Hot News

What to do in HIV Patients on a Failing Regimen With Limited Therapeutic Options?

Current HIV treatment guidelines recommend changing to a more powerful regimen in case of virologic failure. Nevertheless, patients with no fully active treatment options left are often kept on a failing regimen because switching would burn the few drugs still active. Some drugs in the failing regimen may continue to have some antiviral activity, and cessation of therapy may be harmful. However, antiretroviral therapy that is not fully suppressive is prone to further accumulation of drug resistance in HIV. Therefore the dilemma arises: i) do we need to change anyway, despite not having an optimal rescue therapy, risking also blowing up the next line therapy; ii) do we stay on the current regimen, hoping that further accumulation of drug resistance will be limited; or iii) do we need an entirely new strategy, picking a suboptimal maintenance regimen with less selective pressure for new drug resistance mutations?

To enable intelligent decisions in this matter, the EuroSIDA Study Group estimated the amount of accumulated drug resistance mutations during a continued failing regimen (viral load > 400 HIV-RNA copies/ml) and evaluated possible determinants (Cozzi-Lepri, et al. AIDS 2007;21:721-32). They retrospectively studied genotypic resistance profiles at two time points (t_0 and t_1) in a failing regimen in 110 patients enrolled in EuroSIDA. Accumulation of drug resistance was quantified by assessing changes in genotypic susceptibility scores (GSS) provided by the Rega algorithm and counting the number of drugs listed by the International AIDS Society (IAS 2005).

On average, there was a loss of 1.25 active drugs after six months of being on a failing therapy. In comparison with patients with extensive drug resistance to the failing regimen at t_0, patients with low resistance at t_0 seemed to lose more future drug options (Δ = 1.24; 95% CI: 0.04-2.44; p = 0.04) than patients with intermediate drug resistance (Δ = 1.08; 95% CI: 0.03-2.13; p = 0.04). The authors also found that the CD4 cell count nadir may influence the accumulation of drug resistance ('gain' of 0.34 active drugs per 100 cells per µl; 95% CI: 0.03-0.65; p = 0.03), though there could be some confounding factors not fully addressed in this study. Finally, if lamivudine was included in the failing regimen, then there were less mutations accumulated after six months (p = 0.008), though this could not be translated into a significant conservation of treatment options (GSS).

Cozzi-Lepri, et al. concluded from their analysis in heavily pretreated HIV patients failing their current regimen that a rapid switching to a new drug combination consisting of at least two active drugs is the preferred option. However, this is not always possible and, in some cases, even two fully active drugs is not enough to reach undetectable viral load. Another possibility is a maintenance strategy with lamivudine monotherapy, trying to maintain the failing strain, with its presumed reduced fitness, as the major circulating strain, without adding new drug selective pressure which may drive further accumulation of resistance. Some preliminary findings suggest that such a strategy might be acceptable. The E-184V study (Castagna, et al. AIDS 2006;20:795-803) showed that in case of lamivudine-resistant virus, lamivudine monotherapy may lead to a better immunologic and clinical outcome than complete therapy treatment interruption. However, this is a difficult and controversial concept that needs further investigation.

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Absence of HIV-1 Antibody Response in HIV Patients: What is the Foe, the Virus or the Host?

Diagnosis of HIV infection is mainly based on the detection of specific antibodies by screening with commercial enzyme immunoassays (EIA) or rapid tests, and further confirmation by Western blot. The major limitation of these tests is their inability to identify infection during the "window period", when antibodies have still not been produced. In addition, infection with distant HIV variants such as groups O or N may occasionally yield false-negative results using some antibody tests. It is noteworthy that in the last situation the problem is related to antibody detection and not with antibody production. There is a third rare situation in which HIV infection can be missed, represented by subjects in which HIV antibody response is lacking despite detectable viremia. These cases have been a subject of intensive studies in order to determine which factors are responsible for this lack of specific humoral immune response.

The first case of persistent HIV antibody negativity in a patient with HIV-1 subtype C infection has

Table 1. Main features of 15 HIV-infected individuals with persistent nonreactive EIA despite detectable viremia

Sex	Age	HIV-1 clade	CD4 counts (cells/µl)	p24 antigen	Plasma HIV-RNA (103 copies/ml)	IgG concentrations	Reference
Male	26	B	120-208	+	34,000	N	Soriano, Vox Sang 1994
Male	19	ND	4-208	+	ND	N, ↑	Martin-Rico, AIDS 1995
Female	38	A	0-10	+	1492->1600	N	Montagnier, J Infect Dis 1997
Male	31	B	180-230	+	199-7943	N	Michael, J Infect Dis 1997
Male	36	B	69-129	+	ND	N	Reimer, Clin Infect Dis 1997
Male	30'	B	94	+	337	↑	Sullivan, AIDS 1999
Male	30'	B	15	+	ND	N	Sullivan, AIDS 1999
Man	30'	B	0-11	+	773	N	Sullivan, AIDS 1999
Female	20'	B	8-18	+	480	N	Sullivan, AIDS 1999
Female	20'	B	2-3	+	254-750	↑	Sullivan, AIDS 1999
Female	20'	B	1-30	+	105-310	↓, N, ↑	Sullivan, AIDS 1999
Female	29	A/G	229	+	1500	N	Candotti, J Med Virol 2000
Female	29	A2	102	+	> 500	N	Cardoso, AIDS 2004
Male	34	B	ND	ND	1.3-300	↓*	Padeh, N Engl J Med 2005
Female	46	C	19-38	ND	451->750	N	Novitsky, Clin Infect Dis 2007

ND: no data; +: positive; N: normal; ↓: decreased; ↑: elevated.
*Common variable immunodeficiency.

recently been reported (Novostky, et al. Clin Infect Dis 2007;45:e68-71). The authors performed a comprehensive genetic analysis in order to characterize the potential uniqueness of the strain. No recombinations or mismatches between the HIV-1 antigens in diagnostic kits and in the patient's virus were found. These results suggest that host factors rather than HIV features were the main determinants of this lack of specific HIV antibody response in this patient. The same behavior has been reported for other similar cases. A review of the literature permits to identify up to 15 cases of HIV-infected individuals with persistent nonreactive EIA despite detectable plasma HIV-RNA (Table 1). No single clades or recombinant HIV-1 group M strains have been associated with persistent seronegativity. All these subjects presented IgG levels within the normal range, except for one case that had common variable immunodeficiency. In most of them, the diagnosis of HIV infection was made in late stages of the disease. The clinical course was aggressive in most cases, perhaps in part due to a more pronounced immune impairment. The prevalence of seronegative HIV-1 infections is largely unknown, but the widespread use of nucleic acid testing will most likely increase the number of cases in the near future. This would create new opportunities for care, prevention and research.

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Three-year Extended Follow-up of the 2NN Study: Nevirapine versus Efavirenz

Given their long plasma half-lives, potency against HIV, low pill burdens, and ability to be safely combined with other commonly used medications, the NNRTI nevirapine and efavirenz are widely used in combination antiretroviral therapies. Some prior cohort studies among antiretroviral-naive patients have suggested that efavirenz might be superior to nevirapine in terms of efficacy. However, data from the 2NN study, a large (n = 1216), multicenter, international, prospective, randomized, head-to-head trial comparing efavirenz versus nevirapine (van Leth, et al. Lancet 2004;363:1253-63), found that treatment-

naive patients achieved comparably good antiviral responses using stavudine plus lamivudine as nucleoside backbone. After 48 weeks, 70% of patients taking efavirenz, 65% of those taking nevirapine twice daily, and 70% of those taking nevirapine once daily achieved viral loads < 50 HIV-RNA copies/ml.

At the recent 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, held in Sydney last July, the three-year extended follow-up data from the 2NN trial were presented (de Wit, et al. Abstract WEPEB032). The 2NN investigators retrospectively collected data up to 144 weeks for patients still under active follow-up at week 48. Patients in the nevirapine plus efavirenz arm were not included. The primary endpoint was the percentage of treatment failures between weeks 49 and 144, defined as the occurrence of a CDC category B/C event or death, or virologic failure, or change of allocated NNRTI. Secondary endpoints included percentage of patients with virologic failure, change in CD4 cell count, incidence of CDC category B/C events, and incidence of laboratory grade 3/4 (serious or severe) adverse events.

Two comparisons were made: nevirapine twice daily vs. efavirenz, and nevirapine twice daily vs. nevirapine once daily. Overall, 567 patients were included in the intent to treat analysis (120 nevirapine once daily, 223 efavirenz, and 224 nevirapine twice daily). From week 49 through week 144, treatment failure occurred in 45% of patients taking nevirapine once daily, 35% of those taking efavirenz, and 36% of those taking nevirapine twice daily (nevirapine once daily vs. nevirapine twice daily $p = 0.24$; nevirapine twice daily vs. efavirenz $p = 0.92$). Both comparisons for all secondary analyses yielded no significant differences among treatment regimens.

Virologic failure occurred in 8.3% of patients taking nevirapine once daily, 4.9% of those taking efavirenz, and 5.8% of those taking nevirapine twice daily. The mean changes in CD4 counts from week 49 through week 144 were + 72 cells/mm^3 in patients taking nevirapine once daily, + 130 cells/mm^3 in those taking efavirenz, and + 135 cells/mm^3 in those taking nevirapine twice daily. Rates of grade 3/4 laboratory toxicities were 9.2% among patients taking nevirapine once daily, 7.2% among those taking efavirenz, and 7.1% among those taking nevirapine twice daily. Finally, CDC category B/C events or death occurred in 4.2% of patients taking nevirapine once daily, 6.3% of those taking efavirenz, and 5.8% of those taking nevirapine twice daily.

The study investigators concluded that the virologic and immunologic response between 49 weeks and 144 weeks was comparable for the three study arms. Both the primary and the secondary analyses showed no statistically significant differences for efavirenz vs. nevirapine twice daily and for nevirapine once daily vs. nevirapine twice daily.

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Hopes for New Cyclophilin Inhibitors of Hepatitis C Virus in HIV Coinfected Patients

Cyclosporin A is a widely used immunosuppressor that has been reported to suppress both HIV and hepatitis C virus (HCV) replication. In the HCV model, the drug works by blocking the binding of cyclophilin B to the viral NS5B polymerase. The role of cyclophilin B in the HCV replication complex is not clear yet, but it seems to be essential for the binding of the viral RNA to the polymerase. In the HIV model, cyclosporin A may block cyclophilin A, which acts at multiple steps of the HIV life cycle, especially during the uncoating process that follows the entry of the core within target cells.

New non-immunosuppressive derivatives of cyclosporin have been developed and are being tested in patients with chronic hepatitis C. One of them, NIM811 (Novartis), is currently in phase I clinical trials. Another more promising agent, DEBIO-025 (DebioPharm), has just entered phase II trials. Both molecules are *in vitro* more potent inhibitors of HCV replication than cyclosporin A, although unfortunately do not show any significant antiretroviral activity. Nevertheless, due to their double activity, compounds within this family might be a great contribution for the treatment of HCV/HIV coinfected patients.

In a phase Ib trial, DEBIO-025 was administered as monotherapy to 19 drug-naive HCV/HIV coinfected patients at doses of 1200 mg twice daily during 15 days (Flisiak, et al. Hepatology 2006;44(Suppl 1):609A). Treated patients experienced a slight decrease in plasma HIV-RNA (mean, 1.0 ± 0.1 $\log_{10}$ copies/ml), whereas almost all patients (18 out of 19) showed a decline in serum HCV-RNA of more than 2 $\log_{10}$ IU/ml upon administration, with an average maximal HCV-RNA reduction of 3.6 $\log_{10}$ IU/ml. Indeed, three patients achieved undetectable serum HCV-RNA levels (< 10 IU/ml). Interestingly, the antiviral effect of DEBIO-025 was independent of the HCV genotype. Hyperbilirubinemia was relatively frequent and led to treatment withdrawal in three cases; it resolved spontaneously thereafter.

The combination of cyclosporine A derivatives with interferon or anti-HCV small molecules has not been tested in humans, although some *in vitro* experiments have suggested that they could be synergistic (Paeshuyse, et al. Hepatology 2006;43:761-70; Colemont, et al. Antivir Res 2007;74:A39). But there is also bad news. Two recent studies have shown that HCV may

select for resistance mutations to cyclosporin A *in vitro* and likewise it may confer resistance to the new derivatives (Robida, et al. J Virol 2007;81:5829-40; Fernandes, et al. Hepatology, in press).

In summary, new cyclophilin inhibitors are promising anti-HCV agents endowed with anti-HIV activity. They seem to be well tolerated in animals and humans, which may provide an attractive option for the treatment of HCV infections, particularly in HCV/HIV coinfected patients.

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Nevirapine Once Daily is Moving Further Steps

Two trials are currently ongoing in drug-naive HIV-infected individuals in which the safety and efficacy of nevirapine 400 mg once daily is re-assessed. ARTEN (atazanavir, ritonavir, tenofovir, emtricitabine and nevirapine) is a prospective, international, open-label, randomized study in which 561 drug-naive HIV-positive individuals will be allocated to receive one of the following three arms: atazanavir/ritonavir twice daily, nevirapine twice daily, or nevirapine once daily, in all instances along with Truvada® (tenofovir plus emtricitabine). One of the main goals of the study is to compare the metabolic profile of atazanavir/ritonavir versus nevirapine at 48 weeks, and whether nevirapine once daily is as good as given twice daily. In the 2NN trial, while the efficacy of the nevirapine once daily arm was similar to that of the efavirenz or nevirapine twice daily arms (van Leth, et al. Lancet 2004;363:1253-63), nevirapine once daily was associated with more frequent hepatotoxicity events. However, the nucleoside backbone in the 2NN study was the combination of stavudine and lamivudine, and stavudine has been shown to produce liver damage. Moreover, hepatitis B/C coinfected patients and a geographic cluster of hepatic events in patients enrolled in Thailand were noticed retrospectively, a finding which confounded the interpretation of the safety nevirapine once daily regimen.

The second study, named VERVE, is a phase III trial in which the extended-release new formulation of nevirapine 400 mg will be assessed in 958 drug-naive HIV-infected individuals. In this multicenter, randomized, double-blind study, the comparative arm will receive nevirapine 200 mg twice daily. All patients will receive Truvada® as nucleoside backbone. Besides the main safety and efficacy endpoints at 48 weeks, a pharmacokinetic substudy will be conducted in a subset of patients. If the nevirapine extended-release formulation proves to be as safe and efficacious as the current standard pill, it will represent an important advance to make drug compliance easier, since the most currently given nucleoside backbones (e.g. Truvada® and Kivexa® [Epzicom]) are co-formulations of drugs in a single pill.

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