How Individual Can Personalized Antiretroviral Treatment Be? Deep Salvage in an HIV-1-Infected Patient

Bjoern Jensen^a Stefan Esser^b Rolf Kaiser^c Nadine Luebke^c
Dieter Häussinger^a

^aDepartment of Gastroenterology, Hepatology and Infectious Diseases, Düsseldorf University Hospital, Düsseldorf,

^bDepartment of Dermatology, University of Essen, Essen, and ^cDepartment of Virology, University of Cologne, Cologne, Germany

Key Words

Salvage • HIV-1 • Personalized therapy • Antiretroviral treatment

Abstract

We present an HIV-1-infected male (who is now 52 years old) with a multi-drug-resistant virus and discuss the considerations finally leading to an antiretroviral regimen resulting in long-term viral suppression and excellent immunological response in a deep salvage situation. Even in a desperate situation with high-level multi-class resistance, highly individual, personalized antiretroviral regimes can be tailor-made to achieve unexpected improvements in the health status of a patient.

Copyright © 2012 S. Karger AG, Basel

Case Report

Patient's History

HIV infection (HIV-1 subtype B) was diagnosed in 1994 in a 35-year-old HSM presenting with cachexia, pneumocystis pneumonia and HIV-associated focal encephalitis. An antiretroviral treatment (ART) with the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine (AZT) and zalcitabine (ddC) was initiated. In 1996, a disseminated atypical mycobacteriosis was diagnosed. Consequently, the ART was changed to the first protease inhibitor (PI)-containing regimen containing AZT, ddC and saquinavir (SQV), and then in the same year, it was switched to AZT, lamivudine (3TC) and indinavir (IDV). In 1998, the ART was changed again to AZT, didanosine (ddI) and nelfinavir (NFV), followed by AZT, ddI, SQV and ritonavir (RTV)-boosted indinavir (IDV/r). In 1999, SQV was stopped. A nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen was first started in 2000 with AZT/3TC, abacavir (ABC) and efavirenz (EFV). At this point in time the patient had a CD4 cell count of 211/ μ l and a viral load of 142,000 copies/ml. In July 2001, the patient presented in our department with a CD4 cell count of 259/ μ l and a viral load of 275,000 copies/ml and a genotypic resistance test was performed.

The resistance test revealed an extensive resistance pattern in the reverse transcriptase showing the classical thymidine analog

mutation (TAM)-1 pathway including M41L, L210W, T215Y, and a multi-drug resistance mutation, namely the insertion T69SSG, as well as the typical EFV-induced K103N. In the protease, the following PI-specific resistance mutations were detected: L10I, M36I, L63P, A71V, I84V and L90M.

With the newly available RTV-boosted PI lopinavir (LPV/r), it was decided in July 2001 to change the ART regimen to stavudine (d4T), ddI, ABC and LPV/r, a treatment which had to be interrupted in December 2001 because of persistent elevated liver enzymes. The treatment was then restarted in January 2002 with a quadruple nuke (i.e. AZT/3TC/ABC/tenofovir (TDF)) regimen containing the newly licensed nucleotide reverse transcriptase inhibitor (NtRTI) TDF, still combined with the PI LPV/r. Suppression of the viral load could also not be achieved with this regimen, and in April 2003 the patient presented with a CD4 cell count of 93/ μ l and a viral load of 430,000 copies/ml.

In June 2003, the patient was enrolled in a clinical trial and received a combination of the NRTI ddI, the NNRTI nevirapine (NVP), LPV/r, tipranavir (TPV, study medication) and the fusion inhibitor enfuvirtide (T20). The treatment was continued until May 2004 when it had to be discontinued because of pronounced local injection site reactions caused by the treatment with T20 and because of more than 5-fold elevated transaminases. When this ART regimen had to be stopped after less than 1 year, the CD4 cell count had risen to 338/ μ l and the viral load has fallen to 1,346 copies/ml.

Despite an attempt to reinstate the treatment without NVP (to reduce the risk of hepatotoxicity), the CD4 cell count decreased again (56/ μ l) and the viral load rose (53,019 copies/ml). In November 2004, this ART regimen had to be terminated due to hepatotoxicity, probably caused by TPV. Shortly before the discontinuation of this regimen, another resistance test was performed that shows, in addition to I84V, the PI mutation I54V consistent with the TPV treatment, as well as a mutation in gp41 (N43D) which is associated with a decreased susceptibility to T20. Lacking new treatment options, the patient was then treated with a double PI regime (LPV/r, SQV), which resulted in a further drop in CD4 cell count to 26/ μ l and a viral load above 500,000 copies/ml.

In the absence of other treatment options and the high risk of clinical complications at this point in time, an ART comprising d4T, 3TC, EFV, fosamprenavir (FPV/r) and T20 was started in March 2005, even with the knowledge that past resistance tests showed resistance for every one of these drugs. Nevertheless, this regimen achieved a transient increase in CD4 cells up to 296/ μ l and a decrease of the viral load to 3,180 copies/ml but failed shortly thereafter. After 1 year the CD4 cell count dropped down to 87/ μ l and the viral load rose to 545,000 copies/ml and the patient was enrolled in the next clinical trial. Instead of T20, a treatment with maraviroc (MVC) or a placebo combined with the same 'optimized' backbone regimen as before, of d4T, 3TC, FPV/r and EFV, was started, which resulted in a further drop of the CD4 cells to 59/ μ l and a rise of viral load up to more than 1 million copies/ml. At that time the patient developed progressive cachexia and massive diarrhea, which was consecutively diagnosed as intestinal cryptosporidiosis and CMV colitis. In September 2006, after a bridging regimen consisting of ABC/TDF and TPV/r, the patient was enrolled in the early access program for darunavir (DRV/r). After 1 month, the diarrhea symptoms improved, the CD4 cells increased to 78/ μ l and the viral load dropped to 1,492 copies/ml.

In the next months, however, the situation deteriorated again, the viral load increased, CD4 cells decreased and diarrhea worsened again, despite using loperamide, opium tincture and octreotide subcutaneously, and 900 mg of valganciclovir once daily from April 2006.

Another resistance test was performed to evaluate possible treatment options in the light of the upcoming new antiretroviral drugs like the integrase inhibitor raltegravir (RAL), the second-generation NNRTI etravirine (ETR) and the CCR5 coreceptor antagonist MVC.

Strategic Considerations regarding Possible Treatment Options in This Desperate Clinical Situation in June 2007

The adherence to the past ART regimens was excellent, so that in this respect no further optimization was possible. Adverse events like elevated liver enzymes and pronounced local injection site reactions further constricted the treatment options of the patient.

The Appearance of the ART Resistance Profile in the Different Classes

Nucleoside Reverse Transcriptase Inhibitors

The conserved mutations – M41L, L210W, T215Y and T69SSG – still represent the same high-level resistance to all NRTIs as already shown in 2001. Regarding a possible reduced viral replication capacity of an HIV harboring the insertion T69SSX and/or several TAM mutations, a positive effect of continuing NRTIs seemed very unlikely in this case, as obviously this particular virus was not 'unfit', judging by the fact that viral loads reached over 1 million copies/ml during NRTI-containing regimens.

Nonnucleoside Reverse Transcriptase Inhibitors

The mutations K103N and L100I were observed, indicating high-level resistance to EFV and NVP without reduced viral replicative capacity. When evaluating the ETR resistance score [1], the L100I scored 2.5, which is equivalent to an 'intermediate' susceptibility. Other interpretation systems like HIV-GRADE, Stanford HIVdb and REGA (www.HIV-GRADE.de) also scored this mutation pattern 'intermediate'.

Protease Inhibitors

The mutation profile for PIs appeared as follows: L10I, V11I, I13V, V32I, M36I, S73D, M46I, I54L, Q58E, L63P,

A71V, G73S, T74P, I84V, L89V and L90M. This pattern means that the patient accumulated a huge amount of PI-resistance mutations in more than 10 years on failing PI-containing regimens. Using the information supplied by the respective manufacturing companies the virus harbors at least 6 **DRV**- and 5 **TPV**-associated mutations. Using genotypic prediction tools like geno2pheno (www.genafor.org), high-level resistance was predicted for all PIs including DRV and TPV.

Entry Inhibitors

CCR5 Coreceptor Antagonists

At the time of investigation, genotypic testing with geno2pheno interpretation predicted a CCR5-using virus. But at the time of enrolment in the MOTIVATE trial in March 2006, a dual/mixed-tropic virus was predicted by a phenotypic test (Trofile assay), emerging between screening and baseline. The patient was randomized to the placebo arm in the MOTIVATE trial and the regimen (optimized backbone regimen otherwise unchanged from the previous failing regimen) failed, as we have already mentioned. MVC is mostly tolerated very well and the development of a classic resistance is less frequent, which makes it an interesting option in patients with complex resistance patterns. The majority of cases in the MOTIVATE and MERIT trials with failing MVC-containing regimens are described with a switch of the predominant virus strain using the CCR5 coreceptor to a strain using the CXCR4 coreceptor. The CXCR4-using virus that emerged during the phase 3 MOTIVATE trials of the CCR5 antagonist MVC was interpreted to come from pretreatment CXCR4 reservoirs, not from a real coreceptor 'switching' [2, 3].

Fusion Inhibitors

Discontinuation resulted upon detection of a mutation N43D in October 2004 conferring resistance to T20 and also due to the repeatedly pronounced local injection site reactions. On the other hand, consistent with published data, T20 mutations seem to reduce viral fitness, i.e. recycling T20 could be useful in such a situation with very limited options.

Integrase Inhibitors

No baseline mutation was detected. RAL is the most promising of the available drugs in this case, but the limited background options and the low genetic barrier (single-point mutations resulting in high resistance) in addition to a high viral load made the attempt to administer RAL risky.

Decision Considering the Options

Due to legal restrictions in Germany it was not possible to combine two investigational antiretroviral agents from clinical trials or early access programs, so we decided to start the patient on a retroviral regimen consisting of the two RTV-boosted PIs DRV and atazanavir (ATV), RAL and T20.

We chose DRV because it had been well tolerated by the patient in the past and we rated DRV probably the 'best' of the PI class, even if one has to assume a high-level resistance to DRV with the detection of 6 DRV-associated mutations. We combined it with ATV to get a possible positive effect like in other double PI regimens, based on the different resistance patterns of these PIs, although no resensitizing mutations like the L76V were present. The data concerning the pharmacokinetics of DRV/ATV showed that these drugs can be safely coadministered without dose adjustments. Moreover, in this exceptional situation, we wanted to benefit from the observation that RAL levels are increased [4] ($C_{\max}$ 24% higher, AUC 41% higher, $C_{\min}$ 77% higher) and particularly more stable when combined with ATV due to the interference of ATV with the RAL-metabolizing enzyme UGT1A1. The use of RAL obviously took into account the positive data from the BENCHMRK trials, [5] and also it was the only available substance from a class without pre-existing resistance mutations (neglecting the ambiguity regarding the coreceptor usage in the case of MVC). The patient was thus enrolled into the early access program for RAL. As mentioned before, the additional application of MVC or ETR was not possible at that time because of legal restrictions. We were quite uncertain whether the double PI 'backbone' DRV/ATV/r would have enough potency to protect RAL from failing, so we decided to also administer T20, due to its probable effect on viral replication and because data are available that show a prolonged survival of patients in deep salvage situations when T20 is recycled, even in the presence of resistance mutations or after a previous failure [6]. Modifications of the administration of T20 to make the application tolerable for a longer period of time were warranted, as the injection site reactions of T20 were very pronounced in this patient when used in the past. After administering T20 subcutaneously into the patient's back (instead of the abdomen, upper thighs and arms) by a nursing service under optimized circumstances (like reconstitution, very slow injection) T20 was tolerated much better, with only mild local reactions, and is still now used by the patient after almost 4 years (fig. 1).

Fig. 1. Summary of the development of the CD4 cell count and the HIV viral load from March 2006 to May 2011 in relation to the different drugs administered.

Two weeks after starting this new ART regimen in June 2007, the CD4 cells increased to 76/ μ l, the viral load rapidly dropped to 428 copies/ml, and subsequently declined only slowly to 143 copies/ml after 10 weeks and to 41 copies/ml after 17 weeks.

At this time, MVC was approved and we decided in November 2007 to administer it as well (150 mg b.i.d.) to prevent another failure of an ART regimen in this patient with probably deleterious consequences. Even with the past detection of a dual/mixed tropism HIV by the Trofile assay in March 2006, we decided to give MVC. This decision was based on the available genotypic prediction of a CCR5-using virus and on the theoretical consideration that the resistance pattern could be different in possibly already-existing CXCR4-using viruses. In week 24 (5 weeks after the addition of MVC), surprisingly, the viral load increased slightly to 71 copies/ml, but then in week 28, it dropped below the detection level of 40 copies/ml. Clinically, the patient felt much better and the diarrhea stopped around 10 weeks after the therapy switch. The patient gained 11 kg in weight and the CD4 cells had already reached 419/ μ l in week 28. In April 2008, after the detection of viral loads of 93 and 101 copies/ml in weeks 34 and 38, respectively, a resistance test was performed which could not be achieved on the RNA level, but the prediction of the coreceptor tropism was based on proviral DNA analysis, which still predicted a CCR5-using virus. After RAL was licensed and ETR became available through an early access program, we finally decided to also add ETR to the regimen in April 2008. The main reason for this decision was that in the case

of any failure of the actual regimen there would probably be no treatment options available for some years. ETR, with its predicted intermediate activity and known pharmacokinetic compatibility to this regimen, seemed to be a good option to consolidate the therapy success achieved up to this point. After this add-on, the viral load has now been continuously undetectable for 3 years, and the CD4 cell values have constantly been above 500/ μ l. The tolerability of the regimen is very good apart from the mostly mild local injection site reactions due to T20 and a mild hyperbilirubinemia caused by ATV. The tablet burden was initially 16 tablets/day and therefore quite high but due to new formulations becoming available for ATV, DRV and ETR in the meantime, this burden decreased to 11 tablets/day. This is tolerated without any problems by the patient, since the overall improvement in his quality of life and future prospects is immense.

Conclusion

Even in such a desperate situation with multiclass highly drug-resistant HIV, an individual, personalized ART regimen can be tailor-made, taking into consideration the current and past resistance situation, pharmacokinetics, side effects, comorbidities and the particular life circumstances and wishes of the patient. Unexpectedly positive results like long-term viral suppression, eminent immunological recovery and a distinct improvement in quality life can be achieved.

References

- 1 Vingerhoets J, Tambuyzer L, Azijn H, Hoogstoel A, Nijs S, Peeters M, de Béthune M, De Smedt G, Woodfall B, Picchio G: Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled phase III clinical studies. *AIDS* 2010;24:503–514.
- 2 Westby M, Lewis M, Whitcomb J, Youle M, Pozniak AL, James IT, Jenkins TM, Perros M, van der Ryst E: Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pre-treatment CXCR4-using virus reservoir. *J Virol* 2006;80:4909–4920.
- 3 Lewis M, Simpson P, Fransen S, et al: CXCR4-using virus detected in patients receiving maraviroc in the phase III studies MOTIVATE 1 and 2 originates from a pre-existing minority of CXCR4-using virus. *Antivir Ther* 2007;12:65.
- 4 Sekar VJ, Lefebvre E, De Marez T, Spinoza-Guzman S, De Paepe E, Vangeneugden T, Hoetelmans RM: Pharmacokinetics of darunavir (TMC 114) and atazanavir during coadministration in HIV-negative, healthy volunteers. *Drugs* 2007;8:241–248.
- 5 Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, Loutfy MR, Lennox JL, Gatell JM, Rockstroh JK, Katlama C, Yeni P, Lazzarin A, Clotet B, Zhao J, Chen J, Ryan DM, Rhodes RR, Killar JA, Gilde LR, Strohmaier KM, Meibohm AR, Miller MD, Hazuda DJ, Nessel ML, DiNubile MJ, Isaacs RD, Nguyen BY, Teppler H, BENCHMRK Study Teams: Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008;359:339–354.
- 6 Cossarini F, Galli L, Gianotti N, Hasson H, Clementi M, Soria A, Salpietro S, Lazzarin A, Castagna A: Survival of HIV-1 infected multidrug-resistant patients recycling enfuvirtide after a previous failure. *J Acquir Immune Defic Syndr* 2009;51:179–184.