AIDS Rev 1999; 1: 57-60

Impact of Triple Drug Therapy on Morbidity, Mortality and Cost

Natalie Jahnke, Val Montessori, Robert Hogg, Aslam H. Anis, Michael O'Shaughnessy and Julio S.G. Montaner

BC Centre for Excellence on HIV/AIDS, Canadian HIV Trial Network, Vancouver, Canada

Abstract

Two major advances emerged during the Vancouver International AIDS Conference in 1996: The recognition of the prognostic value of plasma viral load and the clinical benefit associated with triple drug combination therapy. These developments have led to a substantial change in the therapeutic management strategy for HIV disease. We have seen a dramatic decrease in HIV-related morbidity and mortality. Furthermore, preliminary results from pharmacoeconomic analyses indicate that the present therapeutic strategy is highly cost-effective.

Key words

HIV. Morbidity. Mortality. Cost. Antiretroviral drugs.

Introduction

A number of surrogate markers have traditionally been used to predict prognosis, and assess treatment efficacy among HIV infected individuals. Among them the CD4 cell count remains a very valuable marker. Other markers, such as immunoglobulin A, C1Q (as a measure of circulating immunocomplexes), the erythrocyte sedimentation rate, neopterin or ß2-microglobulin have not proven clinically useful. However, the recent availability of sensitive laboratory methods for the measurement of HIV RNA in plasma allowed for its evaluation as a surrogate marker. The prognostic value of a single plasma viral load determination was first demonstrated by Mellors *et al*[1]. The same authors later demonstrated that the prognostic value of a plasma viral load determination was enhanced if the CD4 cell count was also taken into account[2].

Having demonstrated the prognostic value of plasma viral load and CD4 cell count in the context of natural history studies, the door was opened for their evaluation as surrogates of therapeutic efficacy. O'Brien *et al*[3], initially reported the results of a study of 270 symptomatic HIV-infected subjects who were randomly assigned to receive either zidovudine or placebo. In this study, each 0.5 $\log_{10}$ decrease of plasma viral load following the initiation of therapy was associated with a reduced risk of progression to AIDS of approximately 30%. Also, each 10% increase in the CD4 cell count following the initiation of therapy was associated with a reduced risk of progression to AIDS of approximately 15%. Similar

Correspondence to:
Prof. Julio S.G. Montaner
667-1081 Burrard Street
Vancouver, B.C. V6Z 1Y6
Canada

results were reported by Hughes *et al*[4], who found that among 198 HIV-positive patients with CD4 cell counts below 350 cells/mm^3, the magnitude of the plasma viral load reduction was proportional to the reduction in the risk of disease progression. More recently, a subset analysis of 487 patients enrolled in the CAESAR trial demonstrated that the 57% reduction in disease progression for the 3TC-containing arm of the study was reliably predicted by the combination of reductions in plasma viral load and increases in the CD4 cell count[5].

This has allowed for the development of a new therapeutic strategy. As of the summer of 1996, several International Panels endorsed the adoption of plasma viral load driven strategies[6]. Although the strategy has evolved substantially since originally crafted, the fundamental aim remains the same: To suppress viral replication as measured by the plasma viral load as much as possible for as long as possible using combinations of antiretroviral agents.

Triple-drug therapy in clinical trials

The introduction of the potent protease inhibitors has probably been the single most important therapeutic development in the field of HIV therapeutics. Already in the early clinical trials, when used in combination with two nucleoside reverse transcriptase inhibitors, these agents were shown to substantially reduce viral replication, increase CD4 counts, decrease morbidity and increase survival, even among patients with very advanced HIV disease[7].

The AIDS Clinical Trials Group (ACTG) Protocol 320 involved 1,158 HIV-infected patients with low CD4 counts and fairly advanced disease who also had a history of prior zidovudine treatment. Study participants received lamivudine and zidovudine or stavudine and they were randomly assigned to indinavir or an identical placebo in a double-blinded fashion. Results of this study showed a substantial and statistically significant decrease in the rate of progression to AIDS and death with the triple-drug regimen. Of note, the surrogate value of CD4 cell count and plasma viral load was again confirmed in this study[8]. In a similar smaller study, 97 zidovudine-experienced patients were randomized to either indinavir monotherapy, zidovudine plus lamivudine or zidovudine, lamivudine and indinavir. At 52 weeks, 90% of patients in the three-drug arm had shown a reduction in serum viral load to below 500 copies/mL. As expected, greater increases in CD4 counts were seen among patients receiving triple drug therapy[9]. Comparable results have now been obtained in the AVANTI 2 and 3 studies using combinations of zidovudine, lamivudine and indinavir or nelfinavir, respectively[10,11]. More recently, comparable surrogate marker effects have been described when two nucleosides and a non nucleoside reverse transcriptase inhibitor (NNRTI), such as nevirapine, delavirdine or efavirenz, were used. Finally, preliminary results of ongoing trials have shown that comparable surrogate marker changes can be obtained with a triple nucleoside-containing regimen of zidovudine, lamivudine and abacavir. These results have substantially expanded the number of treatment options available.

Triple-drug therapy in the real world

The impact of combination therapy in the community has now been well documented. Early on a study was undertaken within the British Columbia Treatment Program to characterize antiviral effect and predictors of response to double and triple-drug combinations[12]. A total of 420 consecutive patients initiating antiretroviral treatment through the provincial program between June 1996 and February 1997 were evaluated. Of note, patients were treated according to contemporary guidelines with two or three drugs. All treatments were distributed free of charge by the program. A total of 264 subjects received dual-drug therapy and 156 subjects received triple-drug therapy. As expected, subjects receiving dual nucleoside therapy had a more benign laboratory profile at baseline (i.e.: higher CD4 cell count and lower plasma viral load). Despite this, triple-drug combination therapy achieved a more substantial and sustained suppression of viral replication. In fact, triple drug treated subjects were nearly four times more likely than dual therapy treated subjects to have a sustained reduction of plasma viral load to levels below 500 copies/mL. Furthermore, subset analyses failed to identify a subgroup of patients who could benefit from dual nucleoside therapy. Based on these and other similar results, dual nucleoside therapy is no longer recommended even when the baseline plasma viral load is quite low.

A separate study was recently reported comparing the mortality and AIDS free survival of HIV-infected subjects treated with two and three drug combinations[13]. This was a prospective, population-based cohort study among a population with free access to antiretroviral therapy within the province of British Columbia. All HIV-infected subjects aged 18 years or older in the province who started antiretroviral therapy between October 1994 and December 1996 were evaluated. A total of 500 (312 dual, 188 triple drug therapy) subjects were studied. Triple-drug treated subjects showed a significant survival benefit as compared to those receiving two-drug therapy. As of December 31, 1997, a total of 40 deaths (35 dual, 5 triple-drug therapy) were identified, yielding a crude mortality rate of 8.0%. Product limit estimates of the cumulative mortality rate at 12 months were 7.4% (± 1.5%) and 1.6% (± 0.9%) for dual and triple-drug therapy subjects, respectively (log rank p = 0.003). Two-drug therapy treated subjects were more than three times more likely to die than triple-drug therapy treated subjects with a mortality risk ratio of 3.82 (95% CI: 1.48 – 9.84; p = 0.006). After adjusting for *P carinii pneumonia* or *M avium* prophylaxis use, AIDS diagnosis, CD4+ cell count, sex and age at initiation of therapy, two-drug therapy treated subjects were 3.21 times (95% CI: 1.24, 8.30; p =

0.016) more likely to die than triple-drug therapy treated subjects. Product limit estimates of the cumulative progression to AIDS or death at 12 months were 9.6% (± 1.9%) and 3.3% (± 1.5%) for dual and triple drug therapy treated subjects, respectively (log rank p = 0.006). After adjusting for other prognostic variables (*P carinii pneumonia* or *M avium* prophylaxis use, CD4+ cell count, gender and age), dual drug therapy treated subjects were 2.37 times (95% CI: 1.04, 5.38; p = 0.040) more likely to die or progress to AIDS than triple-drug therapy treated subjects. These results confirm the effectiveness of triple-drug therapy. Furthermore, these results demonstrate the actual benefit associated with the wide implementation of triple-drug therapy on a given population.

Similar results have now been reported from the USA and Europe. Palella *et al*[14] recently published data on 1,255 clinic based, HIV-positive patients followed for 42 months. Their results demonstrate a striking decrease in quarterly mortality rates between January 1994 and June 1997. This was inversely correlated with the intensity of the antiretroviral regimen prescribed and independent of demographic variables such as gender, age or risk category. In a separate European study, Brodt *et al* evaluated 1003 HIV-positive homosexual men with CD4 cell counts below 200 cells/mm3 between January 1992 and December 1996[15]. In this study, again, AIDS-related morbidity and mortality decreased steadily during the study period as a direct result of the implementation of triple drug therapy regimens.

The cost-effectiveness of triple-drug therapy

Going beyond "efficacy" demonstrated in clinical trials, it is important to assess "effectiveness" of these complex therapeutic regimens. Observational databases containing both clinical prognostic variables and drug utilization data have been used to assess effectiveness and cost-effectiveness of HIV therapies. Evidence regarding this issue was recently presented by Anis *et al*[16], who reported the results of a study relating drug cost and survival following the initiation of antiretroviral therapy among HIV infected individuals in British Columbia. The aims of the study were to go beyond the observed efficacy, given the current duration of therapy, and estimate survival gains expected over the long run. To do this, short-term efficacy data was modeled on "survival" data from a longitudinal cohort. All HIV-positive adults enrolled in the province-wide drug treatment program were studied. Annual costs, survival and cost-effectiveness ratios of successive regimens were calculated using 1997 Canadian Dollars. Total drug related costs at 12 months were $6,373 and $11,823 when dual and triple drug regimens were considered, respectively. Survival at 12 months was 91% and 97.6% when dual and triple drug regimens were considered, respectively. The incremental cost-effectiveness ratio of dual to triple drug therapy was $39,047 per life year gained. These results suggest that triple drug therapy is well within the range of other currently funded/reimbursed therapies. Of note, the study did not take into account indirect costs associated with triple-drug therapy (such as costs associated with additional safety monitoring, possible adverse effects or the use of symptomatic medications). Despite this, these results are likely to represent a conservative estimate of the cost-effectiveness of antiretroviral regimens. This is particularly the case because several important beneficial effects of triple-drug therapy, such as decreased morbidity associated costs (including absenteeism, hospitalizations, rehabilitation, and opportunistic diseases related treatments or prophylaxis), and increased productivity were not taken into account. This assessment is shared by Bartlett *et al*[17], who recently referred to triple drug therapy as one of the most cost-effective medical interventions that has been introduced in the past decade.

In summary, the last two years have seen a dramatic progress in the treatment of HIV disease. The implementation of triple therapy has been associated with a very substantial decrease in morbidity and mortality. Furthermore, there is now objective evidence that the incremental cost-effectiveness of this therapeutic strategy is well within the range of other currently funded/reimbursed therapies.

References

1. Mellors J, Rinaldo C Jr, Gupta P, *et al.* Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996; 272:1167-70.
2. Mellors J, Munoz A, Giorgi J, *et al.* Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997; 126: 946-54.
3. O'Brien W, Hartigan P, Daar E, *et al.* For the VA Cooperative Study Group on AIDS. Changes in plasma HIV RNA levels and CD4+ lymphocytes counts predict both response to antiretroviral therapy and therapeutic failure. Ann Intern Med 1997; 126: 939-45.
4. Hughes M, Johnson V, Hirsch M, *et al.* Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. Ann Intern Med 1997; 126: 929-38.
5. Montaner J, DeMasi R and Hill A. The effects of lamivudine treatment on HIV-1 disease progression are highly correlated with plasma HIV-1 RNA and CD4 cell count. AIDS 1998; 12:F23-F28.
6. Carpenter C, Fischl M, Hammer S, *et al.* Antiretroviral therapy HIV infection in 1996: Recommendations of an international pannel. JAMA 1996; 276: 146-54.
7. Hirsch M, Meibohm A, Rawlins S, *et al.* Protocol 039 (Indinavir) Study Group. Indinavir (IDV) in combination with zidovudine (ZDV) and lamivudine (3TC) in ZDV-experienced patients with CD4+ cell counts < 50 cells/mm^3 - 60 week follow-up. [Abstract 383] In: Program and abstracts of the 5th conference on retroviruses and opportunistic infections, February 1-5, 1998, Chicago, Ill.
8. Hammer S, Squires K, Hughes M, *et al.* A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997; 337:725-33.
9. Gulick R, Mellors J, Havlir D, *et al.* Treatment with indinavir, zidovudine and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med 1997; 337: 734-9.
10. Goebel F, on behalf of the AVANTI Study Group: AVANTI 2. A randomized, double blind, comparative trial to evaluate combi-

nation antiretroviral regimens for the treatment of HIV-1 infection: AZT/3TC vs. AZT/3TC/Indinavir in Antiretroviral Naive Patients. [Abstract 211] In: Abstracts of the Sixth European Conference on Clinical Aspects and Treatments of HIV Infection. 1997, Hamburg.

11. Clumeck N, for the AVANTI Study Group: AVANTI 3. A randomized, double blind comparative trial to evaluate the efficacy, safety and tolerance of AZT/3TC vs. AZT/3TC/Nelfinavir in antiretroviral naive patients. [Abstract 8] In: Abstracts of the 5th Conference on Retroviruses and Opportunistic Infections, February 1-5, 1998. Chicago Ill.
12. Hogg R, Rhone S, Yip B, *et al*: Antiviral effect of double and triple drug combinations amongst HIV-infected adults: Lessons from the Implementation of viral load-driven antiretroviral therapy. AIDS 1998; 12: 279-84.
13. Hogg R, Yip B, Kully, *et al*. Improved survival among HIV-infected individuals following initiation of triple combination antiretroviral regimens. CMAJ (in press).
14. Palella F, Delaney K, Moorman A, *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998; 338: 853-60.
15. Brodt H, Kamps B, Gute P, *et al*. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS 1997; 11: 1731-8.
16. Anis A, Hogg R, Wang X, *et al*. The cost effectiveness of current antiretroviral regimes. [Abstract OP6.5] In: Abstracts of the 4th International Congress on Drug Therapy in HIV Infection, November 1998, Glasgow. AIDS 1998; 12:S1-S113.
17. Bartlett J, Chaisson R, Kerruly J, *et al*. HAART: One of the most cost-effective therapies of the past decade. [Abstract 24380] In: Abstracts of the 12th World AIDS Conference, June 28-July 3 1998, Geneva.