune system. The use of lamivudine compared with emtricitabine was also associated with an increased risk of tenofovir resistance, a finding that might reflect the longer intracellular half-life that is associated with the active form of emtricitabine compared with lamivudine.[2] The finding that HIV drug resistance has occurred at higher than expected levels indicates a need to develop treatment regimens that will be less prone to this problem, which is one that should probably have been anticipated as an unavoidable outcome of the successful HIV drug rollout programmes that have helped to save millions of lives around the world in the past several decades.

Among other considerations, a new pro-drug of tenofovir termed tenofovir alafenamide fumarate might be less prone to development of drug resistance because of lower toxic effects than tenofovir itself, which is associated with loss of bone mineral density and raised creatinine concentrations.[3] However, this might not necessarily translate into lower levels of drug resistance because the same mutation at position K65R in reverse transcriptase causes resistance to both drugs and might be more prone to develop in subtype C viruses that were assessed in this and other studies.[4–8] Unfortunately, subtype C viruses are predominant in many low-income and middle-income countries[8] and limited availability of integrase inhibitors in such settings for use in first-line therapy despite the fact that their use is now recommended by almost all treatment guidelines, will potentially exacerbate this problem.

Another important finding of this study is that drug resistance was more likely to develop in individuals who have low CD4 cell counts due to HIV disease progression. Aside from focusing attention on the important role that a functional immune system can play in mitigating disease progression and development of drug resistance, we also know that an individual has the best chance of attaining long-term treatment success by starting treatment as soon as possible after diagnosis when CD4 concentrations are high.[9] Therefore, the identification of individuals as HIV positive as efficiently and as soon as possible is important; WHO has recently introduced a strategy termed 90-90-90 that seeks to identify 90% of people in the world who are HIV positive, to treat 90% of such people, and to attain a non-detectable viral load in 90% of such cases after treatment initiation. The hope is that this will also serve to prevent onward HIV transmission because individuals who have undetectable viraemia are unlikely to be infectious for their partners.[10–12]

Of course, the success of the WHO 90-90-90 guidelines depends on convincing a very high proportion of high-risk individuals who are unaware of their HIV status to agree to be tested. In this context, a sound argument can be made that more effective incentivisation is urgently needed and perhaps a financial offering could make a difference. Although the costs of such a programme could be high, these would almost certainly be dwarfed by the costs involved in providing antiretroviral treatment to people who might become infected by those who have not yet undergone therapy because their HIV status is unknown.

Altogether, the results of this study are a reminder that the problems of HIV drug resistance and transmitted drug resistance are very real, especially in developing country settings, and that there is a need for enhanced, cost-effective tests that can screen for drug resistance in parts of the world in which such tests are often not affordable as well as for more effective screening for HIV infection in the first place.
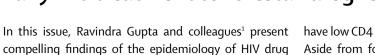
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I declare no competing interests.

Ton Koene/DPA/Press Association Images

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