injecting drug users. The introduction of PrEP for HIV prevention in injecting drug users should be considered as an additional component to accompany other proven prevention strategies like needle exchange programmes, methadone programmes, promotion of safer sex and injecting practices, condoms, and HIV counselling and testing. PrEP as part of combination prevention in injecting drug users could make a useful contribution to the quest for an AIDS-free generation.

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After first-line ART: towards an evidence-based SECOND-LINE


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Access to antiretroviral therapy in low-income and middle-income countries has been scaled-up effectively in the past decade; however, failure of the first-line regimen is increasing.[1] In *The Lancet*, the SECOND-LINE Study Group[2] provide a high-quality evidence-based strategy for safe and effective treatment of patients in whom first-line treatment has failed.[3] They did a randomised clinical trial to compare a WHO-recommended second-line treatment regimen—a ritonavir-boosted protease inhibitor (lopinavir) plus two or three nucleoside or nucleotide reverse transcriptase inhibitors (NtRTIs)—with a novel dual-treatment approach that combined ritonavir-boosted lopinavir with the integrase inhibitor raltegravir. The investigators showed that the efficacy of the new regimen was non-inferior to standard treatment: 223 (83%) of 270 patients in the raltegravir group versus 219 (81%) of 271 in the control group had a plasma viral load of less than 200 copies per mL at week 48 (difference 1·8%, 95% CI −4·7 to 8·3). No major safety issues emerged in either group. Patients who took raltegravir had significantly larger increases in CD4 T-cell count than patients who took the control regimen.

These findings are important because they show that the WHO-recommended second-line treatment is an efficacious rescue regimen. Furthermore, they suggest that the new regimen has equal efficacy, but with other potential advantages. First, use of a single treatment based on only two different compounds for all the patients failing first-line treatment will ease demand on drug supply and stocks. Second, simple regimens might enable treatment to be delivered by trained, but non-medical, health-care workers, improving access to HIV care in settings with limited resources.[4] Third, because the rescue treatment consists of two drugs from antiretroviral classes to which patients have not been previously exposed, genotypic resistance testing is not needed, saving time, money, and effort. Finally, the raltegravir regimen is likely to cause fewer toxic effects than NtRTI-based treatments.

Nevertheless, these advantages are counterbalanced by the higher cost of raltegravir—at present, it is prohibitively expensive in many low-income and middle-income countries. The study by Boyd and colleagues[2] provides a tradeoff, instead of settling for only what is readily available at a reasonable price in resource-constrained settings.[3] However, although the cost of raltegravir will hopefully drop owing to competition with other integrase inhibitors soon to be licensed, new mechanisms to provide wider access to raltegravir are needed if it is to be included in second-line regimens.

Progress in expanding HIV care in the past decade has been based on a public health approach, especially the introduction of a simple, effective, safe, and tolerable standardised first-line antiretroviral treatment regimen.[5] According to guidelines,[6] three regimens could be used sequentially, with exponentially increasing costs, in case

of treatment failure: two NtRTIs plus one non-nucleoside reverse transcriptase inhibitor, two NtRTIs plus one boosted protease inhibitor, and ritonavir-boosted darunavir plus etravirine and raltegravir.[7] Including raltegravir in second-line treatment, as in the strategy used by Boyd and coworkers, could limit the number of class-independent treatment options in case of treatment failure to just two regimens; therefore, the durability of the two alternative second-line regimens needs to be investigated. Conservative[8] and innovative[9] approaches—rigorously assessed in prospective clinical trials and cost-benefit analyses—could help expert panels and policy makers to define the best strategies to manage treatment failure.[10]

Although the SECOND-LINE study[2] offers a simple approach to ensure that first-line and second-line regimens are from independent antiretroviral classes, a crucial problem in HIV treatment remains: how to define failure of a first-line regimen. The use of clinical or immunological criteria for virological failure lacks sensitivity and specificity and continued use of ineffective drugs could lead to the development of resistance, thus jeopardising the efficacy of NtRTIs in second-line treatment; conversely, the apparent absence of an immunological benefit of a virologically effective first-line treatment could lead to unnecessary switching to a more expensive second-line regimen. So, even if the best second-line treatment is identified in clinical trials, it would be difficult to apply without a widely available method for monitoring viral load.[11,12]

Although not providing an ultimate solution to these issues, the SECOND-LINE study is an important guide for clinical and public health decision making for thousands of patients who, because of a failing treatment regimen, are at risk of AIDS and death.

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Hepatitis C treatment: interferon free or interferon freer?

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Pegylated interferon alfa-2a (peginterferon) and ribavirin are the standard of care for all six genotypes of hepatitis C virus. Hepatitis C virus (HCV) does not integrate into the human genome. Thus a sustained virological response (SVR) is tantamount to virological cure and reduces the likelihood of progressive liver disease.[1] About 45% of patients with HCV genotype-1 achieve SVR. Single nucleotide polymorphisms in the human genome affect response to interferon. However, patients with cirrhosis have lower response rates. Many side-effects occur during treatment and therefore peginterferon and ribavirin are contraindicated in many patients. The first generation NS3/4A protease inhibitors, telaprevir and boceprevir, improve response rates in treatment-naive as well as previously treated patients with HCV genotype-1; their use is complex,