British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy

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BHIVA Writing Committee on behalf of the BHIVA Executive Committee*

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1.0 Synopsis

This synopsis represents a consensus from the writing committee based upon the evidence given in detail in the full guidelines. It aims to offer a pragmatic approach to some difficult questions concerning HIV therapy. Some aspects of this synopsis are controversial and clinicians are advised to read the current guidelines in full, alongside those regarding adherence to treatment and hepatitis B and C co-infection [1,2].

1.1 When to start treatment

In asymptomatic patients this decision should be driven primarily by the CD4 count. A value of 200 cells/mm^3 represents the minimum level at which treatment should be advised. Treatment should be initiated when the CD4 count is between 200 and 350 cells/mm^3, and the exact timing should depend on individual factors such as symptoms, patient preference, likely adherence and potential toxicity. In this range, the rate of CD4 decline, viral load (VL) level and age provide additional information to the CD4 count on the short-term risk of progression. Severely symptomatic disease is unusual at CD4 counts above 350 cells/mm^3 in chronic HIV infection, but provides a rationale for treatment when it occurs.

For patients with primary HIV infection, treatment is only recommended for the purpose of resolving severe symptoms. Otherwise the committee feels there is insufficient evidence to recommend treatment outside clinical controlled trials.

1.2 Initial therapy

When choosing therapy, the committee takes the view that in the present state of knowledge more weight should be given to ease of adherence and minimisation of toxicity, including development of lipodystrophy, than to the likely pattern of resistance mutations emerging following treatment failure.

There is more evidence and experience available in support of initial regimens which include two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus either a protease inhibitor (PI) or an non-nucleoside reverse transcriptase inhibitor (NNRTI) than for other combinations, so we generally support the use of such combinations for starting therapy. Combinations including stavudine (d4T) are not recommended for initial therapy due to possible risks of more rapid development of lipodystrophy. Several recent studies have shown excellent surrogate marker responses for combinations containing lamivudine (3TC) and efavirenz. On current data, the nucleoside-only combination abacavir (ABC)/3TC/zidovudine (ZDV) should not be considered as a first line option for initial therapy (but see section 4.2.3 where this is discussed more fully).

NNRTI regimens produce equivalent or superior surrogate marker responses compared with unboosted PI regimens. There are no studies of sufficient size that directly compare NNRTIs with boosted PIs, which the committee recommend when a PI containing regimen is used. Therefore, the choice between these needs to be based on other considerations. The advantages of NNRTIs over currently licensed PIs include suitability for use in once daily regimens, lower pill burdens, fewer clinically important lipid abnormalities, and a lower frequency of central fat accumulation. There is no evidence of a difference in clinical effectiveness between PI and NNRTI regimens in late disease. PIs may have advantages in that broad cross class resistance is less likely than for the NNRTIs and have less hepatotoxicity and rash.

Hence at present the writing committee considers that NNRTIs are more suitable as the agents of first choice for initial regimens. The choice of NNRTI will need to be made by clinicians interpreting a range of studies, including the 2NN trial. The latter study indicates that there is little difference in potency between nevirapine (NVP) and efavirenz (EFV). NVP treatment was associated with more rash and hepato-toxicity, whereas the disadvantages of EFV are a variable rate of psychological disturbances and the possibility of teratogenesis. A number of options for once a day therapy are now available and these regimens are likely to become increasingly popular.

1.3 When to switch therapy for virological failure

A number of strategic studies are in progress to address this issue. Until they report, the committee takes a pragmatic view.

In cases where tolerable treatment options are available that are likely completely to inhibit viral replication, these should be used as soon as virological rebound has been confirmed by two consecutive VLs > 400 copies/ml. The committee emphasizes that before therapy is changed, factors other than resistance, such as poor adherence and pharmacokinetic effects reducing plasma levels of drugs to below optimum levels, need to be examined carefully in this group.

In cases where it is unlikely that further treatment will produce complete inhibition of viral replication, continuation of current therapy is reasonable if the imminent risk of death is low, judged by the CD4 count. However, there is a rationale for switching – albeit to a less than optimally suppressive regimen - in those individuals in whom the imminent risk of death is high, in order to try to improve viral suppression with the aim of raising the CD4 count.

1.3.1 Which drugs to use following failure of initial therapy

Wherever possible one or two different drugs of the NRTI / PI / NNRTI classes should be included in such a switch regimen. Resistance testing should be used to inform the choice of regimen, particularly for those with prior experience of NAs and PIs or NNRTIs. Patients whose therapy fails with adherence problems may benefit from simpler but effective regimens to which their virus is still sensitive.

1.4 When to switch therapy in the absence of virological failure

When an individual drug as part of a regimen is causing toxicity the choice of agents to switch to is often self evident and is usually within class, particularly for patients on complex regimes who are finding complete adherence difficult. Regimen simplification, for example to a triple NRTI pill of ZDV, 3TC and ABC appears to be safe in those whose previous antiretroviral treatment has not failed and may improve adherence. Switching because of the development of abnormal lipids or the fat redistribution syndrome is more complex and of less certain benefit. It is dealt with in detail in the guidelines. Any improvements in fat redistribution that occur as a result of such switching are likely to be slow.

1.5 Resistance testing

There is variable evidence for a benefit of resistance testing for treatment-experienced patients in controlled trials. However, the level of resistance to a regimen predicts the response to a new regimen and the cost of such testing is low compared with that of drug treatment. We recommend testing at each virological rebound. Although it will be difficult to design trials to establish the value of resistance testing in drug-naive individuals, such testing prior to therapy may be of crucial value for a proportion of patients who carry mutations, especially in the context of demonstrable transmitted drug resistance. In view of this, resistance testing is recommended for all drug-naive patients prior to commencing treatment using the nearest available sample to seroconversion or presentation.

1.6 Therapeutic drug monitoring (TDM)

Evidence for the clinical value of TDM remains limited although the committee recognises that it may have a role in reducing toxicity in individual patients and in adjusting doses in those with significant hepatic or renal impairment or at extremes of body weight, and may help to explain treatment failures. It may also be of value in individuals with advanced disease who are limited to using combinations that may have the potential for unknown pharmacokinetic or drug interactions.

1.7 New drugs likely to be used in the near future

1.7.1 Atazanavir

The main interests in this drug lie in its once-daily dosing, its lack of effect on lipid metabolism and, by implication, low probability of an association with lipodystrophy. Present studies indicate similar potency to an NNRTI or unboosted PI in treatment-naive patients. If these early results are confirmed, many clinicians may find this drug an important option when choosing a first PI.

1.7.2 Enfuvirtide (T20)

This drug has recently been licensed for patients with treatment failure. It is the first of a new class of compounds interfering with HIV cell entry. Its main disadvantage will be mode of administration (by injection twice a day). Wherever possible it should be reserved for use after second or subsequent treatment failure, in combination with one or preferably two other new drugs that are expected to be active on the basis of resistance data, to give a realistic prospect of suppressing viral replication completely. This may mean keeping some patients on their current regimen while waiting for other new drugs to become available for use alongside T20.

In individuals at imminent risk of clinical disease and death, T20 might have a limited role as additional therapy in a failing regimen where there are no other active drugs available.

2.0 Introduction

The BHIVA executive is committed to producing updates on the antiretroviral treatment guidelines for adults on a regular basis. Over a 1- to 2-year period, much can change in clinical practice as new scientific evidence is published. To reflect these changes the guidelines have been extensively revised and some sections removed and new sections added. The sections on co-infection with HIV and hepatitis B or C now form separate guidelines which can be found at the BHIVA website (http://www.bhiva.org). New guidelines on tuberculosis co-infection, paediatric HIV care, and adherence to treatment are also in preparation, while guidelines on the management of HIV and pregnancy will be updated over the coming year.

The principles of consensus that overarched the previous guidelines [3,4] were upheld in the production of this, the latest version. We believe it is important that the process by which the guidelines have been revised is made clear. As in the previous guidelines each section was designated to two members of BHIVA, and the Executive Committee have taken on the bulk of this work. The members were asked to revise the guidelines in line with new evidence that had been published either in peer reviewed journals or as peer reviewed abstracts at international meetings. The authors were asked to consult widely with colleagues and co-opt other BHIVA members if need be.

2.1 Purpose of the guidelines

Guidelines for the treatment and management of HIV infection have been produced in a number of countries in Europe, as well as in Australia and the USA [5-8].

The BHIVA guidelines have a number of important roles which are:

(1) To promote a uniformly high standard of care in all HIV treatment centres in the UK.

(2) To set out the strengths, weaknesses and relevance of recent research findings.

(3) To assist in discussions between purchasers and providers regarding funding for HIV/AIDS diagnostic testing, care and treatments.

(4) To act as a basis for clinical audit within clinical governance.

(5) To act as a source of reference on antiretroviral treatments for those physicians caring for patients infected with HIV.

(6) To act as a source of reference for HIV-positive people.

The cost of drugs has not been considered in preparing these guidelines, but basic NHS costs are shown in [Table 1]. Clinicians will be aware that actual costs may vary especially where bulk purchases have been arranged.

These guidelines should not be seen as a substitute for research, nor as a manual for managing an individual. While the guidelines attempt to represent the current state of knowledge it is inevitable that, as HIV/AIDS is a rapidly evolving medical field, new data will change therapeutic choices and preferences. Consequently, the guidelines will require modifications as important new data emerge and the website version (found at *www.bhiva.org*) will be amended at regular intervals to reflect these data. Revisions are planned annually.

Recommendations made within these guidelines have been graded according to the level of evidence on which they are based [Table 2]. Recommendations range from 'essential' to 'optional' and the quality of evidence from 'at least one randomized trial with clinical endpoints' through to 'expert opinion'. They are to be found in parentheses in the document, for example (AII).

2.2 Basing recommendations on evidence

The committee used an evidence-based medicine approach to produce these guidelines. In reality, if only the most reliable form of clinical evidence was taken into account (i.e. results of one or more randomized controlled trials with clinical endpoints), it would be impossible to formulate these guidelines. Many important aspects of clinical practice remain to be formally evaluated and very few trials with clinical endpoints are ongoing or planned. Results from clinical trials with viral load and CD4 count changes as endpoints were included as, in many instances, they are the only source of evidence. However, most such trials have been performed in order to obtain drug approval and are not ideally suited to addressing questions of clinical usage. The most significant drawbacks of such trials are their short duration and the lack of follow-up data on patients who switch therapy. In most cases the only available data on long term outcomes are from routine clinical cohorts. While such cohorts are representative of routine clinical populations, the lack of randomization to different regimens means that comparisons between the outcomes of different regimens are highly susceptible to bias [9,10] opinion forms an important part of all consensus guidelines; however, this is the least valuable and robust form of evidence.

2.3 Use of evidence published as abstracts

The authors of these guidelines recognize that there is often a considerable time lag between initial presentation of important data, whether orally or in abstract/poster format, and full publication. Consequently, there is danger in relying on data that have not been subjected to formal peer review and published in full. We have therefore avoided citing any research findings that appeared only in abstract format more than 3 years ago (i.e. before mid 2000).

2.4 Implications for research

Unless guidelines are interpreted and applied cautiously and sensibly, valuable research initiatives that might improve standards of care will be stifled. It would be wrong to suggest that certain clinical controlled trials would be unethical if they did not conform to the guidelines, especially when these guidelines are based mainly upon expert opinion rather than more reliable evidence. The National Health Service (NHS) executive has stated that clinical guidelines cannot be used to mandate, authorize or outlaw treatment options [11].

2.5 Use of surrogate marker data

CD4 cell counts and plasma viral load are used as markers of the biological activity of antiretroviral therapy in Phase I and II trials. Reduction in viral load leads to a rise in peripheral blood CD4 count,

with greater rises being seen in those with greater and more sustained viral suppression [12]. Changes in these markers in response to therapy are strongly associated with clinical response [13-16]. CD4 counts measured in people on antiretroviral therapy have been associated with a risk of AIDS defining diseases no higher than that expected in untreated individuals with similar CD4 counts [17-21]. The CD4 count is a better indicator of the immediate risk of AIDS defining diseases than the viral load in those on antiretroviral therapy [22].

Favourable responses to therapy, i.e. a decline in plasma HIV-1 RNA and increase in CD4 cell counts, have led to accelerated licensing of antiretroviral agents since it is impracticable to wait years for large clinical endpoint trials to be completed before drugs are approved [13, 14, 23]. Drugs are given full approval on the basis of trials lasting 48 weeks and, in some countries, accelerated approval based on data to 16 weeks.

Most clinicians would agree that a drug licensing policy based on surrogate markers is reasonable and humane. However, it should be remembered that CD4 count and viral load responses do not precisely reflect the expected clinical outcome and are not perfect surrogates of the clinical response [24-26]. This is because the drugs have other effects with clinical consequences besides those reflected in viral load and CD4 count changes. The relatively short length of trials designed to obtain drug approval means that, at the time of licensing, little may be known about the drugs' long term consequences.

2.6 Issues concerning design and analysis of clinical trials

2.6.1 Trial designs

Most antiretroviral drug trials are performed by pharmaceutical companies as part of their efforts to obtain licensing approval and the designs are often not ideally suited to deriving information on using the drugs in clinical practice. Besides the short duration of follow-up, their key limitation is the lack of data on outcomes in people who change from the original randomized regimen, along with a description of what those new regimens are. The results are therefore only clearly interpretable as long as a high proportion of participants remain on the original allocated regimens. Clinical questions about which drugs to start with or switch to require longer term trials that continue despite changes to the original treatment. From a clinical perspective it makes no sense to ignore what happens to patients after a regimen has been discontinued. Moreover, use of a given drug can affect outcomes long after it has been stopped. For example, it may select for virus resistant to drugs not yet encountered or cause toxicities which overlap with those caused by other drugs. However, interpretation of such trials is not straightforward, and account must be taken of which drugs were used subsequent to the original regimen in each arm. Planned or ongoing trials adopting such an approach include Community Programs for Clinical Research on AIDS (CPCRA)'s FIRST and the Initio trial [which is being run in the UK by the Medical Research Council (MRC)].

Study design may significantly influence the discontinuation rate of trial drugs. An open trial design may result in higher levels of discontinuation from what is perceived to be the least effective regimen, while a double blind, placebo controlled study may reduce adherence in all groups because of the large pill burden. It is also important to recognize that controlled clinical trials provide an optimal treatment setting but results from the use of regimens in clinical practice are usually not as good.

The committee generally favours entry into well-constructed trials for patients whose clinical circumstances are complex, with a number of specific instances being mentioned in these guidelines. NAM maintains a list of trials currently recruiting in the UK at www.aidsmap.com, and treatment units should work to ensure arrangements are in place to enable eligible patients to enter trials at centres within or indeed outside their clinical networks.

2.6.2 Methods of analysis

Several methods have been used to analyse viral load and CD4 count responses, including the change from baseline at a given time and the time-weighted change from baseline or the area under the curve (AUC). For virological response, however, the most common approach relates to whether the viral load is below a certain level, usually 50 HIV-1 RNA copies/mL, which is the approximate lower limit of quantification for most viral load assays in routine use. The proportion of people with

viral load <50 copies/mL at a given time point is assessed. One reason for the choice of this outcome measure is that some studies have indicated that if this minimum level is not achieved then subsequent viral load rebound is more likely [27, 28]. However, when comparing treatment regimens, differences in viral load between treatment groups, provided levels are >50 copies/mL, are highly predictive of subsequent differences in clinical outcome [29]. Restricting comparison to those with viral load <50 copies/mL would not utilize other information contained in the viral load measurement. A related method of assessing response to an initial regimen is calculating time to virological failure. Virological failure is typically defined by failure to achieve viral suppression or viral load rebound after achieving <50 copies/mL, but there is no consensus on precise definitions [23, 30].

2.6.3 Intention to treat and on treatment analysis

Randomization in a trial ensures balance in prognosis between the treatment arms at baseline. Inability to assess outcomes for some patients can disturb this balance and create bias in the comparison between the treatment arms. In order to avoid risk of such bias, analysis by intention to treat includes outcomes for all randomized patients. For this purpose, it is necessary to continue collecting data on all patients even if they have switched from the original regimen. As this is rarely done, the intention to treat principle is maintained by imputing values for those patients who have dropped out of the trial. When the outcome is the proportion of people with viral load <50 copies/mL at a given time point, the approach almost universally adopted is to assign >50 copies/mL to all patients who have earlier switched therapy or have the viral load value missing for any reason. This is known as the missing=failure approach [31]. Such an approach implicitly equates failure of a regimen due to inadequate potency and/or viral drug resistance with inability to tolerate a regimen due to pill burden, inconvenience and/or adverse effects, even though the implications of these two outcomes are likely to be substantially different. This approach is often labelled conservative because it gives a minimum proportion <50 copies/mL for any given treatment group over all possible approaches. However, the primary purpose of an endpoint is to compare treatment arms and, in this context, this approach is not conservative in any general sense.

On treatment analyses consider outcomes only in those still receiving the original allocated treatment. In the context of the proportion of people with viral load <50 copies/mL at a given time point, this makes little sense because therapy is switched in patients who experience viral load rebound during a trial. Given this management policy, the proportion of people remaining on the original regimen who have a viral load >50 copies/mL will reflect the speed with which clinicians decide to switch therapy in response to the first viral load value(s) >50 copies/mL. It is difficult to see how it provides a useful means to compare the efficacy of different regimens. Within the context of time to virological failure, the on treatment analysis may be more revealing.

In situations where there is a high (>25%) proportion of patients who do not have a viral load value at a given time point (except where this occurs due to staggered entry), interpretation is inherently difficult and no analytical approach is entirely satisfactory.

2.6.4 Equivalence

Large numbers of patients are usually required to show equivalence between regimens (i.e. to demonstrate no or a small difference in response between treatments). Many surrogate marker studies are underpowered to demonstrate this. Stating that studies have shown no significant difference between the treatment arms is very different from saying that the arms show equivalence. Graphical representations that show overlapping increased CD4 cell counts or decreased viral loads in response to therapy may hide differences in efficacy between drugs. The confidence interval (CI) for the difference in outcome between treatment arms should be examined carefully in such studies. Lack of adherence to allocated regimens is an even greater issue in equivalence trials because an intention to treat analysis would tend to dilute the difference in outcome between treatment groups. Unless discontinuations and treatment changes during the trial reflect what would happen in clinical practice, the results from intention to treat analysis would be biased towards equivalence.

2.6.5 Cross-study comparisons: presentation of data

It is tempting to compare results of individual drug combinations assessed in different trials. Such comparisons are, however, difficult to interpret because of differences in entry criteria (particularly

with respect to viral load and CD4 cell counts), methods of analysis (e.g. intention to treat versus on treatment), degrees of adherence and sensitivities of viral load assays.

2.7 Adverse event reporting

Many previously unsuspected side effects of antiretroviral therapy have been reported only after drug licensing. It is vital that prescribers report any adverse events as soon as possible so that these events are swiftly recognized. A blue-card scheme, organized by the Medicines Control Agency, the Committee for Safety of Medicines (CSM) and the MRC, operates in the UK for reporting adverse events relating to the treatment of HIV
http://www.mca.gov.uk/aboutagency/regframework/csm/csmhome.htm

3.0 When to start treatment

With currently available antiretroviral agents, eradication of HIV infection is not likely to be possible [32]. The main aim of treatment is thus to prolong life and improve quality of life by maintaining suppression of virus replication for as long as possible.

The three groups of treatment naive patients for whom treatment guidelines are required are: patients with symptomatic HIV disease or AIDS, patients with asymptomatic HIV infection and patients with primary HIV infection.. The recommendations are summarised in Table 3.

3.1 Primary HIV infection

3.1.1 Treatment of primary HIV infection to alter the natural history

There is one placebo-controlled study of ZDV monotherapy in primary HIV infection (PHI) [33] and it showed short-term benefit only. As yet, there is no evidence of long term clinical benefit from any study of treatment of PHI compared with deferring treatment until later, however. If it is recognised clinically, the diagnosis of PHI may represent a unique opportunity for therapeutic intervention. It is likely that, at the time of PHI: (1) there is a narrowing of the genetic diversity of the infecting virus compared with the virus in the index case [34,35]; (2) viral ability to infect different cell types may be limited; and (3) the capacity to mount an immune response is usually greater than it is later on. Therefore, the treatment of PHI may preserve HIV specific immune responses and it has been hypothesized that long term benefit may ensue. A variety of triple drug therapy regimens appear able to suppress viral replication in the plasma, lymph nodes and gut for the majority of patients treated within a few months of PHI [35, 36]. Recent studies have demonstrated that shortly after PHI there is a specific and strong CD4 helper HIV response [37-40]. This is in contrast to chronic infection where, with the exception of long term non-progressors [39], the HIV specific CD4 helper response is generally lost [41]. These CD4 helper responses may be important in maintaining an adequate CD8 response. Such immune responses appear to be maintained in people treated with potent antiretroviral therapy shortly after PHI and perhaps represent the best biological evidence that treatment at this time might be beneficial. Recent data suggest that there is more rapid and complete immune reconstitution in patients starting therapy during PHI than in those starting later [42]. There is still no answer to the question of whether treatment at such an early stage will influence the longer term natural history.

Control of viral replication with no return of viraemia after withdrawal of antiretroviral therapy has apparently occurred in a few patients treated very soon after PHI [43].

The role of drugs that are known to inhibit CD4 activation, such as hydroxyurea [44] and cyclosporin A [45], in the suppression of viral replication and boosting of CD4 lymphocyte responses in this setting is unclear and requires further evaluation. Given the present lack of clarity, it remains reasonable to consider treating PHI, ideally within a clinical trial. These putative benefits of treatment during PHI should be tempered by the known risks of toxicity, including lipodystrophy [46, 47] and the potential for developing drug resistance at an early stage. The potential difficulties of long term adherence to available regimens cannot be overstated. It is possible that short-term antiretroviral

therapy in PHI may be of some immunological benefit [48], but it is not known if this is associated with improved clinical outcome.

3.1.2 Use of structured treatment interruption in acute infection

Although earlier data proposed a possible role for structured treatment interruptions (STIs) in stimulating the host immune response and reducing the virological set point in patients treated very early during PHI [49], longer follow-up of the same cohort suggested that viral rebound subsequently occurred with no apparent impact on the natural history [50]. This supports data from others suggesting that discontinuing therapy initiated during PHI had no apparent effect upon the set point that would have been expected in the absence of any treatment [51]. Treatment cessation has been used rather than multiple treatment interruptions [52], demonstrating that a significant percentage of persons are able to control viraemia spontaneously.

In conclusion, although multiple anecdotal reports as well as small clinical trials and data on macaques [53] suggest that STIs offer transient benefits in PHI, the few data we have suggest this does not bring any long term immunological benefit. The exact window of opportunity remains to be defined and will likely require larger clinical trials.

3.1.3 Treatment during PHI for immediate clinical benefit

Individuals who present with severe or prolonged symptoms (such as meningoencephalitis) due to PHI may improve if treated with antiretrovirals. However the duration of therapy needed is unknown, and the possibility of further acute retroviral syndrome on withdrawal of therapy must be considered.

3.1.4 Treatment during PHI to reduce onward transmission

One study has suggested that many recently infected patients have acquired the infection from others who were themselves recently infected with HIV. Identification and treatment of PHI might thus have some effect on reducing HIV incidence [54]. Even if treatment is not started during PHI, there are many benefits of recognizing early HIV infection. These include recognition and monitoring of primary drug resistance, partner notification and contact tracing and the possibility of preventing HIV transmission. Particular effort should thus be directed to identifying patients with PHI who may present to a wide range of healthcare providers.

3.1.5 Recommendations for starting treatment in PHI [CIII]

At the time of PHI patients and physicians should make the most appropriate decision based on the limited data available.

- The biological plausibility that early treatment may be beneficial for the immune system should be balanced against considerations of adherence to long term therapy, potential toxicity and development of resistance. The committee's first choice would be for patients to enter a clinical controlled trial, where available.
- For those who are treated at this time there is no current available data as to the best therapeutic regimen. Thus a regimen appropriate for treatment of chronic HIV infection should be used.
- If treatment is started the decision to stop or continue may be reviewed in the light of evolving data or poor adherence.
- Patients who are currently being treated with antiretroviral therapy started during PHI who may wish to stop treatment should be encouraged to do so in the context of a clinical study.

3.2 Symptomatic HIV infection

All patients with late disease and/or symptomatic HIV infection with a CD4 lymphocyte count consistently <200 cells/mm^3, or who have been diagnosed with AIDS or severe/recurrent HIV related illnesses* or tumour at any CD4 count, should start therapy. This is because of the high risk of

further opportunistic infections which, although treatable, may cause irreversible damage or be life threatening.

*With the possible exception of pulmonary tuberculosis

3.3 Asymptomatic HIV infection

There are no ongoing controlled studies that address the optimum time to start therapy [55]. Current guidelines are therefore based upon previous studies of monotherapy and data from large clinical cohorts. Since the quality of evidence is relatively poor, opinion is divided on this question. The absolute CD4 count forms the basis of these guidelines, but treatment may also be considered for patients with a CD4 percentage below 12%.

In the UK, patients are diagnosed with HIV infection at a late stage. Over 30% present with a CD4 count of <200 cells/mm^3 [56] and, consequently, the 'early versus late' debate is irrelevant to many. The decision on when to start treatment will be influenced principally by two considerations: the short term risk of developing AIDS prior to treatment and the potential efficacy of starting treatment at various CD4 counts. Although it may be biologically plausible to start treatment early, this has to be tempered by the known potential for significant drug toxicity, difficulties with long-term adherence, and the selection of drug-resistant virus.

3.3.1.1 Individuals with CD4 counts <200 cells/mm^3

Patients with CD4 counts <200 cells/mm^3 have a high short-term risk of disease progression and death [57]. Several cohort studies have suggested that patients who initiate therapy when the CD4 count is <200 cells/mm^3 have an increased mortality [58-60] compared with those starting with CD4 counts above this level. Some prospective studies have suggested that for some antiretroviral regimens, patients with a low baseline CD4 count have a poorer virological response [61, 62]. All of these strands of data suggest that it is better to start therapy before the CD4 count has fallen to <200 cells/mm^3.

3.3.1.2 Individuals with CD4 counts >350

If the CD4 count is > 350 cells/mm^3, the risk of clinical progression in the short term is generally low [57] although individuals with a high viral load have a greater (but still small) short-term risk of disease progression [Table 3].

One unrandomised retrospective case-control study [63] has suggested that patients who commenced therapy with a CD4 count >350 cells were less likely than those who commenced later to experience disease progression or death. However, a large cohort study [64] has suggested no difference in disease progression in individuals commencing therapy with CD4 counts >350 versus 201-350 cells/mm^3. For the majority of patients with CD4 counts >350 cells/mm^3 it is reasonable to defer therapy until the CD4 count is below 350 but above 200 cells/mm^3.

3.3.1.3 Individuals with CD4 counts 201-350 cells/mm^3

Ideally, most individuals with established HIV infection should start therapy when the CD4 count is in the range 201-350 cells/mm^3. It is important not to let the CD4 count fall below this level before starting treatment for the reasons outlined above. Whilst it may be safe to monitor the CD4 count in some individuals with counts in this range, in others there will be an unacceptable risk of disease progression or of CD4 count falling to <200 cells/mm^3. These individuals may include those with a high viral load (e.g. > 60,000 copies/ml [65], >100,000 copies/ml [57]. Patients with a rapidly falling CD4 count (e.g. falling >80 cells/mm^3 per year on repeated testing [66] have an increased risk of CD4 cell count decline to <200 cells/mm^3 in the next 6 months. People in these groups may thus be considered for initiation of therapy relatively earlier within the CD4 count range 200–350 cells/mm^3. People who wish to take therapy for a limited period of time and subsequently interrupt treatment may also be advised to start early to ensure a high CD4 nadir. A further group in whom earlier initiation of therapy may be considered are those with hepatitis C co-infection, since progression of liver disease occurs more rapidly with lower CD4 counts [67, 68] and antiretroviral treatment is associated with a reduced rate of progression of liver disease [69]. An alternative strategy may be to treat the hepatitis C before it becomes necessary to treat the HIV.

3.3.2 Recommendations regarding asymptomatic chronic HIV infection

- Currently, our recommendation is that patients start therapy before the CD4 count falls to <200 cells/mm^3. (AIII)
- Given the available data and the limitations of currently available treatment, treatment is not indicated in asymptomatic individuals with a CD4 count >350 cells/mm^3. (AII)
- Within the range 200–350 cells/mm^3, individuals with a rapidly falling CD4 count (AII), a high viral load (AII) or hepatitis C co-infection (CIII) may be considered for earlier intervention.

If patients to whom these recommendations apply choose not to go on treatment, it is suggested that their CD4 count and viral load be monitored intensively (e.g. every 2 months) and the decision to start treatment be reviewed at regular intervals. (AIII)

4.0 What to start with

4.1 Choices of initial therapy

There is overwhelming evidence from cohort studies that the very dramatic fall in AIDS-related mortality and frequency of AIDS events seen in the developed world over the last 6 years coincides with the introduction of HAART [18, 70]. Any HAART regimen should be individualized in order to achieve the best potency, adherence and tolerability; to minimize potential long-term toxicity; and to avoid any likely drug–drug interactions (*www.hiv-druginteractions.org*).

A measurement of a regimen's success is achieving a viral load of <50 HIV-1 RNA copies/ml within 3-6 months of starting therapy and maintaining this out to 48 weeks. Regardless of the baseline viral load, a level of 1000 copies/ml has been found to be achievable in the majority of people by 4 weeks from start of therapy. Failure to achieve this is strongly associated with failure to reach viral load below 50 copies/ml within 24 weeks. Therefore, if the viral load measured 4 weeks after the initiation of therapy remains above 1000 copies/ml, this should prompt questions over possible poor adherence or other reasons such as reduced drug levels or primary drug resistance.

4.2 Which HAART regimen is best?

There have been no definitive controlled trials to demonstrate the clinical superiority of a HAART regimen used as initial therapy containing a boosted protease inhibitor (PI) when compared with a regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI). Patients should continue to be informed about and encouraged to participate in available clinical trials to further clinical practice. It is very important to select a regimen, which is best for the individual patient, and therefore to fully assess baseline risk factors for hepatitis B/hepatitis C co-infection, cardiovascular disease, diabetes, and psychiatric disease. In addition lifestyle issues such as smoking, obesity and recreational drug and alcohol use need to be taken into account. Several regimens will be discussed below and the advantages and disadvantages of each will be assessed. Their relative merits in terms of potency, adherence, toxicity, salvageability and potential drug–drug interactions are summarised in (Table 4). Previous guidelines suggested that patients with high viral loads may need more than three active drugs to achieve a rapid decline in viral load. There has been no new evidence from any clinical study to date for us to continue to recommend this strategy.

4.2.1 Two NRTIs plus an NNRTI

Efavirenz (EFV) and Nevirapine (NVP) are both recommended for initial therapy. These combinations have now been evaluated in a controlled, comparative trial using surrogate marker endpoints [71]. The 2NN study [62] yielded data comparing the two drugs in a randomized manner, showing that EFV and NVP were comparable in potency. However, equivalence was not formally proven, with a small chance that NVP was superior to EFV and a rather greater chance of the reverse. Two drug related deaths occurred in the nevirapine arm.

4.2.1.1 Efavirenz (EFV)

Impressive surrogate marker data have been obtained using EFV with two NRTIs (ZDV/3TC) [72-75]. One of the main advantages of an EFV containing regimen is that this can be prescribed once daily, and with the new formulation is only one pill, both of which may improve adherence. EFV has a long plasma half life ensuring that drug levels far exceed the concentration determined in vitro required to inhibit 90% of viral growth. This advantage however, may be a problem on stopping EFV. The long half life in comparison to some of the NRTIs means that the drug may remain in the plasma for several days effectively exposing the patient to monotherapy and the associated risk of drug resistance. To obviate that, many people would add a short acting protease inhibitor, e.g. nelfinavir (NFV), to the regimen for two weeks, discontinuing EFV under this umbrella and then stopping all other drugs at the same time. In an early randomized open-label study, ZDV/3TC/EFV was compared with ZDV/3TC/indinavir (IDV) and showed either no difference or superior surrogate marker endpoints up to 144 weeks of follow-up when analysed in a variety of ways (including intention to treat and on treatment analysis) [75]. The major drawback of this study however was the high discontinuation rate in both arms. By week 48, 35% of the IDV group and 25% of the EFV group had withdrawn from the study. This, along with the open nature of the study, may have biased the intention to treat analysis in favour of EFV. It also needs to be noted that the comparison drug, unboosted IDV, has a high pill burden requiring three times a day dosing, fasting, and therefore major adherence issues. It is no longer the normal standard of care for patients on a PI based regimen.

The major side effect of EFV is dysphoria. Manifestations include vivid dreams, depression, drowsiness and, in some, insomnia. Most are self-limited and it is unusual for patients to discontinue the drug for this reason within trials [76], though this may be more common in clinical practice. Rashes do occur, but severe rashes with EFV are unusual (the incidence of Stevens-Johnson syndrome is 0.1%). Lipid abnormalities, mainly rises in cholesterol above baseline values, have been observed in patients on EFV containing combinations [77]. EFV appears to be potent when used in patients with high viral titres, >100 000 copies/ml and low CD4 counts [76]. This drug may be teratogenic, so women of childbearing potential should be warned about becoming pregnant whilst on EFV. It should be avoided in women who may contemplate pregnancy.

4.2.1.2 Nevirapine (NVP)

NVP has been compared with EFV in the 2NN Study and has shown to be of comparable potency. However as mentioned above there was more serious toxicity in the NVP arm with two drug related deaths, one from liver failure and one from multi-resistant Staphylococcus aureus septicaemia in a patient with Stevens-Johnson syndrome. The major side effects are rash which occasionally manifests as Stevens-Johnson (incidence 0.3%) with occasional fatalities. The rash with NVP can be made worse by the co-administration of steroids [78-80] and these should not be prescribed. Hepatitis is the other major side effect in patients treated with NVP and reports of fulminant liver failure and deaths have been described. NVP is currently used twice a day, but the pharmacokinetics and now clinical trial data indicate that once daily dosing is possible, although there are more abnormalities of liver function as a result of using it once a day [62]. As with EFV, caution is needed when stopping NVP due to its long half-life in comparison with NRTIs.

4.2.1.3 Delavirdine

Delavirdine is currently unlicensed in the UK. It is not recommended for initial therapy in view of the high pill burden (though this is likely to fall shortly when a larger pill is produced). Delavirdine may have potential uses in boosting PIs since it inhibits the cytochrome P450 pathway.

4.2.2 Two NRTIs plus a PI

The dramatic decline in clinical progression and HIV related deaths followed the introduction of the PI class of antiretrovirals. These agents have shown clinical and surrogate marker efficacy in clinical practice. Sustained suppression of plasma HIV-1 RNA levels for more than 6 years has been seen in most patients within the Merck 035 study taking IDV and two NRTIs [81]. AIDS Clinical Trials Group (ACTG) protocol 320 was a clinical endpoint study that demonstrated long-term virological suppression and improved clinical outcome in patients taking ZDV/3TC/IDV [82]. Improvement in clinical outcome has also been seen in studies with ritonavir (RTV) added to background

antiretroviral therapy (containing NRTIs) in late disease [83]. The hard gel formulation of saquinavir (SQV) has also shown clinical benefit when used in combination [62].

4.2.2.1 Two NRTIs plus a boosted PI

Most clinicians now use a PI in combination with low dose RTV to provide a pharmacokinetic boosting effect when they start antiretroviral naive patients on a PI based regimen. The disadvantage of this approach is a possible risk of greater lipid abnormalities, particularly raised fasting triglycerides. Recent data from the 863 study [62] showed superior surrogate marker endpoint for patients using a boosted PI (lopinavir/RTV) when compared to nelfinavir (NFV) with low numbers discontinuing for side effects. Additionally, patients receiving lopinavir/RTV who developed virological failure had no evidence of PI resistance, only 3TC resistance, whilst most patients on the NFV arm had PI mutations in addition to 3TC resistance. The advantage of using RTV as a pharmacokinetic booster is that it enhances the pharmacokinetic profile of PIs either by extending the half-life or by increasing absorption. This may improve potency and may be associated with a reduced risk of the development resistance. It also aids adherence as regimens can often be simplified.

The committee feels that currently enough data are now available to suggest that a boosted PI should be the standard of care if a PI is chosen as part of an initial regimen (with the possible exception of atazanavir).

The two regimens suggested by the committee are lopinavir/RTV (as Kaletra®[1]) and RTV combined with SQV HGC (Table 4). RTV/SQV HGC and RTV/IDV showed equal efficacy in a randomised open study [84], but the toxicity of the IDV dose was unacceptably high in this and other RTV-boosted IDV studies [85]. Lower dose regimes (RTV 100 mg/IDV 400 mg) have been suggested and have shown good potency [86]. A further randomised study will report shortly when RTV/SQV is compared to Kaletra [87]. In the meantime, either combination can be recommended, although there is currently an advantage in pill burden with Kaletra®. Both regimens have pharmacokinetic profiles which suggest that once daily dosing is possible and surrogate marker data from clinical studies have confirmed these findings.

4.2.3 Three NRTIs

There is now surrogate marker endpoint data suggesting that ZDV/3TC/ABC (usually combined as Trizivir is less potent than combining two NRTIs with either a NNRTI or a PI [88]. In ACTG 5095 the 3 NRTI arm has recently been stopped by the DSMB [73], as Trizivir® was less potent than the other two arms (Trizivir®/EFVor Combivir®/EFV). Fewer patients had suppressed their viral load to <200 copies/ml by 16 weeks in the Trizivir® arm when compared to the other two arms. This finding was found both at high and low entry viral loads. Adherence was unlikely to have been a factor in these results as the pill burden was low in all groups.

Previous studies indicated that the combination of ABC, ZDV and 3TC was capable of producing long-term suppression of virus, in patients with lower viral loads [89]. A double blind, placebo controlled study (CNA 3005 study) [89] of ZDV/3TC/ABC compared with ZDV/3TC/IDV showed no significant difference in viral load suppression between the two arms. In those patients with high viral loads >100,000 copies/ml, though, there was a better response in the IDV arm than the ABC arm. This study was again a double blind, placebo controlled trial with a high pill burden. When a similar study was performed in an open fashion, no significant differences were seen in the high viral load strata [90], but there was much higher adherence in the ABC arm. The committee now feels that Trizivir® should only be considered as a starting regimen in special situations, for example informed patient choice based on likely poor adherence if alternative options are used, or concomitant medication such as for TB.

D4T/didanosine (DDI) and 3TC is a triple nucleoside analogue combination and has been compared with the same D4T/DDI backbone with either NFV or NVP. This study had only a small number of

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[1] Generic drug names are used where possible in these guidelines. However proprietary names are used where the choice of a combination formulation may be relevant to ease of adherence.

patients with high viral load, and showed a trend for less suppression to fewer than 50 copies by 48 weeks in the triple nucleoside arm [74].

4.3 Choice of NRTI backbone for initial therapy

In the context of HAART, there is no conclusive data to show which NRTI backbone to use, the choice of which is governed by issues of adherence and toxicity. Primary drug resistance, especially to ZDV, may affect the choice of initial NRTIs. This may be of particular relevance when considering a combination of ZDV/3TC or an NNRTI because of the relative ease with which resistant mutants are acquired, although there is a possible association between ZDV resistance and EFV hypersusceptibility [73, 74]. Although ABC has been used most often in triple NRTI combinations, it may also be used as part of an NRTI backbone and studies suggest that ABC/3TC is a potent combination [91]. For initial therapy, combinations including D4T are not recommended because of increasing evidence of its role in the development of lipodystrophy and abnormal lipid profiles. Even in subsequent therapy, toxicity data suggests that combinations of D4T with DDI should be avoided where possible and are definitively contra-indicated in pregnancy. Tenofovir is now available for initial use and a good safety profile was seen in a blinded clinical study with 96 week follow up in a group of patients for whom pre-existing renal damage was an exclusion criterion. In this study in which D4T/3TC/EFV and tenofovir/3TC/*EFV* were compared, both regimens were shown to be highly effective with more than 80% of patients having an undetectable viral load using a 50 copy assay in an intention-to-treat analysis at 96 weeks. Tenofovir was not associated with a rise in triglycerides seen in the D4T treated group. Longer term toxicity data is still limited, however. Tenofovir is recommended for use as first line therapy with lamivudine in patients with hepatitis B co-infection.

Increasingly, regimens that can be administered once daily are being used. DDI, 3TC and TFV are each licensed for once daily use, and there are ongoing studies for ABC.

4.4 Conclusions

We therefore believe that there remain insufficient data to make **definitive** recommendations on best initial treatment. However data now exists on less favourable combinations, which include D4T (because of toxicity) and triple nucleosides such as Trizivir (because of lack of potency). Initial therapy must be individualized for each patient and the risks and benefits of the treatment considered, including toxicity, adherence, resistance, immunological benefit, long term safety, clinical trial data and stage of disease. Most clinicians in the UK favour an NNRTI based regimen for initial therapy [92], reserving boosted PIs for later use, based upon the perceived risks of toxicity and ease of administration. There is no comparative evidence to support this stance, which may change when low pill burden PI containing regimens are available which do not produce lipid abnormalities.

5.0 Issues concerning antiretroviral use

5.1 Follow up of the HIV patient

Although there is only limited evidence on which to base recommendations relating to the use of laboratory tests in follow up of the HIV patient, the committee notes that the BHIVA national audit showed variable recording of routine tests and feels that some guidance would be helpful. A recommended summary schedule for specific laboratory tests is included in (Table 7), and a wide variety of additional tests should be used as clinically indicated. Monitoring is not a substitute for thorough clinical assessment, and it is important also to weigh patients, measure their blood pressure and do urinalysis on a regular basis as well as ensuring periodic gynaecological examinations and an annual cervical smear in women. Checks should be offered as well as vaccination against hepatitis A and B in those at risk.

5.2 Adherence

The committee views supporting adherence as an extremely important aspect of clinical care for patients receiving antiretroviral therapy, and BHIVA and the Medical Society for the Study of

Venereal Diseases (MSSVD) have produced specific guidelines on this topic [93]. These are currently available in draft format from the BHIVA website (http://www.bhiva.org/guidelines.htm).

In addition to addressing the role of adherence in HIV disease and the importance of adherence support from the perspective of health economics, the guidelines recommend a series of measures for adoption within HIV clinical care settings, based on evaluation of existing data.

Very high levels of adherence to antiretroviral drugs are a prerequisite for a successful and durable virological and immunological response while low adherence increases the risk of treatment failure and disease progression and contributes to the development of resistance.

High adherence is a process, not a single event, and therefore adherence support must be integrated into clinical follow-up. This is difficult to achieve unless a patient has some understanding of the way their treatment works and the importance of maintaining a minimum concentration of each of their drugs. This is also dependent on clear and accurate information being provided for each drug in relation to timing and flexibility of doses and the importance of dietary restrictions if applicable. For example, when a drug needs to be taken 'with food', this includes providing an indication of whether this is based on minimum calories or fat content.

Adherence support is likely to be different for a patient just starting therapy compared to someone who has been on treatment for several years.

Every prescribing unit should have a written policy on provision of adherence support, and ensure staff are appropriately trained to make delivery of such services possible.

5.3 Toxicity

A wide range of toxicities have been associated with individual drugs used in the treatment of HIV disease, and are beyond the scope of these guidelines. Clinicians are advised to refer to the British National Formulary, Electronic Medicines Compendium (http://www.emc.vhn.net) and HIV-Druginteractions.org (http://www.hiv-druginteractions.org/).

5.3.1 Lipodystrophy

The characteristic morphological changes of lipodystrophy [94] are highly stigmatising to individuals and may lead to consideration of delaying commencement of therapy, modification of established therapy to alternative regimens or decisions to stop therapy to prevent or attempt to manage the problems.

Arguments continue as to the linkage of the main components of the syndrome and indeed as to whether several different, overlapping syndromes may exist. The main components, which may be observed individually or in combination in persons on antiretroviral therapy, include:

- Dyslipidaemia with raised total cholesterol, low HDL cholesterol and raised triglycerides with increased lipid cycling or turnover
- Insulin resistance with hyperglycaemia, particularly in susceptible individuals
- Visceral, breast and/or local fat accumulation
- Generalized diminution of subcutaneous fat mass possibly with fat cell loss.

In addition, other metabolic and physical changes may also be present in individuals on long term antiretroviral therapy including raised serum lactate, low bone mineral density, hypogonadism (and possibly other endocrine abnormalities) and hypertension. The linkage of these problems to metabolic and morphologic changes remains to be elucidated.

A clinical case definition, based on physician and patient agreement regarding significant and characteristic morphological changes, potentially enabling more homogeneous populations to be studied and comparisons made across intervention studies has now been developed [95].

Only through understanding the etiology can optimal management of these problems be established. The etiology specifically of peripheral lipoatrophy and, to some lesser extent other clinical and metabolic consequences of antiretroviral therapy remains speculative. Evidence from

cross sectional surveys point to an interaction between HIV disease and/or immune recovery and antiretroviral medication [96]. Both PIs and nucleoside analogues have been associated with the changes and theories published hypothesizing how they may play a role [97-99]. Evidence to date suggests these hypotheses to be, at best, incomplete [100, 101]. Patients with the syndrome who have never received PIs [102, 103] or have never received (or have developed the syndrome whilst not receiving) nucleoside analogues [104-106] have been reported, indicating that these agents alone are not sufficient to cause the problem. The highest cumulative prevalence of morphologic abnormalities in these studies appear to be in persons receiving both PIs and nucleoside analogues together, relative to dual or triple nucleoside or nucleoside plus non-nucleoside regimens. As nucleoside analogues remain the backbone drugs of antiretroviral therapy, these data may encourage consideration of PI-sparing regimens for initial or long term therapy. Additionally, as D4T appears to have the highest relative risk of the lipoatrophy or is associated with more rapid fat loss, its use should be reserved for individuals not suitable for alternative agents such as ABC, DDI, tenofovir and ZDV. Details of other relevant data and debate are included in references [107-130].

5.3.1.1 Management of Lipodystrophy

Broadly, management approaches to lipodystrophy depend on the current assumptions of etiology. Actions that diminish the chance of lipodystrophy occurring may be key as treatment of established lipoatrophy is limited. Issues for prevention lie in:

- Choice of regimens that avoid combining PIs and NRTIs.
- Choice or regimens that prefer tenofovir or ZDV (and probably ABC and DDI) to D4T
- Commencing therapy before 200 CD4 cells/mm3 and before AIDS is diagnosed
- Consideration of early intervention for metabolic changes as these may be harbingers of lipodystrophy
- Dietary advice, possibly dietary supplementation (fibre, omega-3 fatty acids) and exercise.

Benefits for these suggestions are not fully established from randomised clinic trials but are extrapolated from cross-sectional and limited prospective data with their incumbent limitations.

Once established, the management of lipodystrophy falls into four categories:

- Lifestyle such as diet, possibly dietary supplementation and exercise
- Additional therapies, generally focussing on managing individual manifestations
- Modifying the treatment regimen away from D4T (and possibly ZDV) to ABC (and possibly tenofovir)
- Corrective procedures.

The risk versus benefit of these approaches has not been comprehensively tested, although the risk of diet and exercise can be considered minimal. Broadly, dietary advice should include a Mediterranean diet rich in omega-3 fatty acids, fresh fruit and vegetables. Fibre is known to improve insulin sensitivity. Evidence of benefit for specific food supplements is not established. Regular exercise, a mixture of cardio and weight training may also improve some metabolic parameters and abdominal shape [131].

Individuals switching therapy must consider that they may risk their long-term HIV management in exchange for an uncertain outcome with regard to their lipodystrophy. Specifically benefits in terms of clinically evident lipoatrophy have not been consistently observed in trials and, anecdotally, do not appear evident with even prolonged (>6 months) of treatment interruption. The majority of switch studies that have reported data have focused on switching away from PIs [107]. As mentioned, whilst metabolic benefits are achieved by switching away from PIs to NNRTIs or ABC in many patients, morphological benefits are more limited or absent. Switching away from D4T and possibly ZDV to ABC is associated with some gain in fat detectable by DEXA scanning over 24-48 weeks. It is not know if this recovery of fat is complete or durable. Improvements in metabolic parameters with this switch are not impressive.

Switching away from a PI-NRTI based regimen to a PI-sparing regimen does, however, currently represent the first step in management of metabolic abnormalities when ever feasible. NVP, EFV

and ABC perform similarly virologically in treatment naive persons but ABC should be avoided in those with prior NRTI resistance or mono/dual therapy exposure. Additionally, consideration should be given as to whether ABC should be used as an alternative to an NNRTI or PI or to another NRTI. Lipids and insulin sensitivity generally improve with all these approaches; cholesterol improvement may be greatest with ABC although HDL may rise most with NVP.

Switching away from PI-based regimens may be most beneficial with regards to metabolic parameters but is not particularly effective at managing peripheral lipoatrophy. Switching away from thymidine analogues, especially d4T, to ABC appears the only successful approach in this regard.

5.3.1.2 Other Therapies

Interest exits in the use of glitazones (for insulin resistance with weight loss), metformin (for insulin resistance with weight gain) and growth hormone (for lipoaccumulation) [132]. Metformin may benefit fat accumulations, insulin resistance and may improve some lipid and coaguability factors. Benefits on peripheral lipoatrophy have not been reported. Studies with glitazones are now underway in the US, Australia and the UK. Evidence of their efficacy, increasing fat mass in familial lipodystrophy [133] provides no guarantee of benefit in HIV-associated lipodystrophy. In HIV associated lipodystrophy a small randomized trial of rosiglitazone showed no benefit during short-term follow up, although larger studies are now in progress. Additionally, the safety and potential for pharmacokinetic interactions with these drugs in people with HIV requires clarification before their use can be considered or recommended in persons with HIV, especially those with a hepatitis co-infection [134, 135].

Growth hormone may improve fat management [136] and lead to improvements in appearance of both fat accumulation and lipoatrophy, including facial changes. However its use is likely to be limited by expense and by the evidence that unfortunately these benefits appear at least partially lost on stopping growth hormone. Additionally, growth hormone may preferentially increase lean body mass (hence its use in wasting) and is accompanied by adverse events including the risk of diabetes mellitus. Nor is the optimal dose of growth hormone for lipodystrophy established but it is likely to be lower than the 4-6mg/day recommended for wasting. Combining glitazone agents with growth hormone is an attractive idea that is currently under pilot investigation.

Anabolic steroids may be best avoided, due to concerns regarding worsening lipid profiles, fat loss and potential for liver function disturbances, although testosterone replacement for repeatedly hypogonadal and symptomatic men, who are not hypogonadal due to previous anabolic steroid, use may be considered.

The use of statins and fibrates is appropriate for the management of dyslipidemia but no benefits have been described with regards to morphologic changes. The benefits of these agents appear similar to improvements in cholesterol or triglycerides described in endogenous dyslipidemia [137, 138], hence are like to be associated with reduction in cardiovascular disease risk. However, relatively few individuals in reported studies have achieved response goals as outlined in NCEP guidelines [139]. Pravastatin is the most well studied agent due to the low likelihood of drug interactions with protease inhibitors. Lovastatin may also be suitable. Simvastatin is contraindicated due to substantial risk of drug interactions with PIs and atorvastatin levels may be increased about 2-fold suggesting caution should be used when using this agent. Interactions between statins and NNRTIs have not been described. Interactions with fibrates and PIs or NNRTIs are not expected to be clinically important. Advice from a lipidologist should be sought before combining fibrates and statins.

Corrective surgery remains the mainstay of management of other acquired lipodystrophies such as Barraquer-Simons syndrome albeit that they do not address the etiology. Only one randomized study evaluates outcomes of these approaches [140, 141]. The use of Polylactic acid injections (New-Fill) has attracted considerable interest. Polylactic acid is hypo-allergenic and biodegradable over the course of about 2 years (hence does not trigger chronic inflammatory reactions which may accompany silicone injections) and stimulates fibroblasts to produce collagen (hence is not really a 'filler' such as transferred fat or collagen which may rapidly disappear). Injections may be given after a short training session and involve use of local anaesthetic followed by injection of the substance via several puncture points on each side. Patients are advised to massage the area after use to spread the substance evenly in the tissue plane. Bruising and rarely local skin infections are the main adverse effects. Objective improvements in facial appearance and patient well-being were noted in one study. Other similar products such as hyaluronic acid are also being used. Additionally,

the other 'traditional' approaches, such as fat transfer, collagen, implants carry considerable expense and fat transfer is only feasible if fat is available to 'harvest' from other body areas. Facial implants may also be used but risk fat loss occurring around the implant leading to a lumpy appearance. Plastic surgery is largely suitable for facial changes most reports focusing of the naso-labial folds and buccal fat pad area although the temporal area may also be filled. The limitations of plastic surgery underline the need for more specific treatments that addresses etiology and whole body changes.

5.3.1.3 Conclusions

Lipoatrophy is best avoided as it is difficult to treat. Its appearance may be delayed by avoiding D4T in the initial regimen.

- Insulin resistance should be treated with metformin.
- Abnormal lipid profiles should be treated by switching drugs wherever possible and by the use of both statins and fibrates.
- Exercise and diet may have a modest effect on both body habitus and lipid abnormalities.
- Controlled trial evidence exists for the use of New Fill injections in established lipoatrophy.

5.3.2 Mitochondrial toxicity and lactic acidosis

The link between NRTIs and mitochondrial damage was first suggested in 1989 in relation to myopathy in patients on ZDV. Subsequently, mitochondrial toxicity has been implicated in a wide range of other NRTI associated toxicities, including neurological disease in infants, peripheral neuropathy, hepatic steatosis and lactic acidosis. The role of mitochondrial toxicity in causing these NRTI associated toxicities has yet to be established in most cases. However, the link for which evidence appears strongest, lactic acidosis, is one with a potentially fatal outcome.

5.3.2.1 Aetiology of NRTI induced mitochondrial toxicity

NRTIs inhibit gamma DNA polymerase, the enzyme responsible for copying mitochondrial DNA [142]. Inhibitory effects of NRTIs on other enzymes key to normal mitochondrial function have also been described. Evidence to support DNA polyermease inhibition has been shown by studies that demonstrate reduced mitochondrial respiratory chain enzyme complex activity, reduced mitochondrial DNA concentrations, as well as electromyographic changes seen previously with mitochondrial muscle damage [143-145]. Different NRTIs preferentially affect different cell lineages leading to a variety of clinical syndromes. Hence there appears to be an hierarchy for which NRTIs cause DNA polymerase gamma inhibition, with D4T, DDC and DDI causing more inhibition of mitochondrial DNA replication [142, 146] whereas ZDV may inhibit other mitochondrial enzymes [147] and cause more cytotoxicity in some cell lines [148]. Some evidence for this is suggested by the improvement in laboratory findings and clinical features when D4T was switched to ZDV or ABC in patients with symptomatic hyperlactataemia [149]. Mitochondrial toxicity may, however, represent only one mechanism by which NRTIs cause adverse effects [147].

5.3.2.2 Lactic acidosis and hyperlactataemia

These two terms are not interchangeable. Hyperlactataemia may occur in physiological as well as pathological circumstances and is not necessarily accompanied by changes in blood pH or anion gap. The clinical significance of hyperlactataemia is not established and routine screening of asymptomatic individuals is not currently recommended. Lactic acidosis is always a serious condition requiring immediate withdrawal of antiretroviral therapy and other supportive therapy. Definitions are as follows:

Hyperlactataemia: venous lactate > 2.5–5 mmol/L.

Lactic acidosis: arterial pH <7.35, venous lactate >5 mmol/L.

5.3.2.3 Incidence

Fatal lactic acidosis associated with NRTI use was first reported in 1993 [150]. A review of a heterogeneous group of patients receiving antiretroviral therapy in the 5-year period beginning 1989 showed that the risk of developing lactic acidosis with hepatomegaly and hepatic steatosis was approximately 0.1% per patient per year [151]. More recent estimates are higher, at 1% to 2% per year, particularly if 'symptomatic hyperlactataemia' is included [152-154]. The definition of symptomatic hyperlactatemia is unclear and in general has included a range of symptoms also present in persons with consistently normal lactates (e.g. fatigue). Asymptomatic hyperlactataemia may present in up to 16% or more of individuals on therapy and may be intermittent in nature [155, 156]. This compares to a reported incidence of 2% of those not on ART [156] (as would be expected by normal ranges being set at 2SD from the median). The duration of the ART is important in some studies, and certainly an exposure of at least several months appears to be the norm for most reported cases [157]. It also appears that there is a greater risk of developing lactic acidosis amongst females [158, 159].

5.3.2.4 Clinical and laboratory features

Hyperlactataemia, defined as between 2 or 2.5 and 5 mmol/L, is often asymptomatic. Intervention is not required but the individual should be carefully monitored with repeat lactate samples taken uncuffed and at rest. If accompanied by symptoms such as nausea, malaise, weight loss, abdominal pain, tender hepatomegaly, worsening of hepatic enzyme abnormalities and/or biochemical changes, therapy should be interrupted.

Clinical features commonly accompany lactate levels of >5 mmol/L. Features of lactic acidosis include weight loss, fatigue, abdominal pain, tender hepatomegaly, respiratory distress and failure. As well as a raised lactate and acidosis and an anion gap that is usually widened ($\geq$18 mmol/L), other laboratory features that might be present include raised hepatic aminotransferases, raised creatine kinase, lactate dehydrogenase and amylase [107]. The anion gap is calculated as [Na+ + K+] – [Cl- + HCO_3-] and should be <12 mmol/L.

Lactic acidosis has been reported in infants of mothers receiving ZDV or ZDV+3TC during pregnancy. Additionally, d4T+ddI has been associated with several reports of lactic acidosis in women who became pregnant while taking these medications. Consideration should be given to monitoring lactate in women receiving antiretroviral therapy during pregnancy.

5.3.2.5 Management of hyperlactataemia and lactic acidosis

There is currently no rationale for performing routine serum lactate measurements. The predictive value of a single lactate measurement for the development of lactic acidosis is not established but appears limited. Additionally, there is no evidence to support the routine use of anion gap or lactate : pyruvate ratios. Instead, it is important to maintain a high index of suspicion for lactic acidosis on the basis of associated symptoms and signs that could justify the measurement of serum lactate.

A clinician's decision to reintroduce NRTIs in patients who have had previous acidosis would justify monitoring serum lactate in those patients. However, there is insufficient evidence to establish whether NRTIs can be safely re-introduced following hyperlactataemia and, if so, for which group of patients.

The management of lactic acidosis is cessation of antiretrovirals (and any other possible contributory agents) and exclusion of other causes. Supportive measures such as ensuring adequate perfusion, providing oxygen or if necessary assisted ventilation, haemodialysis or dichloracetate may also be useful [160]. Components required by the mitochondrial respiratory pathway, such as thiamine [161], riboflavin [162] and co-enzyme Q and carnitine, have been administered without apparent toxicity, but the evidence for their use is limited.

5.3.2.6 Recommendations for managing lactic acidosis

The recommended minimum requirements for managing lactic acidosis are*:*

- All patients should be informed of possible signs and symptoms and encouraged to attend an available clinic.

- All clinicians should be fully conversant with the clinical presentations of lactic acidosis and symptomatic hyperlactataemia and have immediate access to means of measuring lactate levels in specified patients.
- All clinicians should be familiar with means of managing lactic acidosis. Identifying symptomatic patients whose current antiretroviral medication should be immediately stopped is of particular importance.

5.4 Resistance testing

Resistance interpretation is continually updated. Readers are referred to the latest IAS-USA algorithm [163].

Antiretroviral drug resistance has been described retrospectively, in vitro and in vivo, to be associated with poor virological and clinical outcomes. Short-term prospective, randomized controlled trials have, in some studies, demonstrated the short term benefits of resistance testing over standard of care [164-174]. It is likely that the relatively modest benefits demonstrated are due to in part to inadequate interpretation of results at the time of the study. Other factors leading to differences between studies include the proportion of patients who are NNRTI naive at time of therapy switch, the availability of expert advice (EA), and the overall therapy experience of participants. A meta-analysis of the VIRADAPT, GART, HAVANA, ARGENTA, NARVAL and VIRA3001 has been undertaken, (Table 8) [175] and showed a higher proportion of patients had undetectable viral loads at 3 and 6 months in the genotype testing groups. This particular analysis supports the use of genotypic but not phenotypic resistance tests and shows that EA can increase the virological response. Further, the recent MRC ERA Study: a one year RTC of genotypic (n=152) versus genotypic plus phenotypic (n=159) testing to guide patient therapy, in a relatively experienced group of patients (average exposure to 7.7 previous drugs) found no clear evidence of added value (in terms of virological and immunological markers) of phenotypic resistance testing against a background of genotypic resistance testing [176]. Genotypic assays are cheaper than phenotypic assays, and can be normally undertaken within specialist clinical virology laboratories. By contrast, real time phenotypic assays are generally provided by a few commercial laboratories and currently require dedicated category 3 facilities.

It is unlikely that randomised, controlled studies of resistance assays will be undertaken in the future, and further insight into the best use of resistance tests may come from large cohort studies and clinical database analysis.

In recently infected individuals resistant virus prevalence rates in a small number of subjects range from 2% in Denmark [177] to 21% in the UK [178]. In these individuals the results of a resistance test are likely to reflect the actual transmitted virus and so may help regimen selection. Further, recent studies suggest that time to virological suppression in patients infected with a resistant virus is longer than for patients infected with wild-type virus [179-181]. Therefore, knowledge of such resistance prior to initiating therapy will allow optimisation of first line therapy. In chronically HIV-infected patients not on treatment, the prevalence rate for primary mutations associated with protease or RT inhibitors ranged from 3.7% in the French Nationwide study [182], to 15% in a Spanish study [183] and >10% in the USA [184]. Overall, the prevalence of resistance appears less than studies on primary infections, which may be explained by the fact that the time of infection for these individuals could have occurred some years previously, prior to the upsurge in transmission of resistance. Alternatively, transmitted resistant virus may subsequently evolve, with reversion to wild type, although recent studies demonstrate that many such resistant viruses appear to persist in the absence of therapy [185]. Moreover, cost effectiveness analyses have shown that when prevalence rates of between 4% and 10% are reached for mutated virus there is an advantage to test for resistance in antiretroviral-naive patients [186, 187].

Resistance testing has technical limitations. Both genotypic and phenotypic testing depend on polymerase chain reaction (PCR) amplification of virus from plasma, and therefore do not address the properties of different virus components (i.e whole virus vs reverse transcriptase/protease genes alone). The likelihood of generating sufficient genome product to undertake the further analysis depends on the starting concentration of virus. Therefore, most current assays require in the order of 1000 copies/ml to reliably provide a result. Although some improvements may be possible, ultimately, greater sensitivity will only be possible with a larger starting quantity of blood. Secondly, the nature of current gene sequencing techniques limits the detection of minority strains of virus (within the plasma virus population) to 20%. Smaller proportions of mutant virus may contribute to subsequent

therapy failure; these will not be detected. These tests are technically demanding, and external quality control is essential. This is addressed by national and international pathology laboratory accreditation programmes.

HIV-1 genetic diversity within the UK is widening. In 2002, heterosexual infection from Sub-Saharan Africa represented the majority of new diagnoses. These individuals are infected with viruses with significant genetic difference from the subtype B virus common within the gay epidemic. The impact on resistance testing is two-fold. Firstly, PCR-based assays require optimisation of efficiently produce results from such viruses, and secondly, the presence of "secondary" resistance mutations as normal variants in such viruses may require modification of resistance interpretation systems.

In drug experienced patients who stop therapy, pre-existing "wild type" virus, archived from prior to therapy, can rapidly emerge within 1 month [188], and resistance testing subsequent to this time will only yield this non-resistant strain. It is therefore un-informative. If possible testing should always be undertaken on virus from a patient while receiving therapy.

A recent study has shown that NNRTI-naive patients with NNRTI-hypersusceptible virus had an improved virological (and immunological) response after starting an NNRTI-containing regimen [189]. A further study has shown there is a significant association between the presence of NRTI mutations and NNRTI hypersusceptibility [190], in particular the duration and number of previous NRTI used and resistance to ZDV and ABC. Such findings may not yet be represented within interpretation algorithms.

5.4.1 Recommendations

- Resistance testing should be undertaken at each point of viral rebound on therapy (although, as stated above, a viral load of at least 1000 copies/ml is required for a reliable assay), unless a patient is on a treatment interruption (AIII).
- As transmission of viruses with reduced sensitivity to drugs is well documented, testing should be undertaken at time of presentation (BIII).
- There is little evidence for an advantage of phenotypic over genotypic testing. Both require interpretation of complex data, and the interpretation systems for fold resistance (phenotype, and phenotypic interpretation of genotype –virtual phenotype) and mutations (genotype) are subject to change as more clinical outcome data becomes available. Genotypic assays are currently cheaper than phenotypic.
- It is essential that interpretation of resistance testing, and choice of new therapy is taken in the light of all clinical information, including prior therapies and toxicities. Previous resistance test results must be considered, and resistance apparent at that previous time must be assumed to be permanently represented within the virus population. Samples taken for viral load should be stored frozen within the laboratory, in order that retrospective resistance testing can be undertaken.
- In drug experienced patients, resistance testing should be undertaken while the patient is receiving therapy, to avoid misleading results.
- Laboratories undertaking resistance testing should be equipped to provide clinical support to HIV clinics, and demonstrate participation in external quality control programmes and accreditation by national/international agencies. They should store samples and assay data according to guidelines of the Royal College of Pathologists.

5.5 Therapeutic drug monitoring

This section discusses the role of TDM for PIs and NNRTIs. TDM is likely to be of little value for NRTIs as these agents require intracellular activation and levels of intracellular drug-triphosphate bear little relationship to plasma levels of the parent compound. The abbreviations Cmin, Cmax and AUC refer to the plasma trough (usually at end of the dosing interval), peak plasma levels and area under the concentration-time curve, respectively.

Europe has seen increasing uptake of TDM and incorporation of TDM into national HIV treatment guidelines in several countries. This is despite a surprising lack of data to confirm the benefit of TDM in routine clinical use, and the opportunity to conduct these trials has largely passed. Nevertheless,

prospective surveys suggest ~20% patients in clinic have sub-therapeutic (below target for wild-type HIV) plasma concentrations of PIs and NNRTIs [191-193]. Moreover, the inter-individual variability in plasma concentrations is immense (≥ 100-fold difference) despite standard dosing [191].

5.5.1 Drug levels and efficacy

A large number of observational studies have confirmed that drug exposure (Cmin or AUC) of PIs correlate with virological suppression in patients prospectively followed up in Phase II studies (SQV, IDV, amprenavir (APV)), treatment-naive patients (including phase III studies) commencing therapy (SQV, NFV, IDV, RTV), dual PI regimens (SQV, NFV, RTV), salvage antiretroviral therapy (SQV, IDV, RTV) or else a broader population of clinic patients on antiretroviral therapy (SQV, NFV, IDV, RTV) [191, 194, 195]. In general, the association between drug concentrations and virological response varies according to patient group, and is less apparent in very heavily pre-treated patients (in whom resistance is likely).

For NNRTIs the data are less convincing - one group of investigators reported an association between NVP concentrations and treatment response in treatment-naive patients in the INCAS trial, but no correlation in clinic patients who may have had a previous therapy failure [196, 197]. Concentration-effect relationships have also been reported for EFV [198].

5.5.2 Drug levels and toxicity

High plasma drug concentrations have been associated with some toxicities, e.g. urological toxicity including flank pain, haematuria or elevated creatinine (IDV; related to C_{max} and AUC), gastrointestinal (RTV; related to C_{max}) [199], elevated lipids (RTV, and possibly LPV) [200-202] and hepatotoxicity (NVP- although it is unclear if elevated drug concentrations were a consequence or cause of abnormal LFTs) [203]. An association between CNS toxicity and EFV concentrations has been reported [198] in a cross-sectional study of 130 patients receiving the drug for an average of 8 months. However, a recent small study reported no association between EFV concentrations and sleep disturbances [204]. There are also preliminary data reporting an association between NFV concentrations and lipodystrophy [205].

5.5.3 Use of TDM

Intervention studies where doses are adjusted to therapeutic and non-toxic levels on the basis of TDM have been sparse and difficult to interpret. An intensive study [206] of 49 adults commencing ZDV, 3TC and IDV randomised patients to receive conventional therapy vs TDM, where full plasma profiles for all 3 drugs plus subsequent multiple sampling was performed. Patients in the TDM arm had significantly more rapid and durable virological responses to therapy. In the ATHENA study [207], a subset of treatment-naive patients randomised to receive TDM had improved efficacy (NFV) or reduced toxicity (IDV). However, these analyses were post-hoc, and in the overall study cohort, analysis was complicated by 'unblinding' of controls as well as low compliance to TDM recommendations by attending clinicians. Two French studies (Genophar and Pharmadapt) have failed to observe any benefit of TDM [208, 209] in a group of pre-treated patients. Assessment of TDM was limited by only a short window in which to observe any effect, since any dose modification was only instituted at 8 weeks for TDM arm, while all patients in the non-TDM arm received TDM from week 12 onwards. A further Canadian trial is recruiting slowly. No association has been shown between CD4 cell response and TDM.

Many of the potential problems with TDM have been overcome. A consensus of what efficacy targets should be for each drug is emerging [194, 195] (although toxicity targets are more problematic). An international quality assurance programme is now in place. Most centres utilise a trough measurement (+/- post-dose concentration), although random levels have also been assessed. TDM should not be performed during acute illness when concentrations of the acute phase protein a1-acid glycoprotein (to which PIs bind) may be elevated. BHIVA recommendations for TDM are shown in [Table 9].

5.5.4 Inhibitory quotients

Inhibitory quotients (IQs) comprise the Cmin of drug divided by some measure of resistance (phenotype, 'virtual' phenotype or genotype). Several different formulas for calculating IQ exist.

Although IQs have yet to be prospectively evaluated as a tool for managing HIV infection, they have been shown to be better predictors of virological response in moderately or extensively pre-treated patients than plasma drug concentrations and/or resistance testing alone [210]. It is important to recognise that the target IQ for optimal response is likely to be different for different drugs- thus cross comparisons between different agents is probably not valid. At present, there are insufficient data to recommend the use of IQs in clinical practice.

5.6 Structured treatment interruption (STI)

The role of structured or supervised treatment interruption (STI) in first and subsequent therapy is still under investigation, even though it has been used in a number of clinical trials. It is important to define what is meant by STI and in which clinical settings it is being studied, since the aims may be very different for each setting (Tables 10, 11, 12). The three settings are acute infection, chronic infection with virological suppression and chronic infection with treatment failure. STI is discussed in more detail in sections relating to these settings. The three main objectives are immune enhancement, limiting drug exposure/toxicity and reducing resistant virus by repopulating with wild type virus.

The potential problems of STIs include disease progression, induction of an acute antiretroviral syndrome similar to PHI, and induction of resistance mutations if drugs of differing half lives are stopped simultaneously. As viral load rises with STI, individuals who engage in unsafe sex may become relatively more infectious to others and there has been a report of an enhanced risk of sexual transmission of HIV during STI [211].

6.0 Changing or stopping therapy in the absence of virological failure

6.1 Patients started on regimens that are not currently recommended for initial therapy

Many patients are currently established on regimens that are no longer recommended for initial therapy. Such patients should be advised of recent study results and should have explained to them where changes in therapy may reduce the risk of virological rebound and improve their quality of life. Those who are stable with evidence of sustained virological suppression (viral load < 50 copies/ml for 6 months or more) and who are not experiencing side effects (including lipoatrophy), may prefer to remain on their current therapy as the longer the period of complete suppression, the lower the risk of subsequent virological rebound is likely to be.

6.1.1 2NRTI plus unboosted PI regimens

Patients who are on PIs suitable for boosting (i.e. IDV or SQV) may find a boosted regimen simpler to take, with fewer daily doses and food restrictions. Although switching to a boosted regimen may improve quality of life [212], some studies have shown evidence of a significant increase in toxicity [85]. NFV is not suitable for boosting and can be continued if the patient is stable with undetectable viral load.

6.1.2 3NRTIs

Patients taking triple NRTI regimens should be advised of recent trial results indicating a higher risk of virological rebound as compared with currently recommended regimens. A change in therapy should be considered for those who have not achieved sustained virological suppression (< 50 copies/ml for more than six months) or who have achieved viral suppression but have previously received mono or dual nucleoside therapy.

6.1.3 Regimens containing stavudine

D4T is no longer recommended for initial therapy largely because of data from several studies suggesting that it is associated with an increased risk of lipoatrophy [213]. Patients who are on a

D4T-containing regimen should consider switching if treatment history and resistance data suggest that an alternative drug is likely to be active. A switch to ZDV may delay but is not likely to prevent the development of lipodystrophy. However a switch to ABC is associated with an increase in subcutaneous fat, [214] and switching to tenofovir is also being studied [215].

6.1.4 Non-HAART regimens

A small number of patients may still remain on non-HAART regimens (e.g. 2 NRTIs). Even if plasma viral load is undetectable or low, there is likely to be significant ongoing viral replication [216] and thus evolution of drug resistance, which will limit future options. Consideration should thus be given to switching all remaining patients to HAART regimens. Patients currently on a non-HAART regimen who started therapy with a high nadir CD4 count (e.g. above 300) should be considered for treatment interruption (see section 5.6).

6.2 Patients on recommended regimens

Patients who have difficulty with adherence should be assessed individually in accordance with the adherence guidelines. Where appropriate, they may be switched to simpler regimens such as once daily therapy. This appears to be safe, except in those who have had either sub-optimal therapy or therapy which may have produced viruses with reduced sensitivity (resistance) to drugs involved in the simplification regimen.

When switching because of life-threatening toxicity, eg fulminant hepatic failure, all drug therapy should be stopped until the patient has recovered.

6.2.1 Switching from PI-based regimens

A number of studies have evaluated the approach of switching the PI in a HAART regimen to a NNRTI [217] or to ABC in patients who have a persistently suppressed viral load . There are several potential advantages of such an approach, including the reduction of central adiposity and hyperlipidaemia . A variable proportion of patients in such studies have experienced early virological failure, often because of pre-existing NRTI resistance before switching [218]. It is very important to consider the possibility of NRTI resistance, particularly in patients who have previously experienced virological failure, by reviewing treatment history and the results of resistance tests (carried out on stored samples if available), as switching one or more NRTIs may also be necessary at the same time to ensure continued virological suppression.

6.2.2 Switching between NNRTIs

For a serious skin rash in individuals taking an NNRTI containing regimen, the drug needs to be stopped immediately. It is probably safe to switch to an alternative NNRTI, although patients who develop a severe rash after starting NVP and switch to EFV may have an increased risk of developing a rash due to EFV.

The optimum policy for switching from EFV to NVP remains to be determined in large studies. On small study has indicated that switching to full dose NVP immediately produces drug levels of a therapeutic range [219]. This is because EFV also induces cytochrome P450, enhancing the metabolism of NVP.

6.2.3 Stopping NNRTI-based regimens in non-emergency situations

EFV and NVP have long plasma half-lives. If all the drugs in a regimen containing 2 NRTIs and one of these drugs are stopped at the same time, levels of the NRTIs are likely to fall more rapidly that the NNRTI, leaving a period of functional NNRTI monotherapy. This may be sufficient to select NNRTI-resistant virus [220, 221]. Ways to limit this risk are to switch the NNRTI to a PI for 1-2 weeks before stopping the whole regimen or to continue with the two NRTI drugs for 7 further days after stopping the NNRTI.

6.3. Stopping therapy in individuals with complete viral suppression (structured treatment interruption)

STI has been investigated in chronic therapy both to enhance immune responses and as a means of decreasing drug exposure with the potential of limiting toxicity and perhaps reducing costs. Results have varied depending on the pattern of treatment interruption used.

6.3.1 Intermittent on-off therapy cycles of one month or longer

The largest study of longer intermittent therapy cycles is the Swiss–Spanish Intermittent Treatment (SSIT) trial of patients who had had <50 copies/mL for longer than 6 months [222]. The patients then stop therapy for 2 months, followed by 8 weeks back on therapy. After four such cycles, therapy is stopped until the patient's HIV RNA load increases to >5000 copies/ml. There was no significant difference between the continuous and intermittent therapy groups on the primary outcome of the study, which was the change in viral load pre- and post-treatment.

Another controlled trial of 70 patients being treated with cycles of one month on followed by one month off therapy [223] was abandoned after the virus rebounded with each interruption in the first 15 subjects, leading to the development of drug resistance in several patients.

6.3.2 Intermittent on-off therapy cycles of one week

Another approach involved a cohort of 11 subjects given cycles of intermittent therapy, consisting of 1 week on followed by 1 week off therapy [224]. The viral load has remained <50 copies/ml in all patients, except two who were non-adherent. Follow-up was as long as 44 weeks and there has been no development of detectable resistance. Further follow-up will be required before any conclusions can be drawn about the effect of this approach on the development of metabolic abnormalities.

However, data from a sub-group of the SSIT Trial showed that even after one week of treatment interruption significant viral replication can be induced [225]. The HIVNAT 014 study was also unsuccessful in respect of a group of treatment experienced patients using one-week on-off therapy cycles, 20-30% of whom showed viral breakthrough, with development of resistance in some cases. In conclusion, the committee feels there is insufficient data to recommend intermittent cycling of treatment outside rigorously controlled clinical trials.

6.3.3 Discontinuation of therapy with re-start based on CD4 count [CII]

In individuals with complete virological suppression, treatment interruption tends to lead to viral load rebound in a few days and CD4 count decline within weeks, with little evidence of any longer term benefits resulting from single or multiple STIs. However, in individuals whose CD4 count never fell to low levels (perhaps a CD4 count of 300 /mm3), interruption is unlikely to rapidly result in CD4 count decline to levels associated with substantial risk of clinical disease. Interruption of therapy is therefore an option in such patients, if there is a strong desire to do so, due to toxicity or other reasons. The HIVNAT 014 study used this approach and a larger study with similar CD4 count guidance is being undertaken by the CPCRA [226]. It should be understood that it may require years of therapy after the interruption to re-attain the CD4 count level prior to the interruption.

We would recommend that any structured treatment interruption should be planned, that particular care should be taken with withdrawal of drugs with extremely long half-life such as efavirenz, and that treatment should be re-started based on the CD4 count. Patients should be counselled and understand these issues. The issues associated with treatment interruption should all be discussed in detail, including the need for relatively frequent CD4 monitoring during an interruption, the risk of developing an acute antiretroviral syndrome similar to PHI, and the risk of onward transmission which will probably increase as the viral load rises.

7.0 Changing or stopping therapy for virological failure

7.1 Virological failure

The viral load nadir achieved within the first few months on treatment is predictive of the subsequent risk of virological failure [227]. To limit the risk of virological treatment failure an objective of initial therapy (and subsequent treatment regimens if achievable) is to suppress viral load to <50 copies/ml. Once suppressed, patients may subsequently experience transient rises in viral load to just above detectable (blips) or sustained viral load rebound.

Recommendations on action to be taken on first virological failure are shown in (Table 11).

7.1.1 Viral load blips

Once a patients shows a rise in viral load to just above detectable ,they should be clinically assessed to determine factors which may have reduced plasma drug levels to below optimal levels such as drug-drug interactions, poor adherence, incorrect dosing or factors which may have increased viral replication such as inter-current infections and vaccinations.

Transient rises in viral load to levels to just above detectable (viral blip) are reported to occur in a significant proportion of patients on treatment over time [228, 229]. Patients who are developing sustained virological rebound (failure) would show further increases in viral load whereas those whose viral load is transiently detectable because of assay related problems or other factors will show no further rise or revert to undetectable usually within 4-6 weeks. It is controversial whether viral blips are associated with an increased future risk of virological failure in those who have already achieved viral suppression. One study showed no such association [229] but another [228] suggested that although a low level viral blip was not a predictor of failure those with repeated episodes or sustained low level viral rebound were more likely to experience virological failure in the future. Patients with frequent blips related to possible inadequate drug potency and absence of genotypic resistance to their current regimen may be candidates for intensification or change of therapy . This strategy is being assessed in ongoing trials.

7.1.2 Sustained viral load rebound

A clinical assessment of factors potentially contributing to reduced plasma drug levels should be undertaken and managed appropriately where possible.

Falls in CD4 count and clinical disease progression are not usually seen in patients experiencing low level viral load rebound but are the usual eventual outcome in patients whose viral load continues to rise towards pre treatment levels [230]. Although resistance to all drugs in a treatment regimen may not be detected in patients experiencing virological failure, it is likely that the higher the copy number the more probable the development of resistance . For some drugs (eg. 3TC, NNRTIs) mutations at one position in the reverse transcriptase gene can cause high level phenotypic resistance and usually emerge at low levels of viral load rebound. Reduced susceptibility to other drugs requires the accumulation of two or more mutations in the viral genome and occurs with ongoing viral replication in the presence of drugs . Thus if significant levels of viral replication develop and persist on therapy and other options are available which can completely suppress it then therapy should be changed. The lower limit for a definition of significant levels of viral replication is somewhat arbitrary. For practical reasons many clinicians would accept a persistent (two values greater than one month apart) viral load level of >400 copies/ml for consideration of a treatment switch. This may change as further information is gained on the frequency and the emergence of genotypic mutations at low level viraemia on different drug combinations and how this may influence the treatment response to subsequent regimens, together with improvement in the sensitivity of assays to detect drug resistance, which is presently only reliable with viral loads of >1000 copies/ml.

7.2 Changing therapy [BII]

Patients should be considered for a change of therapy if they show sustained rebound in viral load levels, having previously been undetectable, or have never achieved undetectable levels on their current treatment regimen. The likelihood of achieving an undetectable viral load on changing therapy is predicted by the number of active drugs in the new regimen [231, 232] plus factors

influencing tolerability and adherence. The decision to change therapy should be guided by the availability of a treatment option which is likely to have the potency to suppress viral load to undetectable levels (<50 copies/ml) and which the patient is likely to be able to adhere to and tolerate.

Occasionally it happens that there is no available effective treatment option after virological failure of an initial regimen. Although this is infrequent it may be a factor in continuing the initial regimen. Factors contributing to a decision to delay switching therapy may also include situational and psychological factors potentially affecting adherence, fear of side effects from the new drugs and a patient's wishes and acceptance of the need to change therapy. If the VL is stable and the CD4 count is at a level not associated with a high and immediate risk of clinical disease progression then a decision to delay switching therapy may be acceptable but must be balanced by the likelihood of accumulation of further mutations and the consequence of this on future therapeutic options.

Although the addition of a single new agent in individuals experiencing low level viral load rebound may result in a proportion becoming undetectable [233] this strategy is not recommended as the disadvantages in terms of added toxicity and development of resistance to the new drug are probably greater than the likelihood of achieving a sustained undetectable viral load.

7.2.1 Failure of two nucleoside analogues plus a protease inhibitor [BII]

There is no clear evidence to guide the optimal treatment strategy in this situation. Resistance testing is of importance to identify which NRTI(s) will be of most benefit in the new regimen and help select new PIs if these are to be included.

One option in first-line failure is to change both NRTIs and switch the PI to an NNRTI. If there is extensive cross-resistance amongst the NRTIs, limiting the benefit of new NRTIs, there is likely to be a high risk of more rapid virological failure with this strategy. In this situation a more effective option would be a new PI (ritonavir boosted) plus an NNRTI and 1 or 2 new NRTIs . In a number of cohort studies lopinavir, enhanced with low dose RTV in combination with either EFV or NVP, reduced viral loads to below detectable limits in NNRTI naive, PI experienced patients [234, 235]. The primary reason for efficacy of ritonavir boosted PIs in patients who have experienced treatment failure to single PI based regimens is probably improved pharmacokinetics, resulting in higher plasma drug levels which are effective against low level increases in phenotypic resistance. There is some comparative data assessing which ritonavir boosted PI regimen is more effective and further data will be available from ongoing trials. Results of a head to head comparison of this lopinavir/RTV regimen with RTV/SQV will be available towards the end of this year [84]. The comparison between RTV-boosted SQV versus RTV-boosted IDV showed similar efficacy but significantly more toxicity in the IDV arm [85].

APV may retain activity after prior PI failure. From one study comparing the use of boosted APV with lopinavir in patients failing the other four licensed PIs, the viruses remained sensitive to APV in half to three-quarters of isolates from 108 patients [236]. However the virological outcome was slightly better in the lopinavir arm of this study.

7.2.2 Failure of two nucleoside analogues plus a non-nucleoside reverse transcriptase inhibitor [BIII]

No randomised strategic comparative study has addressed this issue. A PI-based regimen improves the clinical outlook after NRTI therapy [237] and is likely to do so after 2NRTIs and an NNRTI. Most physicians would treat virological failure of this type of regimen by discontinuing the NNRTI, and guided by resistance testing change the two NRTIs and add a boosted PI component.

7.2.3 Failure of triple nucleoside analogue therapy [BIV]

There are too few clinical data to guide the optimal regimen to use following virological failure of a triple NRTI regimen. The number and pattern of genotypic mutations in the reverse transcriptase gene will determine the extent of cross resistance amongst the NRTIs and whether 2 active and potent NRTIs could be included in the new regimen. If there is limited cross resistance then an option is to switch to a regimen comprising two new NRTIs plus a ritonavir boosted PI or a NNRTI. If

the likelihood of cross resistance amongst the NRTIs is high a more effective option would be to switch to a regimen comprising both a PI (preferably ritonavir boosted) and a NNRTI with new NRTIs.

7.3 Patients whose therapy fails having used at least three classes of drugs ("salvage therapy")

The term salvage therapy is commonly by both physicians and patients, but is not always clearly defined. One possible definition is treatment following exposure to multiple drugs from all available classes of antiretroviral agents, yet many so-called 'salvage studies' have been carried out in patients who are naive with respect to one class of drugs. Moreover, this definition of salvage becomes a moving target as more classes of drugs (e.g. fusion inhibitors) become available.

The reasons for drug failure are complex. To date, most studies of therapy after more than one treatment failure have not distinguished between virological failure due to poor adherence and failure due to other causes, such as poor pharmacokinetics. Individuals who have been poorly adherent to therapy but have not developed resistant virus may be effectively treated if adherence is improved. Enhanced adherence counselling and directly observed rather than self-administered therapy result in significantly better surrogate marker responses, demonstrating the importance of adherence [238, 239]. Low blood levels of PIs, either because of poor absorption or unforeseen pharmacokinetic interactions, may also lead to failure without the development of resistance to PIs.

7.3.1 Criteria for success in patients exposed to multiple drug classes

Suppressing viral load to below detectability (ie to below 50 copies/mL) at 24–48 weeks has become an accepted measure of success in antiviral therapy. This criterion may not be useful in determining success in highly antiretroviral experienced patients in whom the potency of subsequent regimens is attenuated because of the presence of resistant virus. However, data from a number of large clinical endpoint studies, mainly in treatment naive patients, show that much more modest declines in viral load correlate with improvements in clinical outcome. Viral load reductions of greater than 0.5 log10 copies/mL may be responsible for clinical improvement and may imply that such a regimen is worth pursuing [16, 29].

Many salvage studies have been of short duration with little follow-up data, making it difficult to judge whether or not any viral suppression will be maintained over the long term. In late disease, the immediate risk of death is much more closely associated with the CD4 count than with the viral load and thus, perhaps, a more important criterion in salvage studies is the degree to which the CD4 count rises.

7.3.2 Principles of optimizing success in highly treatment experienced patients

Despite these difficulties, both cohort and clinical controlled studies identify a number of general principles to consider when deciding upon a salvage regimen. First, success is most likely if individuals are naive to one class of drugs. It seems to be particularly important to give these agents whenever possible as part of a fully suppressive regimen to avoid the rapid emergence of resistance. New classes of drugs such as fusion inhibitors [240] are being introduced prior to licensing by expanded access and named patient programmes; such drugs may be used together in salvage patients to optimize the chance of success or in combination with drugs from pre-existing classes to which resistance has not been demonstrated.

Second, improved outcome is more likely with the use of drugs within classes to which the patient has not been exposed and to which resistance is unlikely or proven to be absent.

Third, therapy is more successful at reducing the viral load to undetectable levels in those who commence at a lower viral load (e.g. <5000–10,000 copies/mL). This has been attributed to an accumulation of additional mutations within the viral population in those who continue on failing therapy with a high viral load, which increases the likelihood of cross-resistance to new agents tried subsequently. Additionally, the potency of new regimens may be sub-optimal but enough to suppress low viral loads.

Fourth, resistance testing is strongly recommended in all cases where there are difficult choices to make concerning the most beneficial treatment. A number of retrospective and prospective studies demonstrate that responses to drugs in failing regimens can be predicted by genotype or

phenotype. These tests are clearly useful at first failure [164, 241, 242], and although data on patients with subsequent failure has been conflicting [243, 244] they can give useful information regarding which drugs may give some benefit. A resistance result suggesting that the virus remains sensitive to a particular drug does not guarantee a long term response, as drug exposure history and previous resistance test results are important factors.

Finally, plasma drug concentrates may influence therapy outcome. The Viradapt study [245] demonstrated the best virological response in patients who had optimal drug concentration as well as genotyping to guide future choices. The use of TDM and the relationship of drug levels to the viral inhibitory concentration of 50% (IC5O) have led to the theoretical possibility of optimizing drug levels for a particular patient's dominant viral strain [246].

7.3.3 Management of patients with multiple class resistance

A number of approaches have been tried in this situation. These include stopping therapy long term, using new drugs (see section 8) and treatment intensification, which has a limited use at any stage of virological failure and is not generally recommended.

Although responses in viral load are likely to be very small when using a drug to which the virus is resistant, it is possible that using a number of such drugs together might have a cumulative benefit which outweighs the potential toxicity [247]. Varying success has been reported by combining five or more drugs [248], so-called mega-HAART or giga-HAART [249], despite resistance to many of the individual components. A number of small cohort studies have reported successful maintenance of the viral load below 400 copies/mL for up to 2 years in individuals exposed to all three classes of drugs [250] using a mega HAART approach. Such studies are difficult to analyse and, in the long term, toxicity is likely to outweigh benefit. Although the regimens contain multiple drugs, drug adherence was often relatively good in these studies, partly because the drugs were taken only twice a day.

While we are waiting for new drugs to be made available, it appears best for patients to be maintained on some form of antiretroviral therapy rather than have a prolonged treatment interruption with its associated rise in viral load, drop in CD4 count and potential for disease progression [251, 252]. This type of strategy probably relies on the poor fitness of a virus with multiple mutations to maintain the status quo.

A possible alternative strategy for managing patients who have failed treatment with HIV resistance to multiple drugs is the use of STI to allow drug sensitive virus to outgrow and replace resistant virus, with the hope of enhancing responses to subsequent therapy. Unfortunately, resistant virus that had previously evolved may re-emerge during subsequent therapy despite STI. There can be an immunological price to pay for STI. In 22 heavily experienced patients, after a median STI of 20 weeks, there was a mean CD4 decrease of 88 cells/mm^3 and three patients developed opportunistic infections. After restarting a new salvage regimen, most patients increased their CD4 counts to the pre-STI level [253]. With STI, the short term risk of a fall in the CD4 count and the development of OIs does not appear to be balanced by any long term benefit, but this is being evaluated in the OPTIMA study.

In those patients who have other antiretroviral options then we would not recommend a structured treatment interruption. In these patients structured treatment interruption may lead to an increase in the rate of progression to AIDS and large falls in CD4 counts, which may not be regained for up to 48 weeks after restarting treatment [254].

In those patients who have no obvious treatment options then the ANRS study [254] of an 8 week interruption followed by GIGA HAART using minimum of seven drugs appears to give an advantage at 48 weeks in term of surrogate marker responses over those patients who did not have a structured treatment interruption. The median baseline CD4 count was only 25 cells in this study. Tolerability was a problem with just under half the patients remaining on treatment at 1-year, but there were reasonable virological benefits from this. T20 was not used in this study. In conclusion, STI can be considered for patients without other reasonable options but may lead to disease progression and should be restricted to carefully controlled research settings wherever possible.

7. 3.4 Recommendations for subsequent virological failure (third or more regimen) [BIII]

Assess reasons for failure. Test for genotypic resistance: a phenotypic assay or virtual phenotype may be necessary if the genotype assay is difficult to interpret.

Change as many drugs as possible.

Introduce a new class of drugs if possible, but not if the chance of success by combining a new class with other drugs is small. It may be better to defer a change until new treatment options are available.

STI is not recommended as standard care. It needs to be evaluated in clinical trials.

Mega-HAART or recycling of NRTIs may be of value to some patients. Consider stopping all drug treatment if toxicity outweighs any likely benefit.

A viral load <50 HIV-1 RNA copies/mL may not be possible and a significant reduction in the viral load and an increase in the CD4 count are more achievable goals.

8.0 New therapies

Particular emphasis is given below to drugs which are likely to be available within the coming year, but clinicians should be aware that a number of other new drugs are also in development, including tipranavir, TMC114, capravirine and TMC-125. As new information emerges, it may influence decisions on when to maintain patients on existing failing regimens while awaiting these new drugs.

8.1 Enfuvirtide (T20)

T20 (enfurvirtide) is a 36 amino acid peptide derived from HIV GP41. It inhibits GP41 mediated fusion and its active in nanomolar ranges in T-cell lines. It is active against NSI and SI viruses and is synergistic with reverse transcriptase inhibitors, PIs and other entry inhibitors. It is self-administered by subcutaneous injection, the usual dose being 90 mg twice daily. So far it shows no cross-resistance with other antiretroviral classes. It is active against wild-type and virus resistant to the three currently available classes of antiretrovirals. Because it works extra-cellularly it has a low potential for both drug/drug interaction and for any interaction with cellular metabolic processes. Its activity is independent of co-receptor usage. T20 is a large molecule with a total of 106 separate steps in its manufacture.

In the TORO 1 and TORO 2 studies, the T20 group had a 0.93 $\log_{10}$ and a 0.78 $\log_{10}$ advantage in viral load drop compared with the optimised background alone in individuals with triple class experience. In the Toro 1 study, patients previously naive to lopinavir were more likely to achieve good outcomes, illustrating the importance of combining T20 with other new drugs wherever possible.

The most common side effect of T20 are injection site reaction, which they can last up to a week or even longer. Some patients found keeping, preparing and giving injections difficult.

Resistance to T20 does occur. Most of it is around a specific motif from amino acid 36 to 45 in the binding area of GP41. However the relevance of these changes to the phenotypic changes have yet to be elucidated.

It seems inappropriate to use the drug as an add-on for patients failing therapy as resistance may occur rather rapidly. However, there may be situations where patients are extremely advanced with very poor prognosis where the addition of T20 might be seem suitable to produce a viral load drop, which may be translated into a clinical benefit allowing time for the availability of new compounds to enter the clinical arena

8.2 Atazanavir

The protease inhibitor atazanavir is an azopeptide, which is either additive or synergistic in combination with other antiretrovirals. Its oral bioavailability is between 57-80%, its half-life is 4-7 hours and it is 86% protein bound. Blood levels are enhanced by a boosting dose of RTV. Atazanavir's PK profile supports once daily dosing with food and the normal dose is 400mg (2 tablets) a day. The major side effect is an increase in unconjugated bilirubin, which is dose-dependent and is related to drug plasma levels and the patient's glucoronidation enzyme genotype. The numbers of patients who have discontinued because of hyperbilirubinaemia have been small. The BMS 007 study compared three different doses of atazanavir with NFV, and showed that atazanavir had very little affect on lipids but led to a VL drop of just over 2 log [255, 256].

The BMS 008 study randomised patients to either 400 or 600 mg of atazanavir versus NFV for 48 weeks [257]. For all three arms, viral load drops to week 48 were 2 _ log10 and CD4 rises were over 200 cells/mm3. The major differences seen in the study were that the atazanavir arms had little affect on total cholesterol and triglyceride compared with NFV. In [258] atazanavir was compared with EFV in a randomised double blind controlled trial in naive patients with HIV RNA greater than 2000 copies/ml and a CD4 count greater than 100 cells/mm3. In this large multinational study both arms had a similar less than 400 copies/ml end point at 64 and 70% on intent to treat analysis with 32% and 37% achieving less than 50 copies/ml.

Atazanavir may be an attractive drug either in first line use or in first line PI use because of its once a day formulation and because of its freedom from lipid abnormalities. Its role in subsequent therapy and salvage is less clear but RTV boosting may be needed for optimal activity [259].

8.3 Extended release stavudine (D4T)

Extended release (XR) stavudine can be taken once a day and has been compared with the standard twice-daily immediate release (IR) capsules in a randomised double blind placebo control trial of 797 treatment naive subjects [260]. The study showed similar antiviral and immunological profiles in those on extended release compared to those receiving the standard formulation. Discontinuations due to adverse events were 4% in both arms but grade 2 peripheral neurological symptoms were reported in 3% of XR and 5% of the IR subjects.

8.4 Emtricitabine (FTC)

FTC emtricitabine is a fluorinated cytidine analogue similar to lamivudine (3TC) and is also suitable for once a day dosing. In a double blind study 571 treatment naive patients were randomised to receive either daily FTC or twice daily stavudine with open labelled ddI and efavirenz. After a mean follow up of 42 weeks, 81% of the FTC containing arm had undetectable viral load (less than 50 HIV RNA copies/ml) compared with 70% of the D4T treated patients. The increase in CD4 count was significantly higher in the FTC arm, mean 152 cells/mm3 compared with the stavudine mean 117 cells/mm3 and the FTC was well tolerated [261].

8.5 Tenofovir

Although the European license for tenofovir has recently been extended to cover its use in first line therapy, it has been included in this section as many clinicians will only have used this drug in patients whose previous therapy has failed and it has not been reviewed in detail in previous guidelines. Tenofovir is a nucleotide, being a mono-phosphorylated thymidine derivative. The original studies leading to the licensing of this compound showed that in treatment-experienced patients with failing therapy, the addition of tenofovir produced approximately a 0.7 log reduction in viral load which was sustained for a number of months [233]. The number of additional patients who achieved virological undetectability as a result of this treatment intensification was 22% at 24 weeks.

Subsequently a short term monotherapy study [262] indicated that tenofovir was highly active in treatment naive patients, producing a mean viral load drop in excess of 1.6 log over a 21 day treatment period. The pivotal study which has led to licensure of tenofovir in Europe for the treatment of patients who have not previously had antiretroviral therapy was a study in which tenofovir/3TC/EFV was compared with d4T/3TC/EFV [74]. High levels of undetectability by a 50 copy viral load assay were obtained for up to 96 weeks using either treatment regimens, with a lower rate of investigator-defined lipodystrophy, lipid abnormalities and other side effects related to

mitochondrial toxicities in the tenofovir treated group. Tenofovir has the advantage of being given once a day, and in the treatment naive study did not produce significant side effects. Individuals with a creatinine clearance of <60ml/min or baseline creatinine >136 □ mol/l were excluded from this study as *was* the use of concomitant potentially reno-toxic medication. As tenofovir is secreted by the renal tubules as a result of transport by the organic anion transporter (OAT 1) and as a sister compound, adefovir, produced significant renal toxicity, caution should continue to be exercised about the use of concomitant potentially reno-toxic medication when this drug is used. Rare reports of reno-toxicity, possibly associated with tenofovir, have occurred as increasing clinical experience with tenofovir has developed. However, potential lack of mitochondrial toxicity and the once a day use and the excellent surrogate marker results obtained in the pivotal study all indicate that this drug may rapidly become the treatment of first choice in combination with other drugs which can also be used once a day, provided the safety profile continues to be satisfactory and there are no unexpected drug interactions which limit its versatility.

8.6 Fosamprenavir

Fosamprenavir is a pro-drug of APV. The parent drug was associated with considerable gastrointestinal side effects, particularly in the first few weeks of its use. These side effects are reduced in the pro-drug preparation. The levels of fosamprenavir are boosted by the concomitant use of RTV. In the main registrational study [263] fosamprenavir boosted with RTV given once a day was compared with NFV. The proportion of patients undetectable using either at the 400 copy or the 50 copy assay were similar at 48 weeks. In a smaller study in which unboosted APV was compared with NFV, superior virological results were obtained with APV [264]. In a treatment-experienced study [265], patients with treatment failure on one or two previous PIs were given either lopinavir boosted *with* RTV or APV, also boosted with RTV, and were compared using the area under the curve of the viral load fall minus baseline. Although the outcome between the two drugs was similar, there was a tendency for the undetectability rates to be higher in the lopinavir arm. The degree of lipid abnormalities induced by APV boosted with RTV and the gastrointestinal abnormalities were comparable with those seen with NFV. NFV is less used now as part of initial PI containing regimes and comparisons are not presently available between boosted APV and NNRTI containing regimes or other more currently favoured boosted PI regimens.

Tables

Table 1
Basic net NHS costs of antiretroviral drugs[1]

Drug	Tablet/capsule size	Quantity/day	Price/30 days
Abacavir (ABC, Ziagen®)	300 mg	2	£238.50
Amprenavir[2] (APV, Agenerase®)	150mg	16	£510.00
Amprenavir[2] (APV, Agenerase® - boosted dose)	150mg	8	£255.00
Didanosine[3] (DDI, Videx®)	200 mg	2	£176.00
Efavirenz (EFV, Sustiva®)	600 mg	1	£224.09
Indinavir (IDV, Crixivan®)	400 mg	6	£205.71
Lamivudine (3TC, Epivir®)	150 mg	2	£163.59
Nelfinavir (NFV, Viracept®)	250 mg	10	£321.37
Nevirapine (NVP, Viramume®)	200 mg	2	£168.00
Ritonavir (RTV, Norvir®)	100 mg	6	£404.35
Ritonavir (RTV, Norvir® - booster dose)	100 mg	2	£67.39
Saquinavir (SQV SGC, Fortovase®)	200 mg	18	£313.02
Saquinavir (SQV HGC, Invirase® - boosted dose)	200 mg	10	£321.37
Stavudine[3] (D4T, Zerit®)	40 mg	2	£184.26
Tenofovir (Viread®)	245 mg	1	£255.00
Zalcitabine (DDC, Hivid®)	750 □g	3	£136.41
Zidovudine (ZDV, Retrovir®)	250 mg	2	£179.00
Combination formulations:			
Lamivudine/zidovudine (Combivir®)	150/300 mg	2	£342.58
Lopinavir/ritonavir (Kaletra®)	133.3/33.3 mg	6	£332.31
Abacavir/lamivudine/zidovudine (Trizivir®)	300/150/300 mg	2	£581.08

1: Source: British National Formulary 45 (March 2003).

2. Lower doses apply for adults under 50 kg.

3. Lower doses apply for adults under 60 kg.

Table 2

Grading of recommendations and levels of evidence	
Recommendation	**Quality of evidence for recommendations**
A: Required, should always be followed B: Recommended, should usually be followed C: Optional	(I) At least one randomized trial with clinical endpoints (II) At least one randomized trial with surrogate markers (III) Observational cohort data (IV) Expert opinion based on other evidence

Table 3

Recommendations for starting treatment		
Presentation	Surrogate markers	Recommendation
PHI		Treatment only recommended in a clinical trial, or if severe illness (CIV)
Established infection	CD4 <200, any viral load	Treat (AI)
	CD4 201-350	Start treatment, taking into account viral load (BIII), rate of CD4 decline (BIII), patient's wishes, presence of hepatitis C (CIV)
	CD4 >350	Defer treatment (BIII)
Symptomatic disease or AIDS	Any CD4 count or viral load	Treat (AI)

Table 4

Initial HAART regimens

Choices of initial therapy: summary of recommendations

Regimen	Recommendation	Advantages	Disadvantages
2NRTIs + NNRTI*	Recommended	1. Equivalent or superior in surrogate marker trials compared with PI based regimens at 104 weeks of follow-up 2. Easier adherence	1. No RCT clinical endpoint data 2. Shorter follow-up 3. Single mutations may lead to cross-class resistance
2NRTIs + boosted PI‡	Recommended	3. Evidence of improved surrogate endpoint efficacy for lopinavir/ritonavir compared with a single PI 4. Better PK 5. Easier adherence 6. Less resistance at virological failure	4. No RCT clinical endpoint data 5. Possible increased toxicity and drug interactions
3 NRTIs	Not ordinarily recommended except for patients with low VL and major adherence concerns, but see section 4.2.3.	7. Spares PI and NNRTI classes 8. Fewer drug interactions 9. Low pill burden	1. No RCT clinical endpoint data 2. Short term surrogate marker data suggests less potent than NNRTIs or PIs 3. Is less effective at high viral loads

*Recommended NNRTIs are efavirenz or nevirapine.

Table 5

Currently available non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
NNRTI	Dose/frequency	Daily pill burden	Dietary restrictions	Major side effects
Efavirenz	600 mg once daily*	1 tablet	None	CNS effects, hepatitis CI: pregnancy
Nevirapine†	200 mg twice daily or 400 mg once daily	2 tablets	None	Rash, hepatitis, Stevens-Johnson syndrome
CNS = central nervous system; CI = contraindication				
*Take at night				
†The initial dose is 200 mg/day for 2 weeks, increasing to 400 mg/day.				

Table 6

Currently advised protease inhibitors (PIs) for initial therapy				
PI	Dose/frequency	Daily pill burden	Dietary restrictions	Major side effects
Ritonavir/saquinavir HGC†	100/1000 mg twice daily	12 capsules	Within 2 hours following a meal	Diarrhoea, nausea, bloating
Ritonavir/saquinavir HGC†*	100/1600 mg once daily	9 capsules	Within 2 hours following a meal	Diarrhoea, nausea, abnormal lipids
Ritonavir/lopinavir	3 capsules twice daily	6 capsules	With food	Diarrhoea, nausea, abnormal lipids
†Pharmacokinetics for RTV/SQV soft gel capsules are equivalent to hard gel capsules [266].				
*This dosage schedule is unlicensed in Europe.				

Table 7

Routine tests and examinations in the HIV patient[1,2]			
Test	**Newly diagnosed patient**	**Untreated patient**	**Treated patient**
HIV viral load	✓	2-4/year	After treatment initiation, at months 1 and 3, then 4/year
CD4 cell count	✓	2-4/year	4/year
Complete blood count	✓	2-4/year	4/year
Biochemical profile including CPK, liver and renal function	✓		4/year
Lipid profile[3]	✓		4/year
Glucose[3]	✓		4/year
Serology: HAV[4], HBV surface antigen, core antibody, HCV, VDRL, TPHA (syphilis IgG if available), toxoplasmosis (IgG), CMV (IgG)	✓	Re-test yearly if negative at outset	Re-test yearly if negative at outset
Chest X-ray	✓ As baseline		
Dilated fundoscopy[5]	If CD4 <100	2-4/year if CD4 <100	2-4/year if CD4 <100

1. For HIV resistance testing recommendations, [see 5.4.1].
2. These and other tests to be additionally performed when clinically indicated.
3. If raised, do fasting
4. If no previous vaccination
5. To be performed by a competent individual – refer if necessary. There is no data on which to base a recommendation on what level of CD4 should prompt routine fundoscopy, but 100 cells/mm^3 is a reasonable consensus.

Table 8

Meta-analysis of trials of HIV resistance testing [175]		
	Proportion of patients with viral load undetectable at 3 months (based on analysis of 6 trials [refs])	**Proportion of patients with viral load undetectable at 6 months (based on analysis of 4 trials [refs])**
Genotype testing against standard of care (SOC)	42.6% v 33.2% (OR 1.7)	38.8% v 28.7% (OR 1.6)
Phenotype testing against SOC	37.5% v 33.8% (OR 1.1)	
Genotype testing plus expert advice against SOC		50.7% v 35.8% (OR 2.4)

Table 9

Proposed indications for therapeutic drug monitoring (TDM)		
Indication	**Recommendation**	**Rationale**
Routine use	Insufficient (CIII)	Studies are urgently required, particularly given the large inter-individual variability and significant minority of patients in clinic who may have sub-optimal drug exposure. TDM may be considered where a drug is being used outside doses recommended in the manufacturer's Data Sheet, or where drug interaction data are lacking.
Virological Failure	Limited (CIII)	TDM is of little value once high level antiviral resistance has developed. TDM may be considered when treatment intensification is an option (e.g. suboptimal viral load response early in a new regimen), when viral resistance testing suggests that resistance is unlikely or to overcome a low level virological rebound.
Monitoring adherence	Limited (CIII)	The half-life of most PIs is relatively short even with RTV. Near/complete absence of detectable drug in plasma is a good indicator of poor adherence. Sub-therapeutic levels are of limited usefulness except on a background of repeatedly optimal concentrations. An adequate or high plasma drug level only provides information about adherence to the preceding few doses rather than over the long term.
Drug interaction	Recommended (BIII)	PIs and NNRTIs are extensively metabolized by cytochrome P450 3A4 and other CYP isoenzymes. Not only may they affect the metabolism of other drugs that share the same metabolic pathway, but they may themselves be affected by those drugs. Individual drug interactions are beyond the scope of this discussion and are found elsewhere (e.g. http://www.hiv-druginteractions.org). Drug interactions are increasingly difficult to predict, especially with multiple drugs which have direct and indirect interactions with each other. TDM could be considered in these situations, e.g. PI(s) + NNRTI with/without other inducer/inhibitor of

		CYP3A4.
Children	Recommended (BIII)	Useful in children aged < 2 years and may also be considered in those aged 2–5 years on PIs/NNRTIs. Neonates and very young children have liver function, metabolic rates and apparent volumes of drug distribution that differ from adults, and which alter as they grow. Underdosing of infants is not uncommon.
Minimizing toxicity	Consider (CIII)	Many toxicities e.g. rash / hypersensitivity are idiosyncratic and probably not related to plasma drug concentrations. TDM may be useful for dose-related toxicities including urological (renal colic, haematuria and dysuria) symptoms (IDV), hepatotoxicity (NVP), gastrointestinal intolerance (RTV C_{max}). TDM is possibly useful with CNS symptoms (EFV) and high lipids (LPV, RTV). Most importantly, TDM may be utilised to allow dosage reduction in patients who are most at risk of drug toxicity because of previous intolerance, concurrent medication with overlapping toxicities or other pre-existing disease.
Liver impairment	Recommended (BIII)	Recommended with severe liver impairment, or where there is evidence of abnormal liver function tests. It is reasonable to consider TDM in HCV co-infected patients with pre-existing abnormal LFTs receiving NNRTIs.
Malabsorption	Recommended (BIII)	Consider with chronic gastrointestinal disease e.g. cryptosporidiosis or other evidence of malabsorption.
Once-daily regimens	Consider (CIII)	Once-daily boosted PI regimens containing SQV, NFV, IDV, LPV and APV may not be sufficiently robust in some patients.

Table 10

Potential objectives of structured treatment interruptions (STI) in different clinical settings

Potential objectives of STI	Setting
Enhance immune responses	Acute infection
	Chronic infection
Limit drug toxicities	Acute infection
	Chronic infection
	Treatment failure
Repopulate with wild type virus	Chronic infection with treatment failure

Table 11

Changing therapy on first virological failure [BIII]		
Presentation	**Viral load pattern**	**Recommended action**
Inadequate virological response to initial regimen	Failure to achieve VL < 50 copies/ml	Consider factors affecting plasma drug levels[1]. If drug exposure optimal and likelihood of resistance low, consider augmenting treatment regimen. If likelihood of resistance high, consider changing all drugs
Persistent viral load rebound where previously < 50 copies/ml	Viral load >50 and <400 copies/ml	Consider factors affecting plasma drug levels[1].
	Sustained viral load rebound to >400 copies/ml[2]	Consider: 1. Changing all drugs if effective option available likely to reduce viral load to undetectable levels 2. Continue regimen and monitor if no effective option currently available for reasons of drug potency, likely poor adherence or tolerability[3].

1. Factors affecting plasma drug levels include poor adherence, intolerability, drug interactions and incorrect dosing.
2. A viral load rebound to >1,000 copies/ml will allow resistance testing to be performed. Resistance testing with expert interpretation has been shown to have a benefit on short term virological response to the subsequent regimen.
3. There is a risk of developing further mutations by allowing a patient to remain on a virologically failing regimen, which could limit further options for treatment.

Table 12

What to change to after first virological failure: summary of recommendations [BII/IV]

- Change all drugs if possible
- Resistance test recommended

Initial regimen	Options to consider
2NRTIs + PI	2NRTIs[1,2] + NNRTI or 2NRTIs[1] + boosted PI[3] or 2NRTIs[1] + NNRTI[4] + boosted PI
2NRTIs + NNRTI	2NRTIs[1] + boosted PI
3NRTIs	2NRTIs[1,2] + NNRTI or 2NRTIs[1] + boosted PI or 2NRTIs[1] + NNRTI[4] + boosted PI

1. Change to 2 new and active NRTIs guided if possible by resistance testing.
2. This could lead to rapid development of resistance to NNRTIs if the potential exists for extensive NRTI cross-resistance.
3. Low does ritonavir boosted PI should be considered if primary reason for failure is poor adherence or pharmacokinetics (resistance to PIs will often not be found on testing).
4. Studies with low dose ritonavir boosted PI + an NNRTI have shown good results.

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Conflict of interest

The Writing Committee are conscious of the importance that should be attached to the guidelines being written by individuals with no financial ties to the pharmaceutical industry. However, in the context of HIV, most active researchers and major prescribers of antiretrovirals do have such connections and we believe that for the present full disclosure of such financial relationships guards against the possibility of bias.

Jane Anderson has links with Bristol-Myers Squibb (Advisory group and speaker) and GlaxoSmithKline (speaker, member of Embrace strategy group).

Simon Collins works for HIV i-Base, which has received funding including grants towards conference attendance from Abbott Laboratories, Boehringer-Ingelheim, Bristol-Myers Squibb, DuPont, GSK, Gilead Sciences, Merck Sharp & Dohme and Roche.

Dr Duncan Churchill has sat on advisory panels for, received sponsorship to attend scientific meetings from, or acted as a paid speaker for: Bristol-Myers Squibb, GSK, Merck Sharp & Dohme, Gilead Sciences, Boehringer Ingelheim, DuPont, Abbott Laboratories, and Roche.

Dr Hilary Curtis is paid by BHIVA for editing these guidelines, conducting clinical audit and other editorial work.

Dr Martin Fisher is an adviser to or receives research/educational funding from the following companies: Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, GSK, Gilead Sciences, Roche.

Professor Brian Gazzard has been paid for speaking engagements, has been paid for advice or has had research grants from the following pharmaceutical companies: GSK , Bristol-Myers Squibb, Abbott Laboratories, Boehringer Ingelheim, Gilead Sciences, Johnson & Johnson.

Dr SH Khoo has received research and travel grants from GSK, Roche, Gilead Sciences and Bristol-Myers Squibb and consulting agreements with Bristol-Myers Squibb and Vertex. Therapeutic drug monitoring for HIV drugs in the UK is supported by GSK, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, and Abbott Laboratories.

Dr C Leen has received unrestricted research and travel grants, honoraria for lectures and/or consultancy advice from various pharmaceutical companies including Abbott Laboratories, Agouron, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, GSK, and Roche. He has at some time been a member of the UK medical advisory boards of Abbott Laboratories, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, GSK and Roche.

Professor Clive Loveday is the Clinical Director of the International Clinical Virology Centre (ICVC; a registered charity no. 1091046). The charity has received grant awards from Roche Molecular Systems, GSK, Bayer Diagnostics, Abbott Diagnostics, MRC and EU. Professor Loveday is not currently a consultant , a share-holder, or in receipt of an honorarium from any company.

Dr Graeme Moyle has consultancy agreements, acts as speakers bureau, or has research grants from the following companies: Bristol Myers Squibb, Glaxo SmithKline, Merck Sharp and Dhome, Gilead Sciences, Boehringer Ingelheim, Johnson & Johnson, Vertex pharmaceuticals,Abbott, Agouron pharmaceuticals (a division of Pfizer), Pfizer, TriPEP pharmaceuticals, Aventis, Roche pharmaceuticals and Serono.

Dr Mark Nelson has been paid for speaking engagements, sat on advisory boards or received educational grants from: Merck Sharp & Dohme, Roche, GSK, Bristol-Myers Squibb, Abbott Laboratories, Gilead Sciences, Virco, Virologic and Chiron.

Dr Deenan Pillay is or has been a paid advisor to Bristol-Myers Squibb, GSK, Gilead Sciences and Roche, and his laboratory has been funded by educational grants.

Dr Anton Pozniak has received educational and travel grants, as well as speaker and consultancy fees and honoraria from: GSK, Roche, Boehringer Ingelheim, Bristol-Myers Squibb, Abbott Laboratories, Gilead Sciences.

Dr Ian Williams within the last two years has, through his employers University College London, received research grants from Agouron, Roche and Gilead Sciences and unrestricted educational and travel grants for conference attendance from Roche, Bristol-Myers Squibb and Gilead Sciences; been a member of UK Medical advisory boards for Bristol-Myers Squibb, Abbott Laboratories, Roche, Gilead Sciences and Johnson and Johnson and participated in industry sponsored symposia and educational events for which both he and his employers University College London have received honoraria.

Dr Mike Youle accepts speaking engagements on behalf of various pharmaceutical companies.

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