Antiretroviral Treatment Strategies and Immune Reconstitution in Treatment-Naïve HIV-Infected Patients with Advanced Disease

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Summary: Treatment-naïve advanced HIV-infected patients have a lower life expectancy than those treated early with highly active antiretroviral therapy (HAART). Early treatment allows greater immunological recovery, a reduction of AIDS progression, a reduced risk of related illnesses, and lower mortality compared with HAART initiation in advanced disease. Given the numbers with advanced disease worldwide and the high cost of care, strategies encouraging early detection may be life saving and cost effective. Factors associated with increased clinical progression include higher baseline HIV viral load and older age, emphasizing the need for early viral load suppression. HAART initiation faces many challenges; interactions between antiretroviral agents and drugs used to treat life-threatening opportunistic infections may cause subtherapeutic antiretroviral exposure and the development of resistance or supratherapeutic levels resulting in adverse effects. Immune reconstitution inflammatory syndrome can be another cause of suboptimal outcomes. The management of patients with advanced HIV infection should include rapid short-term immune reconstitution to limit the risk of disease progression plus aggressive antiviral treatment to achieve rapid virological suppression. Clear evidence on the optimal regimen and agents to use to target advanced HIV disease is lacking. Therefore, antiretroviral treatment for these patients has to be carefully tailored to the individual according to many variables.

Key Words: highly active antiretroviral treatment, immune reconstitution, late-presenting AIDS, treatment-naïve advanced HIV infection

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INTRODUCTION

Advanced treatment-naïve HIV-infected patients can be defined as individuals presenting with a CD4 lymphocyte count of less than 50–200 cells/μl, or having an AIDS-defining condition. The dramatic improvement in life expectancy for HIV-infected individuals who begin highly active antiretroviral therapy (HAART),[1–3] has led some healthcare authorities to recommend routine HIV testing.[4,5] The early detection of HIV infection, when followed by the proper initiation of HAART according to current guidelines, allows greater immunological recovery and a reduction in progression to full-blown AIDS, as compared with treatment initiation in advanced disease.[6,7] In a recent cohort analysis in England and Wales among heterosexual individuals diagnosed with HIV in the period 2000–2004, short-term mortality within a year from diagnosis was considerably higher in individuals presenting late, having CD4 cell counts less than 200 cells/μl at the time of diagnosis (6.1 versus 0.7%; $P < 0.01$). Earlier diagnosis would have reduced short-term mortality by 56% and overall mortality by 32%.[8] Similar findings have previously been described by the same research group in men who have sex with men, with a far more striking likelihood of short-term mortality for late presenters [adjusted odds ratio 10.8; 95% confidence interval (CI) 7.7–15.9].[9] Considering the high frequency of late presenters in different settings worldwide,[10–14] and the high cost of medical care associated with advanced stage disease,[15] public health strategies encouraging the active detection of HIV-infected individuals may be life saving and cost effective. Nevertheless, late presenters are part of everyday clinical practice, and specific treatment strategies are not yet codified in official guidelines.[16,17]

The relationship between the baseline CD4 cell count and the risk of death, or the occurrence of AIDS-defining events, has been documented by a large collaborative cohort analysis ($n = 12\,000$):[18] in addition to late presentation, high levels of HIV replication at baseline, older age, a history of AIDS, and infection through injected drug abuse, are also associated with increased rates of clinical progression.[18] Moreover, the initial response to HAART over the first 6 months has been associated with a probability of progression at 3 years ranging from 2.4% in patients in the lowest risk stratum to 83% in patients in the highest risk stratum.[19] These findings emphasize the need for rapid suppression of the viral load and an increase in CD4 cell count out of

the 'high-risk zone' of less than 200 cells/μl as soon as possible.

Late presentation of HIV infection may coincide with the presentation of clinical AIDS-related illnesses. AIDS presenters are commonly defined as individuals who had a first positive HIV test in the month of, or immediately before, the AIDS diagnosis. *Pneumocystis jiroveci* pneumonia (PCP) is still one of the most frequent opportunistic infections in AIDS presenters, usually accompanied by oral candidiasis and general signs of wasting. Tuberculosis is the second most common opportunistic infection in some European settings, and is definitely the leading cause of AIDS and death in patients with HIV worldwide. The frequent severe pulmonary involvement of AIDS presenters is often the indication for intensive care unit admission.[20] Treatment-related issues are particularly delicate in these patients, for two main reasons: initiation timing for different treatments, and drug–drug interactions. Acute illnesses should be treated first, but deferral of HAART initiation could be detrimental for the short-term prognosis. Moreover, immune reconstitution inflammatory syndrome (IRIS), occurring days to weeks after HAART initiation, may lead to a paradoxical worsening of the underlying respiratory disease. Interactions between drugs used to treat opportunistic infections and antiretroviral agents should be taken into account, in order to avoid subtherapeutic exposure to antiretroviral drugs leading to the development of resistance or, conversely, supratherapeutic levels causing adverse effects. This paper aims to address some specific questions concerning the management of advanced treatment-naïve HIV patients and AIDS presenters, especially focusing on the choice of a correct antiretroviral regimen.

CHALLENGES IN INITIATION OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

Although the very first objective in patients with advanced disease who are treatment naïve is clear, HAART initiation faces many challenges.

Need for Rapid Viral Load Decay

Advanced treatment-naïve patients usually present with high plasma HIV-RNA (viral load) values, often greater than 100 000 copies/ml. Although potent HAART regimens capable of achieving this goal are widely available, the longer period that is necessary to reach an undetectable plasma viral load leaves the replicating virus exposed for a longer time to selective pressure exerted by the drugs, potentially favouring the selection of resistant variants. A high genetic barrier for the initial regimen may thus be preferable, in order to minimize the risk of resistance and failure.

Drug-resistant variants may pre-exist before HAART is initiated. The increased prevalence of transmitted resistance that has been observed after the first years of HAART[21–23] may have direct clinical consequences on the response to first-line antiretroviral treatment. Resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) is particularly dangerous, as one single mutation is sufficient to determine high-level cross-resistance to this potent class of drugs.

Performing a genotypic resistance test may be particularly helpful in guiding the choice of first-line regimen, although the sensitivity of the test may be very low; in the absence of drugs, wild-type virus overgrows the resistant variants, especially if a long time has elapsed since the primary HIV infection, as in advanced treatment-naïve patients. Mutations not affecting viral fitness may, however, persist for a long time, even in the absence of drugs. Furthermore, resistant variants are archived in latently infected CD4 cells, and may re-emerge as a result of selective pressure. As a resistance test in treatment-naïve patients might not provide a complete panel of mutations, it could be argued that testing is not necessary and would only delay treatment initiation. In routine clinical settings, the results of virological sequencing may be available after 3–4 weeks, a period too long for a patient at imminent risk of disease progression. Therefore, results from resistance tests should not delay treatment, but a viral genotype should be obtained, in order to predict a possible, although rare, early virological failure.

A boosted protease inhibitor (PI)-based regimen needs the accumulation of multiple mutations to be virologically ineffective. In advanced treatment-naïve patients, in whom a rapid viral decay is crucial but more difficult to obtain, boosted PI regimens offer an improved likelihood of success, thanks to their intrinsic high genetic barrier; however, a theoretically lower risk of early virological failure is not supported at present by clear clinical evidence. Many other factors may intervene in early virological failure, making the choice of first-line treatment a far more complex issue.

Management of Accompanying Diseases and Drug–Drug Interactions

The choice of initial HAART regimen may be problematical when it overlaps a complex drug regimen for concomitant pathologies, especially for opportunistic infections, tuberculosis, and malignancies. Besides the issue of drug interactions, which may preclude the simultaneous usage of some molecules, the risk of drug toxicity and the scarce acceptance and tolerance of a too high medication burden make the task of choosing the right drugs all the more difficult.

The most frequent opportunistic infection in western countries is PCP, usually treated with cotrimoxazole (and steroids), without relevant drug–drug interactions with antiretroviral agents. In our opinion, however, the high rate of cutaneous rash with cotrimoxazole, usually observed in the first 2 weeks of treatment, contraindicates the concomitant initiation of NNRTI-based HAART. Nevirapine and efavirenz cause rash leading to discontinuation with rates of 7 and 1.7%, respectively; in the case of rash it would be difficult to identify which out of cotrimoxazole and NNRTI is the culprit.

When advanced treatment-naïve patients present with tuberculosis, two strictly unrelated conditions have to be

treated urgently. Tuberculosis treatment cannot be deferred and should receive priority; however, the initiation of antiretroviral treatment cannot wait for 6 months, especially if the CD4 cell count is very low. Early antiretroviral treatment also favours a cure for tuberculosis, because it enhances a depressed immune function that contributes to tuberculosis development. If antiretroviral treatment is started too early, however, the risk of IRIS could counterbalance the benefit of immune reconstitution, because it may worsen the tuberculosis. Moreover, rifamycin-based regimens are commonly used to treat tuberculosis, especially in resource-limited settings where rifampicin is used in fixed-drug combination pills. This drug is known to have interactions with protease inhibitors and nevirapine. Although the interaction with efavirenz usually requires dose adjustment, recent data provide evidence that the concurrent administration of rifampicin and efavirenz may be safe and effective.[24] If efavirenz cannot be used, rifabutin and a boosted PI may be co-administered, with the necessary dose adjustment. Treatment of the co-infection tuberculosis/HIV needs to take into account both the timing and the choice of drugs. No definite recommendations can be made, although a deferral of 2 months in HAART initiation would be advisable, and data from pharmacokinetic studies should help choose the best treatment regimen.

The optimal timing for treating both HIV infection and its related conditions is thus a fine tuning process that has to consider a plethora of clinical, pharmacokinetic and pharmacodynamic aspects.

Need for Short-Term Immune Reconstitution

Achieving a robust immunological recovery rapidly is of the utmost importance for the clinical outcome because of the close relationship between the CD4 cell count and mortality. In the large cohort study of the Antiretroviral Therapy Cohort Collaboration, the current CD4 cell count (but not the baseline CD4 cell count) was strongly associated with subsequent disease progression 6 months after starting HAART.[19] Similar findings were obtained in different settings, notably in sub-Saharan Africa, where the late presentation of AIDS patients is even more frequent. This can explain the higher mortality observed in patients starting HAART in resource-limited settings, with respect to cohorts in industrialized countries.[25] Despite a similar virological and immunological response with first-line treatment, early mortality was higher in developing countries. In a large community-based setting in rural Malawi, nutritional status, CD4 cell count < 50 cells/μl and World Health Organization stage IV disease have been associated with a greater risk of very early mortality (within 3 months) among patients initiating HAART.[26] Similar findings were reported in patients in Ethiopia.[27] Therefore, achieving a 'safer' threshold of CD4 cell count should be the objective of the early phase of HAART. This goal may be more difficult to reach for advanced treatment-naïve patients who commence treatment with very low baseline CD4 cell counts.

Advanced pre-treatment immunodeficiency is reported to be associated with a diminished capacity for the restoration of CD4 cell counts and CD4 cell functional responses during HAART;[28–33] however, despite concerns about the limited potential for immune recovery, even patients who start HAART while severely immunosuppressed may show a great immunological response. The rate of CD4 cell recovery may vary over time, usually being more pronounced at the beginning. A gradual reduction in increase in CD4 cells to a plateau is usually observed thereafter. This phenomenon is usually outlined in two phases of immunological recovery: phase 1 corresponds to immune redistribution, and phase 2 to immune reconstitution. The rapid phase 1 CD4 cell recovery has been reported to be strongly associated with the baseline viral load.[34,35] Better immunological responses for patients with higher baseline plasma viral loads may be explained by the rapid redistribution of CD4+CD45Ro+ memory T cells sequestered in lymphoid tissue, and the reduction in apoptotic cell death, triggered by the suppression of viral replication during the initial weeks of HAART.[36,37] The rate of viral load recovery may vary according to the baseline CD4 cell count level. Lawn and colleagues[38] recently reported a quite unexpected finding from a study on a South African cohort: the rate of CD4 cell recovery was calculated for different CD4 cell count strata. Although the phase 1 increase in CD4 cell count was similar across all CD4 cell strata, the slope of the phase 2 CD4 cell increase was steeper for patients who started treatment with CD4 cell counts of less than 50 cells/μl. Moreover, the risk of immunological non-response (defined as the failure to achieve ≥ 50 cells/μl increase in CD4 cell count from baseline) was significantly lower among patients with baseline CD4 cell counts of less than 50 cells/μl. Nevertheless, these patients were less likely to attain a CD4 cell count greater than 200 cells/μl at 48 weeks. A prolonged period below a 'safe' CD4 cell count threshold, rather than a diminished rate of immunological recovery, is thus likely to account for the high rates of morbidity and mortality observed among those with advanced disease during the early months of HAART,[39] as emerged from a longer follow-up study conducted in Spain.[30]

The sustained suppression of viral replication is also critical to continuous immunologic recovery.[34,35] This association was confirmed in the study by Lawn and co-workers,[38] in which the viral load at 6 weeks was a strong independent predictor of subsequent immunological recovery.

Cohort studies addressing the consequences of persistently elevated low-level viraemia showed an increased risk of virological failure,[40] with the further selection of resistance mutations, possibly affecting CD4 cell count recovery.[41] The long-term impact of resistance on mortality has been extensively described.[42–44]

The choice of components for triple combination therapy should take into account the need for a profound and rapid increase in the CD4 cell count. Determining the best combination for this purpose is not yet possible, but data

from comparative trials and cohort studies may offer some hints to identify the possible candidates for the regimen for advanced treatment-naïve patients. In the large AIDS Clinical Trials Group (ACTG) 384 trial,[45] initial treatment assignment did not affect total CD4 cell recovery, naïve/memory CD4 cell reconstitution, or the decline in T-cell activation at 144 weeks.

The magnitude of immunological reconstitution may depend on many other factors, not strictly related to the degree of virological response to HAART. For example, increasing age is associated with poorer immunological recovery,[46] for a reduced thymic CD4 cell reserve,[47] further consumed in advanced HIV disease.[6,48] A proportion of immunological non-responders is frequently described in many cohorts, and mechanisms underlying this poor CD4 cell count increase have not yet been fully elucidated. Persistent CD4 T-cell activation and residual viraemia may contribute to incomplete immunological response in patients with full virological response to HAART.[49–54] Strategies of HAART intensification might be appropriate, although poorly investigated as yet.[55]

Adjuvant therapy has been advocated for this cluster of patients. Whereas immune stimulation with IL-2 is reported to give some improvement in the CD4 cell count increase,[56,57] it still lacks proof of solid immunological advantage in the routine setting, and it is not currently recommended.[16]

Recent reports on an adjuvant effect of micronutrients deserve more interest as a simple and effective strategy, although their role may be marginal.[58–60]

Robust immunological recovery may by followed by IRIS, known to be linked to fast immune reconstitution derived from severe immunodepression.[61–65] Although difficult to anticipate, special attention should be paid to the possible occurrence of IRIS, as it may be one of the events arising in the first months of treatment, when the early interruption of HAART should be undertaken with caution, to avoid the selection of resistance mutations.[66] Furthermore, the occurrence of IRIS may raise the question as to whether a rapid and consistent immune reconstitution is always desirable. Conversely, a slower pace towards viral suppression might reduce the risk of IRIS, obtaining the same long-term immunological results; however, data supporting this hypothesis are lacking, and these considerations remain purely speculative.

STRATEGIES FOR MANAGEMENT OF INITIAL HIGHLY ACTIVE ANTIRETROVIRAL THERAPY REGIMEN

The exact timing to start HAART is not well established; despite the urgent need to obtain a fast increase in the CD4 cell count, waiting for the resolution of acute medical conditions (notably PCP or tuberculosis, as well as HIV-related malignancies) is commonly undertaken in clinical practice, for reasons of poor tolerance and toxicity of concomitant treatment administration. Therefore, the choice of HAART components has to be balanced between potential drug–drug interactions and the need for a rapid decrease in the viral load and a robust short-term immune reconstitution. In the absence of specific guidelines for this selected category of patients, current strategies are based on available data from randomized clinical trials and cohort analyses, considering clusters of patients with high viral loads ($> 100\,000$ copies/ml) and low CD4 cell counts (< 50 cells/μl). Many open questions thus still remain unresolved, leaving the clinician to tailor the treatment carefully on a case-by-case basis.

Choice of First Antiretroviral Regimen

One of the most compelling questions in general antiretroviral treatment is 'what to start with'. Current clinical guidelines recommend, as a preferred regimen, either a PI boosted with low-dose ritonavir or efavirenz, the NNRTI, to be administered with a double nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone.[16,17] This issue is far more crucial in advanced treatment-naïve patients, when there is no time to waste and no room for error. A recent intercohort analysis at 6 months on 590 Italian and Spanish AIDS presenters showed no difference in terms of clinical, virological and immunological outcomes between patients treated with a PI-based regimen and patients treated with a NNRTI-based regimen. Interestingly, even the timing for starting the treatment seemed to have no impact on the immunovirological outcome at 6 months (Figure 1).[67]

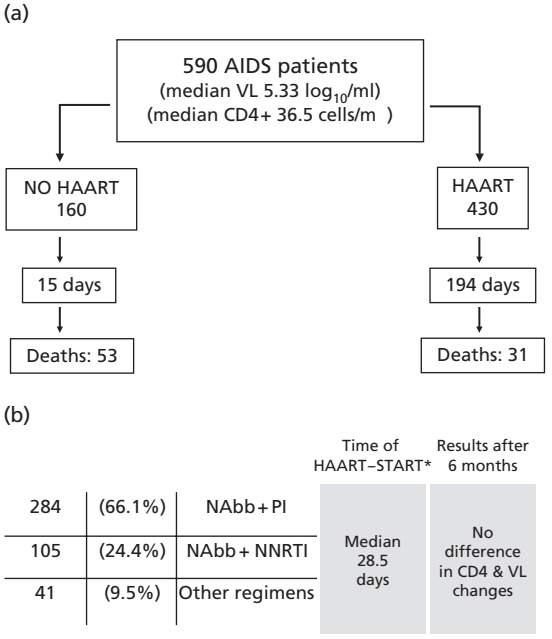

Figure 1. Deaths of patients with AIDS according to the timing of the initiation of highly active antiretroviral therapy (HAART) in an intercohort analysis of Italian and Spanish patients (a). Immunovirological outcome according to initial drug combination in the 430 patients with AIDS who initiated HAART (b).
NAbb, nucleoside analogue backbone; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load. *Main reason for delay *Pneumocystis jiroveci* pneumonia or tuberculosis. Adapted from Mussini et al.,[67] with permission.

When considering data from randomized clinical trials, the first study that directly compared a NNRTI-based regimen with a PI-based regimen[68] showed a better virological outcome for patients treated with efavirenz, although the immunological recovery was similar between the two groups. The better virological performance of efavirenz compared with unboosted indinavir was also obtained for high viral load values, greater than 100 000 copies/ml. By contrast, unboosted indinavir plus two NRTI (zidovudine and lamivudine) showed a better virological suppression in patients with viral loads greater than 100 000 copies/ml, compared with three NRTI (zidovudine, lamivudine and abacavir).[69]

When tested in advanced treatment-naïve patients with CD4 cell counts of less than 100 cells/μl, efavirenz-based HAART resulted in an effective immunological and virological outcome,[70] reaching more than 90% of patients with viral loads of less than 50 copies/ml in an on-treatment analysis.

In the NEAT study,[71] which compared unboosted fosamprenavir with nelfinavir, a full suppression of viral loads in patients with CD4 cell counts less than 50 cells/μl was achieved only in 48 and 24%, respectively.

In a direct comparison between efavirenz-based HAART and a triple NRTI regimen,[72] the NNRTI-based regimen confirmed its better virological performance, even in patients with viral loads greater than 100 000 copies/ml. In the EfaVIP 2 study, which retrospectively compared the outcomes of efavirenz with non-boosted PI-based HAART, in severely immunosuppressed treatment-naïve patients (median CD4 cell count at baseline 34 cells/μl), the former resulted in a superior virological response with no difference in immunological or clinical effectiveness.[73]

When considering boosted PI compared with unboosted PI, better virological response was achieved in advanced treatment-naïve patients. The results of the SOLO study showed a greater proportion of patients with undetectable viral loads at 48 weeks, in the group with baseline CD4 cell counts of less than 50 cells/μl, if treated with boosted fosamprenavir once a day compared with nelfinavir (73 versus 51%, respectively).[74] The definitive superiority of boosted over unboosted PI was established by the comparative trial between lopinavir boosted with low-dose ritonavir and nelfinavir.[75] Beyond the better virological performance (67 versus 52% of patients with viral loads < 50 copies/ml at week 48), lopinavir/ritonavir also offered the advantage of not selecting for protease mutations at failure, thus preserving future treatment options in the same class. Conversely, the higher rate of resistance to lamivudine and the development of HIV protease mutations in nelfinavir-treated patients may undermine the response to subsequent treatment regimens. The baseline median viral load in that study was almost 5.0 $\log_{10}$ copies/ml; the boosted PI advantage was highlighted in highly viraemic patients. As there was no difference in the number of discontinuations for adverse events, the better virological outcome could be attributed to the intrinsic higher potency. Interestingly, the one-year immunological recovery was no different between the two treatment groups.

In order to assess whether the viral load success of NNRTI-based therapy could be assured in advanced treatment-naïve patients, a post-hoc analysis within the 2NN trial evaluated the treatment response for different CD4 cell strata.[76] The risk of virological failure was increased at very low CD4 cell counts (< 25 cells/μl) compared with CD4 cell counts greater than 200 cells/μl [hazard ratio (HR) 1.28; 95% CI 0.93–1.77]. The same was seen for a plasma viral load of 100 000 copies/ml or greater compared with a lower plasma viral load (HR 1.20; 95% CI 0.96–1.50). There were no statistically significant differences between nevirapine and efavirenz in the risk of virological failure within any of the CD4 cell or plasma viral load strata, although the latter performed slightly better in the low CD4 cell stratum. These findings have been confirmed elsewhere in a retrospective analysis of a small dataset of advanced treatment-naïve patients.[77]

Boosted PIs offer the advantage of yielding a rapid viral load decay; in advanced treatment-naïve patients a fast viral load suppression may be crucial to guarantee durable treatment efficacy.[78] Boffito *et al*.,[79] in a pilot study on 32 severely immunosuppressed patients, accurately described the very initial phase of viral decay; despite a similar viral load decrease over the first week between patients treated with efavirenz, indinavir or lopinavir/ritonavir-based regimens, the latter demonstrated a faster clearance of circulating viral biomass in the first 24 h (Figure 2).

If we consider just lopinavir/ritonavir, pooled data from Abbott studies 720, 863, 046, 418 that put together 654 patients, show a very good rate of viral suppression at every CD4 cell stratum, even in patients with baseline CD4 cell counts of less than 25 cells/μl[3,80] in contrast to a previous analysis of NNRTI-based regimens.[76]

A direct comparison between a boosted PI (indinavir boosted with ritonavir) and efavirenz, in 66 severely immunosuppressed patients, has been carried out in the

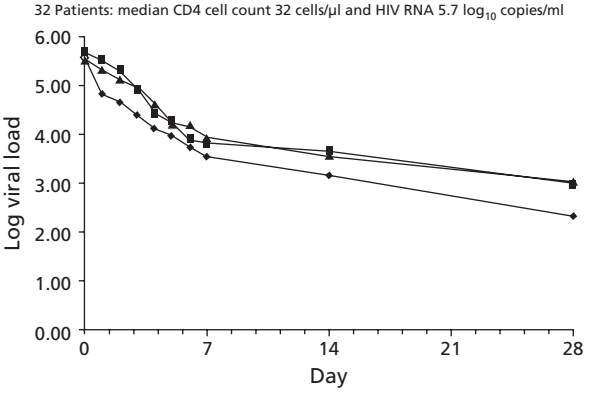

Figure 2. Viral load decay in the first days of highly active antiretroviral therapy: comparison between efavirenz, indinavir and lopinavir/ritonavir-based regimens.
The latter showed a more pronounced early clearance of viral biomass. —•— Lopinavir/ritonavir; —■— efavirenz; —▲— indinavir. Reproduced with permission from Boffito *et al*.[79]

ADVANZ trial; 50% of patients had a diagnosis of AIDS at baseline, and the median CD4 cell count and plasma viral load were 40 cells/μl and 5.5 $\log_{10}$ copies/ml, respectively. Patients treated with an efavirenz-based regimen had a better virological response at 24 months in the intention-to-treat analysis, and the CD4 cell count increase was greater although not statistically significantly so in the on-treatment analysis.[81] These conflicting data leave us wondering whether the choice of boosted PI could affect the virological and immunological results; a direct comparison between efavirenz and lopinavir/ritonavir in advanced treatment-naïve patients is warranted to address this question ultimately. Data on the direct open randomized 2-year comparison between lopinavir/ritonavir plus two NRTI, efavirenz plus two NRTI and lopinavir/ritonavir plus efavirenz, have recently been presented by the ACTG study 5142.[82] A slightly better virological performance was achieved by efavirenz plus two NRTIs than with lopinavir/ritonavir plus two NRTIs (89 versus 77% of patients with viral loads < 50 copies/ml, respectively). By contrast, the median 96-week increase in the CD4 cell count was significantly greater for both lopinavir-containing arms (lopinavir/efavirenz: +268 cells/μl; lopinavir: +285 cells/μl) than for efavirenz (+239.5 cells/μl; $P = 0.01$). The viral resistance tests performed at failure showed that resistance mutations (M184I/V and K103N) were more common in the efavirenz plus two NRTI arm than the two lopinavir arms (10, two and two patients in the efavirenz plus two NRTI, lopinavir plus two NRTI, and lopinavir/efavirenz arms, respectively). Although the numbers are rather small, lopinavir/ritonavir confirmed its high genetic barrier, which leaves more chances open after the first therapeutic failure.

The results of different comparative trials are summarized in Table 1.

In the large ACTG 384 trial, which prospectively assessed immunovirological endpoints for different antiretroviral strategies in treatment-naïve patients,[83] all the subjects underwent a longitudinal evaluation of T-cell counts, and a majority also had a testing of naïve and memory CD4 cell subsets, natural killer and B cells, and T-cell activation. The results of this extensive analysis on factors influencing the magnitude of immunological recovery showed that younger age, female sex, higher naïve/memory CD4 cell ratio, higher baseline viral load, and virological suppression were associated with a greater CD4 cell increase, whereas persistent T-cell activation was associated with impaired CD4 cell recovery after HAART initiation. Initial treatment assignment did not affect CD4 cell reconstitution.[45] This longer evaluation confirmed previous reports.[84]

Nevertheless, in the ACTG 384 trial, the outcome of the PI-based regimen was penalized by the use of a non-boosted PI, notably nelfinavir, currently no longer recommended as a preferred choice in initial treatment. Conversely, there is evidence of a continuous and robust immunological recovery in subjects treated for a long time with lopinavir/ritonavir-based HAART.[85] The M97-720 study was a phase II trial of lopinavir/ritonavir in combination with stavudine and lamivudine in antiretroviral-naïve and experienced HIV-1-infected subjects, in which patients were enrolled with no CD4 cell count restriction. Immunologic analyses were performed to week 312 for all subjects ($n = 63$) who remained on study during this time period. The CD4 cell increase appeared to be consistent regardless of the

TABLE 1. Summary of clinical trials comparing different antiretroviral regimens in treatment-naïve patients.

Study	Comparison	Outcome
Staszewski et al. 1999[68]	IDV vs. EFV	VL < 50: 70% vs. 48% CD4 increase: no difference
Staszewski et al. 2001[69]	IDV vs. ABC in VL > 100 K	VL < 50: 45% vs. 31%
Arribas et al. 2002[70]	EFV in CD4 < 100	VL < 50: 68% (ITT) CD4 > 100: 70% (ITT)
NEAT Study 2004[71]	NFV vs. FosAPV in CD4 < 50	VL < 50: 24% vs. 48%
Gulick et al. 2004[72]	EFV vs. 3 NRTI in VL > 100 K	Virological failure 21% vs. 11%
Pulido et al. 2004[73]	EFV vs. PI in CD4 < 50	VL < 50: EFV better than PI CD4 cell increase: no difference
SOLO Study, 2004[74]	FosAPV/r vs. NFV in CD4 < 50	VL < 50: 73% vs. 51%
Walmsley et al. 2002[75]	LPV/r vs. NFV	VL < 50: 67% vs. 52% CD4 cell increase: no difference
Van Leth et al. 2005[76]	EFV vs. NVP	Increased risk of virological failure at CD4 < 25 vs. CD4 > 200
King et al. 2005[80]	LPV/r in CD4 < 25	No increased risk of virological failure
ADVANZ Trial, 2005[81]	IDV/r vs. EFV in CD4 < 100	VL < 200: 61% vs. 74% ITT CD4 cell increase: no difference
ACTG 5142 Study, 2006[82]	LPV/r vs. EFV	VL < 50: 77% vs. 89% CD4 cell increase: 285 vs. 239.5

ABC, abacavir; CD4, CD4 cell count (cells/μl); EFV, efavirenz; FosAPV, fosamprenavir; IDV, indinavir; ITT, intention-to-treat analysis; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; /r, boosted with low-dose ritonavir; VL, viral load (copies/ml).

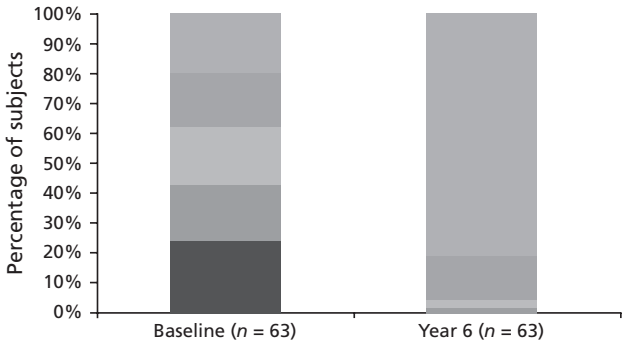

Figure 3. Decreasing proportion of HIV-infected individuals with low CD4 cell counts after 6 years of continuous therapy with lopinavir/ritonavir plus two nucleoside/nucleotide reverse transcriptase inhibitors. 500+; 350–499; 200–349; 50–199; 0–49. Adapted from Landay et al.[85]

baseline CD4 cell count. The mean CD4 cell count increased from 280 to 808 cells/μl, an increase of 528 cells/μl. The largest rate of increase in CD4 cell counts occurred early in the study, from weeks 0 to 12 and weeks 12 to 48; however, increases were also observed in other time periods (years 1–2, years 2–4, and years 4–6). Although 39 out of 63 subjects had baseline CD4 cell counts of less than 350 cells/μl, only three of these subjects had CD4 cell counts of less than 350 cells/μl at year 6 (Figure 3). A substantial improvement in immunological function was also seen in other immunological parameters, such as B and natural killer cells, the CD4 : CD8 cell ratio, and the normalization of CD4 and CD8 cell activation. The latter two findings are particularly important, as they provide some evidence that immune reconstitution continues for 6 years in subjects who are virologically suppressed and receiving a lopinavir/ritonavir-based antiretroviral regimen. Furthermore, an inverse correlation of the CD4 : CD8 cell ratio with the HIV-1 proviral reservoir has been described previously,[86] and the scarce immune reconstitution observed in some subjects has been associated with enhanced T-cell activation and heightened levels of intracellular HIV-DNA in CD4 cells.[52]

In the choice of the first antiretroviral regimen in advanced treatment-naïve patients, a rapid viral decay must be achieved, in order to limit the potential selection of viral-resistant strains, which may hamper long-term virological response. Particularly in cases of high viral load, the use of a low genetic barrier drug is at a greater risk of virological failure. Furthermore, regimens with a low virological performance in clinical trials should be abandoned, as pointed out in the last versions of treatment guidelines: triple nucleoside regimen, unboosted PI-based regimen, tenofovir/didanosine or tenofovir/abacavir as a backbone in NNRTI-based regimens; all these combinations should be avoided as an initial choice. The use of efavirenz is still controversial in the advanced treatment-naïve population. An efavirenz-based regimen theoretically has a low genetic barrier, and considering the risk of transmitted resistance in treatment-naïve patients, particularly involving NRTI and NNRTI,[87] it can result in a more risky combination. On the other hand, all the comparative trials in which efavirenz was used showed equal or better virological results for this NNRTI, with respect to its comparator (even, recently, lopinavir/ritonavir);[82] however, in terms of salvageability, failing a NNRTI-based regimen could preclude future treatment options more quickly, whereas boosted PI-based regimens may allow an easier sequencing with less concern about selected resistance mutations.

Concerns for early treatment interruption should also be considered when introducing HAART in advanced treatment-naïve patients. On the one hand an NNRTI-based regimen has a higher risk of allergic rash, both for nevirapine and efavirenz. Conversely, boosted PI-based regimens are generally less well tolerated at the beginning as a result of gastrointestinal side effects, thus potentially limiting adherence. Managing the latter, however, could be easier than facing an early rash, especially when confounding factors might be present, such as during PCP treatment with cotrimoxazole. Therefore, the choice of initial regimen should take into account the complex interplay of all these factors.

Choice of Nucleoside Reverse Transcriptase Inhibitor Backbone: Risks and Benefits

Different degrees of immune reconstitution can also depend on the nucleoside/nucleotide analogues that constitute the backbone of triple combination therapy. Recent data from direct comparisons in randomized clinical trials suggest a significantly higher change in the mean absolute CD4 cell count for patients treated with tenofovir/emtricitabine with respect to zidovudine/lamivudine (both in combination with efavirenz),[88] and for patients treated with abacavir/lamivudine with respect to zidovudine/lamivudine (both in combination with efavirenz).[89] Direct comparison between these two thymidine analogue mutation-sparing regimens is still lacking. Considering the long-term drug-related toxicity of thymidine analogues, the zidovudine-related risk of anaemia, and the lower immunological recovery by using zidovudine instead of tenofovir or abacavir in the nucleoside/nucleotide analogue backbone, there is a growing body of evidence that places fixed-drug combination tenofovir/emtricitabine or abacavir/lamivudine as the preferred backbone in initial HAART. Actually, the latter combination is still the second choice because of the consistent risk of hypersensitivity reaction, occurring at a variable rate of 5–8%. Even if the exclusion from abacavir therapy of HLA-B 5701 allele carriers will hopefully minimize this risk,[90,91] the narrow time frame for initiating HAART in a severely immunocompromised patient may leave no time to wait for genetic screening results. Tenofovir is well tolerated, but should be used with caution or avoided in patients with preexisting renal insufficiency. Moreover, in advanced treatment-naïve patients treated for acute medical conditions, caution should be taken not to use simultaneously potentially nephrotoxic drugs (such as foscarnet or pentamidine). In patients undergoing

chemotherapy for lymphomas, caution is warranted for the risk of renal damage caused by hyperuricemia derived from massive tumour lysis. In this particular situation, potentially nephrotoxic drugs should be avoided.

The choice of antiretroviral therapy in advanced treatment-naïve patients also has to take into consideration the need for central nervous system (CNS) penetration. This issue has recently been reviewed by Boffito and coworkers.[92] Zidovudine is the only drug for which solid data on CNS penetration are available, and cognitive impairment in advanced HIV disease is directly correlated with viral load suppression in the CNS compartment.[93] Whether viral load suppression is achieved by a direct action on virus in that compartment, or as a consequence of general viral load suppression, is not yet known.[94,95] Furthermore, data on lopinavir/ritonavir monotherapy show suppressed viral loads in the CNS compartment.[96] Moreover, in advanced HIV disease, the inflammation of the blood brain–barrier may favour drug penetration. On the basis of these considerations, the use of zidovudine in advanced stages of HIV disease should no longer be viewed as mandatory.

Improving Current Strategies

Considering the importance of rapidly achieving a suppressed viral load and short-term immunological recovery, strategies using four drugs as initial treatment have been compared with standard triple combination HAART. In the ACTG 384 trial no advantage has been seen in a regimen including stavudine, didanosine, efavirenz and nelfinavir over a three-drug regimen composed of zidovudine, lamivudine and efavirenz.[97] By contrast, the ACTG 388 trial, conducted in advanced HIV patients (mean CD4 cell count 161 cells/μl, mean viral load 5.42 $\log_{10}$ copies/ml), showed better results in a four-drug regimen containing efavirenz compared with a three-drug regimen containing indinavir. Drug-related toxicity and tolerability have actually penalized the virological outcome of the three-drug arm and the four-drug arm with double PI (nelfinavir and indinavir).[98] The INITIO trial,[99] by contrast, found a better outcome in a three-drug arm containing efavirenz, reinforcing the evidence that tolerability is crucial in determining the long-term virological outcome. The ACTG A5095 study was a randomized double-blind clinical trial that compared a regimen of zidovudine/lamivudine plus efavirenz with zidovudine/lamivudine/abacavir plus efavirenz.[100] After a median of 3 years follow-up, the virological endpoint and the immunological recovery were very similar between the two groups, without a statistically relevant difference. No advantage has been seen in a four-drug regimen with respect to classic three-drug HAART. The mean baseline CD4 cell count was 240 cells/μl, quite different from the very low CD4 cell counts of advanced treatment-naïve patients. At this time, data from randomized clinical trials supporting a four-drug strategy in late presenters are lacking. Nevertheless, considering the wider availability of potent and convenient options for first-line treatment, strategies of induction/maintenance with a four/three-drug scheme should not be abandoned *a priori*. Past trials had used less convenient PI in testing the four-drug strategy, and the recent ACTG A5095 study simply did not find a benefit in adding abacavir to a standard zidovudine/lamivudine plus efavirenz regimen.

Beyond the need for comparative trials specifically targeted to an advanced treatment-naïve population, new solutions could be suggested to manage initial treatment in AIDS presenters. Enfuvirtide is the only approved antiretroviral among the new class of entry inhibitors, and has shown a dramatic antiviral activity in multidrug-experienced patients. Data from TORO-1[101] and TORO-2[102] studies have demonstrated the immunological and virological advantage of enfuvirtide when coupled with another fully active drug. The RESIST[103] and POWER[104] studies have confirmed this trend, making enfuvirtide the cornerstone of salvage therapy in patients experiencing multiple virological failures.[105] Although offering enfuvirtide-based treatment may be considered outrageous as the first HAART regimen (many far more convenient alternatives are available), there is a strong rationale in rapidly reducing the high viral load of advanced treatment-naïve patients, and pilot experiences have shown promising results.[106] The advantage of these 'hit hard' strategies, beyond limiting the potential selection of resistance and producing a robust short-term immune reconstitution, could also be to spare long-term metabolic toxicity, usually derived from prolonged boosted PI use.[107,108] The use of more potent drugs, such as enfuvirtide, is not currently licensed for treatment-naïve patients. Strategies aimed at verifying the rationale of the early short-term use of enfuvurtide can only be tested in investigational studies. A comparative randomized trial between the standard lopinavir/ritonavir plus two NRTIs approach and enfuvirtide plus two NRTIs, switched to three NRTIs after 3 months (induction/maintenance strategy) is currently ongoing in advanced treatment-naïve patients in Italy (T20 naïve study).

Perspectives

New investigational agents are on the horizon. It is possible that the new input coming from their use will lead us to reconsider our fixed dual scheme for initial antiretroviral treatment. Completely new treatment algorithms might rapidly outweigh the ongoing debate between the boosted PI and the NNRTI strategy, because the availability of oral compounds of different classes will compel us to reformulate the mainstays of antiretroviral treatment. Integrase inhibitors and CCR5 antagonists are currently being compared with a standard efavirenz-based regimen for initial treatment in phase III randomized clinical trials. As maraviroc is active on R5 but not dual-tropic HIV strains, its use in advanced treatment-naïve patients, who are probably already infected with a CXCR4-using strain of HIV, may be less effective than the standard treatment. Moreover, in a phase I study on treatment-naïve patients,

breakthrough viral rebound has been observed in the arm treated with vicriviroc compared with efavirenz.[109] Therefore, CCR5 antagonists are not currently candidates for treating advanced HAART-naïve patients. By contrast, preliminary data recently presented on the integrase inhibitor raltegravir (MK-0518) have shown efficacy comparable to efavirenz, but a more pronounced early viral decay in treatment-naïve patients.[110] These findings are extremely promising for the potential consequences on an advanced treatment-naïve population, in which a rapid viral decay is of the utmost importance. It remains to be seen if this compound will provide the same performance as boosted-PI or efavirenz in terms of CD4 cell recovery.

CONCLUSION

Although HAART has had a beneficial impact on morbidity and survival even among individuals with AIDS, advanced treatment-naïve HIV-infected patients are at a high risk of death or full blown AIDS progression. Epidemiological data are not reassuring: both in the western world and in resource-limited countries, the AIDS pandemic is growing every year. More worrisome, individuals who present late at diagnosis are a consistent part of newly detected HIV infections. This rather new epidemiological picture has raised public health concerns. In order to tackle the medical risk and the economic cost of unawareness, in the United States HIV testing is now routinely offered to sexually active individuals when accessing primary health-care services.

Having the means, practitioners should know how to manage the treatment of late diagnosed HIV-infected individuals. A short-term immune reconstitution should be obtained rapidly in order to limit the risk of disease progression, which is directly linked to the duration of a CD4 cell count less than 200 cells/μl. A fast viral decay to achieve complete and stable virological suppression is mandatory, and should be pursued immediately. Current strategies offer many options for initiating effective treatment, but a number of questions concerning the best treatment options still remain unresolved. Comparative clinical trials designed to choose the best first-line treatment in treatment-naïve patients usually fail to address specific questions of advanced HIV and AIDS populations. Evidence to support the optimal treatment combination is thus often derived from subgroups of patients within clinical trials, and from retrospective cohort analyses. The great variability of case presentation makes the task of adopting common and codified strategies for this type of patient more difficult. Drug management has to take into account concomitant pathologies, with their specific and case-variable medication burden. Also the optimal timing of initiation is influenced by many variables, including the type of concomitant pathology, the risk of drug toxicity, and the threat of IRIS. All these variables taken together are major obstacles to the design of clinical trials that will identify better treatment strategies to target advanced HIV infection. Therefore, antiretroviral treatment for advanced treatment-naïve HIV-infected patients still has to be tailored according to multiple variables, and may require expert advice to tailor it more effectively to these vulnerable recipients.

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