

Multidrug resistance: a clinical approach

Yazdan Yazdanpanah

Service Universitaire des Maladies Infectieuses et du Voyageur, Centre Hospitalier de Tourcoing and EA 2694, Faculté de Médecine de Lille, Tourcoing, France

Correspondence to Yazdan Yazdanpanah, MD, PhD, Service Universitaire des Maladies Infectieuses et du Voyageur, Centre Hospitalier de Tourcoing (Faculté de Médecine de Lille), 135, rue du Président Coty – B.P.619, F 59208 Tourcoing, France
Tel: +33 320 69 46 16; fax: +33 320 69 46 15; e-mail: yyazdan@yahoo.com

Current Opinion in HIV and AIDS 2009, 4:499–506

Purpose of review

New antiretroviral agents have recently become available within existing and new drug classes, increasing treatment options for patients with multidrug-resistant virus. This review discusses the challenges that these new agents pose for the management of treatment-experienced patients.

Recent findings

Recent studies of the efficacy and safety of new antiretroviral drugs illustrate that drug regimens containing new agents are well tolerated and can suppress viremia in even the most drug-resistant patients. The goal of any new regimen should therefore be suppression of plasma HIV RNA levels to less than 50 copies/ml, even in treatment-experienced patients. Patients should be given a regimen with at least two, or preferably three, fully active drugs after careful consideration of their treatment and adherence history, current and prior genotype tests, comorbidities, and concomitant medications. Newer and more tolerable agents also offer the possibility of regimen simplification among patients with multidrug-resistant HIV who are virologically suppressed.

Summary

Clinicians must optimize the pairing and sequencing of recently available antiretroviral agents. Future studies should continue to investigate the optimal use of new agents in order to further improve long-term treatment efficacy in patients with multidrug-resistant HIV infection.

Keywords

HIV, multidrug-resistant virus, treatment-experienced patients

Curr Opin HIV AIDS 4:499–506
© 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins
1746-630X

Introduction

Over the past two decades, thanks to combination antiretroviral therapy (cART), the HIV has become a treatable chronic disease, with HIV mortality rates approaching those of the general population [1–3,4[•]]. Using data from Concerted Action on SeroConversion to AIDS and Death (CASCADE) study, a collaboration of 23 cohorts of HIV seroconverters in Europe, Australia, and Canada [5], Bhaskaran *et al.* [4[•]] recently reported that mortality rates among HIV-infected patients are similar to the general population in the first 5 years of infection. As the duration of infection increases, however, mortality rates among HIV-infected patients increase compared with the general population [4[•]]. The authors state that this long-term excess mortality is likely to persist because cART-related toxicity, nonadherence, and drug resistance are likely to increase with time on cART. Others have demonstrated that HIV drug resistance, particularly multidrug class-wide resistance, is associated with an increased incidence of AIDS-defining events and death [6].

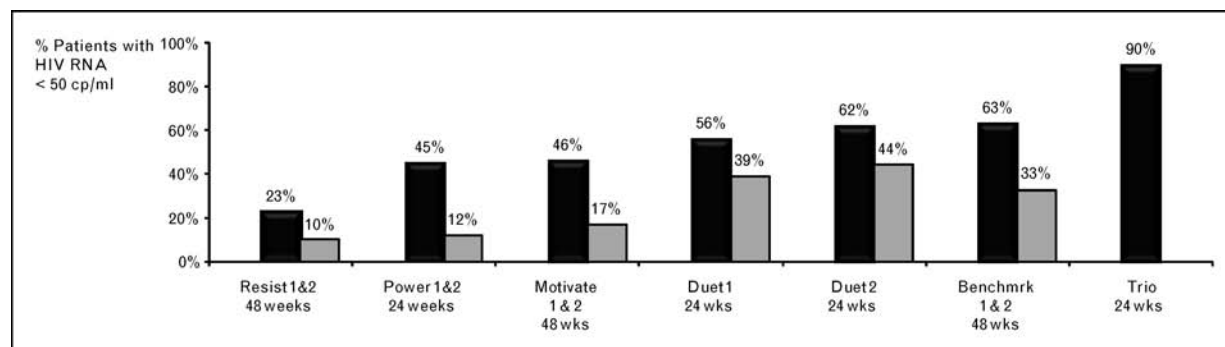
New antiretroviral agents that have recently become available within existing and new drug classes have

increased treatment options, improved the durability, tolerability, and long-term efficacy of cART, and will likely reduce the incidence of AIDS and death, even among patients with extensive treatment experience and high levels of drug resistance.

Recent clinical trials in patients with multidrug-resistant HIV

In the last 2 years, two new classes of antiretroviral drugs and two new drugs within previously available classes almost simultaneously became available. Raltegravir was the first integrase inhibitor (Fig. 1) [7,8,9[•],10,11,12[•],13[•],14]. In the BENCHMRK (Blocking Integrase in Treatment Experienced Patients with a Novel Compound against HIV, Merck) randomized clinical trials, conducted in HIV-infected patients with limited treatment options, 61.8% of patients who took raltegravir along with optimized background therapy (OBT) achieved HIV RNA levels of less than 50 copies/ml at week 48 [12[•]]. Maraviroc was the first chemokine (C–C motif) receptor 5 (CCR5) antagonist [9[•]]. In Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and

Figure 1 Results of clinical trials evaluating new classes of antiretroviral drugs and new drugs within previously available classes in treatment-experienced patients with multidrug-resistant HIV infection



RESIST 1 and 2 studies: Tipranavir/ritonavir along with optimized background therapy (black bar) versus placebo along with optimized background therapy (gray bar) [7]. Power 1 and 2 studies: Darunavir/ritonavir along with optimized background therapy (black bar) versus placebo along with optimized background therapy (gray bar) [8]. Motivate 1 and 2 studies: Maraviroc twice daily along with optimized background therapy (black bar) versus placebo along with optimized background therapy (gray bar) [9^{*}]. Duet 1 and 2 studies: Etravirine along with darunavir/ritonavir as well as optimized background therapy (black bars) versus darunavir/ritonavir along with optimized background therapy (gray bars) [10,11]. Benchmrk 1 and 2 studies: Raltegravir along with optimized background therapy (black bar) versus placebo along with optimized background therapy (gray bar) [12^{*}]. Trio study: Raltegravir, etravirine, and darunavir/ritonavir along with optimized background therapy [13^{*}].

2 studies, randomized clinical trials conducted in treatment-experienced patients infected with R5 HIV-1 only, 47 and 45% of patients taking maraviroc twice daily along with OBT achieved HIV RNA levels of less than 50 copies/ml at week 48, respectively [9^{*}]. Darunavir is a new protease inhibitor, and etravirine is a new non-nucleoside reverse transcriptase inhibitor (NNRTI). DUET 1 and 2 trials randomized treatment-experienced individuals to darunavir, etravirine, and OBT or darunavir and OBT. Of the patients who took darunavir, etravirine, and OBT, 56.0% in DUET 1 and 62.0% in DUET 2 reached HIV RNA levels below 50 copies/ml at week 24 [10,11].

Studies conducted to date on the efficacy and safety of new antiretroviral drugs have generally limited the use of other investigational agents than the new agent being studied, limiting the ability to provide multiple active drugs. Subgroup analyses of data from these studies illustrate that the proportion of patients reaching an undetectable viral load is higher when they initiate three, or at least two, fully active drugs [10,11,15]. The TRIO trial, a phase II, noncomparative, multicenter trial, was the first clinical trial with the a-priori objective of evaluating the efficacy and tolerability of a regimen containing three new agents, namely raltegravir, etravirine, and darunavir/ritonavir (darunavir/r), in multidrug-resistant patients. At week 24, 93 out of 103 patients (90%) had plasma HIV-1 RNA of less than 50 copies/ml [13^{*}]. The suppression rates found in this trial are higher than in all previous studies of multidrug-resistant patients and are comparable to rates reported among antiretroviral-naïve patients [16–19].

Treatment goals for patients with multidrug-resistant HIV infection

The results of the BENCHMRK, MOTIVATE, DUET, and TRIO studies have opened the doors to a new era in HIV therapy. They illustrate that cART regimens with new agents can suppress viremia in even the most drug-resistant patients. Clinicians should therefore strive to improve cART efficacy and durability and reduce viral loads to below limits of assay detection at similar rates in cART-naïve and drug-resistant patients.

Management of patients with multidrug-resistant HIV who are not virologically suppressed on combination antiretroviral therapy

Treatment-experienced patients can fail cART virologically due to either incomplete virologic response or virologic rebound, defined as the repeated detection of HIV RNA above the assay limit of detection after virologic suppression [20]. The United States treatment guidelines define incomplete virologic response as two consecutive HIV RNA measurements of more than 400 copies/ml after 24 weeks of therapy, or more than 50 copies/ml after 48 weeks of therapy [20]. Other countries use stricter definitions (Table 1) [21–23].

On the basis of the trials reported above, recent guidelines for the management of treatment-experienced patients recommend maximizing viral suppression by constructing a regimen consisting of at least two, and preferably three, fully active agents [10,11,15,24]. When selecting fully active agents for patients with multidrug-

Table 1 Definition of incomplete virologic response after treatment initiation by country and/or international organization

Country or international society	Year	Definition of incomplete virologic response
Department of Health and Human Services, United States [20]	2008	2 consecutive HIV RNA measurements >400 copies/ml after 24 weeks of therapy or >50 copies/ml after 48 weeks of therapy
European AIDS Clinical Society [21]	2008	A confirmed HIV RNA measurement >50 copies/ml 6 months after initiating or modifying a regimen
British HIV Association [22]	2008	No undetectable HIV RNA measurements 24–36 weeks after initiating a regimen
French Ministry of Health [23]	2008	HIV RNA decrease <2 log copies/ml 1 month after treatment initiation (<1 log if the regimen was initiated after virologic failure) or a confirmed HIV RNA measurement >50 copies/ml 6 months after initiating a regimen

resistant HIV, clinicians should first examine their patients' treatment history and identify classes of antiretroviral drugs to which they have not been exposed. Clinicians should pay particular attention to drugs with new mechanisms of action (i.e., integrase inhibitors, CCR5 antagonists, and fusion inhibitors).

The clinician should then identify fully active agents within classes of antiretroviral drugs to which the patient has been exposed [i.e. protease inhibitors, NNRTIs, and nucleoside reverse transcriptase inhibitors (NRTIs)] A genotypic resistance test should be performed, keeping in mind that viral sensitivity to an agent based on the most recent resistance test does not guarantee antiretroviral activity. Previous studies [25,26] have shown that reliance on results from the most recent genotype test underestimates the level of resistance to specific drugs because these tests detect only the most prominent HIV-1 variant(s) (Fig. 2). Undetected drug-resistant minority species are known to persist when individuals discontinue or change cART regimens, and the rapid reappearance of these mutations on reinitiation of therapy has been demonstrated [27]. It is, therefore, important to assess the patient's cART history and prior genotype analyses.

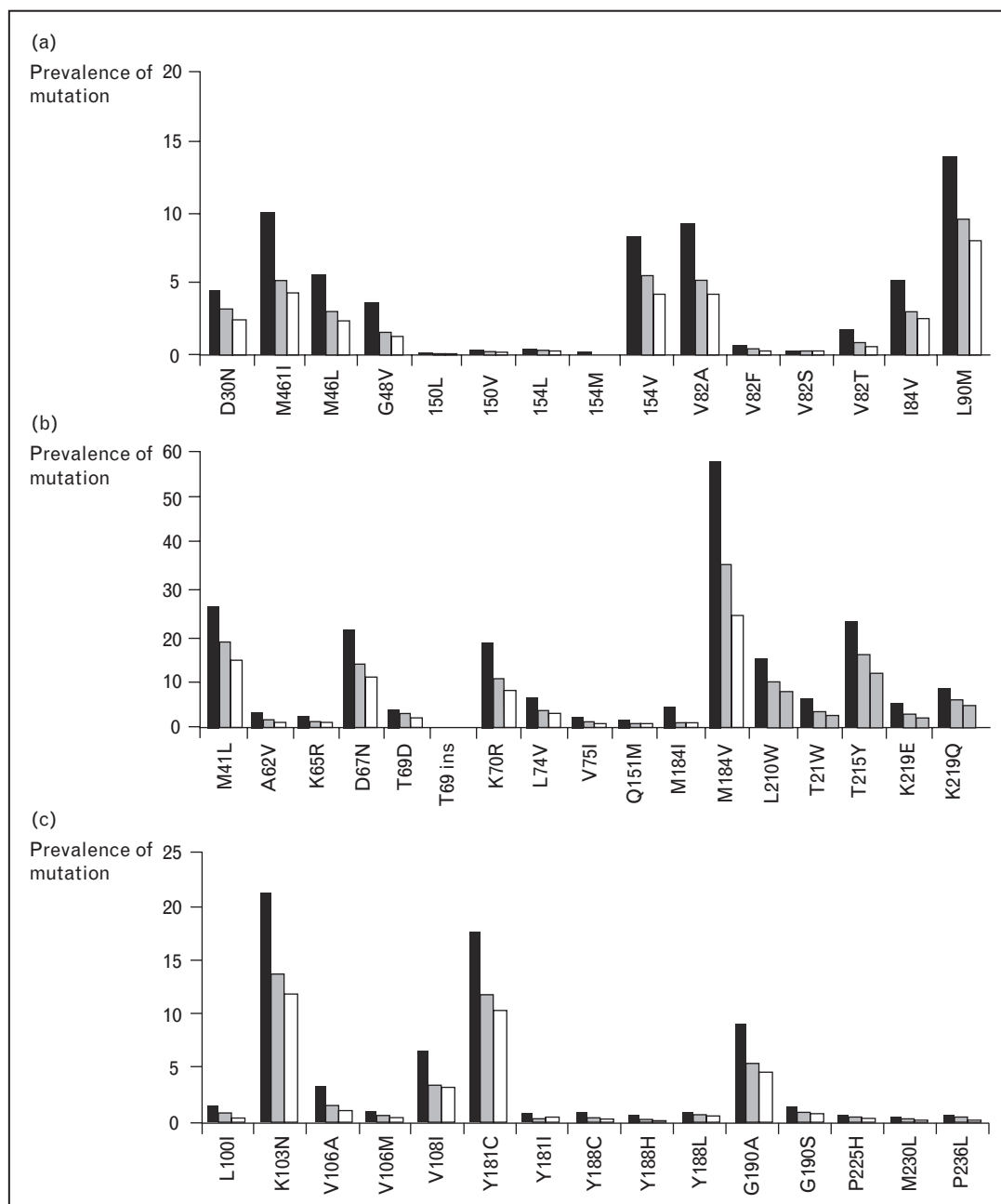
Patients with R5 virus may also benefit from CCR5 antagonists. When selecting fully active agents, the clinician should perform a tropism assay to determine whether the patient has X4-tropic or DM-tropic infection and therefore should not initiate CCR5 antagonists.

After identifying fully active agents, the clinician should review the patient's medical history for tolerability of antiretroviral medications and medication-taking behavior to anticipate toxicities and degree of adherence. The patient's comorbidities and concomitant medications should also be reviewed to prevent drug–drug interactions. Once the clinician has considered the potential efficacy and tolerability of cART, the patient's adherence level, comorbidities, and concomitant medications, multiple scenarios are plausible: more than three fully active agents can be identified for use; two or three fully active agents can be identified for use; and fewer than two fully active agents can be identified for use.

If more than three fully active agents can be identified for use, the clinician must consider how to sequence these drugs. The clinician might choose combinations of drugs such as darunavir/r–etravirine or raltegravir–darunavir/r–etravirine for earlier use because of the larger amount of virologic, immunologic, and safety data for these drugs [10,11,13^{*}]. The patient might prefer agents that are generally well tolerated or have more convenient dosing frequencies and/or food/fasting requirements. The clinician should also anticipate future drug options in case the new cART regimen fails. Agents such as enfuvirtide, requiring twice daily injections and causing painful injection site reactions, should be used later in patients who are resistant to new protease inhibitors and NNRTIs or who have failed new classes of antiretroviral agents. Tipranavir/r should also be used later in patients who are resistant to new protease inhibitors such as darunavir/r. Tipranavir/r has been shown to cause more hyperlipidemia and hepatotoxicity than comparator protease inhibitors [28], presumably because it requires a higher dose of ritonavir (200 mg twice daily). As darunavir and tipranavir resistance mutation patterns are partly distinct [29], tipranavir can remain a potential future drug option, even after a cART regimen containing darunavir/r fails [30]. It may be preferable to use CCR5 antagonists earlier and in patients with higher CD4 cell counts. R5 virus is most prevalent in the earlier stages of disease and in patients with higher CD4 cell counts and CD4 cell nadirs (Fig. 3). In addition, tropism can shift over time, with the emergence of X4 virus [31,32].

It is unclear whether new regimens for patients with multidrug-resistant HIV and at least three fully active drug options should include NRTIs, unless they are coinfecting with hepatitis B virus, which is sensitive to some NRTIs [33]. The results of several studies [34–36] conducted in patients with multidrug-resistant HIV who were not on fully active regimens have led to the belief that NRTIs may have persistent antiretroviral activity, even when fully active agents are available, which is not at all evident. In TRIO, for example, 84% of patients were given NRTIs in addition to the three fully active agents being evaluated, even though genotype tests performed prior to treatment initiation frequently showed resistance to NRTIs [13^{*}]. An AIDS Clinical Trials Group (ACTG)

Figure 2 Prevalence of antiretroviral drug resistance mutations in HIV-1 disease by drug class: latest genotypic resistance test versus history of genotypic resistance tests

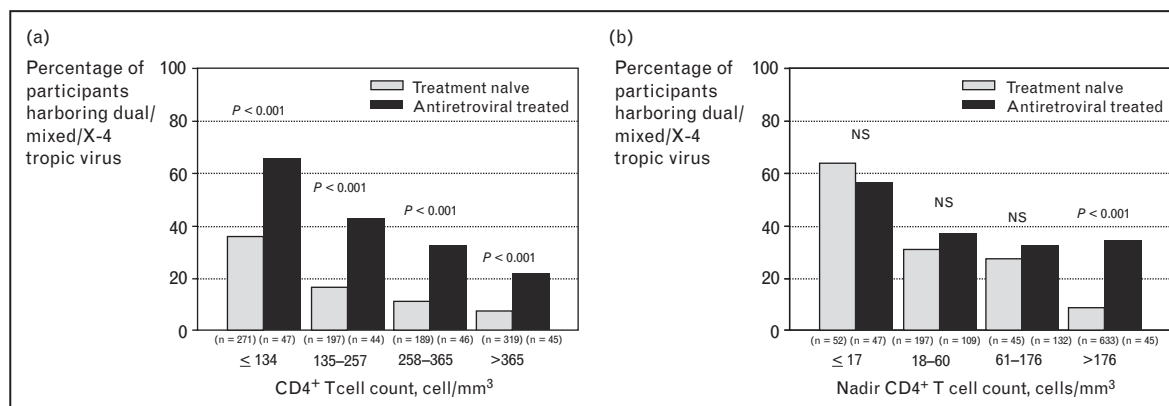


The figure shows the prevalence of the major mutations recognized by the International AIDS Society, USA as conferring resistance to protease inhibitors (a), nucleoside reverse transcriptase inhibitors (b), and nonnucleoside reverse transcriptase inhibitors (c). The figure compares the prevalence of mutations derived from genotypic histories (black bars; 11 404 genotypic resistance tests; 1734 individuals), latest genotypic resistance test performed while on antiretroviral therapy (gray bars; 1571 individuals), and latest genotypic resistance test, regardless of treatment status (white bars; 1734 individuals). Reproduced with permission from [26].

randomized trial among treatment-experienced patients is ongoing to determine the benefit of adding an NRTI to an antiretroviral regimen that includes new generation drugs (<http://clinicaltrials.gov>, identifier NCT00537394).

In patients for whom at least three fully active agents can be identified, most guidelines recommend constructing a

regimen consisting of two, or preferably three, fully active agents [20]. Patients with multidrug-resistant HIV are very likely to achieve virologic suppression in the short term, thanks to new drug options, but long-term suppression is uncertain and future treatment options might be scarce. Using a regimen with two, rather than three, fully active drugs may avoid toxicity, decrease costs of care, and

Figure 3 Prevalence of dual/mixed/X4 tropism by treatment status and current or pretreatment nadir CD4⁺ T cell count

The percentage of participants harboring dual/mixed or X4 tropic virus is plotted by quartiles of current CD4⁺ T-cell count and pretreatment nadir CD4⁺ T-cell count among 976 treatment-naïve (gray bars) and 182 treated (black bars) participants with chronic HIV infection. Lower pretreatment nadir CD4⁺ T-cell counts are associated with a higher prevalence of dual/mixed/X4 tropism among both treatment-naïve ($P < 0.001$ for trend) and treated participants ($P = 0.03$ for trend). (a) The prevalence of dual/mixed/X4 tropism is higher at lower current CD4⁺ T-cell counts ($P < 0.001$ for trend) and is higher for treated patients, regardless of current CD4⁺ T-cell count ($P < 0.01$ within each CD4⁺ T-cell count stratum). (b) After controlling for pretreatment nadir CD4⁺ T-cell count, there is no evidence of an association between treatment status and dual/mixed/X4 tropism among patients with CD4⁺ T-cell count nadirs in the lowest three quartiles (≤ 176 cells/ μ l). However, among participants with pretreatment nadir CD4⁺ T-cell counts above 176 cells/ μ l, treatment was independently associated with a higher prevalence of dual/mixed/X4 tropism ($P < 0.001$ for interaction). NS, not significant. Reproduced with permission from [31].

preserve future drug options. Future randomized controlled trials should therefore evaluate whether patients with multidrug-resistant HIV should receive two or three fully active drugs. These studies [10,11,15,24] should primarily target subgroups of patients with lower HIV RNA levels and higher CD4 cell counts who have shown higher rates of response to cART.

The proportion of patients with multidrug-resistant HIV for whom less than two fully active drugs can be identified for use has dramatically decreased in the last 2 years as the availability of new agents has increased. However, this proportion may increase in the future after treatment-experienced patients fail regimens containing new classes of antiretroviral agents. The clinician should keep these patients on the same nonsuppressive regimen rather than introducing a new regimen with a single active agent. Continuing nonsuppressive therapy has been shown to decrease the risk of disease progression [37]. However, the clinician must be cautious when administering nonsuppressive NNRTI-based and integrase inhibitor-based regimens because accumulation of additional mutations could affect the patient's susceptibility to next generation NNRTIs or integrase inhibitors. Nonsuppressive CCR5 antagonist-based regimens should also be discontinued. In MOTIVATE study, over 50% of patients who received maraviroc, compared with 6% of patients who received placebo, had virus binding to chemokine (C–X–C motif) receptor 4 (CXCR4) at the time of the failure [24]. This result can partly be attributed to detection of low levels of preexisting CXCR4-binding virus when CCR5 tropic variants are selectively

suppressed. Emergence of CXCR4-binding virus has been shown to be associated with CD4 cell decline and clinical progression [38]. Although manifestations of the X4 virus acquired during treatment with a CCR5 antagonist may be different from those of the X4 virus acquired during the natural course of infection, CCR5 antagonists should be interrupted in patients failing regimens that contain these drugs until this issue is studied more in depth.

Clinical progression is very likely among patients who are on a failing cART regimen when HIV-1 RNA is more than 100 000 copies/ml, CD4 cell counts are less than 100 cells/ μ l, and there is an ongoing opportunistic infection or a history of opportunistic infection [39]. In these patients, the addition of a single drug may reduce the risk of immediate clinical progression by temporarily decreasing HIV RNA levels and/or increasing CD4 cell counts [37], but risks and benefits of this decision should be evaluated with the help of an expert [20]. Preliminary data have also illustrated the potential benefits of foscarnet in combination with a thymidine analog, especially when patients have thymidine-associated mutations (TAMs) [40–42]. In a recent study, Charpentier *et al.* [40] demonstrated that 61% of patients with severe immunodeficiency and multidrug-resistant HIV achieved HIV RNA levels below the detection limit of 40 copies/ml at week 24 when they took a salvage regimen containing foscarnet, zidovudine, and OBT with only one fully active drug (enfuvirtide or raltegravir) [43]. However, as the data are scarce and foscarnet needs to be administered intravenously and frequently leads to nephrotoxicity, the use of this combination should be

restricted to situations in which drug switches are necessary and no other options are available.

Before the recent availability of new drugs belonging to old and new classes, double-boosted protease inhibitor regimens were used for patients with extensive treatment histories and multidrug-resistant HIV. The theoretical bases for using full doses of two protease inhibitors were the following: their synergistic (lopinavir–saquinavir/r; atazanavir–saquinavir/r) or additive (lopinavir–atazanavir/r) activity against HIV *in vitro* [44,45]; the possibility of achieving high plasma concentrations of both protease inhibitors with only one booster [46,47]; and varying patterns of resistance to protease inhibitors among viral subpopulations (i.e., if the patterns of resistance to two drugs overlap but are not identical, then the antiretroviral activity of each drug is diminished, but the genetic barrier created by the two drugs combined is increased) [48]. No randomized controlled trial has evaluated these regimens in treatment-experienced patients, and pilot studies in treatment-naïve patients have shown poor success rates [49]. Most of the studies [50,51] involving treatment-experienced patients are observational, noncomparative, and include only a small number of patients. These studies suggest some degree of efficacy with certain double-boosted protease inhibitor combinations such as lopinavir–saquinavir/r and atazanavir–saquinavir/r. Tipranavir/r should not be combined with other protease inhibitors because it markedly decreases the plasma concentration of the added protease inhibitor [52]. Data on the efficacy of darunavir/r in the presence of other protease inhibitors are scarce [53,54], but given its potency, high genetic barrier, and resistance profile, it is unlikely that a second protease inhibitor would provide additional clinical benefit. Clinicians should in general avoid the use of double-boosted protease inhibitors, as this strategy has no proven antiviral benefit and may increase both the cost and toxicity of a regimen.

Management of patients with multidrug-resistant HIV who are virologically suppressed on combination antiretroviral therapy

The clinician should simplify, if possible, the patient's cART regimen in order to reduce the pill burden and dosing frequency, enhance tolerability, and ensure maximal adherence [20]. Thanks to the recent availability of new agents, the regimens of multidrug-resistant patients can be simplified, especially if the regimens were prescribed prior to the availability of newer, more tolerable options. In a recent randomized controlled study [55[•]], 170 patients with multidrug-resistant HIV-1 infection and plasma HIV RNA levels of less than 400 copies/ml while on enfuvirtide-based regimens were randomized to maintaining enfuvirtide or switching to raltegravir.

At week 24, switching to raltegravir was noninferior to maintaining enfuvirtide, with virologic failure rates of 1.2% in both arms in the intent-to-treat analysis. Grade 3–4 adverse events and laboratory abnormalities were uncommon and did not differ between the treatment arms. This study suggests that switching from enfuvirtide, an often poorly tolerated drug, to raltegravir is well tolerated and efficacious.

Replacing protease inhibitors with raltegravir to reduce protease inhibitor-related toxicities such as lipid abnormalities has also been considered. Two recent, multicenter, double-blind, randomized controlled trials (SwitchMRK randomized virologically suppressed patients taking lopinavir/r-based regimens to maintaining their current regimen or replacing lopinavir/r with raltegravir and OBT, which included at least two NRTIs [56[•]]). Although switching to raltegravir was well tolerated and resulted in improved lipid parameters, HIV RNA below 50 copies/ml at week 24 in the raltegravir arm was not noninferior to the lopinavir/r arm (80.8 versus 87.4% of patients in SwitchMRK 1; 88.0 versus 93.8% of patients in SwitchMRK 2). A large proportion of the patients who had virologic rebounds after switching to raltegravir were treatment experienced (84%) and/or had a history of prior virologic failure (66%). Multidrug-resistant patients are likely resistant to many agents, including NRTIs. The treatment-experienced patients who were enrolled in the SwitchMRK trials may therefore have been on the equivalent of boosted protease inhibitor monotherapy. As boosted protease inhibitors have a much stronger genetic barrier to resistance than raltegravir, a switch from boosted protease inhibitor monotherapy to raltegravir monotherapy may have led to virologic rebound. The results of the SwitchMRK studies suggest that clinicians should be cautious when replacing protease inhibitors with raltegravir, especially in patients with multidrug-resistant HIV who are already virologically suppressed. Before switching a protease inhibitor with raltegravir, the clinician should review the patient's treatment history, treatment responses, and resistance tests to ensure that the OBT contains active drugs.

Although it may be possible to simplify regimens with maraviroc, it is difficult to determine viral tropism in virologically suppressed patients. Results of substitution studies using this agent are limited. The clinician should also be cautious when considering substitutions with etravirine because it is difficult to ascertain etravirine resistance in virologically suppressed patients. The presence of three or more NNRTI-associated resistance mutations is associated with decreased etravirine activity [57].

One other approach to treatment simplification may be to reduce the number of drugs in the regimen. The clinician could, for example, discontinue NRTIs, especially if the

cART regimen contains at least three other fully active agents. The ACTG randomized trial cited above (<http://clinicaltrials.gov>, identifier NCT00537394) may help determine whether to adopt this strategy. The clinician might also switch the patient from a regimen with three fully active drugs to a regimen with two fully active drugs, thus reducing the likelihood of toxicity, decreasing the costs of care, and preserving future drug options. This approach cannot be recommended, however, until a trial evaluates it.

Conclusion

The recent availability of new antiretroviral agents has marked a paradigm shift in the approach to treating patients with multidrug-resistant HIV. These new agents not only provide more treatment options but also have efficacies among treatment-experienced patients that are comparable to those among treatment-naïve patients. Development of resistance mutations to these new agents may limit their long-term benefit. Clinicians must, therefore, pay particular attention to optimizing the pairing and sequencing of these new drugs, especially as investigational agents with new mechanisms of action will not be available in the near future. It is also important to adequately monitor the efficacy of and adherence to these regimens. Future studies should continue to investigate the optimal use of new agents in order to further improve long-term treatment of patients with multidrug-resistant HIV.

Acknowledgements

We thank Caroline Sloan for editing and reviewing the manuscript. We acknowledge the assistance of Dr Nathalie Viget for manuscript review.

Dr Yazdanpanah has received travel grants, honoraria for presentation at workshops, and consultancy honoraria from Bristol-Myers Squibb, Boehringer Ingelheim, Gilead, Glaxo-SmithKline, Merck, Pfizer, Roche, Schering-Plough, and Tibotec.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 548).

- 1 Keiser O, Taffe P, Zwahlen M, *et al.* All cause mortality in the Swiss HIV Cohort Study from 1990 to 2001 in comparison with the Swiss population. *AIDS* 2004; 18:1835–1843.
- 2 Lohse N, Hansen AB, Pedersen G, *et al.* Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med* 2007; 146:87–95.
- 3 Jaggy C, von Overbeck J, Ledergerber B, *et al.* Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. *Lancet* 2003; 362:877–878.
- 4 Bhaskaran K, Hamouda O, Sannes M, *et al.* Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* 2008; 300:51–59.

This study demonstrates that mortality rates for HIV-infected persons have become much closer to general mortality rates since the introduction of highly active ART.

- 5 CASCADE Collaboration. Changes in the uptake of antiretroviral therapy and survival in people with known duration of HIV infection in Europe: results from CASCADE. *HIV Med* 2000; 1:224–231.
- 6 Cozzi-Lepri A, Phillips AN, Clotet B, *et al.* Detection of HIV drug resistance during antiretroviral treatment and clinical progression in a large European cohort study. *AIDS* 2008; 22:2187–2198.
- 7 Hicks CB, Cahn P, Cooper DA, *et al.* Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multidrug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet* 2006; 368:466–475.
- 8 Clotet B, Bellos N, Molina JM, *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 randomised trials. *Lancet* 2007; 369:1169–1178.
- 9 Gulick RM, Lalezari J, Goodrich J, *et al.* Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008; 359:1429–1441.
- In two large randomized controlled studies, in previously treated patients with R5 HIV-1 who were receiving OBT, maraviroc, as compared with placebo, resulted in significantly greater suppression of HIV-1 and greater increases in CD4 cell counts at 48 weeks.
- 10 Madruga JV, Cahn P, Grinsztejn B, *et al.* Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; 370:29–38.
- 11 Lazzarin A, Campbell T, Clotet B, *et al.* Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; 370:39–48.
- 12 Steigbigel RT, Cooper DA, Kumar PN, *et al.* Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008; 359:339–354.
- In two large randomized controlled studies in HIV-infected patients with limited treatment options, raltegravir along with OBT provided better viral suppression than OBT alone for at least 48 weeks.
- 13 Yazdanpanah Y, Fagard C, Descamps D, *et al.*, editors. High rate of virologic success with raltegravir, etravirine, and darunavir/ritonavir in treatment-experienced patients with multidrug-resistant virus: results of the ANRS 139 Trio trial [abstract #THAB0406]. In: XVII International AIDS Conference; 3–8 August 2008; Mexico City, Mexico.
- This phase II, noncomparative, multicenter trial demonstrates that in patients with multidrug-resistant virus, the combination of raltegravir, etravirine, and darunavir/r is well tolerated and is associated with a similar rate of virologic suppression than that expected in treatment-naïve patients.
- 14 Hazuda DJ, Felock P, Witmer M, *et al.* Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells. *Science* 2000; 287:646–650.
- 15 Cooper DA, Steigbigel RT, Gatell JM, *et al.* Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med* 2008; 359:355–365.
- 16 Molina JM, Andrade-Villanueva J, Echevarria J, *et al.* Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008; 372:646–655.
- 17 Eron J Jr, Yeni P, Gathe J Jr, *et al.* The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised noninferiority trial. *Lancet* 2006; 368:476–482.
- 18 Ortiz R, Dejesus E, Khanlou H, *et al.* Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS* 2008; 22:1389–1397.
- 19 Riddler SA, Haubrich R, DiRienzo AG, *et al.* Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med* 2008; 358:2095–2106.
- 20 Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents; 2008. <http://www.adisinfo.nih.gov/contentfiles/adultandadolescentgl.pdf>.
- 21 European AIDS Clinical Society. Guidelines for the clinical management and treatment of HIV infected adults in Europe; 2008. http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_treatment_of_hiv_infected_adults.pdf.
- 22 Gazzard BG. British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med* 2008; 9:563–608.
- 23 Yeni P. French Guidelines for the treatment of HIV-1-infected patients; 2008. <http://www.ladocumentationfrancaise.fr/rapports-publics/084000593/>.
- 24 Fatkenheuer G, Nelson M, Lazzarin A, *et al.* Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection. *N Engl J Med* 2008; 359:1442–1455.

- 25 Zaccarelli M, Lorenzini P, Ceccherini-Silberstein F, *et al*. Historical resistance profile helps to predict salvage failure. *Antivir Ther* 2009; 14:285–291.
- 26 Harrigan PR, Wynhoven B, Brumme ZL, *et al*. HIV-1 drug resistance: degree of underestimation by a cross-sectional versus a longitudinal testing approach. *J Infect Dis* 2005; 191:1325–1330.
- 27 Izopet J, Souyris C, Hance A, *et al*. Evolution of human immunodeficiency virus type 1 populations after resumption of therapy following treatment interruption and shift in resistance genotype. *J Infect Dis* 2002; 185:1506–1510.
- 28 Hicks CB, Cahn P, Cooper DA, *et al*. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multidrug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet* 2006; 368:466–475.
- 29 HIV-1 French Resistance; 2008. <http://www.hivfrenchresistance.org/>.
- 30 DeMeyer S, Cao Van K, Lathouwers E, *et al*, editors. Phenotypic and genotypic profiling of TMC114, lopinavir and tipranavir against PI-resistant HIV-1 clinical isolates [abstract #42]. In: 4th European HIV Drug Resistance Workshop; 29–31 March 2006; Monte Carlo, Monaco.
- 31 Hunt PW, Harrigan PR, Huang W, *et al*. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. *J Infect Dis* 2006; 194:926–930.
- 32 Wilkin TJ, Su Z, Kuritzkes DR, *et al*. HIV type 1 chemokine coreceptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. *Clin Infect Dis* 2007; 44:591–595.
- 33 Alberti A, Clumeck N, Collins S, *et al*. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005; 42:615–624.
- 34 Deeks SG, Hoh R, Neilds TB, *et al*. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Infect Dis* 2005; 192:1537–1544.
- 35 Campbell TB, Shulman NS, Johnson SC, *et al*. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis* 2005; 41:236–242.
- 36 Castagna A, Danise A, Menzo S, *et al*. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). *AIDS* 2006; 20:795–803.
- 37 Murray JS, Elashoff MR, Iacono-Connors LC, *et al*. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. *AIDS* 1999; 13:797–804.
- 38 Waters L, Mandalia S, Randell P, *et al*. The impact of HIV tropism on decreases in CD4 cell count, clinical progression, and subsequent response to a first antiretroviral therapy regimen. *Clin Infect Dis* 2008; 46:1617–1623.
- 39 Egger M, May M, Chene G, *et al*. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002; 360:119–129.
- 40 Charpentier C, Laureillard D, Sodqi M, *et al*. Foscarnet salvage therapy efficacy is associated with the presence of thymidine-associated mutations (TAMs) in HIV-infected patients. *J Clin Virol* 2008; 43:212–215.
- 41 Canestri A, Ghosn J, Wirden M, *et al*. Foscarnet salvage therapy for patients with late-stage HIV disease and multiple drug resistance. *Antivir Ther* 2006; 11:561–566.
- 42 Mathiesen S, Roge BT, Weis N, *et al*. Foscarnet used in salvage therapy of HIV-1 patients harbouring multiple nucleotide excision mutations. *AIDS* 2004; 18:1076–1078.
- 43 Mathiesen S, Dam E, Roge B, *et al*. Long-term foscarnet therapy remodels thymidine analogue mutations and alters resistance to zidovudine and lamivudine in HIV-1. *Antivir Ther* 2007; 12:335–343.
- 44 Robinson BS, Riccardi KA, Gong YF, *et al*. BMS-232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents. *Antimicrob Agents Chemother* 2000; 44:2093–2099.
- 45 Molla A, Mo H, Vasavanonda S, *et al*. In vitro antiviral interaction of lopinavir with other protease inhibitors. *Antimicrob Agents Chemother* 2002; 46:2249–2253.
- 46 Ribera E, Lopez RM, Diaz M, *et al*. Steady-state pharmacokinetics of a double-boosting regimen of saquinavir soft gel plus lopinavir plus minidose ritonavir in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2004; 48:4256–4262.
- 47 von Hentig N, Muller A, Rottmann C, *et al*. Pharmacokinetics of saquinavir, atazanavir, and ritonavir in a twice-daily boosted double-protease inhibitor regimen. *Antimicrob Agents Chemother* 2007; 51:1431–1439.
- 48 Ribera E, Curran A. Double-boosted protease inhibitor antiretroviral regimens: what role? *Drugs* 2008; 68:2257–2267.
- 49 Landman R, Chazallon C, Descamps D, *et al*, editors. Efficacy and safety of dual-PI regimens for the treatment of ART-naïve HIV subjects: 21P ANRS 127, a randomized pilot study [abstract #779]. In: 15th Conference on Retroviruses and Opportunistic Infections; 3–6 February 2008; Boston, MA.
- 50 Staszewski S, Babacan E, Stephan C, *et al*. The LOPSQAQ study: 48 week analysis of a boosted double protease inhibitor regimen containing lopinavir/ritonavir plus saquinavir without additional antiretroviral therapy. *J Antimicrob Chemother* 2006; 58:1024–1030.
- 51 Ribera E, Azuaje C, Lopez RM, *et al*. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. *AIDS* 2006; 20:1131–1139.
- 52 Walmsley SL, Katlama C, Lazzarin A, *et al*. Pharmacokinetics, safety, and efficacy of tipranavir boosted with ritonavir alone or in combination with other boosted protease inhibitors as part of optimized combination antiretroviral therapy in highly treatment-experienced patients (BI Study 1182.51). *J Acquir Immune Defic Syndr* 2008; 47:429–440.
- 53 Sekar VJ, Lefebvre E, Marien K, *et al*. Pharmacokinetic interaction between darunavir and saquinavir in HIV-negative volunteers. *Ther Drug Monit* 2007; 29:795–801.
- 54 Sekar VJ, Lefebvre E, Spinosa-Guzman S, *et al*, editors. Pharmacokinetic interaction between the HIV protease inhibitors TMC114 and lopinavir/ritonavir [abstract #0367]. In: 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; 27–30 September 2006; San Francisco, CA.
- 55 De Castro N, Braun J, Charreau I, *et al*, editors. Switch from enfuvirtide to raltegravir in highly treatment-experienced HIV-1-infected patients: a randomized open-label noninferiority trial, Easier – ANRS 138 [abstract #572]. In: 16th Conference on Retroviruses and Opportunistic Infections; 8–11 February 2009; Montreal, CA.
- This study illustrates that a switch to raltegravir is well tolerated and virologically noninferior to the maintenance of enfuvirtide in patients with multidrug-resistant HIV infection receiving a suppressive ART.
- 56 Eron JE, Andrade-Villanueva J, Zajdenverg R, *et al*, editors. Switching from stable lopinavir/ritonavir-based to raltegravir-based combination ART resulted in a superior lipid profile at week 12 but did not demonstrate noninferior virologic efficacy at week 24. In: 16th Conference on Retroviruses and Opportunistic Infections; 8–11 February 2009; Montreal, CA.
- These two multicenter, double-blind, randomized controlled trials show that although switching to raltegravir was well tolerated and resulted in improved lipid parameters when compared with the maintenance of lopinavir/r in patients receiving a suppressive ART, HIV RNA below 50 copies/ml at week 24 in the raltegravir arm was not noninferior to the lopinavir/r arm. A large proportion of the patients who had virologic rebounds after switching to raltegravir were treatment experienced.
- 57 Vingerhoets J, Peeters M, Azijn H, *et al*. An update of the list of NNRTI mutations associated with decreased virologic response to etravirine (ETR): multivariate analyses on the pooled DUET-1 and DUET-2 clinical trial data. In: Program and abstracts of the 17th International HIV Drug Resistance Workshop (Sitges, Spain). College Park, GA: Informed Horizons; 2008.