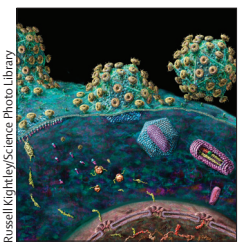
SPRING-2 the future of antiretroviral therapy



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In the past 25 years, the antiretroviral management of HIV-infection has revolutionised the prognosis of people with HIV. From a universally fatal illness in its first decade, HIV has become a readily manageable disorder. In settings where access to antiretroviral therapy is subsidised, the prognosis for good health of a person with HIV can be measured in decades.[1] Effective antiretrovirals are now available in five independent drug classes in high-income countries. In low-income and middle-income countries access is more restricted, with access to drugs in three classes in publicly-funded programmes, but with hopes to extend this number to four.[2]

In *The Lancet Infectious Diseases*, François Raffi and colleagues[3] present the 96 week outcomes of the SPRING-2 study.[3] Results from this randomised, double-blind trial show non-inferior efficacy of once-daily dolutegravir to twice-daily raltegravir in treatment-naive participants with HIV-1 infection over 96 weeks, with a similar safety profile and no evidence of emergent resistance to dolutegravir in those showing virological failure. Our knowledge of the optimum use of antiretroviral combinations has inevitably been constrained by the pathways of clinical development required to gain regulatory approval. We have a very good understanding of the comparative performance of various anchor agents combined with nucleoside or nucleotide reverse-transcriptase inhibitors in first-line therapy. However, the various combinations of drugs possible are more extensive, and the time has come time for us to understand how conventional combination regimens perform compared with feasible and potentially attractive alternatives.

A couple of issues need to be addressed. First, we need to test the place of nucleoside or nucleotide reverse-transcriptase inhibitors in antiretroviral therapy. Recent studies have suggested that although many treatment providers are uncomfortable not including drugs from this class in any regimen, this feeling is based more on belief than on science.[4,5] Another issue is that of pharmacokinetic boosting. Although a neat solution to the problem of the short half-life of the protease inhibitors and elvitegravir, the cost of drug interactions, metabolic dysfunction, and the unknown long-term consequences of interfering with normal hepatic metabolism with boosted regimens demands our concern and attention. What is the potential for potent, tolerable, and safe combination antiretroviral regimens that do not need nucleoside or nucleotide reverse-transcriptase inhibitors or pharmacokinetic boosting? Could dual combination therapies such as once-daily dolutegravir and rilpivirine or once-daily dolutegravir and unboosted atazanavir offer potent, tolerable, safe, and durable antiretroviral regimens in the future? With its high barrier to resistance, what about dolutegravir monotherapy?

Dolutegravir has the potential to have a major effect in low-income and middle-income countries, in which most HIV infections exist. At the Seventh International AIDS Conference on HIV Pathogenesis, Teatment, and Prevention (Kuala Lumpur, Malaysia, June 30–July 3, 2013), WHO launched its new, consolidated guidelines for the use of antiretroviral treatment in people living with HIV.[2] WHO now recommends a preferred single-tablet regimen of efavirenz 600 mg plus tenofovir disoproxil fumerate 300 mg plus lamivudine 300 mg for those starting antiretroviral treatment. While the cost of this single tablet regimen is quite cheap (US$139 per person per year for a quality-assured generically manufactured product[6]), further reductions in cost are constrained by the relatively high doses of active pharmaceutical ingredient required (the total active pharmaceutical ingredient for the single tablet regimen is 1200 mg). Antiretroviral combinations with newer drugs conferring proven efficacy at lower doses might provide not only attractive and more affordable alternatives but also greater tolerability and safety into the bargain, and thereby greater cost-effectiveness. For instance, assuming that the phase 3 development of tenofovir alafenamide fumerate (TAF), a novel prodrug of tenofovir, 25 mg daily is successful (ClinicalTrials.gov, NCT01797445), one can conceive a single-tablet regimen of dolutegravir 50 mg plus TAF 25 mg plus lamivudine 300 mg for a total active pharmaceutical ingredient of 375 mg, which is less than a third that of the currently recommended single-tablet regimen. Although antiretroviral pricing is more complex than this simple comparison implies, and the companies who own dolutegravir and TAF have an important stake in the price of their products in all settings, the

hope of providing universal access to the best possible products at the most affordable price is one we must pursue.

We stand at an important crossroads in the use of antiretroviral therapy worldwide. We have turned HIV-infection into a chronic manageable illness, and we are making universal access to care including antiretroviral therapy a reality. The job, however, is not over. We must find ways to further refine our understanding of the use of antiretroviral therapy to support the modelled life-expectancies predicted by cohort studies[1] while never forgetting that tolerable, safe, and effective antiretroviral drugs should be available to all.

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Laboratory diagnosis of *Clostridium difficile*

Diarrhoea is a common symptom, but most cases are non-infectious and result from a range of underlying diseases or from treatment with one of more than 700 drugs that are known to have this side-effect.[1,2] However, *Clostridium difficile* is responsible for a substantial proportion of cases of diarrhoea and is often indistinguishable from other causes; additional laboratory tests are therefore needed to confirm a presumptive clinical diagnosis of *C difficile* infection. These tests need to be rapid, not only because most hospitals have few side rooms and therefore infected patients can transmit *C difficile* to others while waiting for their results, but also to prevent inappropriate empirical anti-*C difficile* treatment, which could be detrimental to patients not actually infected with the bacterium.[3,4]

The need for a rapid test means that most laboratories do not use either of the two slow, labour-intensive reference methods: cytotoxigenic culture and the cytotoxin assay. Additionally, disagreement persists about which is the more appropriate method to use. This situation has hampered comparison of the performance of different commercially available assays. Instead, laboratories have used toxin enzyme immunoassays to detect free toxin in stool; however, the commercially available assays of this type perform poorly, with low sensitivity. In 2010, more than a third of NHS laboratories in England were using toxin enzyme immunoassays, resulting in a positive predictive value of less than 50%.[5] More recently, the availability of commercial glutamate dehydrogenase and molecular tests has led to the haphazard adoption of several diagnostic algorithms,[5] which, combined with variations in selection of patients and samples to test, has created inconsistent and inequitable practices.[6] In turn, this situation distorts the true epidemiology of the disease and could encourage game playing in hospitals that are subject to targets for infection reduction and financial penalties for failure to meet these.[6]

In *The Lancet Infectious Diseases*, Timothy Planche and colleagues[7] report the results of the largest study so far to define the optimum testing algorithm for the laboratory diagnosis of *C difficile* and to assess clinical outcomes based on the two different reference methods. More than 12 000 samples from four centres were included in the study, and the results confirm that a two-step algorithm comprising a sensitive glutamate


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