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Antiretroviral Salvage Therapy for Multiclass Drug-Resistant HIV-1-Infected Patients: From Clinical Trials to Daily Clinical Practice

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Abstract

Drug resistance is one of the key problems in the management of long-term HIV-1-infected patients. Due to cross-resistance patterns within classes, broad resistance to the three original antiretroviral classes can develop in some patients, mainly those with extensive antiretroviral treatment experience and multiple treatment failures. Triple-class-resistant HIV-1 infection has been associated with a higher risk of clinical progression and death. Additionally, it increases the probability of transmission of multidrug-resistant HIV-1 strains.

Over the last years, the availability of new antiretroviral agents against novel targets (integrase inhibitors and CCR5 antagonists), and new drugs within old classes (nonnucleoside reverse transcriptase inhibitors and protease inhibitors) has opened a range of new therapeutic options for patients with multiclass drug-resistant HIV-1 infection and scarce therapeutic options with previous drugs. In randomized clinical trials, each of these new drugs has shown exceptional efficacy results, especially in patients who received other fully active drugs in the regimen. Indeed, in nonrandomized trials and observational studies, unprecedented rates of virologic suppression similar to those obtained in naive patients have been achieved when three of the currently available new drugs were combined, even in heavily experienced patients who had no viable salvage options with the previous classes. Thus, the goal of suppression and maintenance (plasma HIV-1 RNA < 50 copies/ml) is now also attainable in patients with multidrug-resistant HIV-1 infection.

Treatment failure can still occur, however, and the management of patients with multidrug-resistant HIV-1 infection remains a challenge. Clinicians are encouraged to optimize use of the new drugs to obtain better control of HIV infection while avoiding emergence of new resistance-associated mutations. The aim of this article is to summarize current knowledge on the management of salvage therapy for patients with multidrug-resistant HIV-1 infection by analyzing the evidence extracted from clinical trials, and to review the information on the effectiveness of triple combinations of new drugs provided by non-comparative trials and observational studies. **(AIDS Rev. 2011;13:180-93)**

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Key words

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Introduction

The availability of HAART, which allows complete suppression of viral replication and control of disease progression, has led to an increase in the life expectancy of HIV-infected patients through a significant decline in the morbidity and mortality associated with HIV infection[1-6]. However, many patients may not achieve adequate viral suppression despite receiving antiretroviral therapy (ART), and the ongoing viral replication in the presence of selective pressure from drug exposure favors selection of drug resistance-associated mutations (RAM) in the HIV genome[7-11]. The main drivers of emergent drug resistance are inadequate adherence to ART[12-18], tolerability problems leading to poor adherence[19], and the low potency of some regimens[20].

Drug resistance is one of the key problems in the management of long-term HIV-1-infected patients with extensive ART experience. Emergence of RAM not only compromises the efficacy of the drugs included in the current regimen, but also limits further treatment options due to cross-resistance to drugs within antiretroviral drug classes[8,21-23]. Previous exposure to non-suppressive regimens such as monotherapy or dual therapy in the pre-HAART era[9,19,20], continuation of a failing regimen during a period of time[23-25], and successive additions of a single new agent to a failing antiretroviral, when the availability of more active drugs for salvage therapy are limited, are all factors contributing to selection of multidrug class-resistant HIV-1 strains in a substantial group of heavily pretreated patients[26].

Triple-class drug resistance: definition, prevalence and implications for clinical practice

Multiclass or triple-class drug-resistant HIV-1 infection is usually defined as the presence of phenotypic or genotypic resistance to all three original antiretroviral classes: nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). In clinical and epidemiologic studies, multiclass and triple-class resistance is usually established by at least one major RAM within each drug class present on genotypic resistance testing[19,20,27-29]. However, in HIV-infected patients with considerable antiretroviral experience, multiple virologic failures, and triple-class drug resistance, a high number of RAM for each drug class are usually observed.

Only a few years ago, the emergence of multiclass-resistant HIV-1 in HIV-infected patients had important consequences. Because these patients might have no viable salvage therapy options, their situation was associated with a higher risk of clinical progression and death[27,30]. Furthermore, the probability of transmission of multidrug-resistant HIV-1 strains to newly infected subjects increased.

The availability of modern first-line ART regimens that are more potent, simpler, and better tolerated than regimens from the early HAART era has resulted in higher percentages of patients with complete viral suppression, and decreases in the incidence of resistance[31-34]. Moreover, the use of boosted PI has decreased the emergence of resistance to PI[11,33,35].

Nevertheless, virologic failure and emergence of resistance are still common, in particular NRTI and NNRTI RAM and, to a lesser extent, PI RAM[10,11,36]. In a recent, large cohort study of 45,937 patients starting HAART from 28 cohorts in Europe, the overall prevalence of triple-class virologic failure after a median of three years' follow-up was 1.9%, but the estimated cumulative percentage of patients with triple-class therapeutic failure rose to 3 and 7.8% as the time on ART increased to five and nine years, respectively[37] (Table 1). As compared to patients who received suboptimal regimens before the HAART era, triple-class failure and triple-class resistance rates have declined considerably in patients starting modern HAART regimens[28,31,32,38,39]. However, non-negligible percentages of triple-class resistance up 10% have been reported in several recent series including patients that initiated ART in the early HAART era[19,20,27,41] (Table 1).

Thus, a significant group of HIV-1-infected patients had no therapeutic options with the original drug class, and new drugs were urgently needed to construct optimal salvage regimens.

Salvage therapy for triple-class-resistant HIV-1 infection: time for new drugs

Until recently, only three antiretroviral drug classes, all having extended within-class cross-resistance, were available: NRTI, NNRTI, and PI. Thus, the management of multiclass-resistant HIV-1 infection has been a major challenge for clinicians treating HIV-1-infected patients because of the limited options for combining three, or at least two, fully active drugs, as is recommended in clinical guidelines[42-45]. In an attempt to optimize salvage treatment for these patients and minimize clinical disease progression, several strategies, such as multidrug or "mega-HAART" salvage regimens[46-48], double-boosted PI regimens[49-51], and quadruple NRTI

Table 1. Prevalence of triple-class failure and resistance in the HAART era: Cohort studies

Study	Patients	Follow-up	Outcome
EuroSIDA cohort Mocroft, et al. 2004[38]	3,496 pts initiating HAART (63% previous ART experience)	1994-2002 9,542 patient-year in ART experienced 4,726 patient-year in ART naive	445 pts (12.7%) developed triple-class failure After 6 years on HAART: 16.6% triple-class failure in ART experienced 5.9 % triple-class failure in ART naive
UK collaborative HIV Cohort Phillips, et al. 2007[40]	7,916 pts initiating HAART	1-10 years 27,441 patient-year	167 pts developed triple-class failure Risk of triple-class failure estimated: 3.5% (95% CI: 2.9-4.1%) by 5 years 9.2% (95% CI: 5.0-13.4%) by 10 years
PLATO II Project (COHERE) Lodwick, et al. 2010[37]	45,937 pts initiating HAART	Median 3 years Max 10.2 years	1.9% pts developed triple-class failure Risk of triple-class failure estimated: 3% (95% CI: 2.8-3.3%) by 5 years 7.8% (95% CI: 6.7-9.0%) by 9 years
Richman, et al. 2004[9]	1,099 pts with VL ≥ 500 copies/ml and GRT available	1996-1998	Triple-class drug resistance 13.1% (95% CI: 10.6-16.1%)
UK collaborative HIV Cohort Phillips, et al. 2005[41]	4,306 pts 1,057 (25%) experienced VF, 808 (19%) with GRT available	Since 1996 Median 3.1 years 790 (19%) > 5 years	Cumulative risk of triple-class resistance: 1% (95% CI: 0.7-1.3%) by 2 years 2.7% (95% CI: 2.0-3.4%) by 4 years 4.1% (95% CI: 3.0-5.2%) by 6 years
Zacarelli, et al. 2005[27]	623 pts with GRT after VF available	1999-2002	Triple-class drug resistance 3.9%
Napravnik, et al. 2007[20]	Total 1,587 pts 607 (38%) with GRT available	2000-2006*	Overall: Triple-class drug resistance 8% (95% CI: 6-9%); 3% if HAART initiators (95% CI: 2-4%) Pts with GRT available: Triple-class drug resistance 26% (95% CI: 21-31%) among non-HAART initiators; 10% (95% CI: 7-15%) among HAART initiators
Jones, et al. 2008[19]	3,476 pts	Since 1997†	Triple-class drug resistance 6.6%
Lima, et al. 2010[28]	1,820 pts 833 (46%) with GRT available	2000-2007‡	Among pts with GRT: Resistance to ≥ 2 classes: 17% Resistance to 3 classes: 2%

ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; GRT: genotypic resistant test; pts: patients; VF: virologic failure.
*Patients starting ART with non-HAART regimens were also included: 22% of patients started ART before 1995; 28% in 1995-1997; 28% in 1998-2000; and 21% in 2001-2005.
†The majority started ART between 1994 and 1998.
‡All patients started HAART after January 2000.

regimens[52], have been investigated, but none were able to achieve complete viral suppression in most patients with triple-class resistant HIV-1.

The advent of new antiretroviral drugs against novel targets (fusion inhibitors, integrase inhibitors, and R5 coreceptor antagonists) and new-generation drugs within prior available classes (second-generation NNRTI and new PI), with a higher genetic barrier and a different resistance profile, has expanded the therapeutic options for patients with multiclass drug-resistant HIV-1. The most recently approved agents (the new PI darunavir, the new NNRTI etravirine, the integrase inhibitor raltegravir, and the CCR5 antagonist maraviroc) became available almost simultaneously. Hence, clinicians have been able to design regimens with three fully active drugs even for triple-class-resistant HIV-1-infected patients.

Clinical trials with the new drugs in salvage therapy for multidrug-resistant HIV-1 infection

Firstly, the fusion inhibitor enfuvirtide and the new PI tipranavir, and some years later, etravirine, darunavir,

raltegravir, and maraviroc: all these new agents have been evaluated as integrants of salvage regimens for highly experienced patients with multidrug-resistant HIV infection in randomized clinical trials[53-69], and all have been shown to improve the efficacy of salvage therapy compared to standard of care. The design and main results of these clinical trials are summarized in table 2.

All these trials had a similar design, consisting of two parallel studies (1 and 2) with the same design and conducted in different geographic locations, and association of the new drug with an investigator-selected optimized background regimen (OBR), which is compared with the OBR alone (the standard of care) or with a placebo. In the studies on tipranavir and darunavir, these new PI were compared with an investigator-selected comparator PI, both associated with an OBR. In these trials on new agents, no other investigational drugs were allowed in the OBR, with the exception of the DUET trials, in which darunavir was an integrant of the OBR in both arms before it was licensed. However, as the drugs were approved, they were included in the OBR in successive trials with the newest compounds.

Thus, in the oldest studies (TORO 1 and 2 trials) no new drugs were added to the OBR. At that time, tenofovir and lopinavir/ritonavir were the newest and most active agents available that could be associated with enfuvirtide[53-55]. Enfuvirtide plus the OBR showed superiority compared with the OBR alone, but the percentages of patients with HIV RNA < 50 copies/ml after 48 weeks of treatment were low in both arms (18 and 8%) compared to the most recent studies with the newest drugs (Table 2; Fig. 1).

In subsequent studies with newer drugs, enfuvirtide was available for use in the OBR. However, it has an important limitation: due to its low genetic barrier to resistance and the rapid emergence of resistance mutations when viral suppression is not achieved, enfuvirtide can only be considered a fully active drug in patients who have not previously received it. Thus, the use of enfuvirtide in further salvage regimens is not indicated if previous failure has been documented[70,71].

Later, in the RESIST and POWER trials, enfuvirtide was used in the OBR in association with the investigational PI tipranavir and darunavir, respectively. Both new PI achieved significantly higher rates of virologic suppression than the investigator-selected ritonavir-boosted comparator PI (Table 2; Fig. 1). The efficacy of the regimen improved when enfuvirtide (if not previously used) was included in the OBR[56-61].

Enfuvirtide was also allowed in the DUET, BENCHMRCK, and MOTIVATE trials, where etravirine, raltegravir, and maraviroc were evaluated (Table 2). In addition, darunavir was given to all patients in the DUET trials[62-64], darunavir and tipranavir could be given in the BENCHMRCK trial[65,66], and tipranavir could be used in the MOTIVATE trial[67-69]. When these trials are analyzed together, it is notable that addition of two fully active agents (preferably from new classes) to the investigational drug was associated with the best virologic response rates, in many cases comparable to those achieved in naive patients[62-69]. Thus, when darunavir and enfuvirtide were added to raltegravir in BENCHMRCK, the percentage of patients who achieved < 50 copies/ml HIV RNA at week 48 rose to 89% (Fig. 1).

Triple-drug combinations of new drugs in salvage therapy for multidrug-resistant HIV-1 infection: pilot trials and observational studies

In clinical trials, the new drugs were investigated separately and the use of other new compounds was limited. Thus, clinical trials have provided little information about the efficacy of salvage regimens based on combinations of three new drugs, including drugs of the newest classes.

Nonetheless, the most recently approved drugs became available almost simultaneously, and this has made possible the construction of salvage regimens containing three fully active drugs for patients with multidrug-resistant HIV-1 infection in the setting of daily clinical practice.

The first new drugs licensed, enfuvirtide and tipranavir, have some limitations for inclusion in modern salvage therapy combined with other new agents. The inconvenience of subcutaneous administration of enfuvirtide and its local complications limit long-term use in a substantial portion of patients; therefore, it is now hardly ever used in clinical practice. Tipranavir also has certain limitations, despite its maintained activity resulting from a high genetic barrier to resistance. A clinically relevant interaction has been found between tipranavir and etravirine that reduces etravirine exposure, and for this reason, coadministration of these agents should be avoided[73]. In addition, certain adverse events, such as gastrointestinal intolerance, transaminase elevations, and dyslipidemia, are higher with tipranavir administration compared to darunavir[56-61]. Therefore, the most useful and most widely used new drugs in the deep salvage setting are darunavir/ritonavir, etravirine, maraviroc, and raltegravir.

Several nonrandomized pilot trials and observational studies have evaluated the efficacy of such combinations

Table 2. Randomized clinical trials evaluating the efficacy of the new drugs enfuvirtide, tipranavir, darunavir, etravirine, raltegravir, and maraviroc in salvage therapy for antiretroviral-experienced patients with multidrug-resistant HIV-1 infection

Trial	Design/patients	Inclusion criteria	Baseline characteristics	Outcome at week 48	Remarks
TORO 1/2[53-55]	Open-label, randomized n = 1,013 **Arms**: a) ENF + OBR (n = 661) b) OBR (n = 334) **OBR**: No new drugs available	Patients > 16 yr Plasma HIV-1 RNA > 1,000 c/ml Previous treatment with NRTI, NNRTI and at least 2 PI-based regimens	**CD4**: a) 88 b) 87/µl **VL**: a) 5.2 b) 5.1 lg **OBR GSS = 0**: a) 17% b) 16% **OBR GSS = 1**: a) 29% b) 28% **OBR GSS ≥ 2**: a) 54% b) 66%	**VL < 50 c/ml**: a) 18.3% b) 7.8% (p < 0.0001) **VL < 400 c/ml**: a) 30.4 vs. 12% (p < 0.0001) **Mean CD4 increase**: a) 91 b) 45 cells/µl	**Primary endpoint**: Change in plasma VL at week 24: TORO 1: a) 1.69 b) –0.76 log c/ml (p < 0.001) TORO 2: a) 1.43 b) –0.65 log c/ml (p < 0.001) **Predictors of response**: better response in patients with baseline VL < 5.0 log copies/ml, CD4 count > 100 cells/mm^3, prior experience with ≤ 10 ARV and PSS/GSS ≥ 2 **VL < 50 c/ml at 48 weeks by number of active agents:** 0: a) 4% b) 0%; 1: a) 18% b) 3%: ≥ 2: a) 22% b) 12%
RESIST 1/2[56-58,72]	Open-label, randomized n = 1,529 **Arms**: a) TPV/r + OBR (n = 775) b) PI/r + OBR (n = 754) **OBR**: ENF 20% (first use 15%)	Patients > 18 yr Plasma HIV-1 RNA > 1,000 c/ml Previous treatment with NRTI, NNRTI and at least 2 PI-based regimens	**CD4**: a) 152 b) 174/µl **VL**: a) 4.7 b) 4.7 lg **OBR GSS = 0**: a) 11% b) 14% **OBR GSS = 1**: a) 32% b) 32% **OBR GSS ≥ 2**: a) 57% b) 54%	**VL < 50 c/ml**: a) 22.8% b) 10.2% (p < 0.0001) **VL < 400 c/ml**: a) 43.2% b) 18.5% (p < 0.0001) **Mean CD4 increase**: a) 45 b) 21 cells/µl (p < 0.0001)	**Primary endpoint**: VL reduction ≥ 1 log at week 48: a) 33.6% b) 15.3% (p < 0.0001) **Predictors of response**: Lower baseline VL, lower TPV resistance mutations score, higher TPV C_{trough} , ENF use in OBR (first use) **VL < 50 c/ml at 48 weeks when ENF in OBR:** a) 28% b) 14% (p < 0.001)
POWER 1/2[59-61]	Open-label, randomized n = 255 **Arms**: a) DRV/r + OBR (n = 131) b) PI/r + OBR (n = 124) **OBR**: ENF 44% (first use 31%)	Patients > 18 yr Plasma HIV-1 RNA > 1,000 c/ml on current failing PI-based ART Previous failure to ≥ 1 NRTI, ≥ 1 NNRTI and ≥ 1 PI ≥ 1 primary PI RAM	**CD4**: a) 153 b) 163/µl **VL**: a) 4.6 b) 4.5 lg **OBR GSS 0**: a) 25% b) 18% **OBR GSS 1**: a) 34% b) 40% **OBR GSS ≥ 2**: a) 48% b) 60%	**VL < 50 c/ml**: a) 45% b) 10% (p < 0.0001) **Mean CD4 increase**: a) 102 b) 19 cells/µl (p < 0.0001)	**Primary endpoint**: VL reduction of 1 log at week 48: a) 61% b) 15% (p < 0.0001) **Predictors of response**: Lower baseline VL, higher number of active ARV in OBR, ENF use in OBR (first use), lower number of primary PI RAM, lower number of DRV RAM and lower DRV phenotypic FC **VL < 50 c/ml at 48 weeks by number of active agents:** 0: a) 20% b) 0%; 1: a) 50% b) 3%: ≥ 2: a) 56% b) 17%
DUET 1/2[62-64]	Double-blinded, randomized n = 1,203 **Arms**: a) ETR + OBR* (n = 599) b) Placebo + OBR* (n = 604) **OBR**: DRV/r all, ENF first use 26%	Patients > 18 yr ART-experienced Plasma HIV-1 RNA > 5,000 c/ml, on failing ART ≥ 1 NNRTI RAM and ≥ 1 major PI RAM	**CD4**: a) 99 b) 109/µl **VL**: a) 4.8 b) 4.8 lg **OBR PSS = 0**: a) 17% b) 16% **OBR PSS = 1**: a) 37% b) 39% **OBR GSS ≥ 2**: a) 46 % b) 45%	**VL < 50 c/ml**: a) 61% b) 40% (p < 0.0001) **VL < 400 c/ml**: a) 72% b) 47% (p < 0.0001) **Mean CD4 increase**: a) 98 b) 73 cells/µl (p = 0.0006)	**Primary endpoint**: VL < 50 c/ml week 24: DUET 1: a) 56% b) 39% c/ml (p = 0.005); DUET 2: a) 62% b) 44% (p = 0.0003) **Predictors of response**: Lower VL at baseline, higher CD4 count at baseline, adherence, number of active drugs in OBR, use of ENF (first use) in OBR **VL < 50 c/ml at 48 weeks by number of active agents:** 0: a) 46% b) 6%; 1: a) 63% b) 32%: ≥ 2: a) 78% b) 67% **VL < 50 c/ml at 48 weeks when ENF (*de novo*) in OBR:** a) 71% b) 59% (p < 0.05)

(continue)

Table 2. Randomized clinical trials evaluating the efficacy of the new drugs enfuvirtide, tipranavir, darunavir, etravirine, raltegravir, and maraviroc in salvage therapy for antiretroviral-experienced patients with multidrug-resistant HIV-1 infection *(continued)*

Trial	Design/patients	Inclusion criteria	Baseline characteristics	Outcome at week 48	Remarks
BENCHMRCK 1/2[65]	Double-blinded, randomized n = 699 **Arms**: a) RAL + OBR (n = 462) b) placebo + OBR (n = 237) **OBR**: ENF 38% (first use 20%), DRV/r 40% (first use 36%)	Patients > 16 yr Plasma HIV-1 RNA > 1,000 c/ml Phenotypic or genotypic resistance to ≥ 1 drug in each of the 3 classes NRTI, NNRTI and PI	**CD4**: a) 151 b) 158/μl **VL**: a) 4.6 a) 4.6 lg **OBR GSS = 0**: a) 25% b) 28% **OBR GSS** = 1 a) 38% b) 40% **OBR GSS ≥ 2**: a) 37% b) 32%	**VL < 50 c/ml**: a) 62.1% b) 32.9% ($p < 0.001$) **VL < 400 c/ml**: a) 72.3% b) 37.1% ($p < 0.001$) **Mean CD4 increase**: a) 109 b) 45 cells/μl ($p < 0.001$)	**Primary endpoint**: VL< 400 c/ml week 16: BENCHMRCK 1: a) 78.4% b) 41% ($p < 0.001$); BENCHMRCK 2: a) 78.3% b) 43.3% ($p < 0.001$) **Predictors of response**: Higher number of active drugs in OBR **VL < 50 c/ml at 48 weeks by number of active agents:** 0: a) 51% b) 2%; 1: a) 61% b) 29%: ≥ 2: a) 71% b) 39% **VL < 50 c/ml at 48 weeks when DRV and ENF (both first use) in OBR:** a) 89% b) 68% ($p < 0.001$)[66]
MOTIVATE 1/2[67]	Double-blinded, randomized n = 1,049 **Arms**: a) MVC BID + OBR (n = 426) b) MVC QD + OBR (n = 414) c) Placebo + OBR (n = 209) **OBR**: DRV/r, ETR and RAL not permitted. ENF 42% (first use 25%), TPV/r 15%	Patients > 16 yr Plasma HIV-1 RNA > 5,000 c/ml, on failing ART NRTI, NNRTI and PI-experienced (± ENF) or documented resistance to NRTI, NNRTI and PI R5 coreceptor tropism at screening	**CD4**: a) 167 b) 171 c) 171/μl **VL**: a) 4.9 b) 4.9 c) 4.9 lg **OBR GSS = 0**: a) 24% b) 22% c) 24% **OBR GSS = 1**: a) 32% b) 35% c) 26% **OBR GSS ≥ 2**: a) 43% b) 41% c) 48%	**VL < 50 c/ml**: a) 46% b) 43% c)17% ($p < 0.001$) **VL < 400 c/ml**: a) 56% b) 52% c) 22% ($p < 0.001$) **Mean CD4 increase**: a) 124 b) 116 c) 61 cells/μl	**Primary endpoint**: Mean change in VL at week 48: a) –1.84 b) –1.68 c) –0.79 logs ($p < 0.001$) **Predictors of response**: Lower VL at baseline, higher CD4 count at baseline, higher number of active ARV in OBR, use of ENF (first use) in OBR, use of TPV/r or LPV/r (first use) in OBR (only in univariate analysis) **VL < 50 c/ml at 48 weeks by number of active agents:** 0: a) 33% c) 0%; 1: a) 51% b) 17%: ≥ 2: a) 72% b) 51% **VL < 50 c/ml at 48 weeks when ENF *de novo* in OBR:** a) 61% b) 64% c) 27% **VL < 50 c/ml at 48 weeks when TPV/r *de novo* in OBR:** a) 57% b) 61% c) 29%[68,69]

ART: antiretroviral therapy; c/ml: copies/ml; C_{trough}: trough concentrations; DRV/r: darunavir/ritonavir (600/100 mg twice daily); ENF: enfuvirtide (90 mg twice daily sc); ETR: etravirine (200 mg twice daily); GSS: genotypic sensitive score (total number of antiretroviral drugs used as part of the optimized background therapy to which a patient's HIV was fully susceptible, as determined by genotypic resistance testing); MVC: maraviroc (BID: 150 mg twice daily; QD 150 mg/d once daily); NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; OBR: optimized background regimen; PI: protease inhibitor; PI/r: ritonavir-boosted protease inhibitors (investigator selected); PSS: phenotypic sensitive score, total number of antiretroviral drugs used as part of the optimized background therapy to which a patient's HIV was fully susceptible, as determined by phenotypic; RAL: raltegravir (400 mg twice daily); RAM: resistance-associated mutation; sc: subcutaneous; TPV: tipranavir; TPV/r: tipranavir-ritonavir (500/200 mg twice daily); VL: plasma viral load (HIV-1 RNA); yr: years.

Notes: Trials are in chronological order. In all trials efficacy analysis was performed by intent-to-treat (ITT) approach: all randomized patients who had received at least one dose of the investigational drug were included and non-completion was considered as failure.

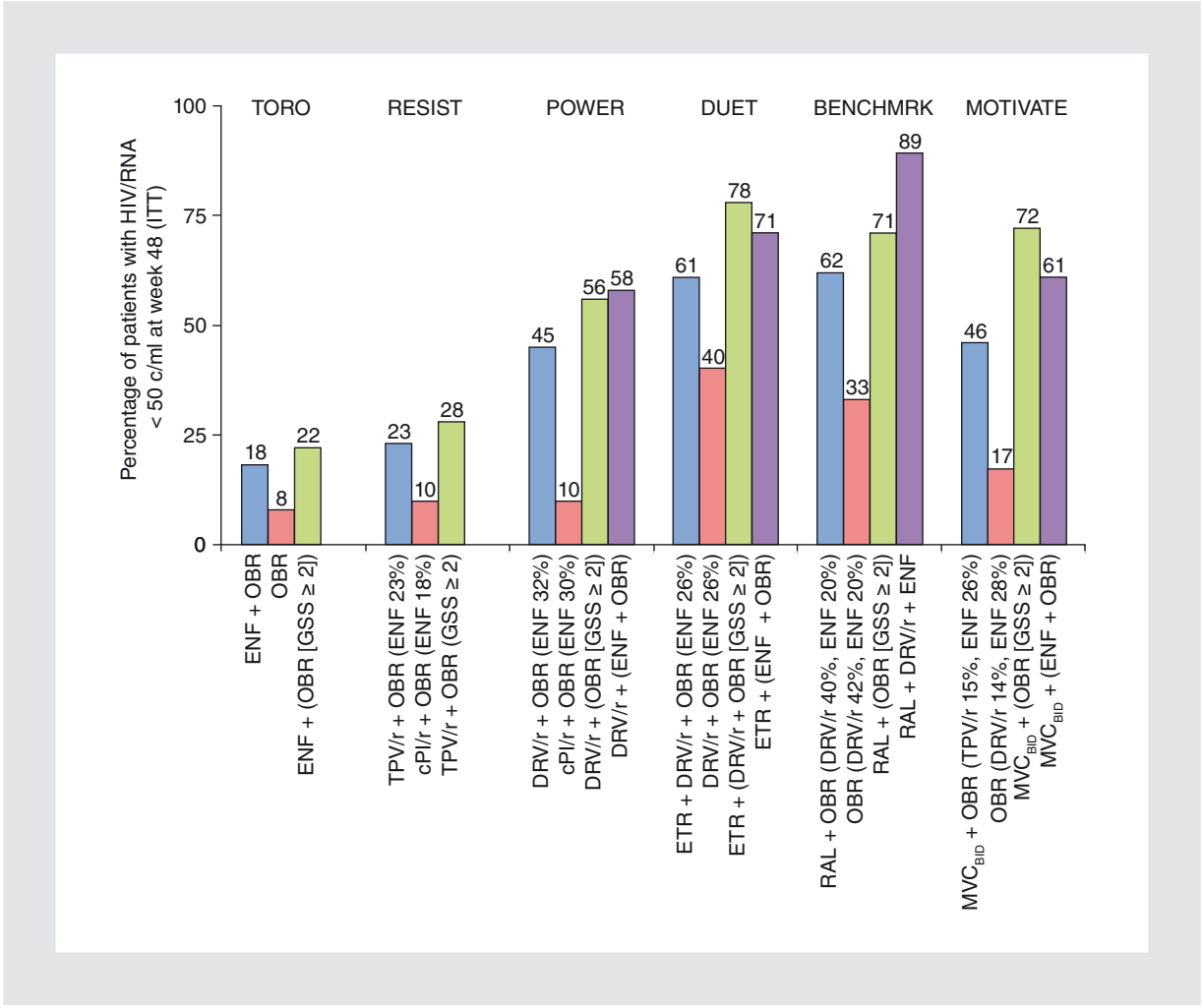

Figure 1. *Percentages of patients with plasma viral load < 50 copies/ml in randomized clinical trials evaluating the efficacy of new drugs (enfuvirtide, tipranavir, darunavir, etravirine, raltegravir, maraviroc) in salvage therapy for patients with multidrug-resistant HIV-1 infection. ITT: intent-to-treat; ENF: enfuvirtide; TPV: tipranavir; DRV: darunavir; ETR: etravirine; RAL: raltegravir; MVC: maraviroc; r: ritonavir; OBR: optimized background regimen.*

in patients with multidrug-resistant HIV-1 infection (Table 3; Fig. 2). All possible combinations of raltegravir, maraviroc, etravirine, and darunavir/ritonavir have been assessed[74], but the one that has received the most attention is raltegravir plus etravirine plus darunavir/ritonavir[75-78].

Clinical studies support the use of etravirine in combination with darunavir/ritonavir and/or raltegravir and/or maraviroc[79-82]. It has been reported that darunavir concentration may decrease when it is coadministered with raltegravir, but the potential clinical effect is uncertain[83,84]. Indeed, a pharmacokinetic study of the raltegravir, etravirine, darunavir/ritonavir combination did not find a deleterious drug-drug interaction, and therefore, there are no recommendations for dose adjustment when this regimen is used[85].

In the ANRS 139 TRIO trial, the efficacy and safety of combined raltegravir, etravirine, and darunavir/ritonavir was investigated in patients with triple-class-resistant HIV-1 infection[75]. At week 48, the percentage of patients with plasma HIV-1 RNA < 50 copies/ml was 86%. Darunavir and etravirine RAM were detected in only one and three patients, respectively, at virologic failure, and no raltegravir RAM were observed[86]. It should be noted that HIV genotypic susceptibility to etravirine and darunavir was required for the study, and 87% of patients also received a background therapy with NRTI and/or enfuvirtide[75] (Table 3; Fig. 2).

Similar results with this combination have been reported in other studies. In a pilot study in Spain, 32 heavily pretreated patients with multidrug-resistant HIV-1 infection who received a salvage regimen consisting

Table 3. Nonrandomized studies evaluating the efficacy of salvage regimens based on combinations of three of the new antiretrovirals in adult patients with multidrug-resistant HIV-1 infection

Study	Design/patients/ treatments	Inclusion criteria	Baseline characteristics	Outcome and remarks
TRIO (ANRS 139) Yazdanpanah, et al. 2009[75]	n = 103 **One arm:** RAL + ETR + DRV/r ± optional OBT **OBT:** 87% (NRTI 84% and/or ENF 12%)	VL > 1,000 c/ml on stable ART ≥ 3 PI resistance mutations but susceptibility to DRV ≥ 3 NRTI resistance mutations Prior failure to NNRTI, but susceptibility to ETR	CD4: 255 (132-351)/mm^3 VL: 4.2 (3.6-4.6) logs Major PI mutations: 5 (1-6) NRTI mutations: 6 (5-7) NNRTI mutations: 1 (0-2) GSS OBT < 1 GSS OBT ≥ 1	**VL < 50 c/ml week 24:** 90% **VL < 50 c/ml week 48**: 86% VL< 50 c/ml at 24 weeks when ENF (first use) in OBT: 90% VL< 50 c/ml at 24 weeks when NRTI in OBT: 88% VL< 50 c/ml at 24 weeks when GSS in OBT < 1: 91% Virologic suppression did not differ according to baseline HIV-1 RNA levels, CD4 cell count, first use of enfuvirtide, or OBT GSS **CD4 increase** at 48 weeks: 108 cells/mm^3
Imaz, et al. 2009[76]	n = 32 **One arm:** RAL + ETR + DRV/r	Consecutive heavily pretreated patients With multidrug-resistant HIV-1 Who started a new salvage regimen with RAL, ETR and DRV/r	CD4: 261 (1-910)/mm^3 VL: 4.3 (2.6-6.2) logs Major PI mutations: 4 (3-4) NRTI mutations: 5 (1-10) NNRTI mutations: 2 (0-4) Prior failure to TPV/r: 44% Prior failure to ENF: 50%	**VL < 50 c/ml week 24 ITT:** 30/32 (94%) **VL <50 c/ml week 24 OT:** 30/31 (97%) **CD4 increase** at 24 weeks: 103 (50-217) cells/mm^3
Etravirine Early Access Program in Europe Florence, et al. 2010[77]	n = 86 **One arm:** ETR + DRV/r + RAL ± optional OBT **OBT: 60**% (NRTI)	Prior experience to NRTI, NNRTI and PI Unable to use currently approved NNRTI (intolerance or resistance)	CD4: 249 (134-415)/mm^3 VL: 4.2 (3.6-4.7) logs	**VL < 50 c/ml week 24:** 70% **VL < 400 c/ml week 24:** 93% No differences between patients receiving or not receiving NRTI in OBT (91 vs. 97% VL < 400 c/ml) **CD4 increase at 24 weeks**: 108 cells/mm^3
Noza, et al. 2010[87]	n = 28 **One arm:** RAL + MVC (600 mg BID) + ETR	Resistance to NRTI, NNRTI and PI CCR5 tropic HIV-1 infection	CD4: 254 (76-399)/mm^3 VL: 4.16 (3.85-5.08) logs Prior exposure to TPV/r: 14% Prior exposure to DRV/r: 36% Prior exposure to ENF: 39%	**VL < 50 c/ml week 48**: 26/28 (93%) **VL < 400 c/ml week 48**: 28/28 (100%) **CD4 increase at 48 weeks**: 267 (136-355) cells/mm^3 No patients discontinued therapy before week 48
Imaz, et al. 2011[74]	n = 122 **Arms:** Three drugs among DRV/r, ETR, RAL and MVC a) with NRTI (n = 63) b) without NRTI (n = 59)	Prior failure to NRTI, NNRTI and PIs Resistance to at least one drug of each class (NRTI, NNRTI and PI)	CD4: a) 254 (104-421) b) 282 (153-409)/mm^3 VL: a) 3.7 (2.4-4.9) b) 4.2 (2.9-4.8) logs Major PI mutations: a) 3 (1-4) b) 2 (0-4) DRV mutations: a) 1 (0-2) b) 0 (0-2) NRTI mutations: a) 5 (3-7) b) 5 (4-6) NNRTI mutations: a) 2 (0-2) b) 2 (1-2) ETR mutations: a) 1 (0-1) b) 1 (0-1) Prior failure to TPV/r: 40% Prior failure to ENF: 43%	**VL < 50 c/ml week 48 ITT**: a) 49/63 (78%) b) 46/59 (78%) (p = 1.00) **VL < 50 c/ml week 48 OT**: a) 82% b) 85% (p = 0.81) **CD4 increase at 48 weeks**: a) 116 (21-259) b) 81 (29-181) cells/mm^3 (p = 0.91)

DRV: darunavir; c/ml: copies per ml; ENF: enfuvirtide; ETR: etravirine; GSS: genonotypic sensitive score (total number of antiretroviral drugs used as part of the optimized background therapy to which a patient's HIV was fully susceptible, as determined by genotypic resistance testing); ITT: intent-to-treat analysis, all missed data equals failure; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; OBT: optimized background therapy; OT: on treatment analysis (missed data excluded); PI: protease inhibitor; PSS: phenotypic sensitive score (total number of antiretroviral drugs used as part of the optimized background therapy to which a patient's HIV was fully susceptible, as determined by phenotypic); RAL: raltegravir; RAM: resistance associated mutations; TPV/r: tipranavir/ritonavir; VL: plasma viral load (HIV-1 RNA); yr: years.

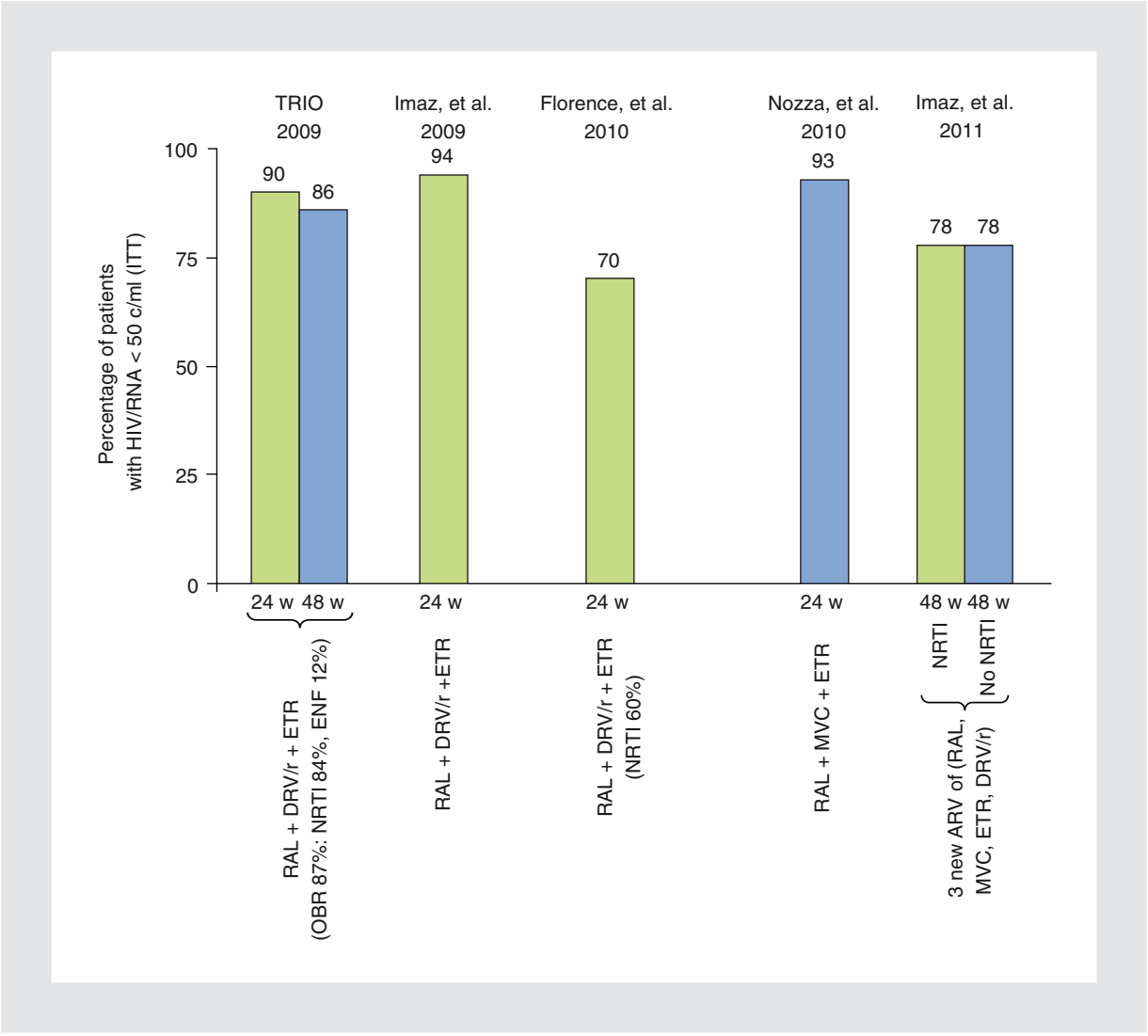

Figure 2. *Percentages of patients with plasma viral load < 50 copies/ml in nonrandomized studies evaluating the efficacy of salvage regimens based on combinations of three of the new antiretrovirals (darunavir, etravirine, raltegravir, maraviroc) in patients with multidrug-resistant HIV-1 infection. ITT: intent-to-treat; DRV: darunavir; ETR: etravirine; RAL: raltegravir; MVC: maraviroc; r: ritonavir; OBR: optimized background regimen; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor.*

of raltegravir, etravirine, and darunavir/ritonavir were analyzed. At week 24, 94% of subjects had plasma viral load < 50 copies/ml. The presence of darunavir and etravirine RAM was allowed in this study, and 66% of patients harbored at least one etravirine RAM, including three patients with three RAM[76]. The high efficacy of combined raltegravir, etravirine, and darunavir/ritonavir with and without background therapy in multidrug-resistant HIV-1-infected subjects has been also been observed in patients included in the etravirine early access program in Europe and the USA[77,78].

Due to their potency and high genetic barrier to resistance, new PI, mainly darunavir/ritonavir, are included in most deep salvage regimens in daily clinical practice. However, highly effective combinations can be also constructed without PI. The efficacy of a raltegravir, etravirine, and maraviroc combination was assessed in 28 patients included in a pilot study in Italy. At week 48, 93% of subjects achieved plasma HIV-1 RNA < 50 copies/ml[87].

A retrospective study has been recently published in Spain, including 122 patients with triple-class resistant HIV-1 infection starting a genotype-guided salvage regimen with at least three drugs, among them, darunavir, etravirine, raltegravir, and maraviroc[74]. Fifty-two percent of patients also received NRTI, although they were partially active or inactive. In the intent-to-treat analysis, 78% of patients with NRTI and 78% of patients without NRTI achieved HIV-1 RNA < 50 copies/ml at 48 weeks.

Management of multidrug-resistant HIV infection in routine clinical practice

Assessment of virologic failure

The goal for patients receiving ART is to achieve complete viral suppression, defined as plasma viral load below the detection limit of ultrasensitive assays (usually HIV RNA < 50 copies/ml), which enables restoration of the immune system and limits resistance emergence. Isolated transient detectable viral loads, typically < 400 copies/ml ("blips"), are not uncommon in successfully treated patients and do not represent true virologic failure[88]. A confirmed viral load > 50 copies/ml in at least two consecutive samples is usually warranted to define virologic failure. In clinical practice, when one or several viral load determinations of > 50 copies/ml are observed in a patient, certain causes, such as adherence, drug-drug interactions, and intercurrent infection, should be assessed and, if possible, corrected. Cases in which viral load becomes undetectable without a treatment change are not considered virologic failures.

Persistent HIV RNA levels > 200 copies/ml and especially > 500 copies/ml are often associated with emergence of drug-resistant mutations[89,90]. Therefore, although drug resistance testing is technically difficult in this viral load range, persistent plasma HIV RNA levels between 200 and 1,000 copies/ml should be considered virologic failure and an indication for a change of ART.

Recently, for the purposes of clinical trials, the AIDS Clinical Trials Group (ACTG) defined virologic failure as a confirmed viral load > 200 copies/ml, which eliminates most cases of apparent viremia caused by blips or assay variability. However, some risk of resistance emergence could exist in patients with persistent viral load at 50-200 copies/ml[91,92], hence, the goal of < 50 copies/ml is still maintained in current clinical guidelines[42-45].

Assessment of resistance and antiviral activity of the drugs in salvage regimens

In the management of patients on ART experiencing virologic failure, resistance testing is recommended for guiding the selection of active drugs to be included in the salvage regimen. Resistance testing has demonstrated a significant benefit in the response to salvage therapy compared with clinical judgment alone, and has been associated with improved survival of ART-experienced patients[93,94]. Drug resistance can be defined by genotypic or phenotypic assays, but in daily clinical practice, genotypic testing is generally preferred because of its lower cost, faster results, and higher sensitivity for detecting mixtures of wild-type and resistant viral strains. As a result of the advances in predicting drug activity by genotypic testing for both old and new drugs, and the current wide availability of these tools, clinicians can select the best salvage combination for each patient attending to the activity profile of each drug[29,95-101]. However, in patients with a long ART history, some archived drug resistance mutations may not be detected by standard drug resistance tests. Therefore, it is important to consider the patient's treatment history and prior resistance testing findings when available, as well as all other clinically relevant information for predicting therapy response[102]. Phenotypic testing can provide additional information in cases of complex drug resistance mutation patterns[43,95,99].

Maraviroc binds only to the CCR5 receptor and has no activity against X4-tropic viruses; hence, the presence of CCR5 tropism must be confirmed before maraviroc is used. Until recently, the only validated tropism test was the Trofile® phenotypic assay (Monogram, USA), but now, several techniques are being developed and validated to predict tropism by genotyping the envelope V3 loop sequence[103-106]. Genotypic assays are faster and less expensive, and can be performed in local laboratories.

Clinical management

The cornerstone in the management of multiclass drug-resistant HIV-1 infection is the combination of at least two and preferably three fully active drugs that allows patients to achieve complete suppression of viral replication and avoids the emergence of new RAM[42-45]. With the availability of the newest antiretrovirals, salvage regimens with three fully active drugs can be given to most patients, and recent studies have demonstrated the high efficacy of these new regimens.

The inclusion of drugs from new classes that have no cross-resistance with older classes, adequate combination of the available drugs, and reinforcement of treatment adherence are essential factors to guarantee efficacy and avoid the emergence of resistance to the new drug classes. The resistance pattern of each drug must be considered to select the most appropriate drugs for the regimen. Thus, the current genotypic resistance tests and all available historical tests, as well as the complete treatment history, should be taken into account when designing a patient's regimen[107].

By proper assessment of the activity of each drug in the salvage regimen, clinicians will avoid including

agents that are not fully active, and this will decrease the risk of drug toxicity and reduce treatment complexity. The high efficacy of these new combinations also has economic consequences. A recent economic analysis of cost versus HIV RNA suppression rates showed that the use of new drugs in salvage regimens reduces the cost of virologic suppression compared with regimens including recycled NRTI or enfuvirtide[108].

It has been suggested that a salvage regimen with two new fully active drugs may be potent enough in some cases[80]. However, randomized studies are needed to define the scenario in which this strategy would be feasible and effective.

Currently, we should recommend giving three fully active drugs to all patients with multiclass drug-resistant HIV-1 infection whenever possible. If three fully active drugs are not available, at least two agents with complete activity associated with one or more partially active drugs should be given. If it is possible, one of the two fully active drugs should be a PI with a high genetic barrier (darunavir or tipranavir), which could help to suppress viral replication earlier and avoid resistance emergence to all the agents in the regimen.

Unresolved issues

The role of nucleoside reverse transcriptase inhibitors

Although the new drugs have changed the management of patients with multidrug-resistant HIV-1 infection, NRTI are often included in salvage regimens for this population. In all the trials that have evaluated new agents in this scenario, an OBR containing NRTI has been added to the investigational drug. Furthermore, there is some evidence that certain NRTI retain activity against HIV even in the presence of resistance mutations, and these may help to guarantee the efficacy of the regimen in this population with scarce treatment options[109,110]. Maintenance of lamivudine in the presence of resistance, as confirmed by the M184I/V mutation, has been associated with at least some degree of viral suppression related to impaired viral fitness[111,112]. However, this benefit of lamivudine has been observed only in patients who received a regimen that was not fully suppressive[111-113]. Other recycled NRTI, such as didanosine, stavudine, and tenofovir, have shown efficacy in some patients with prior failures to NRTI, but their use seems to be limited by toxicity concerns and poor response when there is a large number of RAM[114-117]. Since new agents with potentially full activity are available, the role of NRTI in salvage regimens is controversial. In this setting, partially active or inactive NRTI may be unnecessary if three new fully active drugs are available[74,77,118]. In addition, by avoiding NRTI that are not highly useful, treatment toxicity and complexity can be reduced, as well as cost[108]. In contrast, it seems reasonable to recommend inclusion of partially active NRTI in salvage regimens for patients who cannot receive three fully active agents. Prospective studies restricted only to this population are needed to clarify whether inactive NRTI have a role in this scenario.

Highly drug-resistant HIV

Despite the current availability of several new drugs, in a small subset of patients, a regimen with at least two fully active drugs cannot be designed because of toxicity and/or resistance. In a high percentage of patients who do not receive at least two fully active drugs, an optimal virologic suppression cannot be achieved. The goals in this case are to preserve immunologic function and prevent clinical progression, while avoiding the emergence of new resistance mutations that can limit further use of new drugs. There is no consensus on how to optimize the management of these patients. Maintenance of partial virologic suppression by staying on the same failing regimen could reduce clinical progression[119]. However, this potential benefit must be balanced with the risk of accumulating additional resistance mutations. In this way, the use of transient non-suppressive regimens with NRTI, such as lamivudine alone or combined with other NRTI, may prevent clinical progression and avoid the emergence of new resistance mutations in other drug classes that could be more useful in the future[52,111,112].

Conclusion

Over the last years, several new antiretroviral drugs from novel and old classes have become available to clinical practice and have transformed the approach to salvage therapy for patients with multidrug-resistant HIV-1 infection. Complete and sustained virologic suppression (< 50 copies/ml) has become an attainable therapeutic goal even for this group of patients who had very limited treatment options with older drugs. Indeed, these new possibilities of salvage therapy have resulted in extraordinarily successful rates of virologic suppression in patients with multidrug-resistant HIV infection, comparable to those in patients who receive first-line regimens. As has been observed in

clinical trials and confirmed in recent pilot trials and observational studies, a combination of at least two and preferably three fully active drugs is critical to achieve complete suppression of viral replication and avoid the emergence of new RAM.

Nonetheless, although these new drugs have opened a wide range of salvage options for patients with multidrug-resistant HIV-1 infection, virologic failure can still occur and salvage therapy remains a challenge for clinicians treating HIV-infected patients. Before starting a new salvage therapy, the possible causes of previous failures should be considered and corrected whenever possible. When a salvage regimen is designed, the activity of each drug must be assessed based on current and historical genotypic resistance tests. The complete treatment history and all possible drug-drug interactions should also be taken into account. In summary, each drug in a salvage regimen must be carefully selected in order to achieve complete viral suppression, avoid the emergence of new RAM, and preserve active agents as viable future treatment options.

Conflict of interest

All authors declare no conflicts of interest.

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