Special Aspects of the Treatment of HIV-2-Infected Patients

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Key Words

AIDS · HIV-2 treatment management · HIV-2 drug resistance

Abstract

HIV-2 is responsible for a limited epidemic in West Africa. Around 20% of all infected patients will progress to AIDS, and will need antiretroviral therapy. Unfortunately, antiretrovirals were developed to suppress HIV-1 replication; not all of them are active against HIV-2, e.g. all nonnucleoside reverse transcriptase inhibitors or fusion inhibitors. Moreover, only three protease inhibitors have the same activity in HIV-1 and HIV-2: lopinavir, saquinavir and darunavir. Even if all nucleoside and nucleotide reverse transcriptase inhibitors appear to be equally efficient against HIV-2, different resistance pathways and an increased facility of resistance selection make their use much more difficult than in HIV-1. Integrase inhibitors have a potent inhibitory effect on HIV-2 replication, but questions about the best timing for their use remain unanswered, as well as those regarding the use of entry inhibitors in this setting. The lack of reliable monitoring tools adds to the difficulty of treating HIV-2-infected patients, mostly because the viral load is not as useful as it is in HIV-1, and the incomplete knowledge about resistance pathways limits the clinical usefulness of resistance testing. With all these limitations, HIV-2 treatment remains a challenge.

Further research is urgently needed, since antiretroviral therapy is now becoming available in countries where the HIV-2 prevalence is significant. The need for appropriate guidelines for HIV-2 treatment has become an emergency.

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Introduction

HIV-2, like HIV-1, is a lentivirus from the Retroviridae family that causes AIDS [1]. As opposed to HIV-1, which is responsible for a pandemic, HIV-2 established a limited epidemic in West Africa, infecting 1–2 million people in countries like Senegal, Guinea-Bissau, Gambia, Ivory Coast and Cape Verde [2, 3]. The highest prevalence is in Guinea-Bissau, where 8% of the adult population is infected [4]. The presence of HIV-2 has also been reported in small numbers in other regions of the world, Portugal and France being the countries with the highest prevalence outside West Africa.

There are significant differences between HIV-1 and HIV-2 regarding disease progression. While both viruses can cause AIDS, around 80% of HIV-2-infected patients behave like long-term nonprogressors; only 20–25% of all patients progress to AIDS [5], and are thus the primary target for treatment interventions.

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With access to therapy becoming available in the areas where HIV-2 is more prevalent, guidelines for the appropriate management of HIV-2 treatment urgently need to be established. Unfortunately, most data available on HIV-2 therapy are the result of small, mainly observational studies performed in Europe, which offers incomplete information; most treatment interventions have been done by extrapolation of what is known for HIV-1, often with poor results. In effect, HIV-2 treatment has some aspects that are specific for this virus; most of them are now available in published guidelines [6, 7]. However, there are still a large number of unanswered questions, stressing the need for further research.

Monitoring HIV-2 Therapy

Viral Load and Resistance Testing

One of the cornerstones for treatment monitoring in HIV-1 – viral load – has a limited usefulness for HIV-2 therapy. Viral load is undetectable most of the time, only becoming detectable in the late stages of infection or in rapid progressors. Typically, its value is 2–3 log₁₀ lower than in HIV-1-matched controls; the observation of an undetectable plasma viral load in patients at very late stages of disease, with low CD4 counts and clinical symptoms, is not unusual [8]. As for resistance testing, the incomplete knowledge of all resistance pathways limits its usefulness to fine-tuning new drug choices, even if the major mutations are known. As a result, the recommendations for its use in the clinical setting are not as strong as those for HIV-1 [6].

Immune Recovery

Therapy response in HIV-2 is, in general, worse than in HIV-1. As published by Matheron et al. [9], immune recovery is not as effective, with the increase of CD4 cells significantly lower than in matched HIV-1 controls. The patients included in this study started therapy late in the stage of infection (median CD4 count: 138 cells/mm³); recent data suggest that if therapy is started earlier, at a higher CD4 count, immune response can be more effective. This is one of the reasons why all published guidelines for HIV-2 treatment now recommend starting therapy at a higher threshold of CD4 cell count (350 cells/mm³).

Efficacy of Antiretrovirals

The main therapeutic targets in HIV-2 are protease, reverse transcriptase and, more recently, integrase. At the

amino acid level, HIV-1 and HIV-2 share a 50% identity in protease [10] and 60% in reverse transcriptase and integrase [11, 12]. Despite this identity, not all antiretrovirals developed for HIV-1 treatment are equally effective in HIV-2 infection: the virus is naturally resistant to the whole class of nonnucleoside reverse transcriptase inhibitors (NNRTI) and the fusion inhibitor enfuvirtide (T20) [13]. It also displays varying degrees of natural resistance to some protease inhibitors (PIs). Even for drugs with a similar efficacy in HIV-1 and HIV-2, several aspects may differ significantly.

Resistance Selection

Resistance selection is much faster in HIV-2 than in HIV-1. In an experiment published in 2007 by Ntemgwa et al. [14], HIV-1 and HIV-2 were cultured in the presence of several PIs. After 10–15 weeks in culture, 3 major mutations – I54M, I82F and L90M – were detected in cell cultures exposed to amprenavir, indinavir and nelfinavir; I82L arose in a cell culture exposed to tipranavir. After 25 weeks, 2 additional major mutations were also detected: I50V and I84V. During this time period, no major mutations were found in the HIV-1 cultures, with the exception of D30N (not selected in HIV-2) in the cultures exposed to nelfinavir.

This fast selection of drug resistance means that the time window for a regimen change is narrower than in HIV-1. Unfortunately, without the help of viral load to monitor therapy, a failure can go unnoticed for some time before its detection by the decrease in CD4 cell count; in the meantime, additional mutations may develop, limiting the availability of further treatment options.

Special Aspects of HIV-2 Therapy by Drug Class

Protease Inhibitors

As described above, HIV-2 proteases differ from HIV-1 in 50% of its 99 amino acids. Despite the similarities in the 3-dimensional structure [10], there is a wide variation in the efficacy of PIs against HIV-2. Three independent studies [15–17] showed that only saquinavir, lopinavir and darunavir have a half maximal inhibitory concentration (IC₅₀) value against wild-type HIV-2 in the same range of the one against HIV-1. All other PIs display varying degrees of natural resistance, ranging from 31-fold change (FC) for amprenavir or fosamprenavir, 8 FC for atazanavir, 3–4 FC for nelfinavir and 3 FC for indinavir. There is controversy about tipranavir, with 2 studies [15, 17] showing natural resistance and 1 reporting full efficacy [16].

One of the reasons for these observations could be the fact that several highly conserved amino acids, as well as some common polymorphisms, related to resistance in HIV-1: 10V, 20V, 32I, 33V, 36I, 46I, 47V, 71V, 73A, 89V and 93L [18] are present in wild type HIV-2 in HIV-2. However, this assumption can be an oversimplistic explanation, since differences in the viral genome can be responsible for selection of resistance at different positions than in HIV-1. A fact supporting this possibility is the full efficacy of darunavir in HIV-2 viruses displaying 32I + 47V + 89V, a set of mutations that in HIV-1 would mean intermediate resistance to the drug.

Even the fully active PIs have a low genetic barrier to resistance. The efficacy of lopinavir can be severely impaired by a single mutation (V47A), while saquinavir loses efficacy in the presence of L90M. The V47A mutation makes the virus hypersusceptible to saquinavir [19]. This fact supports the preferential use of lopinavir in first-line therapy, since saquinavir will remain fully active for a second-line regimen.

Even if darunavir can be used successfully in first-line therapy, there is not enough data about its resistance pathways, which affects our ability to use it in sequential therapy. In a few cases, a relative inefficacy in salvage therapy was observed, unlike in HIV-1. Further research will be needed until proper recommendations about the use of darunavir can be established.

Nucleoside Reverse Transcriptase Inhibitors

All nucleoside reverse transcriptase inhibitors (NRTIs) display an in vitro sensitivity in HIV-2 which is similar to that in HIV-1 [13, 20]; however, their use in vivo shows some differences from HIV-1.

Resistance to thymidine analogs – stavudine and, to a much lesser extent, zidovudine – does not follow the usual pathway of selection of mutations at positions 41, 67, 70, 210, 215 and 219. Instead, they select the multi-drug resistance mutation Q151M, which confers varying levels of resistance to all NRTIs with the exception of tenofovir [21]. This mutation is also easily selected by didanosine. In combination with the mutation at codon 111 (V111I) – which can also occur as a natural polymorphism – it confers a high-level resistance to all NRTIs [22]. Consequently, the use of stavudine and didanosine is not recommended for the treatment of HIV-2 infection.

Zidovudine, and to a lesser extent stavudine, also selects resistance by an alternative pathway, which starts, like in HIV-1, with amino acid changes in codon 215. Mutations can rarely be observed at positions 67 and 70, but mutations in positions 41 and 210 have never been re-

ported. Position 219 is highly polymorphic and apparently has no relation with resistance. Instead, several other mutations have been reported associated with zidovudine therapy, but its role in NRTI resistance remains elusive [23].

Lamivudine and emtricitabine select the M184I/V mutation, as they do in HIV-1 [22]. However, in the case of HIV-2, there is no proof that this mutation has an impact on viral fitness.

Tenofovir selects the same mutation as in HIV-1, K65R. The difference is that in HIV-2 this mutation is easily selected, which is not the case in HIV-1. Interestingly, this mutation has an antagonistic effect with substitutions at position 215, as observed in HIV-1 [24].

Finally, abacavir appears to select the same mutations as in HIV-1 – M184V, L74V, Y115F and K65R – but its efficacy is severely affected by the Q151M mutation [22].

Integrase Inhibitors

Raltegravir and elvitegravir have a similar activity in HIV-1 and HIV-2 in vitro [25], with a potent inhibition of both viruses. In vivo, raltegravir has also proved to be a potent inhibitor of HIV-2 replication [26]. However, its use has been restricted to salvage therapy, often in regimens with no other active drugs. In this setting, the benefits were only transient; the low genetic barrier of this drug to resistance allowed the virus to select resistance in a matter of weeks to months, with consequent therapy failure.

The major resistance mutations selected by raltegravir in HIV-2 have so far been similar to those selected in HIV-1 – N155H, Q148H/K/R, Y143R/H/K. In some raltegravir failures without any of these mutations, alternative pathways have been proposed [27], but further research is needed to uncover these mechanisms.

Recently, a potent inhibition of HIV-2 in vitro was described for the second-generation integrase inhibitor dolutegravir [28], but there is no experience on the use of this drug in vivo.

Entry Inhibitors

HIV-2 can use several coreceptors for cellular infection (CCR5, CXCR4, CCR3, BOB, BONZO), but CCR5 and CXCR4 are the major coreceptors for virus entry [29, 30]. There is almost no experience in the use of coreceptor antagonists in vivo. They have proved able to inhibit most R5 strains of HIV-2 in vitro – even if the lack of efficacy against some R5 strains remains unexplained. There is a case report in the literature only describing the use of maraviroc in a highly treatment-experienced pa-

tient, with at least transient efficacy [31]. Recently, the molecular determinants for CXCR4 use were uncovered [32], which will allow a more informed use of maraviroc in the HIV-2 setting.

Conclusions

The treatment of HIV-2 infection must take into account the specificities of this virus. Viral load is not a good tool for monitoring therapy as it is in HIV-1, resistance testing lacks the precision it has in the HIV-1 setting and immune recovery can be impaired if treatment which recommends an earlier start is started too late (CD4 cell count below 200 cells/mm³).

Not all antiretrovirals are effective in the HIV-2 setting. NNRTIs and fusion inhibitors are inactive and the virus is at least partially resistant to some PIs, which have a low genetic barrier to resistance. Even if NRTIs seem to be equally active, different resistance pathways, and an apparently easy selection of at least some resistance mutations must be taken into account when selecting new regimens. Integrase inhibitors are highly effective, but there is no data to allow a recommendation on when to use these compounds, for a first-line or later regimen. Entry inhibitors show some potential in vitro, but whether they are really useful in vivo has yet to be established.

There remain a lot of unanswered questions regarding HIV-2 therapy, clearly demonstrating that further research is needed to optimize the available resources.

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