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Antiretroviral Therapy: When to Start, What to Start With

Brian Gazzard

Chelsea and Westminster Hospital, London, United Kingdom

Abstract

Recent guidelines on initiation of antiretroviral therapy (ART) have been modified because HIV is no longer likely to be eradicated by treatment; toxicity with ART is increasingly recognised and adherence wanes with time. Even late treatment (CD4 count less than 200 cells/µl) is associated with sufficient immune reconstitution in most patients to avoid opportunistic infections.
The optimum starting treatment is unknown. Relatively similar results in terms of viral load reduction at 48 weeks are produced by a wide variety of triple therapy regimes. Factors that can be used to decide optimal first treatment in the absence of controlled studies include potency, durability, salvageability, freedom from side effects, ease of long term adherence and the degree of flexibility around the timing of individual doses (forgiveness).

Key words

Antiretroviral Therapy. When to Start. Strategies.

Introduction

It was Francis Bacon in the early part of the 16th century who first pointed out that personal observations (ordinary experience) could be misleading compared with methodological observations (ordered experience) when deciding optimal therapy. Previously, medical practice had been based upon codes of treatment laid down by Hippocrates and updated by Gallen[1]. Although we now pay lip service to the importance of randomised trials to determine optimal therapy, by necessity much dogma is used to treat individual patients. Nowhere is this more true than in the management of HIV disease where in the understandable desire for speed to license new therapies, there is little objective evidence to guide us about optimum choices.

Correspondence to:
Brian Gazzard
Chelsea and Westminster Hospital
London SW10 9NH
United Kingdom

Fortunately this is now changing and a number of strategic studies looking at eventual outcome, i.e. the development of AIDS or death which should address the issues of when to start therapy and what to start with are being carried out. A careful distinction in all these studies (INITIO, ACTG384 and the SMART study) are made between decision to switch between therapies using surrogate markers and continuing these studies for long enough to arrive at an eventual outcome. This satisfies the frequently voiced criticism that such studies may end up "counting the bodies" rather than giving patients optimal therapy. In the absence of data my comments about when to start and what to start with are, of necessity, both subjective and dogmatic.

Timing of treatment

The 'hit early, hit hard' hypothesis was a scientific rationale for treatment based upon the then current understanding of the pathogenesis of HIV disease[2]. The hit early part of this hypothesis has been modified by experience as a result of four crucial factors.

First, the initial understanding was that HIV infection might be eradicated after approximately three years on complete adherence to therapy. The finding of a pool of long-lived cells (either resting CD4+ cells or macrophages) capable of releasing HIV despite continued antiretroviral treatment, meaning that therapy either has to be lifelong or for such a long period that complete adherence is impractical[3]. Second, the difficulty with taking treatment over the very long-term is two-fold. On one hand, a number of toxicities of antiretroviral therapy have emerged which were not apparent at the time these treatments were licensed. These include the development of lactic acidosis[4], of lipid abnormalities often associated with fat redistribution from the peripheral stores to the visceral compartment[4], rare but fatal skin rashes and hepatotoxicity associated with non-nucleoside reverse transcriptase inhibitors (NNRTI) and, more problematically, the possibility of osteopaenia and osteoporosis[5]. Adherence over the long-term may be another reason for delaying therapy. It is likely to wane with time and a very high degree of adherence (in excess of 95%) certainly with protease inhibitors (PI), is required to maintain suppression of the plasma viral load[6].

The final false premise on which the 'hit early, hit hard' hypothesis was based was that the immune deterioration which occurs with progressive HIV disease, was irreversible. It is now clear, however, that although immunological abnormalities do persist in those individuals who present and are treated late, effective antiretroviral therapy does substantially reduce the risk of subsequent opportunistic infections. The potential impact of infection with opportunistic oncogenic viruses, such as human herpes virus type 8 (HHV-8), Epstein-Barr virus and human papilloma virus, which might be prevented with earlier treatment, is less clear when treatment is initiated late. One study[7] suggested that the risk of lymphoma is low providing the nadir CD4 count, at which treatment is commenced, is above 350 cells/mm^3. Both Kaposi's sarcoma caused by HHV-8 and intra-epithelial neoplasia associated with papilloma virus may regress with effective antiretroviral therapy[8,9].

Important theoretical arguments persist for early treatment which include a lower viral load which makes treatment more successful with at least some therapies, less viral diversity and possibly less viral penetration of so-called sanctuary sites. Thus, if eradication with antiretroviral therapy was possible, clinicians would be in favour of much earlier treatment than is currently the vogue.

Risk-benefit analysis

At the moment, most clinicians pragmatically start treatment when a simple risk-benefit analysis indicates the risks of disease development without treatment outweigh the risks of therapy, both cumulative toxicity and likely non-adherence.

The risk of opportunistic infection developing in individuals with a CD4 count above 200 cells/mm^3 is low but not non-existent. Such individuals may still be more liable to develop virulent infections such as tuberculosis and respiratory tract infections. As such diseases are treatable, many would take the view that a possible increased risk of virulent infection would not be a major reason for early antiretroviral therapy. A number of early randomised clinical controlled trials with clinical end-points did show that the relative hazards of developing clinical events was reduced by an approximately equal amount in both early and late disease[10]. The total number of events prevented in early disease is low and the majority of life-threatening clinical events occur in individuals with CD4 counts below 50 cells/mm^3 [11]. Thus, a number of cohort studies which have been presented recently indicate that early treatment reduces the risk of clinical events but these are unhelpful in deciding a risk-benefit analysis when the potential advantages of preventing a small number of clinical events have to be balanced against long-term treatment and toxicity in those[12] at low risk of progression.

A recently presented and influential cohort study has suggested that survival of patients treated with HAART is related primarily to the CD4 count at initiation with a worse prognosis for those treated when this falls below 200 cells/mm^3 compared with treatment above this level[11]. Further follow-up of this cohort would determine whether this survival advantage for treated patients with a CD4 count of above 200 cells/mm^3 persists in the longer term.

A number of other cohort studies address another important issue: do short-term surrogate markers respond equally well in those treated at relatively late stages of disease as in those treated earlier on?. A consensus across a number of studies would appear to be that above a CD4 count of 200 cells/mm^3, the chances of the viral load falling to below detectable limits of a sensitive assay (less than 50 or less than 400 copies/ml) is about the same whatever the CD4 count at initiation. However, below this cut-off, the chances of achieving viral load undetectability diminish[13]. It is unlikely that the CD4 count of 200 cells/mm^3 represents an actual threshold but nevertheless this does seem to provide a useful baseline and most clinicians would believe that it would be important, to suggest treatment to people with a CD4 count which is falling to this critical point. Some clinicians would take the view that as this lower limit is the one at which opportunistic infections start to become increasingly common, that individuals should take treatment somewhat earlier to provide a cushion of immunological reserve to lessen the risks of the development of opportunistic infections in the early months of treatment.

It is recognized that the height of the plasma viral load predicts the rate of fall of the CD4 count[14]. Thus, while many clinicians now take relatively little notice of the viral load when deciding the most opportune time to begin therapy, in those with a high viral load, the CD4 count should be monitored more closely, and slightly earlier therapy might be recommended in those patients who are likely to adhere

well. Unfortunately, the assessment of adherence is an inexact science. A number of other factors might influence how early we start therapy. Certainly, for combinations containing PIs, the risk of atherosclerotic complications increases in smokers and with age[15] and people who do shift work have difficulties with adherence. My personal view is that by the time the CD4 count has fallen to about 300 cells/mm^3, the risk-benefit analysis for antiretroviral therapy is probably in favour of therapy, and so I would discuss the issues involving treatment with the patients at this stage.

Mathematical modelling

In the absence of strategic studies, mathematical modelling using figures from real controlled trials can be helpful in pointing out the likely long-term consequences of certain modes of action. Thus, treatment early, i.e., above a CD4 count of 500 cells/mm^3 with a viral load of over 30,000 copies/ml compared with waiting until the CD4 count had fallen below 350 cells/mm^3 results in 4 years of extra antiretroviral therapy for the early treated population with no improvement in outcome at 10 years but a higher proportion of patients with virological failure and multi-drug resistant virus[16]. Thus, with the present drug armamentarium, the potential development of widespread resistance may also be a factor in favour of later treatment.

It is also likely, however, that mathematical modelling looking at the reduced risks of transmission in the treated population would be an argument in favour of earlier treatment to reduce the spread of HIV infection.

What to start treatment with

Relatively few comparative studies have been performed to answer this question. Most drugs have been licensed because of superior surrogate marker results at 48 weeks when compared with a sub-optimal combination. The exceptions to this are that in an open labelled study, a combination of AZT/3TC and Efavirenz was superior to AZT/3TC and Indinavir[17], and in a second study, a ritonavir-boosted PI, Lopinavir (Kaletra) was superior to Nelfinavir[18]. In another open comparison trial, Nelfinavir combined with AZT/3TC produced similar responses to AZT/3TC/Nevirapine, although too small numbers in this study were included to prove equivalence[19].

In a cross study comparison, surrogate marker results at 48 weeks are fairly similar with all triple therapy combinations containing either two nucleosides and one PI or two nucleosides and one NNRTI or three nucleosides[20]. These comparisons are fraught with difficulties because of different entry criteria, but do indicate that any differences in terms of viral load reductions at 48 weeks between currently available therapies is small.

It is far from clear that viral load undetectability at 48 weeks is the best way to decide what therapy to begin with. Long-term tolerability and durability of the first regime are clearly important as is the ability to salvage this regime with subsequent therapy to again produce HIV-RNA undetectability in the plasma. It is also clear that the immunological improvement produced by antiretroviral therapy may have more impact than reduction in viral load on the development of subsequent clinical events. However, the present clinical paradigm is that if at all possible, treatment should attempt to prevent viral replication as this will prevent the development of viral resistance and is most likely to be associated with a sustained rise in CD4 count. With subsequent therapies when viral load undetectability is not an attainable goal, it may be more important to adjust therapy so as to ensure that the CD4 count remains above a dangerous level. In the absence of definitive data as to which therapy is the optimum to start with, a number of factors have to be taken into account.

Clinical potency

This concept includes not only the *in vitro* potency of the drugs but also a number of pharmacokinetic parameters including the ability of the drug to be absorbed orally, the plasma protein binding and, in some instances, the ability to activate the drug by cellular enzymes. An important part of the pharmacokinetic profile of the drug is the latitude around time of dosing which would not result in drug levels falling below those required to continue to inhibit viral replication completely. Those drugs with long plasma half-lives or long intracellular half-life of active components, are likely to have advantages in this regard. For some NNRTIs and some nucleoside analogues, the daily timing of taking the dose may not be crucial for continuing activity. While for the PIs, particularly those not boosted by Ritonavir, the timing of the dose may be much more important.

Clinical potency as assessed by viral load undetectability over 48 weeks also includes the ability of the patient to adhere to the drug regime on a regular basis which is likely to relate to the complexity of the treatment and specific food requirements. Short-term toxicities, even if not serious, are likely to reduce adherence as well. Cross study comparisons would indicate the clinical potency of a whole variety of regimes is similar, but the reasons the regimes still fail in a significant proportion of individuals will vary depending upon the drugs used.

Some clinicians continue to believe that more drugs or classes of drugs should be given to increase the intrinsic potency of the current regimes. Limited data has been presented that regimes including all three currently available drug classes produce a more rapid fall in viral load during initial therapy[21] and are more likely to be associated with a viral load which is negative by the most sensitive assay (less than 5 HIV-RNA copies/ml) at 48 weeks. None of these data are randomised, and cohort studies are open to a number of biases. It also remains to be seen whether or not a very low plasma viral load (i.e., less than 5 copies/ml) is in fact any

more efficacious at providing long-term control of viral replication than lesser degrees of suppression. Some studies suggest that recurrent low levels of viraemia, i.e., blips (above 50 HIV-RNA copies/ml but below 400 copies/ml) are not associated with an any worse outcome in terms of viral load suppression than individuals who consistently have a viral load below 50 copies/ml[22]. If this turns out to be the case, it would certainly not suggest that there is a particular advantage in having even greater virological suppression with more drugs which will increase toxicity.

Adherence

While a large number of factors are known to be associated with poor adherence, very little data is available that tells us how this might be improved. Largely by analogy with anti-hypertensive medication, it is likely that tablets taken twice a day will be better adhered to than treatment regimes requiring more frequent medication. Similarly many patients complain that requiring to take drug on an empty stomach, e.g., Indinavir or ddI, is less convenient than when there are no food requirements. It has also recently become clear that the results of Nelfinavir treatment can be improved by ensuring that the patient takes the tablet at the same time as a relatively high fat meal which, in practice, may be difficult. Although combination pills have disadvantages from the pharmacologist's point of view, in the context of HIV these may be outweighed by advantages, particularly when the drugs which are combined have similar half-lives. In this situation when the tablets are not taken, resistance may be less likelyto develop as no drug at all is taken rather than in regimes with multiple tablets only some of which are taken.

Toxicity

Continuing toxicities are likely to reduce adherence. Worries about long-term toxicities, particularly when these are stigmatising, may make particular types of therapy unpopular to start and may reduce adherence, even in individuals who agree to start the treatment. Risk assessment with the various long-term toxicities of present therapies are particularly difficult as their prevalence and impact on life is very difficult to assess. Thus, most data indicates that the incidence of severe lactic acidosis with nucleoside analogues is low (certainly less than 2%). Excess death either from myocardial disease or cardiovascular illness have not been clearly associated with the lipid abnormalities that antiretroviral therapy can produce. However, most modelling experiments indicate that the lipid abnormalities are likely to be atherogenic and are likely to have synergistic effects on mortality with smoking and age[15]. It appears that these lipid abnormalities occur occasionally with nucleoside analogue treatment alone but most cohort data would indicate that there is a synergistic effect between nucleoside analogues and PIs in producing such changes, while NNRTIs added to nucleoside analogues do not have this effect[4].

In the United Kingdom the stigmatizing effects of facial atrophy have become firmly associated with PI-containing regimes and is a major reason for a switch to NNRTI treatment as first-line therapy. However, occasionally fatal toxicities may also be an important reason for avoiding particular drugs. Thus, the incidence of Stevens-Johnson syndrome is probably commonest with Nevirapine and hepatic failure probably occurs with both Efavirenz and Nevirapine although the relative frequencies of this complication with the two drugs are debatable.

Abacavir hypersensitivity is also a potentially fatal complication, and ddI-associated pancreatitis in alcoholics and those with pre-existing pancreatic damage, mean that this drug is contraindicated in this group of patients.

Durability

From most of the current regimes, it appears that durability is largely a function of continued good adherence, although it remains possible that some regimes have an advantage as a result of greater potency or the reduced likelihood of resistance development[23]. Obviously some drug regimes have been studied for longer than others and therefore have better data for durability.

Salvageability

There are virtually no controlled trials which give us a clear guide as to whether the virological failure associated with some regimes has a better chance of being reversed by another treatment. A number of cohort studies certainly suggest that some regimes are easier to salvage than others[23]. It is clear that there is relatively little cross-resistance between the various available classes of drugs and so the short-term outcome at least is better when a new class of drug is used in a salvage regime. It also appears particularly important with the NNRTIs that other drugs should be available which are able to assist in completely suppressing viral replication as otherwise the improvements will be short-lived[24]. It is clear that there is little likelihood of salvage with another member of the NNRTI class when treatment has failed with one drug of this family.

On the other hand, with PIs, if a single PI has been used, substituting a ritonavir-boosted PI regime is relatively likely to be successful. Perhaps the commonest reason for this is the improved pharmacokinetics of such a regime and better adherence although, in some cases, it may be because the enhanced plasma levels of the drug are sufficiently high to overcome low level viral resistance. Moreover, it may be that some drugs like Amprenavir or Nelfinavir with relatively unique patterns of initial resistance development, may be easier to salvage than regimes containing Indinavir, Ritonavir or Saquinavir where the initial resistant mutations often produce widespread loss of sensitivity to other PIs[25].

The inability to salvage NNRTI-containing regimes with another member of this class has led to considerable debate as to whether such regimes are more suitable for first-line therapy or salvage. It is likely that during the lifetime of a patient, both NNRTIs and PIs will be used, and so salvageability is probably not a major argument in favour of which drug regime should be used first although using an NNRTI as initial therapy is more likely to be in a regimen where complete suppression of viral replication occurs.

In the absence of clear data, strong opinions about the optimum first therapy are likely to be based upon previous clinical experience. Thus, in the UK the advantages of NNRTIs with a relative freedom from abnormal lipid profiles and long plasma half-lives allowing latitude around the time of dosing has led to their widespread first use, with PI-containing regimes tending to be used following the failure of first-line therapy. The development of new PIs which may have less side effects and have better pharmacokinetic profiles may change this view in the future.

Protease inhibitors do have the advantage of greater clinical experience and randomised controlled trials with clinical end-points attest to their efficacy. Thus, a PI-containing regime continues to be used by some in initial treatment in patients presenting late when the early risk of further clinical events is high. Increasing experience with NNRTIs in late disease, however, suggests that they are also likely to be equally effective in this situation[25].

Although experience in randomised controlled trials with pharmacokinetically boosted PIs is limited and there is less data about how such regimes can best be salvaged, many clinicians are using them as first PI-containing regimes because of the improved pharmacokinetic profile, in particular twice a day regimes and lack of specific food requirements during dosing. However, the addition of Ritonavir may add to the toxicity of some regimes, in particular renal toxicity for Ritonavir/Indinavir combinations[26].

References

1. Trohler U. To improve the evidence of medicine. Royal College of Physicians of Edinburgh, Plenary Lecture 2000.
2. Ho D. Time to treat HIV: early and hard. N Engl J Med 1995;333: 450-1.
3. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. Science 1997;278:1295-300.
4. Carr A, Miller J, Law M, Cooper D. A syndrome of lipoatrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. AIDS 2000;14:F25-F32.
5. Knobel H, Guelar G, Valdecillo I, et al. Osteopaenia in HIV-infected patients: Is it the disease or is it the treatment? 8th CROI. Chicago, February 2001 [abstract 629].
6. Paterson D, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000;133:21-30.
7. Matthews G, Bower M, Mandalia S, et al. Changes in acquired immunodeficiency syndrome-related lymphoma since the introduction of highly active antiretroviral therapy. Blood 2000;96: 2730-4.
8. Wit F, Sol C, Renwick N, et al. Regression of AIDS-related Kaposi's sarcoma associated with clearance of human herpesvirus type 8 with antiretroviral therapy. AIDS 1998;12:218-9.
9. Heard I, Tassie J, Kazatchkine M. Impact of highly active antiretroviral therapy on CIN in HIV-seropositive women. 8th CROI, Chicago, February 2001 [abstract 568].
10. Delta Coordinating Committee and Virology Group. An evaluation of HIV-RNA and CD4 cell count as surrogates for clinical outcome. AIDS 1999;13:565-73.
11. Hogg R, Yip B, Wood E, et al. Diminished effectiveness of antiretroviral therapy among patients initiating therapy with CD4+ cell counts below 200/mm^3. 8th CROI. Chicago, February 2001 [abstract 342].
12. Opravil M, Ledergerber B, Furrer H, et al. Clinical benefit of early initiation of HAART in patients with asymptomatic HIV infection and CD4 counts > 350/mm^3. 8th CROI. Chicago, February 2001 [abstract LB6].
13. Phillips A, Staszewski S, Weber R. Phillips A, Staszewski S, Weber R, et al. Viral load changes in response to antiretroviral therapy according to baseline CD4 count and viral load. V Congress on Drug Therapy in HIV Infection. Glasgow, October 2001 [abstract PL 3.4].
14. Mellors J, Muñoz 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.
15. Klein D, Hurley L, Sorel M, Doe P. Increase in the risk of coronary disease associated with HIV PI therapy follow-up through to the year 2000. 8th CROI. Chicago, February 2001 [abstract 655].
16. Tebas P, Henry K, Nease R, Murphy R, Phair J, Powderly W. Timing of antiretroviral therapy. Use of Markov modelling and decision analysis to evaluate the long term implications of therapy. AIDS 2001;15:591-9.
17. Staszewski S, Morales-Ramirez J, Tashima K, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. N Engl J Med 1999;341:1865-73.
18. Johnson M, Beall G, Badley A, et al. ABT-378/ritonavir (ABT-378/r) *versus* nelfinavir in antiretroviral naïve subjects: week 48 comparison in a phase III blinded randomized clinical trial. V International Congress on Drug Therapy in HIV Infection. Glasgow. October 2000 [abstract PL6.5].
19. Podzamczer D, Ferrer E, Consiglio E, et al. Final 12-month results from the COMBINE study: a randomized, open, multicenter trial comparing Combivir plus Nelfinavir or Nevirapine in *naïve* patients. 1st IAS Conference on HIV Pathogenesis and Treatment. Buenos Aires, July 2001 [abstract 7].
20. Bartlett J, Demasi F, Quinn J, et al. Meta-analysis of efficacy of triple combination therapy in antiretroviral-*naïve* HIV-infected adults. 7th CROI. San Francisco, January 2000 [abstract 519].
21. Hoetelmans R, Reijers M, Weverling G, et al. The effect of plasma drug concentrations on HIV-1 clearance rate during quadruple drug therapy. AIDS 1998;12:F111-F115.
22. Greub G, Cozzi Lepri A, Ledergerber B, et al. Lower level HIV viral rebound and blips in patients receiving potent antiretroviral therapy. 8th CROI. Chicago, February 2001 [abstract 522].
23. Soriano V. Sequencing antiretroviral drugs. AIDS 2001;15:1-5.
24. Hirsch M, Brun-Vezinet F, D'Aquila R, et al. Antiretroviral drug resistance testing in adult HIV-1 infection. Recommendations of International AIDS Society-USA Panel. JAMA 2000;283:2417-26.
25. Tebas P, Patick A, Kane E, et al. Virologic responses to a ritonavir-saquinavir containing regimen in patients who had previously failed nelfinavir. AIDS 1999;13:F23-F28.
26. Nelson M, Staszewski S, Morales-Ramirez J, et al. Successful virologic suppression with efavirenz in HIV-infected patients with low baseline CD4 cell counts: post hoc results from Study 006. X European Conference of Clinical Microbiology and Infectious Diseases. Stockholm 2000 [abstract 3-349].
27. Gatell JM, Lange J, Arnaiz J, et al. A randomized study comparing continued indinavir (800 mg tid) vs switching to indinavir/ritonavir (800/100 mg bid) in HIV patients having achieved viral load suppression with indinavir plus 2 nucleoside analogues: the BID Efficacy and Safety Trial (BEST). XIIIth World AIDS Conference. Durban, July 2000 [abstract WeOrB484].