Consensus statement

1998 revision to the British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals

*Brian Gazzard, Graeme Moyle on behalf of the BHIVA Guidelines Writing Committee**

When the British HIV-1 Association (BHIVA) guidelines on the treatment of HIV-seropositive individuals with antiretrovirals were published in *The Lancet* in April 1997, it was clear that they would require updating on a frequent basis. The guidelines have been useful in ensuring that viral-load testing and combination therapy is widely available in the UK. However, standards of treatment are rapidly changing as new evidence becomes available. Since formulation of the guidelines, data from two large clinical endpoint studies have been presented that show superior clinical benefit for the use of triple therapy compared with dual therapy in treatment of both naïve individuals and patients who have been given zidovudine. Here we update the BHIVA guidelines with a consensus drawn from a wide range of UK medical opinion. The guidelines include input from groups representing individuals living with HIV-1. A more detailed reflection of these views may be found in publications such as the *National AIDS Manual* and the AIDS Treatment Project's Doctor fax.

There is debate on approaches to the long-term management of HIV-1 infection.[1-5] The differing views agree that the virological goal of therapy should be to achieve a viral load below detection limits of standard assays, hence initial therapy should be uncompromising in its activity. However, some physicians feel that with initial therapy we have not just the best chance at achieving the virological goal of therapy, but essentially the only chance of responding well to therapy. A therapy that rapidly achieves a viral load, not only undetectable by standard assays but also by the experimental ultrasensitive assays (reliable cutoff limits around 50 copies/mL), should be instituted. This rapid reduction should be attained because the viral-load nadir on therapy seems to be critical to the durability of treatment response. Viral resistance, the principle cause of treatment failure, is unlikely in such circumstances because continued viral replication is required to generate viral diversity and hence resistance. Therefore, such a regimen would work indefinitely. Others believe that in formulating an initial treatment regimen we should consider that over prolonged follow-up, for most, if not all patients, their initial regimen will fail for many reasons (eg, intolerance, adherence, and viral replication persisting in sanctuary sites) and they will require a second-line regimen. Additionally, a proportion of treatment-naïve patients, generally 15–40% in clinical studies of potent triple-therapy regimens, fail to achieve an undetectable viral load by current assays. Therefore, the initial regimen needs to be both uncompromising in terms of activity and also strategically planned, taking into consideration the likely mechanism of failure, resistance, such that the option of a salvage or second-line therapy is available. This approach is sometimes known as treatment sequencing.[6] Insufficient evidence exists to guide us in deciding which approach is best.

Revised by BHIVA guidelines: initiation of antiretroviral therapy in HIV-infected adults

- **When**

Patient agrees to treatment
Possible risks of therapy outweighed by likely benefit
CD4 count >350 cells/mL
Viral-load value associated with risk of disease progression

- **What**

<50 000 RNA copies/mL: two nucleoside analogues plus a non-nucleoside reverse-transcriptase inhibitor or protease inhibitor
>50 000 RNA copies/mL: two nucleosides plus one or two protease inhibitor(s)

- **Aim of therapy in treatment-naive patients**

Plasma viral load to be less than 4–500 copies/mL (and preferably <50 copies/mL) by 24 weeks of therapy
Improve and extend length and quality of life

Limited prospective data on salvage therapy in patients experiencing virological rebound on an initial protease-inhibitor regimen are available to guide sequence order with these agents.[7] The BHIVA guidelines committee feel that a middle ground between these positions should be sought. Briefly, the aim should be to construct a well considered initial regimen that achieves optimum virological responses and allows potential benefit from subsequent therapy.

Data from clinical trials using the ultrasensitive assay are currently only published in abstract form. More information is required on the rapidity of reliable undetectability with effective treatment, how frequently HIV-1RNA becomes detectable transiently with this assay, whether durability of response is truly longer with this cutoff, and what therapies are required to reliably reach this goal before its use is routinely recommended. However, given understanding of its limitations, pursuit of less than 50 HIV-1 RNA copies seems to be an appropriate treatment goal in principle. Changes in therapy after virological rebound in treatment-adherent patients should be made promptly (eg, at <5000 HIV-1 RNA copies/mL) and should involve change of multiple, preferably all, components of a regimen. At least one agent from a new class should be included.

*Listed at end of paper

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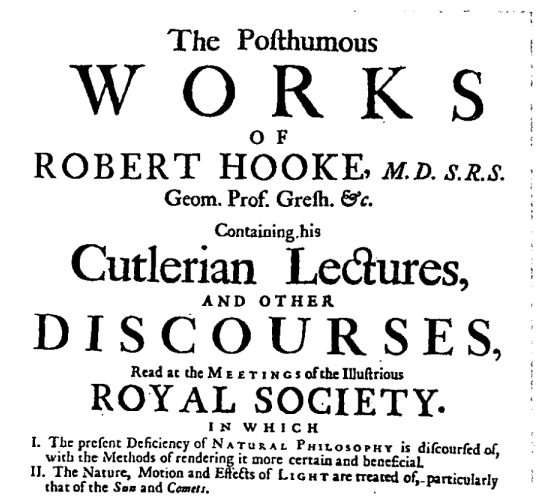
Hooke's anticipation of the stethoscope

There may be also a possibility of discovering the Internal Motions and Actions of Bodies by the sound they make. Who knows but that as in a Watch we may hear the beating of the Balance, and running of the Wheels, and the striking of the Hammers, and the grating of the Teeth, and Multitudes of other Noises; who knows, I say, but that it may be possible to discover the Motions of the Internal Parts of Bodies, whether Animal, Vegetable or Mineral, by the sound they make, that one may discover the Works perform'd in the several Offices and Shops of a Man's Body, and thereby discover what Instrument or Engine is out of order, what Works are going on at several Times, and lie still at others, and the like; that in Plants and Vegetables one might discover by the Noise the Pumps for raising the Juice, the Valves for stopping it, and the rushing of it out of one Passage into another, and the like. I could proceed further, but methinks I can hardly forbear to blush when I consider how the most part of Men will look upon this: But yet again, I have this Incouragement, not to think all these things utterly impossible, though never so much derided by the Generality of Men, and never so seemingly mad, foolish and phantastick, that as the thinking them impossible cannot much improve my Knowledge, so the believing them possible may perhaps be an occasion of taking notice of such things as another would pass by without regard as useless. And somewhat more of Incouragement I have also from Experience, that I have been able to hear very plainly the beating of a Man's Heart, and 'tis common to hear the Motion of Wind to and fro in the Guts, and other small Vessels; the stopping of the Lungs is easily discover'd by the Wheezing, the Stopping of the Head by the humming and whistling Noises, the sliping to and fro of the Joynts in many cases, by crackling, and the like; as to the working, or Motion of the Parts one amongst another, methinks I could receive Incouragement from hearing the hissing noise made by a corrosive Menstruum in its Operation, the Noise of Fire in dissolving, of Water in boyling, of the Parts of a Bell after that its Motion is grown quite invisible as to the Eye, for to me these Motions and the other seem only to differ *secundum magis et minus*, and so to their becoming sensible they require either that their Motions be increased, or that the Organ be made more nice and powerful to sensate and distinguish them [to try the Contrivance about an Artificial Timpanum] as they are, for the doing of both which I think it not impossible but that in many cases there may be Helps found, some of which I may as Opportunity is offer'd make Tryal of which if successful and useful, I shall not conceal.


The Posthumous
WORKS
OF
ROBERT HOOKE, *M.D. S.R.S.*
Geom. Prof. Gresh. &c.
Containing his
Cutlerian Lectures,
AND OTHER
DISCOURSES,
Read at the MEETINGS of the Illustrious
ROYAL SOCIETY.
IN WHICH
I. The present Deficiency of NATURAL PHILOSOPHY is discourfed of, with the Methods of rendering it more certain and beneficial.
II. The Nature, Motion and Effects of LIGHT are treated of, particularly that of the *Sun* and *Comets*.

From the introduction to *The Posthumous Works*[10]

Transcribed from ref 10.

source of inspiration to others but it was also a manifestation of the intellectual restlessness that prevented him from completing the seminal scientific advances to which he was often so tantalisingly close.

Laennec's invention of the monaural stethoscope in 1819,[13] happened through a flash of practical inspiration rather than proceeding from an earlier stage of detailed hypothesis. The particular brilliance of Laennec's achievement was in the clinical application of his methodology and in the correlation with underlying pathology.

Tyndall[14] sums it up well when he says of the passage quoted in the panel, "that another could hardly be found that illustrates so well that action of the scientific imagination which, in all great investigators, is the precursor and assosciate of experiment". As the tercentenary of Robert Hooke's death approaches, it is also a timely reminder of his accomplishments.

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When to start treatment

US guidelines[8,9] state that treatment should begin at any stage when the viral load is either detectable or greater than 10 000 copies/mL irrespective of CD4 cell count.[8,9] However, our advice remains that start of treatment should be individualised and should begin before irreversible damage has occurred to the immune system such as at a CD4 count above 350 cell/mL, when risk of opportunistic infections remains low. Those with high viral loads before treatment are significantly more likely to develop clinical illness over defined periods of follow-up than are CD4-matched people with low viral load.[10] However, HIV-1 therapy should represent risk management. This management should be a balance between the potential benefit of therapy in delaying clinical events and the potential morbidities—both physical and psychological—associated with the commitment to lifelong multidrug therapy. In particular, the impact of late toxicities of protease inhibitors—eg, diabetes,[11] hyperlipidaemia, risk of accelerated ischaemic heart disease, lipodystrophy,[12,13] renal calculi, and crystaluria—on morbidity and mortality have not been fully assessed. Additionally, treatment adherence is poorer in people with symptom-free disease. Adherence is known to decline over prolonged periods of follow-up in other potentially fatal diseases.[14]

What to start treatment with

We believe that it is important to start treatment with regimens that reliably reduce the plasma viral load of individuals below detectable limits of the currently available assays (200–500 copies of virus/mL and preferably to <50 copies/mL; panel). Although the clinical outcome at 1 year in one study[15] was similar whether the viral load was below detectable (<400 copies/mL) or below 5000 copies/mL after start of treatment, most clinicians believe that continuing viral replication will eventually lead to drug resistance, loss of treatment options, and a poorer clinical outcome. There is also evidence that the nadir of viral load achieved in response to treatment is directly related to the length of time that the viral load remains suppressed by therapy.[16,17]

Regimens that are highly effective in reducing viral replication include two nucleoside analogues and a protease inhibitor, two nucleoside analogues and a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or two protease inhibitors with or without nucleoside analogues. The combination of an NNRTI with a protease inhibitor is currently also under assessment. Short-term data from one prospective study indicates, in an on-study analysis, similar antiviral effects of nucleoside analogue (2NA) and either indinavir or the new NNRTI efavirenz but with better tolerability with the NNRTI-containing regimen.[18]

The use of two nucleoside analogues and an NNRTI is attractive because it allows the use of protease inhibitors to be reserved for later. However, evidence has indicated that although treatment with zidovudine, didanosine, and nevirapine causes the viral load of a high proportion of individuals to fall from less than 50 000 copies/mL to below detectable limits, this was less likely to be true in those with higher viral loads.[17] Although this may not be true for newer NNRTI regimens, such as zudovudine and lamivudine with efavirenz,[18] it seems prudent to recommend that patients with viral loads above 50 000 copies/mL should be started on a protease-inhibitor-containing regimen. However, this advice is likely to change once efavirenz becomes more widely available. Additionally, patients with high viral loads and low CD4 counts at baseline as well as those who have had extensive nucleoside-analogue therapy may be less likely to achieve an undetectable viral load on triple therapy[19,20] and therefore may be considered as candidates for multiple-therapy regimens.[20]

An initial combination of two nucleoside analogues is no longer considered a reasonable standard of care and therefore should only be considered in very exceptional circumstances. If the viral load is below 5000 copies/mL at baseline, two nucleoside analogues will cause plasma viral load to fall below detectable limits of standard assays in more than 70% of patients after 1 year of follow-up.[21] Although many physicians and patient advocates believe that the durability of response to two nucleoside analogues—even in selected patient populations—is unlikely to be sustained, continuation of closely monitored short-term trials of some therapies in which the mechanism of failure may not be associated with the development of viral resistance, such as stavudine and didanosine,[22] seems reasonable. Treatment intensification with two additional agents has, in incomplete responders to two or three drugs, yielded a high proportion of optimum responses and may therefore be a useful strategy in these circumstances.[20] However, deintensification in an induction followed by maintenance model,[23] whilst attractive, does not currently represent a feasible approach.

How to monitor treatment

For most patients who have had triple-drug therapy, a plasma viral load that is undetectable on standard assays can be achieved. However, the definition of failure remains elusive. Specifically, it may be important to differentiate between an inadequate treatment response, not achieving a value below assay detection within 24 weeks of initiating treatment, and virological rebound, because treatment approaches may differ depending on circumstances.

It seems appropriate to use measurement of viral load as the primary definer of failure. However, in doing so, it is important to remember that detectable plasma HIV-1 RNA is neither immediately nor inevitably associated with clinical events. Additionally, definitions of failure and the treatment goals may be different for those very experienced with antiretroviral drugs who have few remaining treatment options compared with those receiving initial therapy. A rise in viral load to more than 0·5 $\log_{10}$ above detectable or above the virological nadir have been used in one study[16] and is in keeping with biological variations in viral-load tests.[1] A more conservative view would be to wait until viral load has returned to a concentration in which treatment would normally be initiated (ie, >10 000 copies/mL). However, longer duration on failing therapy and higher viral load at the time of switch seem to be associated with an accumulation of greater numbers of mutations in the HIV genome and a probable greater chance of cross-resistance.[24]

Some patients may experience clinical events despite undetectable viral loads and rising CD4 cell counts. Other patients may have rising CD4 cell counts but

detectable viral load, or falling CD4 counts but undetectable viral load.[25] The management of these individuals is currently unclear but should include consideration of the treatment history, short-term and long-term risks of maintaining current therapy versus switching therapy, the potential benefits of immunotherapy such as interleukin 2, and consideration of the patients' personal goals and quality of life.

The optimum initial protease inhibitor used in combination therapy is unknown. In the original BHIVA guidelines[1] we suggested that a drug with a low potential for cross resistance should be given priority. However, evidence published since those guidelines indicates that accumulation of multiple mutations in the protease gene under the selective pressure of any of the protease inhibitors is associated with cross resistance to all available protease inhibitors. The longer the duration of viral replication in the presence of an inhibitor, the greater the likelihood of multiple mutations occurring.[24] Such a likelihood emphasises the importance of viral-load monitoring because it is still possible that switching from one protease inhibitor to another (or a combination of two protease inhibitors) might be effective in some individuals shortly after initial viral re-emergence in the plasma, but may be less likely after sustained virological failure.[7] Limited evidence from small comparative studies suggests that activity of the four different protease inhibitors now available in the USA is similar.[20,26] Therefore, the choice of initial protease inhibitor should be governed by issues such as its short and long-term toxicity, frequency of drug interactions, and convenience of administration.[1] The same principles apply to selection of nucleoside analogues, a discussion of which was included in the original guidelines.

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