Commentary

Novel agents for the treatment of HIV-2 infection

Kevin Peterson*, Sarah Rowland-Jones

1Institute for Tropical Medicine, Antwerp, Belgium
2Nuffield Department of Medicine, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK

*Corresponding author e-mail: kpeterson@itg.be

Many of the antiretrovirals used against HIV-1 are either ineffective or less effective in HIV-2 infection. There is in vitro evidence of the potency of maraviroc and several investigational agents against HIV-2. We conclude that, whilst specific boosted protease inhibitors combined with nucleoside analogues should still be considered the mainstays of HIV-2 treatment, maraviroc, T-1249, TAK-779 and AMD3100, as well as raltegravir, could contribute to regimens for treatment-experienced individuals. Factors bearing on the use and timing of these alternative agents are discussed.

Although the extent of HIV-2 infection in its natural home in West Africa has been eclipsed by the scale of the worldwide HIV-1 epidemic, it is worth remembering that at its height in the 1980s–1990s estimates suggested that over a million people were infected with HIV-2 [1]. No reliable prevalence data have been gathered in recent years, although reports from several West African countries suggest that HIV-2 prevalence is declining [2,3]. However, even in endemic countries, the national testing algorithms do not reliably diagnose HIV-2 infection [4], so the burden of HIV-2 is probably underestimated. Recent reports of clusters of HIV-2 infection in settings as diverse as New York City [5], southern India [6] and Japan [7] suggest that the potential for HIV-2 to spread worldwide may not have been adequately appreciated. Although epidemiological data suggest that a significant proportion of HIV-2-infected people will experience few, if any, health consequences of this infection [8], there remains a substantial burden of disease in patients for whom antiretroviral therapy (ART) is life-saving. Alongside the welcome increase in the availability of ART in West Africa, the challenges of treating HIV-2 infection have become more apparent in the developing world. The antiretroviral drugs (ARVs) in the current armamentarium for HIV infection were all designed with HIV-1 in mind and there are no randomised clinical trial (RCT) data to guide first- and second-line therapy in HIV-2 infection [9]. Crucially, HIV-2 is resistant to the non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are the mainstay of first line therapy, particularly in resource-limited settings, and furthermore, exhibits naturally occurring resistance mutations to some protease inhibitors (PIs) [10]. Monitoring therapy is complicated by the lack of commercially available viral load (VL) assays, and the interpretation of genotypic resistance data is hindered by the absence of phenotypic resistance studies from the literature.

Against this background, the report by Borrego et al. [11] in this issue provides welcome information about the in vitro potency against HIV-2 clinical isolates of the newer antiretroviral drugs from the coreceptor blocking and fusion inhibitor classes. These include the fusion inhibitors enfuvirtide (formerly T-20) and T-1249, and the coreceptor blockers maraviroc (MVC), TAK-779 and AMD3100. The inhibitory concentration (IC) data they provide form the best available evidence of the potency of these drugs for the treatment of HIV-2 infections, and forms a foundation on which future clinical studies can be based.

Of the currently available drugs, nucleoside reverse transcriptase inhibitors (NRTIs) appear to be as effective for HIV-2 therapy as they are in HIV-1. This includes zidovudine (AZT) [12], previously thought to be less active against HIV-2. Combinations of three NRTIs, while supported by some experts [13,14], appear to be even less effective in HIV-2 than they are in HIV-1. A recent retrospective observational study showed a striking lack of long-term benefit (assessed at 12 months) on either CD4+ T-cell counts or VLs in patients starting a triple NRTI regimen [15]. The Q151M, K65R and M184V mutations are readily generated during drug therapy and result in significant cross-resistance. The low barrier to developing ‘pan-nucleoside’ resistance makes a triple nucleoside regimen more fragile. It also increases the consequences of failure, as remaining options to form effective regimens become more limited. Resistance
genotypes should be obtained whenever possible before making NRTI switches in HIV-2. In the absence of that information one could consider initially using AZT with lamivudine (3TC) and adding tenofovir (TDF) in combination with other active ARVs for the second-line regimen, as TDF retains potency in the face of the Q151M mutation selected for by AZT. Alternatively, one could use TDF with emtricitabine (FTC) initially and add AZT in combination with other active ARVs for the second-line regimen, as the K65R mutation selected for by TDF may render HIV-2 hypersusceptible to AZT [10]. There is one published case of successful treatment of HIV-2 with a regimen of stavudine and abacavir in combination with 3TC and TDF [16]. While this has the advantage of being PI sparing, compared with initial therapy using drugs from two classes it is unlikely to prove as potent.

Among PIs, effectiveness against HIV-2 varies. In general, they should be boosted, and whilst the best available data support ritonavir-boosted lopinavir (LPV/r) and indinavir (IDV/r), either saquinavir (SQV/r) or darunavir (DRV/r) are also likely to yield a good treatment response [10,15,17–20]. Of the four boosted PIs with reliable activity against HIV-2, the daily cost in 2010 in low-income countries of IDV and LPV is less than $2, SQV is under $4, and DRV is over $30 [21–23].

If initial therapy is based on a boosted PI, a second-line regimen in HIV-2 could still be based on another boosted PI, provided the resistance mutations have not compromised the new drug. This is somewhat hazardous, as there are fewer clinical data (and no phenotypic resistance data) on which to base interpretation of HIV-2 genotypic data. LPV failures in HIV-2 tend to select for the V47A mutation that increases susceptibility to SQV, suggesting one possible sequencing of PIs. DRV/r may have advantages over the other boosted PIs, in either treatment-naive or treatment-experienced patients, although little is known about the resistance mutations selected by DRV in HIV-2; this is of greater concern where it is used as part of a first-line regimen if a different PI may form part of a later regimen and resistance testing is unavailable. Of course, multiple PI mutations could ultimately compromise any drug in this class and complicated cases may benefit from phenotypic resistance tests.

The first of the integrase inhibitors, raltegravir (RAL), while used primarily in treatment-experienced individuals, could be considered for the treatment of ARV-naive individuals. It appears to work well in HIV-2 [24–27] although, as yet, there has been little published on its clinical use. Given its low barrier to resistance and demonstrated failures where it is the only active ARV [28,29], it may perform better if deployed earlier. Hypothetically, the risk of evolving resistance would be higher among those with high HIV-2 VLs, suggesting a possible advantage of an induction-maintenance regimen, with a boosted PI as a fourth agent until viral suppression has been maintained for a substantial period of time, such as a year. The benefit of an induction-maintenance approach compared to a more conventional regimen of a boosted PI with two NRTIs has however not been demonstrated.

Confirming prior studies [30,31], Borrego et al. [11] conclude that the fusion inhibitor enfuvirtide is unlikely to be effective against HIV-2. In contrast to earlier conclusions drawn from viral sequencing [31], Borrego et al. [11] show the fusion inhibitor T-1249 to have significant potency against HIV-2, although at twice the IC as HIV-1. Complicating this is their finding that X4 isolates have half the T-1249 50% IC (IC50) of R5 isolates. On the basis of this data, T-1249 would likely be beneficial at any point during the disease course, while prior to the transition to an X4 virus higher doses may be required for HIV-2-infected individuals. Even if one has access to an X4 tropism assay for HIV-2, such as that described by Visseaux et al. [32], this dosing uncertainty argues against its use where good alternatives exist, that is, outside of salvage regimens.

As with HIV-1, HIV-2 transitions from R5 to X4 forms [33,34], although it may not do so with the same frequency. Moreover, it appears much more flexible in its coreceptor utilization than HIV-1 while still nominally an R5 virus [35]. Prior to the transition from R5 to X4, MVC, a CCR5 coreceptor blocker, may be effective even if flexibility in HIV-2’s coreceptor utilization hints that it would not provide as durable a response. There is only one published case of MVC’s use in HIV-2, in a treatment-experienced individual receiving a potent combination of other ARVs [36]. Borrego et al. [11] show that, whilst the IC50 of MVC in HIV-2 is similar to HIV-1, the 90% IC (IC90) is many fold higher, and the ICs from patients with advanced disease are even higher. This has been ascribed to increasing flexibility of R5-tropic viruses over the course of infection [37]. A similar diminished effect in advanced disease was also noted for TAK-779, a mixed CCR5/CXCR3 blocker. On the basis of the data from Borrego et al. [11], it would appear that these CCR5 receptor blockers are more likely to contribute potency to a regimen relatively early in the course of HIV-2 infection, perhaps while CD4+ T-cell counts remain high, following a tropism assay. This suggests that these could serve as adjunctive therapies alongside a potent three-drug regimen in an induction–maintenance paradigm in patients with both high VL and high CD4+ T-cell counts, for example in acute HIV infection; the value of this approach remains speculative, however. Optimal dosing may be higher than in patients with HIV-1 and depend on disease stage. Long-term data from individuals with HIV-2

---

436

©2012 International Medical Press
infection undergoing treatment with MVC are needed to provide reliable estimates of the incidence and mechanism of viral escape.

Based on the findings of Borrego et al. [11], the X4 coreceptor blocker AMD3100 may be expected to function in mixed and X4-tropic HIV-2 virus infection. It gave more consistent results than the other agents they tested and its IC₅₀ in HIV-2 were similar to those in HIV-1. In practice, its role will predominantly be in treatment-experienced patients with advanced disease, preferably following a tropism assay.

In summary, boosted PIs combined with NRTIs remain the initial treatment of choice for HIV-2 infection. NRTI cross-resistance is a serious concern with HIV-2 and genotypic resistance tests are important to optimize their sequential use. With PI sequencing options available in HIV-2, the roles of RAL, MVC, TAK-779, AMD3100 and T-1249 are unclear, and may depend on the patient’s CD₄+ T-cell count or his/her VL. Of the coreceptor blockers, Borrego et al. [11] demonstrate that the CXRX4 blocker AMD3100 gives more consistent results, and similar IC₅₀ in HIV-2 compared with HIV-1; this makes it the most promising of the candidates assessed, as long as it is used in conjunction with an HIV-2 tropism assay. For T-1249, MVC and TAK-779 dosing is more complex and it is unclear what role phenotypic resistance tests and therapeutic drug monitoring (TDM) should have alongside tropism tests in clinical practice with these agents. Lack of information on drug–drug interactions further argues for TDM to ensure predictable treatment responses when these agents are used. Suggestions for potential indications are given in Table 1.

### Disclosure statement

The authors declare no competing interests.

### References


