AIDS Rev. 2007;9:246-53

Treatment of Heavily Antiretroviral-Experienced HIV-Infected Patients

Jan van Lunzen

Infectious Diseases Unit, University Medical Centre Hamburg-Eppendorf and Heinrich-Pette-Institute for Experimental Virology and Immunology, Hamburg, Germany

Abstract

In 2008, the goal of antiretroviral therapy is the suppression of viral load to undetectable levels (< 50 HIV-RNA copies/ml) even in heavily pretreated patients harboring multidrug-resistant viruses. This ambitious goal can be achieved by combining at least two fully active antiretroviral drugs with an optimized background regimen according to genotypic and phenotypic resistance testing. This favorable situation has been accomplished by the advent of new compounds in already known drug classes (e.g. second-generation protease inhibitors and nonnucleoside reverse transcriptase inhibitors) as well as thanks to the development of new drug classes with a different mode of action (e.g. fusion inhibitors, integrase inhibitors, and coreceptor antagonists). Moreover, new diagnostic tools have been developed to better predict virologic response and tolerability of a given regimen in the individual patient, such as weighted mutation scores, virtual phenotypes, viral tropism assays, pharmacogenetics and pharmacokinetic analyses. This new array of therapeutic and diagnostic tools requires a highly specialized training of the treating physician to achieve the ultimate goal of halting disease progression. The purpose of this review is to introduce the new drugs and drug classes, and discuss their safety and use in combination therapy of multidrug-resistant viruses, guided by new diagnostic tools. **(AIDS Rev. 2007;9:246-53)**

Corresponding author: Jan van Lunzen, v.lunzen@uke.uni-hamburg.de

Key words

HIV. Antiretroviral therapy. Tipranavir. Darunavir. Maraviroc. Raltegravir. Etravirine. Drug resistance.

Introduction

Current guidelines recommend that the goal of antiretroviral therapy, even in highly treatment-experienced HIV-1-infected patients, is the suppression of viral load to undetectable levels (< 50 copies/ml)[1,2]. Maintaining undetectable viral load minimizes the risk of virologic failure and the development of additional resistance mutations, AIDS progression, and death[3-7]. This goal is attainable by adding at least two or more fully active agents, as determined by resistance testing and prior treatment history, to an optimized background regimen[2].

New substances from known drug classes (protease inhibitors, PI, and nonnucleoside reverse transcriptase inhibitors, NNRTI) have been developed and licensed, such as second-generation PI (tipranavir, darunavir), or are awaiting approval shortly, such as the second-generation NNRTI etravirine (TMC-125). Moreover, the antiretroviral armamentarium has been expanded by the development of innovative drugs with distinct mode of action, targeting events in the viral replication cycle which are not influenced by current drug classes. Here, the introduction of chemokine receptor-5 (CCR5) antagonists, integrase inhibitors, and fusion inhibitors into clinical practice has clearly proven superior efficacy in heavily pretreated patients.

These developments have been accompanied by the introduction of new diagnostic and predictive tools, which

Correspondence to:
Jan van Lunzen, MD PhD
Infectious Diseases Unit
University Medical Centre Hamburg-Eppendorf
Martinistr. 52
20246 Hamburg
Germany
E-mail: v.lunzen@uke.uni-hamburg.de

further enhance the likelihood of achieving maximal viral suppression in this hitherto difficult to treat patient population. This review will focus on the most relevant clinical issues of these new options with respect to their optimal use as evidenced in recently published clinical trials.

Second-generation PI and NNRTI

Two so-called second-generation PI have been approved so far for the treatment of antiretroviral-experienced patients: tipranavir and darunavir. Both drugs have been developed for the treatment of PI-experienced patients and show little cross-resistance to classical PI. However, each drug has a distinct mutational profile with some overlap, which deserves special attention and directs their differentiated use (see below). In addition, etravirine was developed as a second-generation NNRTI with retained activity against HIV with broad cross-class resistance against "classical" NNRTI.

Tipranavir

Tipranavir is a non-peptidomimetic PI with a reasonable pharmacokinetic profile when boosted with ritonavir (2 x 200 mg)[8]. Two pivotal clinical trials in treatment-experienced patients (RESIST-1 and -2) have lead to the licensing of the drug in this patient population. The RESIST-1 and -2 studies demonstrate that in highly treatment-experienced patients, ritonavir-boosted tipranavir is superior to a comparator PI. When given in combination with a second fully active drug (e.g. enfuvirtide), the virologic response (achieving viral load < 50 copies/ml) can be maximized substantially[8-13]. Durable treatment responses to tipranavir/ritonavir are maintained through 156 weeks, with a similar adverse event profile to ritonavir-boosted comparator PI[8,13]. In addition, the majority of highly treatment-experienced recipients of tipranavir/ritonavir 500/200 mg twice daily did not develop grade 3/4 transaminase elevations; those who did were mostly asymptomatic and manageable, with very few discontinuations of study drug due to hepatotoxicity[14]. Among treatment-experienced patients receiving the approved standard dose of tipranavir/ritonavir 500/200 mg twice daily in phase IIb and III trials through 96 weeks (n = 1299), the large majority did not develop grade 3/4 transaminase elevations (88.9%). Most patients who developed grade 3/4 transaminase elevations were able to continue treatment uninterrupted or resume treatment after temporary discontinuation, with transaminase levels returning to grade ≤ 2 during the treatment period. Clinical hepatic serious adverse events were infrequent (1.1%)[14].

Darunavir

Darunavir (TMC114) with low-dose ritonavir at a dose of 600/100 mg twice daily has demonstrated sustained efficacy and favorable safety in patients with a broad range of treatment experience[15-17]. The results of the POWER 1 and 2 studies in treatment-experienced patients suggested that darunavir/ritonavir at all doses provided a safety profile comparable to that seen with control PI[18,19]. It has been shown that darunavir plasma concentrations are above the EC_{50} target concentration of 55 ng/ml (wild-type virus), and darunavir/ritonavir has a long half-life in the absence of a clear dose/response relationship for safety and tolerability. The data presented in the POWER 1 and 2 studies support the use of darunavir/ritonavir 600/100 mg twice daily in treatment-experienced patients[19]. Here, favorable outcome and superior activity could be demonstrated in patients with previous multiple treatment failures up to 48 weeks. In these randomized, multinational, phase IIB studies, efficacy and safety of darunavir in combination with low-dose ritonavir was evaluated in treatment-experienced HIV-1-infected patients. A pooled subgroup analysis to update results at week 48 for patients receiving darunavir/ritonavir 600/100 mg twice daily compared with those receiving other PI was presented this year[15]. At week 48, 67 of 110 (61%) darunavir/ritonavir patients compared with 18 of 120 (15%) of control PI patients had viral load reductions of ≥ 1 $\log_{10}$ copies/ml from baseline (primary endpoint: difference in response rates 46%; 95% CI: 35-57%; $p < 0.0001$). Based on a logistic regression model including stratification factors (baseline number of primary PI mutations, use of enfuvirtide, baseline viral load) and study as covariates, the difference in response was 50% (OR: 11.72; 95% CI: 5.75-23.89). In the darunavir/ritonavir group, rates of adverse events were mostly lower than or similar to those in the control group when corrected for treatment exposure. No unexpected safety concerns were identified.

Etravirine (TMC-125)

Etravirine (TMC-125) is a NNRTI with retained activity against NNRTI-resistant HIV-1 in phase IIb trials. Thus, a randomized, double-blind, placebo-controlled, phase III trial (Duet-2) was initiated and first results were published in 2007[20]. In this trial, HIV-1-infected patients on failing antiretroviral therapy with evidence of resistance to currently available NNRTI and at least three primary PI mutations were eligible for enrolment if on stable (eight weeks unchanged) antiretroviral therapy with plasma HIV-1 RNA > 5000 copies/ml. Patients were randomly assigned

to receive either TMC-125 (200 mg) or placebo, each given twice daily with darunavir/ritonavir, investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors, and optional enfuvirtide. The primary endpoint was the proportion of patients with confirmed viral load < 50 copies/ml at week 24. By week 24, 51 of 295 (17%) patients in the TMC-125 group and 73 of 296 (25%) in the placebo group had discontinued, mainly because of virologic failure; 183 (62%) patients in the TMC-125 group and 129 (44%) in the placebo group achieved confirmed viral load < 50 copies/ml at week 24 (difference 18%; 95% CI: 11-26; p = 0.0003). The type and frequency of adverse events were much the same in the two groups. It was concluded that the combination of darunavir/ritonavir and etravirine is an attractive future option for heavily pretreated patients with multiple-drug failure[20].

Approval for this combination is awaited in 2008 in this patient population. It should be pointed out that the response rate of patients achieving an undetectable viral load was clearly the best if any of the abovementioned substances was combined with at least one other fully active drug in the combination regimen. In most cases this fully active drug was enfuvirtide, as outlined by the superior responses of patients receiving one of the abovementioned investigational drugs with new enfuvirtide.

Coreceptor antagonists

Maraviroc

Maraviroc is a selective and slowly reversible CCR5 antagonist that is active *in vitro* against a wide range of clinical isolates, including those resistant to existing drug classes. In healthy volunteers and asymptomatic HIV-1-infected patients, monotherapy with maraviroc at doses up to 300 mg twice daily for up to 28 days demonstrated a safety and tolerability profile that was not significantly different to placebo, with a decrease of viral load of approximately 2 $\log_{10}$ in HIV-infected patients[21]. Pharmacokinetic studies suggested that both once and twice daily dosing might be possible. Consequently, this drug was further developed into later clinical stages.

In two phase III studies, MOTIVATE 1 and MOTIVATE 2, it has been demonstrated that a 300 mg dose equivalent of maraviroc, given once or twice daily, when dosed in combination with optimized background therapy in treatment-experienced patients infected with CCR5-tropic HIV-1, leads to a greater and clinically relevant decline in viral load than optimized background therapy alone (placebo), with a mean reduction in HIV RNA from baseline to week 24 of at least 1.8 $\log_{10}$ copies/ml compared to approximately 1.0 $\log_{10}$ copies/ml with optimized background therapy alone[21]. This translated to approximately a twofold increased likelihood of achieving a viral load < 50 copies/ml in patients receiving maraviroc compared to placebo-treated patients. This was achieved in about half of the total heavily treatment-experienced patient population treated with maraviroc. In these studies, enfuvirtide and tipranavir were available for the optimized background therapy, but not darunavir and raltegravir. Again, it was shown that the substance performed best if combined with at least two other active drugs, as judged by sensitivity scores. Especially the combination of maraviroc with enfuvirtide, in patients who were previously naive to it, yielded excellent virologic responses.

The placebo response of > 1.0 $\log_{10}$ copies/ml provides evidence that the optimized background therapy selections for these studies were appropriate, providing these patients with a clinically relevant reduction in HIV-1 RNA from baseline, which was comparable or greater than previous registration trials for approved antiretroviral agents[22-25]. The addition of maraviroc to this optimized background therapy, however, resulted in approximately 1.0 $\log_{10}$ copies/ml reduction in HIV-1 RNA above that of the placebo response. The greater efficacy provided by maraviroc compared with placebo in patients infected with CCR5-tropic HIV-1 was observed regardless of a patient's screening HIV-1 RNA level (< 100,000 copies/ml or > 100,000 copies/ml) or CD4 cell count at baseline. The dose adjustment implemented for patients receiving a PI (except for tipranavir/ritonavir) or delavirdine in their optimized background therapy was appropriate and did not adversely affect the efficacy outcome.

The mean change in CD4 cell count (cells/µl) was greater for the maraviroc treatment groups than placebo. The adjusted mean CD4 cell count increases observed in patients receiving maraviroc once and twice daily were 109 and 106 cells/µl, respectively, compared with placebo where an increase of 57.4 cells/µl was demonstrated. Maraviroc administration in patients infected with dual/mixed tropic or CXCR4-using HIV-1, or in patients whose virus was non-phenotypable, did not result in adverse effects on viral load or CD4 count.

There was no indication of a clinically meaningful difference between maraviroc once and twice daily across the whole population studied, based on the primary and key secondary efficacy endpoints measured following 24 weeks of therapy. However, certain subgroups, notably patients with lower CD4 count, higher viral loads and fewer potentially active drugs in their optimized background therapy, seem to receive greater benefit from maraviroc twice daily.

These studies also demonstrated an acceptable safety and tolerability profile with no significant effect on the corrected QT interval or an increase in the incidence of hepatotoxicity, infections, or malignancies, relative to placebo. Nasopharyngitis and bronchitis were the most common side effects, which were thought to be related to maraviroc treatment. No other infections were reported more often for maraviroc compared to placebo. The maraviroc treatment arms also showed a favorable lipid profile.

Vicriviroc

The clinical development of another CCR5 antagonist, vicriviroc, is not that advanced yet. Here, data from a phase II dose-finding study in treatment-experienced patients indicate an overall good antiviral efficacy of the 10 mg and 15 mg dose groups. In these patients, viral load dropped by 2 $\log_{10}$ after 48 weeks, which was superior to the placebo plus optimized background therapy control arm[26]. The exact optimum dosage of this drug remains to be defined and little is known about interactions with the other substances frequently used in heavily pretreated patients. Moreover, the development of vicriviroc was delayed by some safety issues in the past, which did not appear to be of clinical significance in the abovementioned phase II trial, but these data need further confirmation from ongoing studies with larger patient numbers.

Integrase inhibitors

Raltegravir (MK-0518)

After a long and troublesome time of development, another new class of substances has entered the clinic: the integrase inhibitors. They function through the inhibition of proviral DNA strand transfer, which is an essential step in the integration of viral DNA into the host genome catalyzed by the enzyme integrase. Two substances have currently entered later-phase clinical trials and one of them, raltegravir, is expected to be approved for the treatment of experienced patients in the beginning of 2008.

Raltegravir is being studied in two large, phase III, double-blind, placebo-controlled studies (BENCHMRK 1 and 2) that are evaluating the efficacy and safety of raltegravir plus an optimized background regimen in patients with triple class-resistant HIV-1 virus[27,28]. Eligible participants were those failing antiretroviral therapy with triple-antiretroviral class resistance and documented genotypic or phenotypic resistance to at least one NNRTI, one NRTI, and one PI, with a viral load > 1000 copies/ml. These were randomized 2:1 to raltegravir 400 mg twice daily or placebo. Optimized background therapy was selected by the treating physicians based on genotypic resistance analysis. Select investigational drugs (e.g. darunavir) were permitted to be part of optimized background therapy.

The primary endpoint was the proportion of patients that achieved HIV-1 RNA < 400 copies/ml at week 16. Additional efficacy endpoints included the percentage of patients with HIV RNA < 50 copies/ml as well as change from baseline in HIV-1 RNA levels and CD4 cell counts. At 16 weeks, the raltegravir arm was found to be superior in its antiretroviral effect compared to the placebo arm. About 77% of patients treated with raltegravir achieved the primary endpoint (viral load < 400 copies/ml) compared to 42% in the placebo group (61 vs. 34% for viral load < 50 copies/ml). The mean change in viral load was –1.88 $\log_{10}$ for raltegravir compared to –0.92 $\log_{10}$ in placebo recipients by week 16. This translated into a significantly better CD4 count increase in the raltegravir arm (84 vs. 36 cells/µl). Superior efficacy of the raltegravir arms over placebo was maintained regardless of baseline CD4 count, HIV RNA values, as well as genotypic and phenotypic scores in the optimized background therapy. Adverse events were similar between groups. These impressive antiviral results were underlined by a very rapid initial viral decay in a phase II study in antiretroviral-naive patients, which was superior to an efavirenz-based regimen[29].

Elvitegravir (GS-9137)

The second integrase inhibitor which has entered clinical studies is Gilead's compound elvitegravir, which has shown promising activity in treatment-experienced patients[30], but is somewhat later in development compared to raltegravir. In contrast to raltegravir, it needs boosting with ritonavir, but then can be applied once daily. Unfortunately, both integrase inhibitors are likely to select for the same resistance mutations. Thus development of cross-resistance is highly likely in patients failing either raltegravir or elvitegravir due to integrase inhibitor mutations. Integrase inhibitors have a rather low genetic resistance barrier and should thus be applied only in the context of other fully active drugs.

Combinations of new drugs and new drug classes

Tipranavir/ritonavir can be combined with new drug classes without any need for dose adjustment and with no clinically relevant drug-drug interactions[31-36].

Data from RESIST-1 and -2 (n = 1438) demonstrate that in comparison to ritonavir-boosted comparator PI plus new enfuvirtide patients, more than twice as many tipranavir/ritonavir plus new enfuvirtide patients achieved viral load < 50 copies/ml at 96 weeks (34.7 vs. 14.4%; p = 0.0002)[8,12]. Tipranavir/ritonavir plus enfuvirtide recipients maintained a durable response to treatment, which is superior to ritonavir-boosted comparator PI recipients through 156 weeks; twice as many patients (21.8 vs. 9.3%, respectively) achieved viral load < 50 copies/ml. The same positive effect of adding enfuvirtide to a second-generation PI has been demonstrated for darunavir/ritonavir in the POWER studies.

In addition to enfuvirtide, new drugs that seem likely to contribute to future treatment success include the integrase inhibitors raltegravir (MK-0518) and elvitegravir (GS-9137), and the CCR5 antagonist, maraviroc. Recently presented data show that tipranavir/ritonavir can be effectively combined with both maraviroc and raltegravir, without dose adjustment, to achieve undetectable viral load. In the MOTIVATE-1 and -2 studies, 59.4% of patients who received a combination of sensitive tipranavir/ritonavir and maraviroc, plus an optimized background regimen, achieved viral load < 50 copies/ml at 24 weeks[37,38]. Similarly, data from the BENCHMRK-1 and -2 studies showed good virologic responses at week 24 when tipranavir/ritonavir was combined with raltegravir; 70% of patients achieved viral load < 50 copies/ml[38,39].

As mentioned above, integrase inhibitors have a low genetic barrier to resistance, but supporting their use with other active drugs in the regimen, such as tipranavir/ritonavir or darunavir/ritonavir (which have a high genetic barrier to resistance), should decrease the likelihood of rapid emergence of drug resistance to these new classes[38,40].

In later lines of therapy failure, maraviroc has already proven its superiority over standard salvage therapies. Here, the overall assessment shows comparable benefit for maraviroc and raltegravir. Both drugs have proven to lead to sustained reduction of viral load to below the limit of detection in a high proportion of patients, which is comparable to earlier salvage trials with darunavir (POWER), tipranavir (RESIST), and enfuvirtide (TORO)[22-25]. The combination of both drugs will be highly interesting in this context in order to even increase the percentage of patients with complete control of viral replication to an extent that is observed in treatment-naive patients. Both drugs may be recommended in treatment-experienced patients with multiple drug failure due to resistance or intolerability in combination with two other active drugs. Whether it will be advisable to use maraviroc or raltegravir first, or one or the other even prior to second-generation PI (darunavir, tipranavir), remains to be elucidated. Certainly, there is a great potential for maraviroc to enter these earlier stages of salvage therapy. In later stages of salvage therapy, maraviroc will have an influence on the use of enfuvirtide in patients with the option of two other active drugs remaining. Here, enfuvirtide use will be delayed until maraviroc-based regimens fail. Moreover, in deeper salvage situations, maraviroc can be very efficiently combined with enfuvirtide, enhancing the potential armamentarium in late-stage disease. The combination with integrase inhibitors will be also of special interest in this setting and might even further delay enfuvirtide use[56].

New diagnostic tools

Early virologic response as a predictor of treatment outcome

The ability to determine in advance whether a patient is likely to respond to a particular therapy is a valuable tool for any treating physician. In the RESIST trial, tipranavir/ritonavir recipients with a viral load reduction ≥ 1.5 $\log_{10}$ copies/ml from baseline at week 8 were ten-times more likely to achieve undetectable viral load at week 48. Also, the recently developed tipranavir-weighted mutation score can be used to predict sensitivity to a tipranavir/ritonavir-based regimen. These new predictive tools, along with data demonstrating improved virologic responses when new drugs are used in combination, should encourage the use of these new diagnostic algorithms in the clinical setting.

Moreover, predictors of long-term treatment response can prevent the accumulation of drug-resistance associated mutations and the development of drug-related adverse events by avoiding unnecessary exposure to ineffective regimens[41]. As mentioned previously, resistance testing should be used to determine whether an agent is suitable for inclusion in a patient's treatment regimen.

There is evidence that early virologic responses in highly treatment-experienced patients are predictive of long-term virologic success[42]. In tipranavir/ritonavir recipients, a viral load reduction ≥ 1.5 $\log_{10}$ copies/ml from baseline at week 8 was predictive of achieving undetectable viral load (< 50 copies/ml) at week 48 (OR: 17.15; 95% CI: 9.83, 29.91; p < 0.001)[43]. Nearly half of all tipranavir/ritonavir plus new enfuvirtide patients with viral load reduction ≥ 1.5 $\log_{10}$ copies/ml from baseline at week 8 also achieved a viral load < 50 copies/ml at week 48. In comparison, only 7.4% of tipranavir/ritonavir plus new enfuvirtide recipients who did not have an early virologic response at week 8 went on to achieve viral load < 50 copies/ml at week 48. The same phenomenon can be observed in

patients treated with enfuvirtide; here, the week 4 viral response can be used to predict the later treatment outcome and thus help to guide antiviral therapy. Indeed, patients who do not show an adequate response to enfuvirtide after four weeks of therapy are unlikely to achieve viral suppression at a later time point; therefore it is recommended to stop the drug already in nonresponding patients at this early point in time[57].

This early virologic response criterion for long-term treatment outcome is already well established in the treatment of chronic hepatitis C and is used as a predictive tool to guide antiviral therapy. Whether early virologic responses at week 4 in HIV-infected patients can be generally used in analogy is likely, but remains to be proven in clinical studies.

A very rapid viral decay was demonstrated in antiretroviral-naive patients who received raltegravir, which was more pronounced compared to efavirenz, both used in combination with Combivir® (GlaxoSmithKline) for the first 12 weeks of the respective study. Corresponding studies in treatment-experienced patients are missing so far; thus, the clinical impact of this finding in advanced patients remains to be elucidated.

Virtual phenotypes and weighted mutation scores

Virologic response to tipranavir/ritonavir can be predicted by using the tipranavir-weighted mutation score, developed using data from the RESIST trials[44]. Patients who had a baseline phenotype were randomized and received at least one dose of tipranavir/ritonavir and were included in a base dataset. This group was divided further into score-development and evaluation datasets. Score development consisted of identifying mutations believed to increase sensitivity to tipranavir, applying models which related these mutations to different response variables, cross-validating the models, determining weighting for each mutation, and determining clinical cut-offs. The tipranavir-weighted mutation score was tested on an independent dataset against other commonly used scores and compared favorably, showing a better prediction than the unweighted-tipranavir, Stanford, and REGA Institute scores, while showing similar results to Virco's Virtual Phenotype. The tipranavir-weighted mutation score can be used to determine the course of a patient's HIV treatment[44].

Similar approaches have been undertaken, comparing virologic outcomes with known genotypes in large clinical databases and allowing for the assessment of the potential susceptibility of a given drug based on a virtual phenotype. These algorithms have further helped to individualize the choice of the right combination therapy in all lines of salvage therapies.

Viral tropism

Both preclinical selection experiments and exploratory *in vitro* studies conducted on pre- and post-treatment viruses from patients enrolled in the phase IIa and phase IIb/III maraviroc clinical program have found that maraviroc acts as a highly selective and potent inhibitor of CCR5-tropic viruses. Thus, an assay testing viral tropism (CCR5 versus CXCR4 coreceptor usage) will be mandatory before starting therapy with CCR5 antagonists[45]. Results from clinical phase III trials showed that approximately half of the treatment-experienced patient population screened in these trials harbored CCR5-tropic viral strains, with an unknown percentage of minority quasispecies showing CXCR4-tropic viruses[46]. A background change in tropism result from CCR5 to dual/mixed tropic between screening and baseline occurred in approximately 8% of patients. The clinical outcome in these patients was similar to that of patients with non-CCR5-tropic virus in one of these studies[47]. In patients with a CCR5 tropism result at screening/baseline who failed a maraviroc-containing regimen, emergence of CXCR4-using virus was seen in the majority of cases. However, the clinical relevance of this finding remains to be elucidated, since patients failing on a maraviroc-containing regimen had a larger mean increase in CD4 from baseline compared to placebo, irrespective of tropism result at time of failure. There is no evidence to suggest that changes in tropism result, which occur in the circulating virus from patients on maraviroc-containing regimens, are caused by mutation of a CCR5-tropic virus to a CXCR4-using virus (i.e. no evidence of tropism switch)[48].

The presence of CCR5-tropic strains depends on the stage of the disease; in general it is observed that CCR5-tropic strains occur in less-advanced stages of immunodeficiency and CXCR4-tropic strains will predominate in full-blown AIDS, with a mixed population intermediately[47]. No easy to use surrogate marker for tropism switch exists, leaving phenotypic tests as the ultimate choice for assessment of coreceptor usage[49]. This would argue for the use of CCR5 antagonists in patient populations in less-advanced stages of immunodeficiency, with a high likelihood of the presence of CCR5-tropic strains predominating[50].

Pharmacogenetic testing

Pharmacogenetic assays will play an increasing role in the treatment of HIV-infected patients in order to facilitate

a safer or more effective future use of complex drug regimens. So far, the only test with proven value in the clinical setting is the screening for HLA-B*5701 in order to prevent abacavir-associated hypersensitivity reactions. Here, the screening on this particular HLA haplotype and exclusion of corresponding patients from abacavir treatment has resulted in a significant reduction of hypersensitivity reactions against this drug, with a high predictive value of this test[51]. The same association has been reported for HLA-DRB1*0101 and nevirapine hypersensitivity. Other potential possibilities to apply pharmacogenetics in treatment guidance include the prediction of certain toxicities or pharmacokinetic profiles of a given drug. In this regard, the magnitude of hyperbilirubinemia induced by atazanavir or indinavir is associated with distinct polymorphisms in the UGT-1A1 enzyme[52]. Likewise, efavirenz-induced central nervous system toxicities are dose related and occur more frequently in patients with CYP2B6 allelic variants who display extensively high plasma drug levels due to altered metabolization kinetics of the drug[53]. Numerous other candidate genes are currently under study, which may allow a better prediction of drug safety and efficacy guided by pharmacogenetics in the near future[54,55].

Conclusions

In 2008, treatment of heavily antiretroviral-experienced patients should aim to achieve undetectable viral loads in these patients. This can be accomplished by combining at least two or more active drugs with an optimized background therapy based on phenotypic and/or genotypic resistance testing. New substances from known drug classes as well as new drug classes with distinct mode of action can be combined to allow for the creation of a maximally suppressive antiretroviral combination, even in those patients with multidrug-resistant viruses. This can be further optimized by including new diagnostic tools such as resistance scores, early virologic response kinetics, tropism assays, and pharmacogenetic assays into the decision-making process when starting a new treatment. This will lead to an increased proportion of treatment-experienced patients who can be treated with sustained antiviral potency and acceptable toxicity, minimizing the risk of virologic failure and the development of further resistance mutations.

References

1. U.S. Department of Health and Human Services. Panel on Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Accessed December 5, 2007. http://aidsinfo.nih.gov/.
2. Hammer S, Saag M, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. Top HIV Med. 2006;14:827-43.
3. Phillips A, Lepri A, Lampe F, et al. When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies. AIDS. 2003;17:1863-9.
4. Phillips A. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS. 2004;18:51-8.
5. Cozzi Lepri A, Sabin C, Staszewski S, et al. Resistance profiles in patients with viral rebound on potent antiretroviral therapy. J Infect Dis. 2000;181:1143-7.
6. Mocroft A, Ledergerber B, Viard J, et al. Time to virologic failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA study group. J Infect Dis. 2004;190:1947-56.
7. Zaccarelli M, Tozzi V, Forbici F. Achieving undetectable load after genotypic resistance test dramatically decreases HIV progression and survival even in more advanced patients. 5th European HIV Drug Resistance Workshop. Cascais, Portugal; 2007.
8. De Mendoza C, Morello J, Garcia-Gasco P, Rodríguez-Novoa S, Soriano V. Tipranavir: a new protease inhibitor for the treatment of antiretroviral-experienced HIV-infected patients. Expert Opin Pharmacother. 2007;8:839-50.
9. Gathe J, Cooper D, Farthing C, et al. Efficacy of the protease inhibitors tipranavir plus ritonavir in treatment-experienced patients: 24-week analysis from the RESIST-1 trial. Clin Infect Dis. 2006;43:1337-46.
10. Cahn P, Villacian J, Lazzarin A, et al. Ritonavir-boosted tipranavir demonstrates superior efficacy to ritonavir-boosted protease inhibitors in treatment-experienced HIV-infected patients: 24-week results of the RESIST-2 trial. Clin Infect Dis. 2006;43:1347-56.
11. Hicks C, Cahn P, Cooper D, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimized background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the RESIST studies: an analysis of combined data from two randomized open-label trials. Lancet. 2006;368:466-75.
12. Farthing C, Ward D, Hicks C, Johnson M, Cauda R, Cahn P. Tipranavir/r demonstrates superior and durable treatment response compared with comparator PI/r in highly treatment experienced patients: Week 96 RESIST 1 and 2 results. 46th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, California, USA; 2006.
13. Hicks C, Cahn P, Jelaska A, et al. Tipranavir/r maintains long term virologic suppression – Week 156 results of RESIST. 11th European AIDS Conference. Madrid, Spain; 2007.
14. Pol S, Benhamou Y, Rockstroh J, et al. Hepatic profile of tipranavir in treatment experienced HIV-1 infected individuals. 11th European AIDS Conference. Madrid, Spain; 2007.
15. Clotet B, Bellos N, Molina J, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomized trials. Lancet. 2007;369:1169-78.
16. Molina J, Cohen C, Katlama C, et al. Safety and efficacy of darunavir (TMC114) with low-dose ritonavir in treatment-experienced patients: 24-week results of POWER 3. J Acquir Immune Defic Syndr. 2007;46:24-31.
17. Madruga J, Berger D, McMurchie M, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomized controlled phase III trial. Lancet. 2007;370:49-58.
18. Katlama C, Esposito R, Gatell J, et al. Efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients: 24-week results of POWER 1. AIDS. 2007;21:395-402.
19. Haubrich R, Berger D, Chiliade P, et al. Week 24 efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients. AIDS. 2007; 21:F11-18.
20. Lazzarin A, Campbell T, Clotet B; DUET-2 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomized, double-blind, placebo-controlled trial. Lancet. 2007; 370:39-48.
21. Fatkenheuer G, Pozniak A, Johnson M, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nat Med. 2005;11:1170-2.
22. Cahn P, Villacian J, Lazzarin A, et al. Ritonavir-boosted tipranavir demonstrates superior efficacy to ritonavir boosted protease inhibitors in treatment-

experienced HIV-infected patients: 24-week results of the RESIST-2 trial. Clin Infect Dis. 2006;43:1347-5.
23. Gathe J, Cooper D, Farthing C, et al. Efficacy of protease inhibitors tipranavir plus ritonavir in treatment experienced patients: 24-week analysis from the RESIST-1 trial. Clin Infect Dis. 2006;43:1337-46.
24. Lalezari J, Henry K, O'Hearn M, et al. Enfuvirtide, and HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Eng J Med. 2003;348:2175-85.
25. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Eng J Med. 2003;348:2186-95.
26. Gulick R, Su Z, Flexner C, et al. ACTG 5211: phase II study of the safety and efficacy of vicriviroc (VCV) in HIV-infected treatment-experienced subjects: 48 week results. 4th IAS Conference 2007 [abstract TUAB102].
27. Cooper D, Gatell J, Rockstroh J, et al. Results of BENCHMRK-1, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. Program and abstracts of the 14th CROI; February 25-28, 2007; Los Angeles, California [abstract 105aLB].
28. Steigbigel R, Kumar P, Eron J, et al. Results of BENCHMRK-2, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. Program and abstracts of the 14th CROI; February 25-28, 2007; Los Angeles, California [abstract 105bLB].
29. Markowitz M, Nguyen B, Gotuzzo E, et al. Rapid onset and durable antiretroviral effect of raltegravir (MK-0518), a novel HIV-1 integrase inhibitor, as part of combination ART in treatment naive HIV-1 infected patients: 48-week data. 4th IAS Conference Sydney, Australia, 2007 [abstract TUAB104].
30. Zolopa A, Mullen M, Berger D, et al. The HIV integrase inhibitor GS-9137 has potent antiviral activity in treatment experienced patients. Program and abstracts of the 14th CROI; February 25-28, 2007; Los Angeles, California [abstract 143LB].
31. Vourvahis M, Kashuba A. Mechanisms of pharmacokinetic and pharmacodynamic drug interactions associated with ritonavir-enhanced tipranavir. Pharmacotherapy. 2007;27:888-909.
32. Raffi F, Battegay M, Rusconi S, Opravil M, Kraft M, Sabo J. Co-administering tipranavir/r (500/200 mg BID) and enfuvirtide in the RESIST studies resulted in superior virologic outcomes and a comparable safety profile compared to regimens containing tipranavir/r without enfuvirtide. 4th IAS Conference. Sydney, Australia; 2007.
33. Mathias A, Hinkle J, Enejosa J, Piliero P, Kearney B. Lack of pharmacokinetic interaction between ritonavir-boosted GS-9137 (elvitegravir) and tipranavir/r. 4th IAS Conference. Sydney, Australia; 2007.
34. Abel S, Taylor-Worth R, Ridgway C. Effect of boosted tipranavir on the pharmacokinetics of maraviroc (UK 427,857) in healthy volunteers. 10th European AIDS Conference. Dublin, Ireland; 2005.
35. Wenning L, Hanley H, Stone J. Effect of tipranavir + ritonavir on pharmacokinetics of MK-0518. 46th ICAAC San Francisco, USA; 2006.
36. Markowitz M, Nguyen B-Y, Gotuzzo F, et al. Potent antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, as part of combination ART in treatment -naïve HIV-1 infected patients. XVI International AIDS Conference. Toronto, Canada; 2006.
37. van der Ryst E. Efficacy of Maraviroc in combination with at least one other potent new antiretroviral drug: 24-week combined analysis of the MOTIVATE 1 and 2 studies. 4th IAS Conference. Sydney, Australia; 2007.
38. Jones J, Taylor B, Wilkin T, Hammer S. Advances in antiretroviral therapy. Top HIV Med. 2007;15:48-82.
39. Kumar P, Cooper D, Steigbigel R. Efficacy of raltegravir, an HIV integrase inhibitor, in combination with regimens containing enfuvirtide, darunavir, or tipranavir in patients with triple-class resistant virus: combined results from Benchmrk-1 and Benchmrk-2. 11th European AIDS Conference. Madrid, Spain; 2007.
40. Lederman M, Miller V, Weller I, et al. A new approach for 'deep salvage' trials in advanced HIV infection. AIDS. 2007;21:1503-6.
41. Polis M, Sidorov I, Yoder C, et al. Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy. Lancet. 2001; 358:1760-5.
42. Raffi F, Katlama C, Saag M, et al. Week-12 response to therapy as a predictor of week 24, 48, and 96 outcome in patients receiving the HIV fusion inhibitor enfuvirtide in the T-20 versus Optimized Regimen Only (TORO) trials. Clin Infect Dis. 2006;42:870-7.
43. Ernst J, Farthing C, Cooper D, et al. Week 8 response predicts week 48 virologic responses to tipranavir/r in the RESIST studies. 4th IAS Conference. Sydney, Australia; 2007.
44. Scherer J, Boucher C, Baxter J, Schapiro J, Kohlbrenner V, Hall D. Improving the prediction of virologic response to tipranavir: the development of a tipranavir weighted score. 11th European AIDS Conference. Madrid, Spain; 2007.
45. Petropoulos C, Parkin N, Limoli K, et al. A novel phenotypic drug susceptibility assay for HIV type 1. Antimicrob Agents Chemother. 2000;44:920-8.
46. Moore J, Kitchen S, Pugach P, et al. The CCR5 and CXCR4 coreceptors - central to understanding the transmission and pathogenesis of the HIV type 1 infection. AIDS Res Hum Retroviruses. 2004; 20:111-26.
47. Wilkin T, Su Z, Kuritzkes D, et al. HIV type 1 chemokine receptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. Clin Infect Dis. 2007;44:591-5.
48. Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using HIV-1 variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. J Virol. 2006; 80:4909-20.
49. Whitcomb J, Huang W, Fransen S, et al. Development and characterization of a novel single-cycle recombinant-virus assay to determine HIV type 1 co-receptor tropism. Antimicrob Agents Chemother. 2007;51:566-75.
50. Moyle G, Wildfire A, Mandalia S, et al. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. J Infect Dis. 2005;191:866-72.
51. Rodriguez-Novoa S, Garcia-Gasco P, Blanco F, et al. Value of the HLA-B*5701 allele to predict abacavir hypersensitivity in Spaniards. AIDS Res Hum Retroviruses. 2007;23:1374-6.
52. Rodriguez-Novoa S, Martin-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. AIDS. 2007;21:41-6.
53. Rodriguez-Novoa S, Barreiro P. Influence of 516G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. Clin Infect Dis. 2005;40:1358-61.
54. Soriano V, Puoti M, Garcia-Gasco P, et al. Antiretroviral drugs and liver injury. AIDS. 2008;22:1-13
55. Rodriguez-Novoa S, Barreiro P, Jimenez-Nacher I, Soriano V. Overview of the pharmacogenetics of HIV therapy. Pharmacogenomics J. 2006;6:234-45.
56. Salzberger B, Däumer M, Gute P, et al. Consensus Recommendation from a Group of German Experts for the Use of Enfuvirtide in Heavily Pretreated HIV Patients. Eur J Med Res. 2007 March 26;12:93-102.
57. van Lunzen J. How will CCR5 antagonists influence the recommendations for the antiretroviral treatment of HIV infection. Eur J Med Res. 2007; 12:435-40.