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BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008

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1.0 Introduction

The 2008 BHIVA Guidelines have been updated to incorporate all the new relevant information (including presentations at the 15th Conference on Retroviruses and Opportunistic Infections 2008) since the last iteration. The guidelines follow the methodology outlined below and all the peer-reviewed publications and important, potentially treatment-changing abstracts from the last 2 years have been reviewed.

The translation of data into clinical practice is often difficult even with the best possible evidence (i.e. two randomized controlled trials) because of trial design, inclusion criteria and precise surrogate marker endpoints (see Appendix). The recommendations based upon expert opinion have the least good evidence but perhaps provide an important reason for writing the guidelines to produce a consensual opinion about current practice. It must, however, be appreciated that such opinion is often wrong and should not stifle research to challenge it.

Similarly, although the Writing Group seeks to provide guidelines to optimize treatment, such care needs to be individualized and we have not constructed a document that we would wish to see used as a 'standard' for litigation.

2.0 Methodology

2.1 Basing recommendations on evidence

The Writing Group used an evidence-based medicine approach to produce these guidelines. In reality, if only the most reliable form of clinical evidence were 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. Many trials have been performed in order to obtain licensing approval for a drug. In many cases, they are the only source of evidence for comparing two drug regimens. However, the designs are not ideally suited to addressing questions concerning clinical use. 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 [1,2]. Expert opinion forms an important part of all consensus guidelines; however, this is the least valuable and robust form of evidence.

2.2 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 controlled clinical 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 [3].

2.3 Use of surrogate marker data

CD4 cell counts and plasma viral load are used as markers of the effect of antiretroviral therapy (ART). Reduction in viral load leads to a rise in peripheral blood CD4 cell count, with greater rises being seen in those with greater and more sustained viral suppression [4]. Changes in these markers in response to therapy are strongly associated with clinical response [5–9]. CD4 cell counts measured in people on ART have been associated with a risk of AIDS-defining diseases no higher than that expected in untreated individuals with similar CD4 cell counts [10–13]. The CD4 cell count is a better indicator of the immediate risk of AIDS-defining diseases than the viral load in those on ART [14,15]. However, it should be remembered that CD4 cell count and viral load responses do not precisely reflect the expected clinical outcome and are not perfect surrogates of the clinical response [9,16,17].

This is because the drugs have other effects with clinical consequences besides those reflected in viral load and CD4 cell count changes. Even so, for patients with a given CD4 cell count and viral load, the risk of AIDS disease appears to be similar, regardless of the specific antiretroviral drugs being used [18]. The relatively short length of trials designed to obtain drug approval means that, at the time of licensing, little is known about the long-term consequences of a drug.

2.4 Issues concerning design and analysis of clinical trials

2.4.1 Trial designs

As stated above, 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 and a description of what those new regimens are. The results are, therefore, only clearly interpretable as long as a very 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 following patients despite changes to the original treatment. Such changes in regimen are common in real-life practice and so, from a clinical perspective, it makes little sense to ignore what happens to patients after a specific regimen has been discontinued. The 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 that overlap with those caused by other drugs. However, interpretation of such longer term trials is not straightforward, and account must be taken of which drugs were used subsequent to the original regimen in each arm.

The Writing Group 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.

2.4.2 Viral load outcome measures

In most efficacy trials, treatments are compared in terms of viral load as defined by plasma HIV RNA. Depending on the target population, the primary outcome measure may be defined to include the achievement of viral suppression below a certain limit (usually 50 HIV-1 RNA copies/mL) at a pre-specified time (e.g. 24 or 48 weeks after randomizations), time to viral rebound or time-weighted average change from baseline. To avoid selection bias, all enrolled patients must be included in an analysis comparing the treatments, and all in the group to which they were randomized, even if no longer taking the treatment they were allocated (the intent-to-treat principle). The inability to assess outcomes for some patients, leading to missing data, for example as a result of patient dropout before completion of the trial, is a potential source of bias. The frequency of and reasons for missing outcomes may be affected by many factors, including the efficacy of treatments, toxicity and the length of follow-up. Interpretation of the results of the trial is particularly problematic if a substantial number of patients drop out for reasons related to the outcome whether by design, as in many pharmaceutical industry trials where patients are withdrawn when they change their randomized treatment, or otherwise. This problem can be addressed at three levels: in the design, conduct and analysis stages of the trial. Changes in treatment during the trial must be anticipated and it is necessary to continue collecting data on all patients, even if they have switched from the original regimen, thus avoiding missing data by design and/or poor implementation. While several analytical methods have been published for handling missing outcome in clinical trials, all make assumptions that cannot be completely verified. Whichever method is used for handling missing outcomes at the analysis stage must be pre-specified in the protocol or the statistical analysis plan. When the outcome is the proportion of people with viral load below 50 copies/mL at a given time-point, the approach widely adopted is to

assign an outcome of failure to achieve a value below 50 copies/mL to all patients with missing outcome (and those who have switched from the randomized treatment, regardless of whether they remain under follow-up). This is known as the missing equals failure (MEF) approach [14–21]. This approach to missing outcome is used in trials for drug licensing because it considers anyone who has to stop the drug of interest as having failed and thus prevents any tendency for drugs used by a patient after the drug of interest has failed to influence the trial results. Such an approach implicitly equates failure of a regimen as a consequence of inadequate potency and/or viral drug resistance not only with the inability to tolerate a regimen compared with other possible approaches because of pill burden, inconvenience and/or adverse effects but also with assessments being missing for other reasons, including randomly missing visits, even though the implications of these various outcomes are likely to be substantially different. This approach is often labelled conservative compared with other possible approaches because it gives a minimum proportion of patients with viral load below 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 the reasons for missing outcomes may well differ between treatments. In this context, this approach is not conservative in any general sense and its indiscriminate use without consideration of its inherent limitations involves a degree of risk of bias that could be greater than simply ignoring missing values. For these reasons, trials that are conducted for purposes of licensing a particular drug, and which treat stopping of the drug as treatment failure and ignore outcomes occurring after the drug has stopped, do not always provide the type of information that is most useful for clinical practice.

In the past, trials have generally considered whether the viral load is below 50 copies/mL or not at a given time-point (e.g. 48 weeks). In recent years, the tendency has been to consider whether virological failure (or 'loss of virological response', usually defined as two consecutive values above 50 copies/mL) has occurred by a certain time-point, rather than whether the viral load at the time-point is below 50 copies/mL or not, as described above. In the (common) case where missing viral load values and switches in therapy are treated the same as values above 50 copies/mL, this approach uses a 'time to loss of virological response' (TLOVR) algorithm [20]. The two approaches will give similar but not identical results; for example, patients can fulfil the definition of loss of virological response before 48 weeks but then have a viral load value below 50 copies/mL at 48 weeks itself, without any change in regimen.

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 intent to treat includes outcomes for all randomized patients. So-called 'on-treatment' analyses consider outcomes only in those still receiving the original allocated treatment. Here, the difference between assessing the proportion with viral load below 50 copies/mL at a given time-point and assessing the proportion with viral load above 50 copies/mL by a given time-point becomes greater. In the context of an assessment of the proportion of people with viral load below 50 copies/mL at a given time-point, on-treatment analysis makes little sense because therapy has been switched in patients who experience viral load rebound during a trial, so the only patients who remain on the regimen are those with viral load below 50 copies/mL. Hence, all regimens that lead to a viral load below 50 copies/mL in at least one person should lead to a value of 100%, unless there are patients who have viral load above 50 copies/mL at the time-point but are yet to have their regimen switched. In contrast, an assessment of whether the viral load was above 50 copies/mL by a given time-point (i.e. time to virological failure or loss of virological response), which censors observation on patients once they have switched from the original randomized regimen, may be more revealing, but is still subject to potential bias.

2.4.3 Noninferiority

In contrast to superiority trials where the primary objective is to demonstrate that a new treatment regimen, or strategy, is more efficacious than a well-established treatment, the aim of a noninferiority trial is to show that there is no important loss of efficacy if the new treatment is used instead of the established reference. This is particularly relevant in evaluating simplification strategies where the new treatment strategy is better than the reference treatment in aspects other than efficacy, for example toxicity, tolerability or cost. A critical aspect of noninferiority trials is the judgement of what degree of possible loss of efficacy will be tolerated – the noninferiority margin (sometimes referred to as the delta). The choice of the noninferiority margin depends on what is considered to be a clinically unimportant difference in efficacy taking into account other potential advantages of the new treatment. To demonstrate noninferiority, large numbers of patients are usually required because of the need to exclude the possibility that there is even moderate loss of efficacy with the new treatment. The trial protocol must pre-specify the noninferiority margin (e.g. the proportion with viral load below 50 copies/mL at 48 weeks, in people receiving the new treatment, is not smaller than the same proportion in the reference treatment by more than 5%). As an

illustration of the interpretation of the results of noninferiority trials, we shall consider the case where the primary efficacy outcome is the proportion of participants with viral load below 50 copies/mL at 48 weeks. Conclusions on the noninferiority of a new treatment are then based on the lower confidence bound, which is the lower limit of the one-sided 95% (or sometimes 97.5%) confidence interval for the difference (new – standard) between the outcome for the new treatment and the outcome for the standard treatment. Noninferiority is indicated when this lower confidence bound for the difference between the two treatments excludes loss of efficacy greater than the pre-specified noninferiority margin. So, for example, if the proportion with viral load <50 copies/mL with the standard treatment is 85% and the corresponding proportion with the new treatment is 87%, then the observed difference in proportions (new – standard) is 2%. If the lower confidence bound of this difference is -8%, this can be interpreted as meaning that (within the appropriate level of confidence) the new treatment is at most 8% inferior to the standard treatment. If (and only if) our pre-specified noninferiority margin is 8% or above then this means we would conclude that the new treatment is noninferior to the standard.

If the proportions were instead 85% for the standard treatment and 79% for the new treatment, with a difference of -6% and lower confidence bound of -11%, then noninferiority of the new treatment could again be concluded if the pre-specified noninferiority margin was 11% or higher regardless of whether the observed difference of -6% was significantly different from zero; i.e. even if the proportion of participants receiving the new treatment with viral load <50 copies/mL was significantly lower than the corresponding proportion for the standard treatment. If, however, the pre-specified non-inferiority margin was less than 11% (e.g. 5%) and we obtained the same outcome data, then noninferiority would not be established even if the difference between the two treatments was not statistically significant. This illustrates the importance of a suitable choice of a noninferiority margin. These margins have tended to range from 10 to 15%, which seems high. The smaller the noninferiority margin, the stricter the test for the new treatment but the larger the sample size required.

It should be noted that finding that the response to the new treatment is not significantly inferior to that of the standard treatment in a significance test is not evidence for noninferiority. It is also important to note that a very high standard of trial conduct (e.g. minimizing violations of entry criteria, nonadherence to allocated regimens and loss to follow-up) is more critical in noninferiority than in superiority trials. Such deviations from the protocol would tend to bias the difference between the two treatments towards zero and thus increase the chance of erroneously concluding noninferiority.

Two frequently asked questions are:

- Can we infer superiority or inferiority of a new treatment from the results of a trial designed to establish its noninferiority to the standard treatment?
- What about inferring noninferiority of the new treatment on the basis of the results of a trial designed to demonstrate its superiority?

The answer to the first question is 'yes'. Conclusions of superiority (or inferiority) are based, not on the one-sided confidence interval as for noninferiority, but on the standard 95% two-sided confidence interval. If the proportion of patients with viral load <50 copies/mL with the standard treatment is 85% and the corresponding proportion with the new treatment is 91%, then the observed difference in proportions (new – standard) is 6%. If the 95% confidence interval for this difference is 1–11%, with the lower bound greater than 0, then this can be interpreted as demonstrating the superiority of the new treatment at the 5% level relative to the standard treatment in a straightforward way regardless of the value of the pre-specified noninferiority margin. If the proportions are instead 85% for the standard treatment and 76% for the new treatment, with a difference of -9% and a two-sided 95% confidence interval of -12 to -6%, then this can be interpreted as a demonstration of inferiority of the new treatment provided that the pre-assigned noninferiority margin is 6% or lower. If instead the pre-assigned noninferiority margin is 8%, inferiority is not established, notwithstanding the highly statistically significant lower efficacy of the new treatment, because an 8% difference has been defined *a priori* as a clinically unimportant difference. This again highlights the importance of pre-specifying a sufficiently low noninferiority margin truly reflecting the highest clinically nonsignificant loss of efficacy with the new treatment.

Finally, in answer to the second question, any inference about noninferiority from the results of a superiority trial would not be valid because the noninferiority margin cannot be assigned *post hoc* with knowledge of interim or final data from the trial.

2.4.4 Cross-study comparisons and 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. intent to treat *vs.*

on-treatment), degrees of adherence and sensitivities of viral load assays [22,23].

2.5 Adverse event reporting

Many previously unsuspected side-effects of ART have been reported only after drug licensing. It is vital that prescribers report any unsuspected adverse events as soon as possible so that these events are swiftly recognized. A yellow-card scheme, organized by the Medicines and Healthcare products Regulatory Agency, operates in the UK for reporting adverse events relating to the treatment of HIV (http://yellowcard.mhra.gov.uk).

3.0 When to start

3.1 Primary HIV infection

The rationale for treating with antiretroviral drugs in primary HIV infection is as follows:

(1) Preservation of specific anti-HIV immune responses that would otherwise be lost, and which are associated with long-term nonprogression in untreated individuals.
(2) Reduction in morbidity associated with high viraemia and CD4 depletion during acute infection.
(3) Reduction in the risk of onward transmission of HIV.

Multiple studies have shown conflicting results of therapy [24], with varying short-term effects on immunological markers, viral load and CD4 lymphocyte count. However, in order to make a firm recommendation, the results of a randomized prospective study are needed. The Medical Research Council (MRC) SPARTAC study is fully recruited and initial results are anticipated in 2010. In the meantime, treatment in primary infection (outside a prospective study) should only be routinely considered in those with:

- neurological involvement
- any AIDS-defining illness
- a CD4 cell count persistently <200 cells/μL (i.e. for 3 months or more).

3.2 Established HIV infection

Epidemiological data show that almost one-third of patients with HIV infection in the UK remain undiagnosed [25]. Furthermore, one-third when diagnosed already have a CD4 cell count below 200 cells/μL [25]. In addition, data from two national BHIVA audits have shown that almost two-thirds of patients have CD4 cell counts less than 200 cells/μL when therapy is first started [26]. It has been clearly shown that starting therapy with a CD4 cell count below 200 cells/μL is associated with a substantially greater risk of disease progression and death, and this risk persists for a significant period after treatment is started [27]. Thus the Writing Group believe that every effort should be made to start treatment before the CD4 cell count has fallen to less than 200 cells/μL.

Given that adherence to ART is critical to treatment success, and may be dependent on the patient's perception of the necessity for treatment, discussions regarding the relative advantages and disadvantages of starting treatment should ideally begin at an earlier stage, for example when the CD4 count falls below 500 cells/μL. Data from UK CHIC [28] indicate that, even in patients whose HIV infection is diagnosed relatively early, highly active antiretroviral therapy (HAART) has often not been initiated until the CD4 cell count has dropped below 200 cells/μL (the minimum CD4 count for initiation in the previous iteration of these guidelines). The reasons for this are likely to include the fact that patients and clinicians may both fail to start the sometimes lengthy process of preparing to initiate treatment early enough.

As a means of informing discussions with individual patients, Table 1 gives an estimate of the absolute risk of disease progression over the following 6 months if HAART is withheld or started. This highlights the fact that the absolute reduction in risk is greatest in those patients with a high baseline risk (i.e. those who are older, and who have a low CD4 cell count and high viral load). It is important to point out that these data do not capture serious non-AIDS events that may be in part preventable by earlier initiation of HAART [e.g. non-AIDS malignancies and cardiovascular disease (CVD)]. It may also be that patients who are at a high risk of CVD, for example ($>20\%$ over 10 years), are likely to benefit more from earlier treatment (Table 2).

Data from the SMART study [29] confirm the impression from previous cohort studies [30,31] that there is a continual gradient of increased risk of both death and disease progression associated with lower CD4 cell counts and no specific clear threshold at which risk increases. Furthermore, SMART has shown that untreated HIV infection is associated with greater risks of morbidity and mortality that have not previously been recognized to be HIV-related, including those attributable to non-AIDS-defining malignancies. In those individuals entering the SMART study who were either treatment-naïve or who had not been on therapy for the previous 6 months, the absolute risk of a new diagnosis of opportunistic disease or a serious non-AIDS event in the treatment deferral arm was 7.0 per 100 patient-years, compared with 1.6 in the virological suppression arm [32]. However, this also means that 14 patient-years of therapy were required to prevent one serious progression if treatment was started before the CD4 count fell below 350 cells/μL.

Table 1 Predicted 6-month risk of AIDS in antiretroviral therapy-naïve patients according to current age [(a) 25 years, (b) 35 years, (c) 45 years and (d) 55 years], CD4 cell count, viral load and whether antiretroviral therapy is initiated immediately or deferred

		Risk (%)									
		CD4 count (cells/μL)									
Treatment	Viral load (copies/mL)	50	100	150	200	250	300	350	400	450	500
(a)											
Deferred	3000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
Initiated		2.3	1.2	0.8	0.5	0.4	0.3	0.2	0.2	0.1	0.1
Deferred	10 000	9.6	5.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
Initiated		3.2	1.8	1.1	0.8	0.5	0.4	0.3	0.2	0.2	0.1
Deferred	30 000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
Initiated		4.4	2.5	1.6	1.1	0.7	0.5	0.4	0.3	0.2	0.2
Deferred	100 000	18.6	10.6	6.7	4.6	3.2	2.4	1.8	1.4	1.1	0.8
Initiated		6.2	3.5	2.2	1.5	1.1	0.8	0.6	0.5	0.4	0.3
Deferred	300 000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
Initiated		8.4	4.8	3.1	2.1	1.5	1.1	0.8	0.6	0.5	0.4
(b)											
Deferred	3000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
Initiated		2.8	1.6	1.0	0.7	0.5	0.3	0.3	0.2	0.2	0.1
Deferred	10 000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
Initiated		4.0	2.2	1.4	1.0	0.7	0.5	0.4	0.3	0.2	0.2
Deferred	30 000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
Initiated		5.5	3.1	2.0	1.3	0.9	0.7	0.5	0.4	0.3	0.2
Deferred	100 000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
Initiated		8.0	4.5	2.8	1.9	1.4	1.0	0.8	0.6	0.4	0.4
Deferred	300 000	30.8	18.0	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
Initiated		10.3	6.0	3.9	2.7	1.9	1.4	1.0	0.8	0.6	0.5
(c)											
Deferred	3000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
Initiated		3.6	2.0	1.2	0.8	0.6	0.4	0.3	0.2	0.2	0.2
Deferred	10 000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
Initiated		5.0	2.8	1.8	1.2	0.9	0.6	0.5	0.4	0.3	0.2
Deferred	30 000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
Initiated		6.9	3.9	2.5	1.7	1.2	0.9	0.7	0.5	0.4	0.3
Deferred	100 000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
Initiated		9.5	5.5	3.5	2.4	1.7	1.3	1.0	0.7	0.6	0.4
Deferred	300 000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
Initiated		12.5	7.5	4.9	3.4	2.4	1.8	1.3	1.0	0.8	0.6
(d)											
Deferred	3000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
Initiated		4.5	2.5	1.6	1.1	0.8	0.6	0.4	0.3	0.2	0.2
Deferred	10 000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
Initiated		6.3	3.6	2.3	1.5	1.1	0.8	0.6	0.5	0.4	0.3
Deferred	30 000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
Initiated		8.5	4.9	3.1	2.1	1.5	1.1	0.8	0.6	0.5	0.4
Deferred	100 000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
Initiated		11.5	6.8	4.4	3.1	2.2	1.6	1.2	0.9	0.7	0.6
Deferred	300 000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4
Initiated		14.9	9.2	6.1	4.2	3.0	2.2	1.7	1.3	1.0	0.8

Risk if ART is deferred is taken from [328]. The predicted 6-month risk if ART is initiated is based on the assumption that the rate with immediate therapy initiation is one-third the rate without therapy initiation. This (probably conservative) value is based on considering evidence from multiple sources, including references [32,329–333].

As a result of these factors, our recommendation is that the initiation of therapy should be recommended in all patients with a CD4 count of <350 cells/μL (confirmed on at least one consecutive sample, in the absence of any obvious reason for transient CD4 depletion).

Several studies have suggested that CD4 percentage may have a small additional prognostic value independently of the total CD4 cell count, although the data are conflicting [33,34]. This may prompt deferral of antiretroviral treatment in some patients with CD4 counts <350 cells/μL

Table 2 Recommendations for when to initiate therapy

Presentation	
Primary HIV infection	Treatment in clinical trial or neurological involvement or CD4 <200 cells/μL >3/12 or AIDS-defining illness
Established HIV infection	
CD4 <200 cells/μL	Treat
CD4 201–350 cells/μL	Treat as soon as possible when patient ready
CD4 351–500 cells/μL	Treat in specific situations with higher risk of clinical events – see section 3.3
CD4 >500 cells/μL	Consider enrolment into 'when to start' trial
AIDS diagnosis	Treat (except for tuberculosis when CD4 >350 cells/μL)

but high CD4 percentages, but also may support a decision to start therapy earlier in patients with absolute CD4 counts >350 cells/μL but with low CD4 percentages {e.g. <14%, where *Pneumocystis carinii* pneumonia (PCP) prophylaxis is indicated [35]; some studies have indicated increased risk of disease progression in patients with CD4 percentages <15–17% [36]}.

3.3 Patients with a CD4 count >350 cells/μL

As detailed above, at CD4 counts >350 cells/μL, multiple cohort studies have suggested that there might be benefits to ART. This is supported by data from the substudy of patients not on therapy at entry to the SMART study [32]. Some of the previous concerns about earlier initiation of therapy have been reduced because of the availability of simpler, less toxic and better tolerated antiretroviral regimens, improved pharmacokinetic profiles and increasing options after virological failure. For the majority of patients, the absolute risk of deferring therapy until the CD4 count is <350 cells/μL is likely to be low, but in a subgroup at particularly high risk of clinical events that may be preventable by ART, this is not the case. For all these reasons, in a small number of patients, treatment may be started or considered before the CD4 count is below 350 cells/μL, including the following:

- AIDS diagnosis (e.g. Kaposi's sarcoma); any HIV-related comorbidity;
- hepatitis B infection, where treatment of hepatitis B is indicated (see hepatitis guidelines);
- hepatitis C infection in some cases, where treatment for hepatitis is deferred;
- low CD4 percentage (e.g. <14%, where PCP prophylaxis would be indicated);
- established CVD or a very high risk of cardiovascular events (e.g. Framingham risk of CVD >20% over 10 years).

Additionally, it is likely that successful antiretroviral treatment, by reducing viral load, reduces infectivity irrespective of the current CD4 cell count, and this may be taken into account in deciding on the timing of starting treatment, particularly in discordant couples where the infected partner has a high viral load. This is likely to be an issue in a very small number of patients, and it must be stressed that antiretroviral treatment in this context would be an adjunct rather than an alternative to safer sex.

In patients who do not have an AIDS diagnosis or coinfection with hepatitis B or C virus, and whose CD4 counts are above 500 cells/μL, the benefits of starting therapy remain unclear, the risk of deferring therapy is low, and we recommend that they consider enrolment in the START study, where this is an option.

3.4 Comorbidities

Whilst it has been clearly shown that HAART improves both short- and long-term prognosis, early initiation of antiretroviral drugs in the setting of comorbidity needs to be balanced against the risks associated with drug–drug interactions, overlapping toxicity and the risk of immune reconstitution disease. Despite these potential disadvantages of early introduction of HAART, the recent AIDS Clinical Trials Group (ACTG) 5164 study [37] has suggested that, in the majority of patients presenting with opportunistic disease, ART should be started early (a median of 12 days after starting treatment of the opportunistic infection in the study). This will also allow time for results from resistance tests and human leucocyte antigen (HLA)-B*5701 tests to be available before therapy is started. In patients who present with lymphoma and who are starting chemotherapy, ART should also start immediately (see British HIV Association guidelines for HIV-associated malignancies 2008 [38]).

4.0 What to start with

There is now accumulating evidence of the long-term efficacy of HAART, with more choices of agents and fewer patients failing first-line regimens. The goal of treatment must always be to achieve a viral load of <50 copies/mL and to achieve this within 4–6 months of starting treatment. The trend in viral load reduction should be monitored closely during the early weeks and if there is any concern that the speed of viral load reduction is insufficient then treatment failure should be considered and prompt questioning to identify adherence problems, inadequate drug levels or pre-existing primary drug resistance.

4.1 Which HAART regimen is best?

HAART regimens always need to be individualized for the patient in order to achieve the maximum potency, durability, adherence and tolerability and to avoid long-term toxicities and any likely drug interactions. It is therefore essential to undertake a full baseline assessment before starting treatment and this should include HIV resistance testing, and screening for hepatitis B and C coinfection. In addition, a full cardiovascular risk assessment should be undertaken and patients should be screened for diabetes and renal problems as well as having a psychosocial history taken to identify psychiatric problems, alcohol use and recreational drug use. In women, it is important to enter into a discussion around plans for pregnancy and the use of contraception. Treatment needs to be designed to work within the context of an individual's working and family life and patients must be fully informed of all aspects of therapy prior to commencing treatment. In addition, the comparative costs of individual drugs and the implication of costing in defining treatment pathways are increasingly important [39]. Also, knowledge of the availability of the antiretroviral drugs in the country to which a patient is shortly planning to return is important in deciding the regimen. Lastly, patients should continue to be informed about and encouraged to participate in available clinical trials.

Previously, guidelines have been hampered by the paucity of published data to definitively inform whether HAART based around a nonnucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor (PI) regimen is preferable. In addition, there have been limited data on efficacy comparing individual boosted PIs, and comparing fixed-dose tenofovir and emtricitabine (Truvada) with fixed-dose abacavir and lamivudine (Kivexa). However, significant data have now become available and, as a result, more specific recommendations on drug choice can be made.

It is the Writing Group's view that efavirenz should be considered first line in all patients. This recommendation is based upon its efficacy, durability, toxicity profile, convenience and cost. Boosted PIs should be reserved for specific groups of patients, such as those with primary nucleoside reverse transcriptase inhibitor (NRTI) and/or NNRTI resistance, women who wish to become pregnant, and some patients with psychiatric problems. Nevirapine is another alternative to efavirenz in women wishing to become pregnant and those patients with mental health problems but it should only be used within set CD4 cell count criteria.

It is also the Writing Group's view that both Truvada and Kivexa are appropriate first-choice nucleoside backbones to be used with efavirenz. This recommendation is based upon their efficacy, durability, toxicity profile and convenience. However, Kivexa should be used only in patients who are HLA-B*5701 negative and, in view of recent data, used with caution in those with baseline viral loads over 100 000 copies/mL and in those where there is significant risk of CVD. This advice may change when more detailed study data become available. Combivir remains the coformulation of choice in patients using ART to prevent mother-to-child transmission.

4.2 Recommendations

- Efavirenz should be considered first line in all patients (level Ib).
- Boosted PIs should ordinarily be reserved for specific groups of patients, such as those with primary NRTI and/or NNRTI resistance, women who wish to become pregnant, and some patients with psychiatric problems (level IV).
- Nevirapine should ordinarily be reserved for women wishing to become pregnant and those patients with mental health problems but should only be used within set CD4 cell count criteria (level Ib).
- Truvada or Kivexa should be the first choice for nucleoside backbone to be used with efavirenz (level Ib). However, Kivexa should be reserved for patients who are HLA-B*5701 negative and used with caution in those with viral loads over 100 000 copies/mL or where there is significant risk for CVD (level IV).
- Combivir remains the coformulation of choice in patients using ART to prevent mother-to-child transmission (level Ib).

4.3 Two NRTIs plus an NNRTI

NNRTI-based regimens have now been extensively studied. Compared with boosted PIs, the benefits of efavirenz in terms of virological suppression, good tolerability, low toxicity and convenience are partially offset by genetic frailty, with an increased risk of class resistance on virological failure.

4.3.1 Efavirenz (preferred regimen)

Past studies have shown the superiority of efavirenz over unboosted PIs [40–42]. ACTG 5142 compared a currently recommended boosted PI, lopinavir, with efavirenz in naïve patients [43]. In this study, 757 patients with a median CD4 count of 191 cells/μL and a median viral load of 4.8 $\log_{10}$ copies/mL were randomized in an open-label prospective study to one of three treatment arms: efavirenz with two NRTIs, boosted lopinavir with two NRTIs or NRTI-sparing

boosted lopinavir with efavirenz. The two NRTIs consisted of lamivudine with tenofovir, zidovudine or extended release stavudine. Primary endpoints were time to virological failure (defined as an HIV viral load that had failed to decrease by 1 $\log_{10}$ or rebounded before 32 weeks, or alternatively failed to suppress to <200 copies/mL or rebounded after 32 weeks) and regimen completion (defined as discontinuation because of the first of either virological failure or toxicity of any regimen component). A significant difference in the virological failure rate was demonstrated between the efavirenz and boosted lopinavir arms ($P = 0.006$; significance set at 0.014 for primary endpoints), which was most noticeable in patients with viral loads $>100\,000$ copies/mL ($P = 0.01$). At week 96, the proportion with a viral load of <50 copies/mL was 89% in the efavirenz arm compared with 77% of those on boosted lopinavir ($P = 0.003$). There was no significant difference between the arms in treatment-limiting toxicity or grade 3/4 adverse events. However, less class-emergent resistance was observed in the boosted lopinavir arm compared with the efavirenz arm. In addition, an improved immunological response and less fat loss were seen with boosted lopinavir.

The potency of efavirenz is independent of baseline viral load and CD4 cell count and together with two NRTIs it remains the standard comparator in clinical trials of new agents. It is now available in a fixed-dose combination with tenofovir and emtricitabine allowing a one-pill, once-daily dosing (Atripla). In the 2NN study, efavirenz was compared with nevirapine in a randomized controlled trial which showed that the two drugs were comparable in potency [44,45]. Equivalence was not formally proven, with a small chance that nevirapine was superior to efavirenz and a greater chance of the reverse. However, the principal reason for the recommendation of efavirenz as the preferred NNRTI is related to toxicity in the nevirapine arm.

The major limitation of efavirenz, as for all currently available NNRTIs, is the low genetic barrier to resistance. Although overall transmitted drug resistance in the USA and Europe has remained stable, varying from 8 to 14%, in some groups/countries, including resource-poor nations, it is increasing [46–48]. In ACTG 5142 more class-emergent resistance was observed in the efavirenz arm compared with the boosted lopinavir arm in failing patients. A single mutation is sufficient to confer resistance to efavirenz and also cross-resistance to nevirapine although not to second-generation NNRTIs such as etravirine. NNRTI resistance is almost always accompanied by the emergence of NRTI mutations, reducing options for this class as well.

The major side-effect of efavirenz is dysphoria, which needs to be discussed in detail with the patient prior to commencing the drug. Manifestations include vivid dreams and/or nightmares, sleep and mood disturbance, drowsiness and disorientation. Most are mild to moderate and self-limiting, and can be managed with a short course of hypnotics. Although it is unusual for patients to discontinue the drug for this reason within prospective clinical trials, it has been reported more frequently in cohort analyses and, in a minority, symptoms may persist and be severe enough to warrant switching to an alternative agent [49]. The evidence is conflicting as to whether or not side effects are more common in individuals with a previous psychiatric history. Rashes do occur but severe rashes with efavirenz are unusual (the incidence of Stevens-Johnson syndrome is 0.1%). Similarly, hypersensitivity hepatitis occurs (3.4% in the 2NN study) but fulminant hepatitis is exceptionally rare. Lipid abnormalities, mainly rises above baseline values in total and low-density lipoprotein (LDL) cholesterol, are not infrequently observed in patients on efavirenz-containing regimens.

Efavirenz may be teratogenic and there have been four retrospective reports of neural tube defects in mothers taking efavirenz in the first trimester [50]. Such defects have not been described in prospectively collected data and the relative risk of efavirenz use in early pregnancy remains uncertain. Nevertheless, women of childbearing potential should be warned about becoming pregnant whilst on efavirenz and wherever possible it should be avoided in women who may contemplate pregnancy.

Efavirenz has a long half-life compared with NRTIs and it is important to maintain viral suppression for a period after discontinuation to prevent functional monotherapy and the emergence of resistance. This can be achieved by either substitution of a boosted PI (preferable) or continuing the NRTIs (see '12.0 Pharmacology' section).

4.3.2 Nevirapine

As discussed above, nevirapine has been compared with efavirenz in the 2NN study and has been shown to be of comparable potency. In this study, however, there was more serious toxicity in the nevirapine arm, with two drug-related deaths.

The major side effects are rash and hepatitis. The rash is usually mild and self-limiting but may occasionally manifest as Stevens-Johnson syndrome (incidence 0.3%) with rare fatalities. The rash is not reduced by the co-administration of steroids, which should be avoided [51]. Hepatitis is an infrequent side effect that mainly occurs in the first 6 weeks of therapy but fulminant liver failure and deaths have been reported. Recent analyses have shown a 12-fold higher incidence of symptomatic hepatic events in women with CD4 counts >250 cells/μL (11 *vs.* 0.9%) and a five-fold higher incidence in men with CD4 counts >400 cells/μL (6.3 *vs.* 1.2%): most of these patients had

no identifiable underlying liver disease. This drug should be avoided in these patients, as well as in those with active hepatitis B or C infection and in patients with elevated liver function tests at baseline wherever alternatives are available. Nevirapine is currently used twice a day, but the pharmacokinetics and now clinical trial data indicate that once-daily dosing is possible and patients can be switched safely once the viral load has been suppressed [52]. Nevertheless, when used from the outset, once-daily nevirapine leads to more abnormalities of liver function (13.6 *vs.* 8.3%) [44]. Concerns about the antiviral efficacy of a once-daily regimen of nevirapine, tenofovir and lamivudine which have arisen from two small prospective studies are being addressed in a suitably powered randomized trial comparing nevirapine with boosted atazanavir both dosed with Truvada [53].

Based on these data, nevirapine is not now recommended as a preferred regimen in patients starting HAART, but should be used in patients in whom other regimens would have disadvantages (e.g. women desiring to become pregnant and possibly those with a previous psychiatric history) and only within the CD4 cell count recommendations. It remains a well-tolerated drug with no adverse effect on lipids. Because nevirapine causes induction of its own metabolism, a 14-day lead-in period of 200 mg daily should be prescribed before increasing to twice-daily dosing unless switching directly from efavirenz. In the presence of mild to moderate rash without constitutional symptoms or biochemical hepatitis, the lead-in dose should be continued until rash resolution. However, the drug should be permanently discontinued if constitutional symptoms are present, the rash is severe or hepatitis is present [54]. The same recommendations apply when discontinuing nevirapine as apply for efavirenz.

4.4 Two NRTIs plus a boosted PI

A dramatic decline in clinical progression and HIV-related deaths followed the introduction of the PI class of antiretroviral drugs. These agents have shown clinical and surrogate marker efficacy in clinical practice. When boosted with low-dose ritonavir, they have a high genetic barrier to resistance and may produce a larger CD4 cell count rise than NNRTIs [43,55]. Sustained suppression of plasma HIV RNA levels has been observed with up to 7 years of continued immunological recovery in patients treated with boosted PIs. There is now ample data to recommend that, if a PI is chosen as part of an initial HAART regimen, it should be a boosted agent. Ritonavir boosting increases drug exposure, thereby prolonging the half-life of the drug, allowing reduction in pill burden and dosing frequency and optimization of adherence. It also limits the development of resistance. As discussed in the efavirenz section, ACTG 5142 demonstrated a significant benefit of efavirenz in terms of virological failure when compared with boosted lopinavir [43]. However, those patients who did fail virologically had more resistance in the efavirenz arm than in the lopinavir arm. Overall, significant mutations occurred in 48% of the virological failures in the efavirenz group compared with 21% of those in the boosted lopinavir group ($P = 0.002$), with NNRTI and primary PI mutations occurring in 43 and 0% and NRTI mutations in 33 and 19%, respectively. Hence, a modest benefit in achieving sustained virological undetectability with efavirenz needs to be balanced by the increased potential risk of two-class resistance on failure. This underscores the importance of tailoring the choice of initial drugs to the patient and their circumstances and may be particularly relevant in selecting a regimen in a patient with poor adherence.

4.4.1 Boosted lopinavir

Data from the original licensing study showed superior surrogate marker endpoints for patients using boosted lopinavir compared with nelfinavir, with lower numbers of patients discontinuing for side effects [56]. Additionally, patients randomized to boosted lopinavir who developed virological failure had no evidence of primary PI resistance. Subsequent and separate head-to-head comparisons between boosted lopinavir and other boosted PIs have confirmed the general lack of emergent primary PI resistance in boosted regimens. Although two early studies cast doubt on the efficacy of once-daily dosing in patients with viral loads $> 100\,000$ copies/mL [57,58], a recent large randomized trial did not show any difference (73.8% in the twice-daily arm *vs.* 73.2% in the once-daily arm) [59]. The main adverse effects are dyslipidaemia, particularly hypertriglyceridaemia, and gastrointestinal side effects, with diarrhoea being the predominant symptom. The lack of a need for refrigeration is an advantage. It is licensed in the UK to be dosed twice daily although the evidence now supports its use once daily.

4.4.2 Boosted fosamprenavir

Boosted fosamprenavir has been compared once daily to nelfinavir (SOLO study) and twice daily to boosted lopinavir (KLEAN study) [60,61]. Findings from KLEAN showed fosamprenavir to be noninferior to lopinavir (66% of those randomized to boosted fosamprenavir and 65% of those randomized to boosted lopinavir had viral loads < 50 copies/mL at 48 weeks) with both drugs demonstrating durable antiviral activity out to 96 weeks. Virological failure was low (3.7% in the fosamprenavir arm *vs.* 5.4% in the lopinavir arm) and no major PI mutations were identified in either arm. Data from the SOLO study also demonstrated that boosted fosamprenavir showed durable responses out to 120 weeks in naïve patients, with only one

case of emergent PI resistance reported to date [62]. Several small studies have evaluated once-daily dosing with 1400 mg fosamprenavir and 100 mg ritonavir and demonstrated no loss of virological potency or durability and a trend towards improved lipid parameters [63]. Nevertheless, this dosing strategy cannot be recommended until informed by a suitably powered randomized clinical trial and boosted fosamprenavir remains unlicensed when given once daily. Boosted fosamprenavir dosed twice daily has the same pill burden, dosing, tolerability, and level of dyslipidaemia as boosted lopinavir.

4.4.3 Boosted saquinavir

In a randomized comparative study of ritonavir-boosted saquinavir (100/1000 mg) against boosted lopinavir, both dosed twice daily (GEMINI study), noninferiority was demonstrated at 48 weeks, with 64.7% of those taking boosted saquinavir and 63.5% of those taking boosted lopinavir achieving a viral load <50 copies/mL (the primary endpoint) [64]. Adverse effects were mainly gastrointestinal (27% of those taking boosted lopinavir *vs.* 17% of those taking boosted saquinavir) with the difference mainly being attributable to higher rates of grade 3/4 diarrhoea in the lopinavir arm. Significantly higher triglyceride elevations were also seen with boosted lopinavir. There was a trend towards more virological failures in the boosted saquinavir arm (7 *vs.* 3%) and one poorly adherent patient receiving boosted saquinavir developed new major PI mutations. Several small studies with the soft gel or capsule formulation have examined once-daily dosing with mainly 1600 mg saquinavir and 100 mg ritonavir [65,66]. Results have been generally encouraging and further studies with the tablet formulation are underway to assess the efficacy of this strategy. However, until informed by a suitably powered randomized clinical trial, once-daily dosing cannot be recommended and is not licensed. Boosted saquinavir dosed twice daily represents a well-tolerated alternative to boosted lopinavir or fosamprenavir with less dyslipidaemia and gastrointestinal toxicity but a higher pill burden.

4.4.4 Boosted or unboosted atazanavir

Unboosted atazanavir has been shown to have similar efficacy to nelfinavir and efavirenz in three clinical studies [67–69]. A fourth study comparing boosted and unboosted atazanavir showed less virological failure and the absence of phenotypic resistance in those taking boosted drug at 96 weeks but with greater rates of hyperbilirubinaemia and increases in lipid levels [70]. Recently, a large randomized comparative study has compared boosted atazanavir with boosted lopinavir (CASTLE study) [71]. Noninferiority was demonstrated, with 78% of those taking atazanavir achieving a viral load <50 copies/mL at 48 weeks (the primary endpoint) compared with 76% of those taking lopinavir. Atazanavir was associated with less dyslipidaemia and diarrhoea and was generally well tolerated with a low rate of discontinuation.

The main advantages of boosted atazanavir are that the drug is dosed once daily and has limited effect on lipids. Its main side effects are hyperbilirubinaemia with or without jaundice, but this is not associated with liver enzyme changes and seldom results in the need to discontinue treatment. A disadvantage is its interaction with acid-reducing agents, notably protein-pump inhibitors. This is not overcome by ritonavir boosting, and, where alternative antacid strategies cannot be used, atazanavir should be avoided.

4.4.5 Boosted darunavir (unlicensed for naïve patients)

A phase III open-labelled randomized trial compared once-daily ritonavir-boosted darunavir (100/800 mg) with boosted lopinavir dosed either once daily (17%) or twice daily (77%) with tenofovir and emtricitabine [58]. The primary endpoint of <50 copies/mL at 48 weeks was achieved in 84% of those receiving darunavir compared with 81% of those taking twice-daily lopinavir (not significant) and 71% of those taking daily dosing ($P<0.05$). In a *post hoc* analysis stratifying response by initial viral load, differences were most noticeable in those with a baseline viral load of $>100\,000$ copies/mL, for whom viral undetectability was reached in 79% of those receiving darunavir, 71% of those receiving lopinavir twice daily, and 56% of those on daily administration; however, numbers were small in the once-daily arm. Boosted darunavir was also associated with less gastrointestinal toxicity and dyslipidaemia.

4.5 Three NRTIs

There are now surrogate marker endpoint data suggesting that zidovudine/lamivudine/abacavir (usually combined as Trizivir) is less potent than combining two NRTIs with either an NNRTI or a PI, with higher rates of virological failure, and therefore should not be used [72,73]. Currently no triple NRTI regimen can be recommended. However, data suggest that zidovudine/lamivudine/tenofovir with or without abacavir is a possible option in exceptional circumstances when a PI- or NNRTI-based HAART regimen cannot be administered [74].

4.6 Choice of two NRTIs

Two NRTIs remain an integral component of HAART with either an NNRTI or a ritonavir-boosted PI. There is no

evidence that a further NRTI adds any additional benefits and two-class NRTI-sparing combinations are associated with more discontinuations because of toxicity. There are now seven NRTIs available, four NRTI coformulations (Truvada, Kivexa, Combivir and Trizivir) and one fixed-dose combination of tenofovir, emtricitabine and efavirenz (Atripla). The availability of these fixed-dose combinations has led to the majority of patients starting treatment being prescribed one of the three two-NRTI combinations as their backbone. The merits and limitations of each coformulated two-NRTI combination are discussed below.

The Writing Group recommend the use of either Truvada or Kivexa in initial therapy, with Combivir being reserved for patients with contraindications to the other fixed-dose combinations. However, Kivexa should be used with caution in certain groups (see section 4.1). Combivir remains the coformulation of choice in patients using ART to prevent mother-to-child transmission.

4.7 Coformulated two NRTIs

4.7.1 Tenofovir/emtricitabine (Truvada)

Individually dosed emtricitabine/tenofovir has been compared to Combivir both dosed with daily efavirenz in the Gilead 934 study, in which virological rebound (5 *vs.* 2%) and adverse events leading to discontinuation (11 *vs.* 5%) were seen more frequently in the Combivir arm at 144 weeks. Data for Truvada demonstrate that the individual components are bio-equivalent with the fixed-dose formulation [75,76].

Tenofovir with emtricitabine is generally well tolerated with no significant effect on lipid profile. There have been reports of renal tubular damage and an association between related compounds and nephrotoxicity, raising the possibility of long-term renal toxicity with tenofovir. Numerous studies, including those providing clinical trial, observational cohort and expanded access data, have identified serious renal toxicity in approximately 0.5% of patients, a rate no different to that observed with comparator NRTIs [77,78]. However, other studies have demonstrated a small but significant reduction in renal function over time compared with other NRTIs [79,80]. It is clear that tenofovir should be used cautiously in patients who have, or are at risk of developing, renal disease, including those co-prescribed potentially nephrotoxic agents. Patients should have blood biochemistry [including glomerular filtration rate (GFR) estimation] and urinalysis for total protein performed prior to initiating tenofovir with regular monitoring throughout treatment. When tenofovir has been used as first-line therapy, the K65R mutation has been observed in a minority of patients receiving efavirenz/tenofovir/lamivudine. In the Gilead 903 study, this mutation occurred in 2.4% of patients at 48 weeks (overall virological failure rate 9.7%) [81]. This mutation was mainly observed in those with CD4 counts of <50 cells/μL and viral loads $>100\,000$ copies/mL: K65R has not been observed in patients with pretreatment wild-type virus receiving tenofovir and emtricitabine with either a boosted PI or efavirenz.

4.7.2 Abacavir/lamivudine (Kivexa)

Kivexa is generally well tolerated but a hypersensitivity reaction (HSR) may occur in the first 6 weeks (median 11 days from drug commencement) and all patients need counselling. It has been identified in approximately 5–8% of naïve-patient studies and is independent of dosing frequency. These studies used a case reporting form (where HSR was also reported in 3% of zidovudine-treated patients in a double-blind study) and the summary of product characteristics (SPC) states an HSR rate of 5.4% [82]. Pharmacogenetic analysis has identified a close association between HSR and carriage of the class 1 HLA-B*5701 allele, which to a large extent explains the racially defined differences in susceptibility. A large controlled trial randomized patients prior to planned commencement of abacavir into a group that had prospective screening with exclusion if HLA-B*5701-positive and a standard of care group in which all patients proceeded to receive abacavir [83]. Because of suboptimal specificity when using clinical criteria alone for diagnosing HSR, all patients suspected of having an abacavir HSR had confirmatory skin-patch testing (immunologically confirmed HSR). HLA-B*5701 screening excluded skin-test positive HSR patients (negative predictive value 100%) compared with 2.7% in the control group as well as significantly reducing the rate of clinically suspected HSRs (from 7.8 to 3.4%). Although data in racially diverse populations are limited, a retrospective study in black patients with documented clinical hypersensitivity using skin-patch testing validated the use and negative predictive value of HLA-B*5701 screening in this group also [84]. Abacavir should not be used without prior HLA-B*5701 screening and should be avoided in patients testing positive. A negative test does not rule out the possibility of HSR and the need for careful counselling and monitoring for abacavir HSR remains. A recent analysis of the prospective observational cohort D:A:D study showed an increase in myocardial events in patients while, and shortly after, receiving abacavir compared with patients recently receiving zidovudine, stavudine, or lamivudine [85]. Didanosine was associated with a similar but less marked increase: tenofovir regimens were not investigated. This increased risk was particularly evident in those patients with the highest cardiovascular risk. Although subject to further analysis, these results caution the choice of Kivexa in patients with a high risk of CVD. In

addition, dyslipidaemia is greater than that seen with zidovudine. In terms of the resistance profile the L74V mutation is seen in <1% of patients at 48 weeks (overall virological failure rate 6%) and both K65R and L74V may lead to difficulties in choice of subsequent treatments [86].

Recently, two studies have compared Truvada and Kivexa in naïve patients. HEAT was a double-blinded, placebo-controlled study with boosted lopinavir as the third drug and with primary virological (proportion <50 copies/mL at 48 weeks) and toxicity (96 weeks) endpoints [87]. Noninferiority was demonstrated for Kivexa, with no significant differences between the two fixed-dose combinations being observed in any virological or toxicity analysis including patients with baseline viral loads >100 000 copies/mL. In the second ongoing study (ACTG 5202), which is a phase III randomized trial of open-label efavirenz or ritonavir-boosted atazanavir in combination with a double-blind comparison of Truvada or Kivexa, a higher rate of virological failure was identified in those with baseline viral loads above 100 000 copies/mL who were receiving Kivexa [estimated hazard ratio (HR) 2.33; 95% confidence interval (CI) 1.46–3.72] [88]. As a result of the efficacy findings, the Data Safety and Monitoring Board (DSMB) recommended that blinded follow-up of Kivexa in the subjects within the high viral load stratum be stopped. In view of these results, the Writing Group cautions the use of Kivexa in those with high viral loads and recommends that it should be reserved for patients in whom Truvada is contraindicated. However, this guidance will be informed by further data and analysis of ACTG 5202 and additional studies comparing the two coformulated backbones.

4.7.3 Zidovudine/lamivudine (Combivir)

Considerable experience has been accrued with Combivir but, because of poor early tolerability, compelling evidence implicating zidovudine in extremity fat loss [89], and the availability of potent alternatives, the Writing Group's recommendation is that this combination should no longer be a first-line option for naïve patients, except for patients in specific situations. These would include women who are, or are intending to become, pregnant, and those planning to return shortly to a nation where limited alternative nucleoside backbones are available. When used, ongoing monitoring for long-term toxicity is important.

4.8 Other two-NRTI combinations

Stavudine/lamivudine is a well-studied NRTI combination with equal antiviral effectiveness to tenofovir/emtricitabine and abacavir/lamivudine but with significantly greater stavudine-related mitochondrial toxicity, including peripheral neuropathy and lipoatrophy [90]. Because of this, stavudine is not recommended for initial therapy.

Tenofovir and didanosine is a once-daily, two-tablet combination. However, all studies where this two-nucleoside backbone has been used with an NNRTI as the third agent have demonstrated an unacceptably high failure rate, with the development of early resistance which was more marked in patients with more advanced disease [91]. There is also potential for tenofovir to potentiate didanosine-related toxicity. The combination is not recommended.

Didanosine/lamivudine or didanosine/emtricitabine is well tolerated and effective [92]. However, didanosine-related restrictions on food and the potential for long-term mitochondrial toxicity make this choice less popular.

Zidovudine/didanosine was a common two-NRTI combination prior to HAART. However, no data exist for zidovudine/enteric-coated didanosine in HAART. Similarly, tenofovir/abacavir and abacavir/didanosine have not been evaluated in naïve patients: none of these two-NRTI combinations can be recommended.

4.9 Conclusions

In light of the findings of ACTG 5142, the recommendation of the Writing Group is for use of an efavirenz-based regimen for initial therapy, reserving boosted PIs for later. This is based on the efficacy data, the low risk of toxicity, the ease of administration, and the genetic frailty of an NNRTI in patients failing a boosted PI regimen. However, less class-emergent resistance is observed with boosted PIs, underscoring the importance of individualizing therapy. It is also recommended that Truvada and Kivexa are the nucleoside backbones of choice. However, Kivexa should be reserved for patients who are HLA-B*5701 negative and, based on recent trial data, should be used with caution in

Table 3 Preferred regimens

Regimen	A	B	C
Preferred	Efavirenz*	Tenofovir*,†	Lamivudine‡,§
		Abacavir§	Emtricitabine*,†
Alternative	Lopinavir/r	Didanosine	
	Fosamprenavir/r	Zidovudine‡	
	Atazanavir/r		
	Saquinavir/r		
Specific groups	Nevirapine ‖		
	Atazanavir**		

Choose one drug from columns A, B and C.
Licensing is based on European Medicines Agency (EMEA).
*Coformulated as Atripla (licensed for virologically suppressed patients only).
†Coformulated as Truvada.
‡Coformulated as Combivir.
§Coformulated as Kivexa.
‖Only when CD4 <250 cells/μL in female patients and <400 cells/μL in male patients.
**Where there are established cardiovascular disease risk factors and a PI is required.

Table 4 Comparison of boosted protease inhibitors (PIs) (based upon dose licensed or currently pending licensing approval)

	Lopinavir/r*	Saquinavir/r*	Fosamprenavir/r*	Atazanavir/r	Darunavir/r*†
Potency in naïve patients	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Durability	+ + + +	+ +	+ + +	+ +	+ +
Convenience	+ + +	+ +	+ + +	+ + + +	+ + +
Tolerability	+ +	+ + +	+ +	+ + +	+ + +
Lipid profile‡	+	+ +	+	+ + +	+ + +
Resistance barrier	+ + + +	+ + + +	+ + + +	+ + + +	+ + + +
Interaction profile	+ + +	+ +	+ +	+	+ +

Recommendations for potency, durability, tolerability, resistance barrier, and lipid profile are based on results from the KLEAN, ARTEMIS, GEMINI and CASTLE studies for naïve patients.
Recommendations for convenience are based on tablet formulation for lopinavir/r and saquinavir 500 mg, European Medicines Agency (EMEA) licensed dosing (twice daily for lopinavir/r, fosamprenavir/r and saquinavir/r and once daily dosing for atazanavir/r) and, where pending licensing decisions, once-daily dosing for darunavir/r.
Recommendations for interaction profile are based on the Liverpool HIV Drug Interactions website (www.hiv-druginteractions.org/ last accessed 25 May 2008) particularly with relation to acid-reducing agents, lipid-lowering drugs, and other antiretroviral drugs.
+ + + +, excellent; + + +, very good; + +, moderately good; +, not good; −, poor.
*Not licensed for once-daily dosing.
†Not licensed for treatment of naïve patients.
‡Compared with lopinavir/r.

Table 5 Changing therapy on first virological failure [BIII]

Presentation	Viral load pattern	Recommended action
Inadequate virological response to initial regimen	Failure to achieve viral load < 50 copies/mL*,‡	Consider factors affecting plasma drug levels† If drug exposure optimal and likelihood of resistance low, or resistance not detected, consider augmenting treatment regimen If likelihood of resistance high, or resistance detected, consider changing all drugs
Persistent viral load rebound where previously < 50 copies/mL	Viral load > 50 and < 400 copies/mL‡ Sustained viral load rebound to > 400 copies/mL	Consider factors affecting plasma drug levels† Change all drugs to an effective option likely to reduce viral load to undetectable levels Consider continuing regimen, with monitoring, only if CD4 count > 200 cells/μL and decision to change affected by factors that will influence adherence to and tolerability of new regimen or other situational factors affecting timing of switch§

*Viral load suppression to < 50 copies/mL is usually achieved 4–6 months after starting therapy but may take longer particularly in patients with high baseline viral loads.
†Factors affecting plasma drug levels include poor adherence, intolerability, drug interactions and incorrect dosing.
‡Genotypic resistance testing is frequently possible at viral load < 1000 copies/mL and if available should be considered in patients with low-level viraemia and experiencing virological failure.
§There is a risk of developing further mutations by allowing a patient to remain on a virologically failing regimen, which will limit further options for treatment.

patients with a baseline viral load of > 100 000 copies/mL or where there is significant risk of CVD (Tables 3 and 4).

5.0 Virological failure: after first-line treatment

The viral load nadir achieved within the first few months on treatment is predictive of the subsequent risk of virological failure [93]. 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 viral load has been 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 5.

If a patient on stable therapy for longer than 3 months with an undetectable (< 50 copies/mL) viral load shows a rise in viral load to just above detectable, the patient should be clinically assessed to confirm the viral load rebound. The factors that may have reduced plasma drug levels to below optimal levels, such as drug–drug interactions, poor adherence and incorrect dosing, or that may have increased viral replication, such as inter-current infections and vaccinations, should be determined.

5.1 Viral load blips

Transient rises in viral load to levels just above detectable (viral blip) are reported to occur in a significant proportion of patients on treatment over time [94,95]. They may reflect

technical variations in assay performance, or biological events associated with virus replication. Patients who are developing sustained virological rebound (failure) would show further increases in viral load on subsequent testing whereas those whose viral load is transiently detectable would revert to undetectable (<50 copies/mL) 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. Two studies showed no such association [94,96] but another [95] 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.

5.2 Sustained viral load rebound

The factors potentially contributing to reduced plasma drug levels should be clinically assessed and, where possible, managed appropriately; these include poor adherence, drug intolerance, incorrect dosing and drug–drug interactions.

Falls in CD4 cell 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 pretreatment levels [97]. 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 (e.g. lamivudine and NNRTIs) mutations at one position in the reverse transcriptase (RT) gene can cause high-level phenotypic resistance and usually emerge at low levels of viral load rebound. Reduced susceptibility to other drugs usually requires the accumulation of two or more mutations in the viral genome. In the presence of ongoing viral replication, mutations continue to accumulate in a stepwise fashion; these mutations may improve viral fitness as well as increase cross-resistance to other drugs. Thus, if significant levels of viral replication develop and persist on therapy and other options are available that 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 at least 1 month apart) viral load level of >400 copies/mL for consideration of a treatment switch, although others would consider a switch at sustained rebound between 50 and 400 copies/mL, if resistance is detected. This may change as further information is gained on the frequency and emergence of genotypic mutations at low-level viraemia on different drug combinations and how this may influence the treatment response to subsequent regimens.

5.3 Changing therapy

A change of therapy should be considered for patients if they experience sustained rebound in viral load levels, having either had previously undetectable levels or never achieved undetectable levels on their current treatment regimen after 24–36 weeks. The likelihood of achieving an undetectable viral load on changing therapy is predicted by the number of active drugs in the new regimen [98,99], plus factors influencing tolerability and adherence. The decision to change therapy should be guided by the availability of a treatment option that 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.

Although the addition of a single new agent in individuals experiencing low-level viral load rebound may result in a proportion of these individuals achieving undetectable viral loads [100], 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.

The choice of a new regimen should be guided by the results of current and previous resistance testing, treatment history and the ability of the patient to adhere to and tolerate individual drugs. Resistance testing is important to identify which drugs will possibly be of most benefit, i.e. active. A drug is defined as active where it is likely to have significant antiviral activity *in vivo* based on antiretroviral treatment and virological failure histories and the results of all current and previous resistance testing.

5.4 Virological failure with no resistance

Patients may experience virological failure but have no resistance mutations detected on genotypic resistance testing. Failure here is probably attributable to poor treatment adherence with drug levels that are both insufficient to maintain viral load suppression and inadequate to select out viral mutations associated with drug resistance. However, the absence of detectable resistance mutations does not exclude the presence of mutations in minor virus populations, which may have emerged as a result of treatment experience [101–103].

In this situation, factors affecting adherence and drug exposure should be fully evaluated and the choice of the next regimen guided by previous treatment experience and the

likelihood of the patient adhering to, and tolerating, individual drugs. Additional adherence support should be considered.

5.5 First-line virological failure with PI mutations

Most patients experiencing treatment failure on a boosted PI with two NRTIs as the first-line regimen do not have detectable PI-associated mutations [56,104]. Continuing the same boosted PI and changing the nucleoside backbone has not been evaluated. Most clinicians would consider switching to an alternative boosted PI-containing regimen. For patients with failing treatment and detectable PI mutations there is only limited randomized control trial evidence to guide the optimal treatment strategy.

There are comparative data assessing which ritonavir-boosted PI regimen is more effective in PI-experienced patients with or without detectable PI mutations at baseline and further data will be available from ongoing trials.

Similar virological efficacy at 48 weeks has been demonstrated for lopinavir/r and atazanavir/r in patients who have previously failed at least two regimens including at least one containing a PI [105]. Gastrointestinal side effects and hyperlipidaemia were more common with lopinavir/r. Hyperbilirubinaemia and, in a small number of patients, clinical jaundice were the most common side effects with atazanavir/r.

In treatment-experienced patients, of whom 69% were PI- and 76% NNRTI-experienced and all of whom were lopinavir/r naïve, treatment with darunavir/r twice daily had superior virological efficacy at 48 weeks compared with lopinavir/r. However, in secondary analyses, similar virological efficacy was seen in patients who had no detectable primary PI mutations at baseline and in those who had two or more active agents in the optimized background therapy [106].

In patients who had previously experienced treatment failure on one or two PIs, noninferiority of fosamprenavir/r compared with lopinavir/r using the primary endpoint of time-averaged change in viral load from baseline could not be established [107]. However, similar proportions of patients achieved viral load <50 copies/mL at 48 weeks with lopinavir/r and twice-daily fosamprenavir/r, but not with once-daily fosamprenavir/r. Once-daily fosamprenavir/r is not recommended in patients with previous PI failure.

An alternative option is to change both NRTIs and introduce a new class by switching the PI to an NNRTI. There are no randomized control trial data to support this strategy, although in the absence of any resistance to NRTIs this may be feasible. However, if there is cross-resistance amongst the NRTIs, limiting the benefit of new NRTIs, there is likely to be a high risk of more rapid virological failure and development of resistance to the NNRTI with this strategy. In a number of cohort studies, lopinavir, with low-dose ritonavir in combination with either efavirenz or nevirapine, reduced viral loads to below detectable limits in NNRTI-naïve, PI-experienced patients [108,109].The decision to include an NNRTI or not may depend on the extent of cross-resistance amongst the NRTIs and thus the availability of an active NRTI.

5.6 Virological failure with NNRTI mutations

No large randomized strategic comparative study has addressed the optimal treatment strategy in patients who have NNRTI mutations with or without NRTI mutations, following failure of two NRTIs plus an NNRTI. Unlike PIs, the presence of one or more NNRTI-associated mutations usually indicates cross-resistance to both nevirapine and efavirenz.

A trial evaluating the NNRTI etravirine, which has *in vitro* activity against virus isolates with NNRTI mutations, was stopped prematurely because of increased risk of virological failure in NNRTI-experienced and PI-naïve patients treated with etravirine and two new NRTIs compared with the control group treated with a PI-based regimen [110]. A contributing factor was the high proportion of patients who had a significant number of NRTI- and NNRTI-associated mutations at baseline. Thus, most physicians would switch to a regimen containing two active NRTIs and a boosted PI following virological failure with a first-line regimen of one NNRTI and two NRTIs in the presence of NNRTI and NRTI mutations.

There are few data from studies in patients who are therapy-experienced but PI-naïve to guide choice of the boosted PI. Data from trials in PI treatment-experienced patients (see previous section) and therapy-naïve patients may help to inform choice.

5.7 Virological failure with NRTI mutations alone

Virological failure with NRTI mutations alone may follow treatment with triple NRTI regimens or two NRTIs and a PI. It is unusual to observe failure with NRTI mutations alone in patients experiencing treatment failure on two NRTIs and an NNRTI. In patients who have failed an NNRTI-containing regimen, minor populations of NNRTI mutations may be present that are not detectable on routine resistance testing but are likely to affect response to future NNRTI-containing regimens [101].

The number and pattern of genotypic mutations in the reverse transcriptase gene will determine the extent of cross-resistance amongst the NRTIs and whether two active and potent NRTIs could be included in the new regimen. If no or limited cross-resistance is detected then the preferred option is to switch to a regimen comprising two active and

Table 6 What to change to after first virological failure: summary of recommendations [BII/IV]

Initial regimen	Options to consider
2 NRTIs + 1 PI	2 NRTIs*,† + 1 NNRTI or 2 NRTIs* + 1 boosted PI or 1 NNRTI + 1 boosted PI‡ + 1–2 NRTIs*
2 NRTIs + 1 NNRTI	1 boosted PI + 2 NRTIs*
3 NRTIs	2 NRTIs*,† + 1 NNRTI or 1 boosted PI + 2 NRTIs* or 1 NNRTI + 1 boosted PI‡ + 1–2 NRTIs*

Change all drugs if possible and a resistance test is recommended
*Change to new and active NRTIs guided by resistance testing.
†This could lead to rapid development of resistance to NNRTIs if the potential exists for NRTI cross-resistance.
‡Studies with a low-dose ritonavir-boosted PI + an NNRTI have shown good results.
NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

potent NRTIs plus a boosted PI. The alternative option of switching to a new regimen containing an NNRTI and two active NRTIs is likely, in most cases, to be less successful and can be recommended only rarely. The main reasons for this are the low genetic resistance barrier of an NNRTI or the presence of NNRTI mutations in minor virus populations from previous NNRTI exposure and the possible presence of greater cross-resistance amongst the NRTIs than detected by current genotypic assays.

If the likelihood of cross-resistance amongst the NRTIs is high (i.e. there are not two fully active drugs) then switching to a regimen comprising a boosted PI with two (at least partially) active NRTIs is recommended. In patients who are NNRTI-naïve a regimen containing a boosted PI and an NNRTI and one or two active NRTIs is an alternative. This is a rapidly changing field and many clinicians would now consider adding one new drug class in this situation (Table 6).

6.0 Subsequent virological failure

6.1 The patient with therapy options

In treatment-experienced patients with therapy options, the physician should construct a new HIV treatment that includes at least two (preferably three) active agents guided by HIV resistance testing and by the patient's previous antiretroviral drug history. The use of an agent from a new drug class is likely to be more effective.

The available data for enfuvirtide show that it is most effective when used with other drugs to which the patient is susceptible based on resistance testing and antiviral experience. When used as the only effective agent, resistance to it occurs within weeks and a future opportunity for constructing an effective regimen is lost. If darunavir is used in a similar way, then the regimen is less effective than in combination with other effective drugs such as raltegravir, etravirine, maraviroc or enfuvirtide, as seen in the BENCHMRK, DUET, MOTIVATE and POWER studies [99,111–118].

Although these studies had different designs and entry criteria, they underline the principle that new regimens should contain two or more fully active drugs. However, this strategy may not be a realistic option when managing some highly treatment-experienced patients.

6.2 The patient with few or no therapy options: continue, interrupt or change therapy?

In treatment-experienced patients with few or no therapy options, especially if the CD4 cell count is well maintained, it may be better to wait to change treatment until investigational agents are available that can be put together with drugs, which may have only partial activity at best, to increase the likelihood of constructing a virologically suppressive and durable regimen. Several drugs are in a late phase of development that have activity against currently resistant viruses and will be used to create an effective drug combination but care in their use should be taken to prevent what might be sequential monotherapy.

6.2.1 Continuing the failing regimen

If a suppressive regimen cannot be realistically constructed then even partial virological suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits [93]; however, this must be balanced with the ongoing risk of accumulating additional resistance mutations. There is good evidence that continuing therapy, even in the presence of viraemia without CD4 cell increases, reduces the risk of disease progression [119]. Other cohort studies suggest continued immunological and clinical benefits if the HIV RNA level is maintained between 10 000 and 20 000 copies/mL [15,120].

Virological failure on continuous ART is associated with variable changes in CD4 cell counts that appear to correlate with the viral replicative capacity, the ability of the virus to induce apoptosis in both infected and uninfected CD4 T cells, and the use of the CXCR4 *vs.* CCR5 receptor for entry [121].

There is no test currently that will predict CD4 cell count responses in individual patients continuing a failing regimen. The replicative capacity assay provides only a partial measure of the multiple factors that influence viral fitness and pathogenicity. Once resistant virus has become established as the dominant species, the emergence of further resistance mutations detectable by routine genotypic testing is widely believed to occur slowly. In one study of patients with viral load >200 copies/mL, the

average increase per year in the number of mutations was 0.5 for RT mutations, 0.2 for major PI mutations and 0.3 for minor PI mutations [122]. Within the SCOPE clinical cohort, however, among persons with a viral load >1000 copies/mL while on stable therapy, as many as 44% accumulated at least one new mutation at year 1, and 30% lost at least one active drug [123].

The highest risk for the emergence of further mutations is in persons who initially have limited resistance [123]. Conversely, in some patients with multiple mutations a genetic deadlock may be achieved that limits further evolution of resistance. However, the majority of patients keep accumulating new resistance mutations [123], including mutations present only as minority variants that escape detection by routine testing. A 'V'-shaped relationship exists between the number of mutations and viral load in the setting of treatment failure. Above a certain threshold, the number of mutations is associated with increases in viral load, reflecting compensatory changes that improve viral fitness and pathogenicity [124]. Variants with compensatory changes may carry mutations in several regions of the HIV genome and do not necessarily display further increases in drug resistance [125]. In addition, under prolonged drug-selective pressure, mutations initially present on separate viral variants can accumulate on the same viral genome. Such linkage cannot be detected by standard genotype analysis [126].

Taken together, these observations indicate that continuing a failing regimen can be deleterious and there is no benefit in continuing patients on a failing NNRTI regimen as this may jeopardize the utility of etravirine if multiple resistance mutations are allowed to accumulate. There is no real benefit in continuing a boosted PI in this situation and again it may be deleterious as protease mutations may accumulate and the impact of other PIs such as darunavir may be diminished. Thus, patients lacking effective treatment options should maintain that regimen for the shortest period possible. The issue is what to do with patients while waiting for effective drugs to become available. The options are to interrupt treatment or maintain patients on an NRTI-only regimen.

6.3 Treatment interruption

Until recently, treatment interruptions have been used as one experimental strategy for patients lacking effective treatment options. Four studies confirm that interrupting treatment in an effort to revert to wild-type prior to initiation of a salvage regimen is not associated with significant durable benefits [127–130]. Instead, it may be associated with a rapid increase in HIV RNA, loss of CD4 cells or clinical disease progression. The results of the SMART study would also support the recommendation that total treatment interruption cannot be recommended in the management of the treatment-experienced patient.

6.4 Change

Until investigational drugs that are effective against currently resistant virus are available, it might be possible to change the regimen and recycle drugs previously used or omit drugs from the treatment that are having little antiviral effect and/or contributing to side effects. Partially interrupting components of a treatment regimen may have a role to play in such heavily treatment-experienced patients and may reduce toxicity and the potential for drug interactions.

Data from a small pilot study showed that interruption of PI treatment was associated with stable HIV RNA levels and waning of PI mutations. However, viral replicative capacity and HIV RNA levels started to increase after long-term (more than 6 months) treatment interruption. In contrast, subjects interrupting their NRTI treatment experienced an immediate rise in HIV RNA. Interestingly, most subjects had a subsequent loss of the M184V mutation. These results suggest that NRTIs may retain direct antiviral activity against the resistant variant [131].

One controlled clinical trial that included lamivudine in a subsequent regimen after the development of an M184V mutation has shown no benefit [132]. However, lamivudine retains antiviral activity even in the face of complete phenotypic resistance [133]. Campbell and coinvestigators [134] recently demonstrated that withdrawal of lamivudine from a failing antiviral regimen led to an average increase of 0.5 $\log_{10}$ in viral load. This adds further support to the notion that lamivudine retains some of its activity even in the presence of genotypic resistance. If, on the basis of resistance testing, there are more potent NRTIs available, then these can be used with or instead of lamivudine.

In those patients with no current active therapy options, lamivudine may contribute to a salvage regimen even in the presence of high-level genotypic resistance. This situation has led to the possibility of treating patients with lamivudine monotherapy. This strategy has only been used, however, in the setting of treatment failure in patients with the M184V mutation and a CD4 count >500 cells/μL. In a randomized trial comparing the immunological and clinical outcomes of lamivudine monotherapy and complete therapy interruption, 58 treatment-experienced patients harbouring lamivudine-resistant virus were studied. By week 48, in intention-to-treat analysis, immunological failure (CD4 count falling to <350 cells/μL) or clinical failure (grade B or C clinical event) occurred in 69% (20 of 29) of the persons in the structured treatment interruption group and 41% (12 of 29) of the persons in the lamivudine-monotherapy group. Lamivudine monotherapy

significantly delayed CD4 cell count decline and reduced viral load rebound compared with treatment interruption and only patients in the treatment interruption groups experienced clinical failure. Disappearance of resistant variants was reduced and replication capacity was significantly lower in the lamivudine group, implying a beneficial effect of impaired viral fitness [135].

A judicious selection of maintenance therapy is required in these patients, guided by resistance testing as well as considerations of tolerability. Each case should be judged on its merits, but as general guidance:

- it is preferable to select NRTIs to which the patient already shows extensive resistance;
- attempts should be made to induce or maintain resistance patterns known to be associated with reduced viral fitness, including exploitation of antagonisms between resistance pathways and potential hypersusceptibility effects;
- the immunological efficacy of the regimen should be reviewed closely.

It should be understood that standard genotypic (and phenotypic) testing does not necessarily reflect virological changes that may impact on immunological success and the preservation of future treatment options. It should be remembered that the strategy of using incompletely suppressive regimens will always be a short-term one. It is only relevant until a regimen likely to suppress viral replication completely can be found.

7.0 New drugs

7.1 Etravirine (TMC-125)

Etravirine has activity against both wild-type and NNRTI-resistant HIV. The current dose of etravirine is 200 mg taken twice daily with food and is available as a 100 mg oral tablet formulation. A 25 mg tablet has been developed for use in paediatric trials.

7.1.1 Pharmacokinetics

Etravirine is an inducer of cytochrome P450 3A4 and has some clinically significant interactions with other antiretroviral drugs. With tipranavir/ritonavir, the area under the curve (AUC) for etravirine is decreased by 76%, while etravirine increases the AUC for amprenavir by 69% when given with fosamprenavir/ritonavir. Co-administration of etravirine and raltegravir requires no dose adjustment of either drug. Etravirine can be co-administered without dose adjustment with atorvastatin, methadone, the oral contraceptives ethinyl estradiol and norethindrone, omeprazole, rifabutin, and the H_2-receptor antagonist ranitidine.

7.1.2 Resistance

Etravirine has a higher genetic barrier to resistance than the other NNRTIs. Recent data from the phase III DUET studies have identified 17 NNRTI resistance mutations associated with reduced response to etravirine: V90I, A98G, L100I, K101E, K101H, K101P, V106I, E138A, V179D, V179F, V179T, Y181C, Y181I, Y181V, G190A, G190S and M230L [335]. At least three etravirine-associated mutations must be present for the virological response to be significantly reduced though mutation-weighted scores are being developed and fold change may also be important. The common K103N NNRTI mutation is not on this list.

7.1.3 Efficacy, safety and tolerability

The phase III DUET-1 and -2 trials were important registrational studies of etravirine that compared etravirine 200 mg twice daily with placebo, each combined with an optimized background regimen including darunavir/ritonavir 600/100 mg twice daily plus optimized NRTIs, with or without enfuvirtide, in treatment-experienced patients with documented resistance to NNRTIs and at least three primary PI resistance mutations. After 24 weeks, significantly more patients in the etravirine arm achieved HIV RNA <50 copies/mL compared with those in the placebo group (56 *vs.* 39% in DUET-1; $P = 0.005$ and 62 *vs.* 44% in DUET-2; $P = 0.003$). After 48 weeks, 61% of patients in the etravirine arm achieved HIV RNA <50 copies/mL compared with 40% of those in the placebo group [136].

Etravirine was well tolerated. Apart from rash, there were no other noticeable differences, in particular in central nervous system (CNS) disturbances, between the etravirine and placebo arms. Reported rashes were usually mild with only 1–1.4% of patients having a grade 3 rash while none had a grade 4 rash [110,112,136–140].

7.2 Maraviroc

Maraviroc is the first CCR5 receptor antagonist licensed for the treatment of HIV infection. Maraviroc binds to CCR5, preventing HIV from binding to this receptor. When CCR5 is unavailable, CCR5-tropic HIV cannot engage a CD4 cell to infect the cell. The CCR5-tropic variant of the virus is common in earlier HIV infection, whereas viruses adapted to use the CXCR4 receptor gradually become dominant as HIV infection progresses [141,142]. The recommended dose of maraviroc is 150, 300 or 600 mg twice daily depending on interactions with co-administered medicines and may be taken with or without food.

7.2.1 Pharmacokinetics

Maraviroc is a substrate of the cytochrome P450 enzyme system (CYP3A) and *p*-glycoprotein, and has clinically significant interactions with many medications, including

other antiretroviral agents. Inhibitors of CYP3A such as PIs (other than tipranavir) substantially increase the serum concentration of maraviroc. Inducers of CYP3A such as efavirenz may significantly decrease serum maraviroc concentrations if given without a strong CYP3A inhibitor. However, maraviroc does not appear to cause clinically significant changes in concentrations of other medications. Please refer to the summary of product characteristics (SPC) of maraviroc.

7.2.2 Resistance

Maraviroc was not effective against CXCR4-tropic or mixed- or dual-tropic virus in phase II efficacy studies [143]. Co-receptor tropism should be determined prior to using maraviroc. Current tropism assays may not reliably detect dual or mixed tropism and tropism may change with disease progression. In the MOTIVATE studies, around 8% of patients with exclusively CCR5-tropic virus at the time of screening were found to have dual- or mixed-tropic virus 4–6 weeks later. This may be either because of the emergence of previously undetected CXCR4 or because of tropism shifts. Dual/mixed or CXCR4 tropism was identified in nearly 65% of patients tested after treatment failure compared with approximately 5% of placebo recipients with treatment failure. Emergence of CXCR4 virus therefore appears to be a more common cause of virological failure than the development of resistance mutations [144].

7.2.3 Efficacy, safety and tolerability

Maraviroc was studied in patients with advanced HIV disease, prior exposure or documented resistance to at least three classes of antiretroviral drugs, and an HIV RNA $\geq$ 5000 copies/mL. MOTIVATE 1 and 2 are randomized controlled phase IIb/III studies that compared maraviroc with placebo, each given in combination with an optimized background regimen. All subjects had CCR5-tropic HIV-1. In pooled analysis, the groups that received maraviroc (dosed either once or twice daily) had superior virological outcomes at 24 and 48 weeks. At week 48, the group that received maraviroc twice daily had greater mean decreases in HIV RNA (1.84 *vs.* 0.78 $\log_{10}$ copies/mL) and higher rates of viral suppression to $<$400 copies/mL (56.1 *vs* 22.5%) and to $<$50 copies/mL (45.5 *vs* 16.7%) than the group that received placebo. These differences were statistically significant ($P = 0.0001$) [118].

The correlation of the efficacy of maraviroc-containing regimens with the number of other active antiretroviral agents used concomitantly indicates the importance of including at least two agents with potent activity in the antiretroviral regimen [117,146].

Maraviroc was also studied in a naïve to treatment population with a zidovudine/lamivudine backbone and efavirenz as the comparator arm [145]. The once-daily dosing arm was less effective and was stopped early. In this noninferiority study, the lower confidence limit for noninferiority (10%) at 48 weeks was not reached for the 50-copy viral load assay comparing efavirenz with maraviroc. However, the primary endpoint was reached using the 400-copy assay.

7.3 Integrase inhibitors

Integrase inhibitors target the viral integrase enzyme, which plays an important role in the viral life cycle. The integrase inhibitors that are the furthest in clinical trial development are raltegravir (formerly MK-0518) and elvitegravir (formerly GS9137). Currently, phase III trials of raltegravir in treatment-naïve and treatment-experienced patients are ongoing and it has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for use in treatment-experienced patients. Elvitegravir is going into phase III development for treatment-experienced patients. It is metabolized by CYP3A4 and, in studies carried out to date, it has been administered with ritonavir, allowing once-daily dosing; raltegravir is given twice daily.

7.3.1 Raltegravir in treatment-experienced patients

BENCHMRK-1 and -2 are parallel phase III studies in which patients were randomly allocated in a ratio of 2:1 to receive raltegravir 400 mg twice daily or placebo, each combined with an optimized background regimen (OBR). At week 48, 65 and 60% of patients in the raltegravir plus OBR arms had an HIV-1 RNA $<$50 copies/mL compared with 31 and 34% in the placebo arms ($P <0.001$) in BENCHMRK-1 and -2, respectively. A small subset of patients had received enfuvirtide and/or darunavir for the first time as part of their background regimen in combination with raltegravir ($n = 44$), and 98% had HIV-1 RNA $<$400 copies/mL at 16 weeks. At 48 weeks, among the subgroup with a genotypic sensitivity score (GSS) of $\geq$2, 75% of patients in the raltegravir arm compared with 59% in the placebo arm achieved HIV RNA $<$ 50 copies/mL in a combined analysis of BENCHMRK-1 and -2; figures for a GSS of $\geq$1 were 67 and 37% for the raltegravir and placebo arms, respectively [147,148].

7.3.2 Resistance

Genotype analyses were available for 41 of the 76 patients with virological failure on raltegravir. Two pathways of resistance have been characterized, with either N155H or Q148K/R/H being predominant and arising relatively quickly after virological failure [114,115,149].

7.3.3 Raltegravir in treatment-naïve patients

Protocol 004 is a phase IIb/III dose ranging study of raltegravir combined with tenofovir plus lamivudine for 48

weeks, compared with an efavirenz control arm. At week 24, there were no significant differences in response among any of the arms, with around 80% of patients in each arm having an HIV RNA <50 copies/mL, and this response was maintained through to week 96 [334].

The rate of fall of viraemia was more rapid and the time to reach an HIV RNA <50 copies/mL was shorter with raltegravir than with efavirenz. More than half of the patients in each of the raltegravir arms had HIV RNA levels <50 copies/mL by week 4. Whether this phenomenon has a clinical significance is unknown.

No raltegravir dose-related toxicities have been identified at this time. Lipid increases were observed with efavirenz but not with raltegravir [150–153].

8.0 Treating patients with chronic hepatitis B or C

This section should be read in conjunction with the BHIVA hepatitis B or hepatitis C management guidelines [154,155], which are scheduled for revision in 2009.

Coinfection with HIV increases the rate of progression to cirrhosis and liver cancer by four- to five-fold for people with chronic hepatitis B or C compared with hepatitis mono-infected individuals [156–159]. The mortality rate of untreated dual HIV/hepatitis B virus (HBV)- or HIV/hepatitis C virus (HCV)-infected patients is approximately 10 times higher than that of patients with either infection alone [156–159]. There is accumulating evidence that appropriate ART greatly reduces the rate of progression to cirrhosis and death in coinfected patients [156,160,161]. It is also clear that, in HIV coinfected people, the chance of cure of HCV infection with specific therapy and the ability to suppress HBV viral replication with sustained disease amelioration are significant [162–164]. Therefore, specific consideration for the treatment of patients coinfected with HIV and HBV or HCV has increased in importance, as the prognosis of HIV has so dramatically improved.

8.1 Hepatitis B

8.1.1 When to treat

There is a correlation between CD4 cell count and liver-related mortality in HIV/HBV coinfection [161,165–167] and this mortality is reduced if ART is started at a CD4 count >200 cells/μL. It is unclear if there is an upper limit at which CD4 cell count is associated with better prognosis with regard to liver disease, but treatment should be started at a CD4 count of 350 cells/μL if possible. In patients with a higher CD4 cell count the hepatitis B should be treated according to criteria described in the coinfection guidelines [153]. This would include patients who are HBV 'e' antigen positive (HBeAg + ve), have HBV DNA $>10^4$ copies/mL, have cirrhosis or need to reduce serum HBV DNA levels for other reasons. The choice of therapy currently would be either (a) specific anti-HBV treatment (adefovir, pegylated interferon or telbivudine alone or in combination) or (b) commencing ART with HBV-active antiretroviral drugs (see below) [154,162–164,168]. Entecavir can only be used with ART because monotherapy without concurrent ART can induce the M184V (lamivudine/emtricitabine resistance) mutation in HIV [169].

8.1.2 What to treat with

There are three licensed antiretroviral drugs that also have significant anti-HBV activity: lamivudine, emtricitabine and tenofovir [162–164]. All are very effective at suppressing HBV DNA and normalizing aminotransferase levels when used in the long term, but HBeAg to anti-HBe seroconversion is less likely than in HIV-negative patients. However, acquired resistance to lamivudine or emtricitabine develops rapidly when either drug is used as the sole anti-HBV agent [170]. Tenofovir resistance seems to be very infrequent [162,164,168,170]. Combining tenofovir with lamivudine or emtricitabine is effective in the short term (up to 2 years) at reducing HBV DNA, normalizing aminotransferase levels and inducing HBeAg seroconversion [162,164,168,171,172]. Evidence also suggests that lamivudine or emtricitabine resistance is reduced when lamivudine or emtricitabine is given in combination with tenofovir, with no tenofovir resistance reported [162,164,168,172]. Therefore, all patients given triple ART, who have replicating HBV, should receive tenofovir or tenofovir plus lamivudine or emtricitabine as part of the regimen. This anti-HBV therapy should be continued even if HIV resistance occurs, when up to three other antiretroviral agents should be added to ensure effective HIV therapy.

8.2 Hepatitis C

8.2.1 When to treat

There is strong evidence that in HIV/HCV coinfected patients liver disease progression is worse in patients with high viral loads and low CD4 cell counts. Hepatic fibrosis worsens as the CD4 cell count falls and this effect is seen at CD4 counts <500 cells/μL [173–175]. There is also evidence that ART slows the progression of liver disease and reduces liver-related mortality by about 50% [156,160]. Therefore, all patients with a CD4 count of <350 cells/μL should be started on ART and treatment should be considered for those in the range 350–500 cells/μL. Chronic hepatitis C can be treated effectively in HIV-positive patients with pegylated interferon and weight-based ribavirin with overall response rates varying

from 14 to 73% according to genotype and viral load [176–179]. Response is better in patients with higher CD4 cell counts, but there is an interaction between several antiretroviral drugs and ribavirin (see below). Acute hepatitis C also responds to treatment with pegylated interferon and ribavirin in about 70% of patients [180]. Therefore, in patients with a CD4 count above 350 cells/μL not already on ART and who are being considered for specific anti-HCV therapy, it may be best to defer ART until the HCV therapy has finished.

8.2.2 What to treat with

Because of significant interactions with ribavirin, the following antiretroviral drugs should be avoided if anti-HCV therapy is contemplated: zidovudine (anaemia); didanosine or stavudine/didanosine (lactic acidosis) [181,182]. There is also evidence that abacavir may interact with ribavirin, reducing its efficacy, and therefore abacavir should be avoided if possible until further information is available [183].

8.2.3 Avoiding antiretroviral hepatotoxicity

All antiretroviral drugs have the potential to cause acute and long-term hepatotoxicity and this risk is increased two- to three-fold in the presence of chronic liver disease such as that caused by hepatitis B or C. This increased risk of hepatotoxicity largely disappears if the hepatitis is successfully treated [184]. Patients should therefore be carefully monitored for hepatotoxicity when HAART is commenced or changed. There is some evidence that the risk of hepatotoxicity with nevirapine and high-dose ritonavir (1000 mg/day) is higher than with other ARTs [185,186], and nevirapine may also be linked to increased liver fibrosis [186,187], although not all studies show this [188]. High-dose ritonavir is no longer recommended in ART and low-dose ritonavir (in doses used to boost other PIs) is not associated with significant liver problems. It is therefore recommended that nevirapine is only used cautiously in HIV/HBV or HIV/HCV coinfected individuals.

8.2.4 Recommendations

- All patients with active hepatitis B (HBeAg positive or HBV DNA $>10^4$ copies/mL or cirrhosis with HBV DNA at any level) should be started on ART if the CD4 count is <350 cells/μL.
- All patients who require antiretroviral and anti-HBV therapy should receive tenofovir or tenofovir plus lamivudine or emtricitabine as part of the regimen. Lamivudine or emtricitabine should not be used alone or in combination with each other. If showing continuing anti-HBV activity, tenofovir and lamivudine/emtricitabine should not be stopped when changing the antiretroviral regimen because of HIV resistance. This, therefore, may mean adding three further antiretroviral agents.
- For patients requiring HBV therapy who have a CD4 count >350 cells/μL, the choice of therapy is between the use of non-ART anti-HBV therapy and early commencement of ART as above. Entecavir should be avoided.
- All patients with chronic hepatitis C should be assessed for treatment with pegylated interferon and weight-based ribavirin. Ideally, anti-HCV therapy should be given before ART is commenced and when there is a high CD4 cell count.
- If ART needs to be started then zidovudine, didanosine, stavudine/didanosine and probably abacavir should be avoided in any patient who is going to be commenced on anti-HCV therapy.
- Nevirapine and high-dose ritonavir (>1000 mg/day) should be avoided if possible in all patients with active liver disease including those with chronic HBV and HCV infection.

9.0 Guidelines for the management of metabolic complications in HIV infection

The metabolic complications in HIV infection are multifactorial in origin and may include uncontrolled HIV replication or interrupted HIV replication, coinfection particularly with HCV and the effect of different antiretroviral drugs [29,189–191]. The SMART study [192] has shown excess risk of CVD among patients receiving intermittent ART. A subanalysis of the same study [192] showed that treatment interruptions were associated with a lowering of all lipids, including both total and high-density lipoprotein (HDL) cholesterol, but a large increase in inflammatory and coagulation markers, which correlated with an increase in HIV RNA level [193]. This leaves the reasons for the observed elevated risk of cardiovascular events still uncertain, but inflammatory and atherogenic factors, such as pro-inflammatory cytokines driven by uncontrolled viral replication, may play an important role.

In the absence of robust evidence, treatment plans for metabolic complications in HIV infection are mainly developed from the medical guidelines for general populations.

9.1 Lipid abnormalities

Lipid disorders are common in HIV-infected patients, even in those who are treatment-naïve [194]. Antiretroviral

therapy can ameliorate or worsen the problem. The effects of different antiretroviral therapies can vary [195–198], even in the same class. Kaletra primarily raises triglycerides, whereas atazanavir does not significantly perturb any lipid fraction. Switching from a PI-based regimen often improves lipid parameters [199,200]. Nevirapine but not efavirenz can increase HDL cholesterol (HDL). In the 2NN study, the total cholesterol-to-high density lipoprotein (TC:HDL) ratio improved significantly with nevirapine but remained unchanged with efavirenz. There was initial improvement with efavirenz but the effect disappeared with time, which was not the case with nevirapine [44].

The effects of different NRTIs can also vary. Tenofovir-containing regimens have better lipid profiles compared with regimens containing zidovudine and stavudine [201,202]. Switch studies have shown better TC, LDL cholesterol (LDL) and triglyceride (TG) but not HDL profiles in the tenofovir group compared with the abacavir group [202,203].

9.1.1 Evaluation of risk

Evaluation of CVD risk could begin with a nonfasting lipid profile [199] including TC and HDL (TC:HDL ratio). The lipid profile should be repeated within 3–6 months of HAART initiation, and then annually. In view of the potential for HIV to increase cardiovascular risk, patients naïve to HAART or off HAART should also have cardiovascular risk assessment and appropriate advice or management given to at least Joint British Societies guideline standards [204].

Target lipid levels depend on the cardiovascular risk of the individual (www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm) which include age, sex, cigarette smoking, systolic blood pressure, TC:HDL ratio and family history of premature coronary heart disease.

9.1.2 Which calculator to use

The 10-year risk of developing CVD should be calculated using the Framingham calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp) or from cardiovascular risk prediction charts (Joint British Societies/British National Formulary; http://cvrisk.mvm.ed.ac.uk/calculator/bnf.htm). However, most of the risk calculation is based on data available for people of mainly white ethnic origin. These data may be less accurate for people of nonwhite ethnic origin for whom the ETHRISK calculator (www.epi.bris.ac.uk/CVDethrisk/CHD_CVD_form.html) can be used; however, this risk calculator has not been validated in independent populations.

9.1.3 Treatment of lipid disorders

Therapeutic lifestyle changes in the form of cessation of smoking (referral to smoking cessation clinic), dietary changes (moderation of alcohol intake, more fruits and vegetables, avoidance of saturated fat), and regular physical exercise (30–60 min of aerobic exercise 5–7 days a week) should be considered for each patient (for details, please see http://odphp.osophs.dhhs.gov/pubs/guidecps/pcpstoc.htm).

9.1.4 Switching ART

Viral suppression is the key to success and switching should be considered while keeping viral suppression as the priority.

Switching from a PI-based regimen to an NNRTI regimen [202] or switching to another PI with a better lipid profile has been found to be successful [205,206]. Replacing stavudine and zidovudine with a tenofovir-containing regimen is another option, particularly when lipoatrophy is the main concern [202,207].

An association of abacavir and of didanosine with increased cardiovascular risk was observed in a recent analysis of the D:A:D study. This association has yet to be fully substantiated or explained, but might be a consideration in the choice of therapy, or possible change of therapy, for patients with substantially raised cardiovascular risk [85].

9.1.5 Lipid-lowering treatments

Pharmacological agents are considered when lifestyle changes, with or without modification of ART, fail to lower the lipids to target levels.

The use of statins and fibrates is appropriate for the management of dyslipidaemia, although a relatively small proportion of individuals are reported to have achieved response goals [208] as outlined in the Joint British Societies' guidelines [204].

9.1.6 Which agents to use

Pravastatin and fluvastatin have the least potential for drug interaction but are less potent lipid-lowering agents. Atorvastatin can be used but caution should be exercised in patients taking PIs, as extensive safety data are lacking. Rosuvastatin is very potent but should be used with caution as blood levels can increase with ritonavir. Simvastatin and lovastatin are contraindicated in patients taking PIs. With NNRTIs, higher doses of statins may be needed.

Lipid-lowering agents and antiretroviral drugs may have potential interactions at the level of CYP3A4, but the effect can be different with different drugs and caution should be exercised before use [206–209].

- The metabolism of fluvastatin is not dependent on CYP3A4 and interactions are not expected with unboosted or ritonavir-boosted PIs.
- Co-administration of lovastatin or simvastatin and unboosted or ritonavir-boosted PIs is contraindicated

because of the potential for serious reactions such as risk of myopathy including rhabdomyolysis.
- Fibrates: primarily conjugated with glucuronic acid and excreted in urine, *in vivo* metabolism data indicate that fenofibrate does not undergo CYP450 metabolism. Co-administration with PIs is safe.
- Fish oil: clinically relevant drug–drug interactions between omacor and PIs or NNRTIs are not expected.
- Cholesterol absorption inhibitor: ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation. Inducers and inhibitors of such metabolic pathways may alter ezetimibe concentrations; pharmacokinetic studies evaluating antiretroviral drugs and ezetimibe co-administration are ongoing.
- Nicotinic acid: excreted in urine and drug interactions with antiretroviral drugs are unlikely to occur; further studies are needed.

The probability of developing liver and muscle damage increases when fibrates and statins are used together and expert guidance should be considered before combining these two classes.

Routine laboratory monitoring includes hepatic transaminase levels at baseline, 4–12 weeks after initiation of treatment, and then annually if within normal limits. Lipid levels should be tested 4–12 weeks after initiation and annually when target levels are reached.

9.2 Insulin resistance and diabetes

Insulin resistance is an important and under-recognized consequence of HIV treatment. Diabetes mellitus occurred in 7% of patients with fat atrophy or fat accumulation in one study, which was 14 times commoner than in healthy, matched controls [209,210]. The risk increases further with HCV coinfection [190,211].

Although PIs are the main drug class implicated in insulin resistance, the Women Interagency HIV Study has shown an association of increased risk of diabetes with cumulative exposure to NRTIs [212]. Although most PIs are associated with significant glucose intolerance, saquinavir has relatively little effect, and atazanavir has no discernible effect [213,214]. Another study using boosted lopinavir and tipranavir with a backbone of tenofovir and lamivudine did not show any evidence of insulin resistance at 48 weeks' therapy, but this was present when boosted lopinavir and tipranavir were used with zidovudine [215,216].

9.2.1 Recommendations for assessment and monitoring of insulin resistance

- Fasting glucose should be assessed before starting treatment and then 3–6 months after starting treatment. The recently published International Diabetic Federation (IDF) guideline (www.idf.org) [217] suggests that patients with fasting plasma glucose levels 5.6 mmol/L or above should be offered an oral glucose tolerance test (OGTT).

9.2.2 Treatment

In the presence of an impaired fasting glucose (IFG) level or impaired glucose tolerance test (pre-diabetic), patients should follow dietary advice and do regular physical exercise, and a change of antiretroviral drug, if possible, should be considered.

For patients with persistent hyperglycaemia or established diabetes, guidelines should be followed as in the general population [204,217].

Metformin should be avoided for lipoatrophic patients [218]. Other oral hypoglycaemic agents including sulfonylureas (gliclazide and glipizide), glinides, exenatide and α-glucosidase inhibitors should be used with caution as there is currently no evidence on the use of these drugs in the treatment of HIV-infected patients. If the treatment target cannot be reached with oral agents, insulin should be started.

Acetylsalicylic acid or aspirin (75–150 mg/day) should be considered in all patients with diabetes [204].

9.3 Prevention and management of lipodystrophy

The estimated prevalence of HIV-associated lipodystrophy depends on both the extent of investigation and examination, and the patient population concerned (particularly in relation to age and antiretroviral use). This is reflected in a reported prevalence of between 11 and 83% in cross-sectional studies [219–221].

9.3.1 Assessment of lipodystrophy

Different cross-sectional imaging techniques have been used for the assessment of lipodystrophy [222–225]. Magnetic resonance imaging (MRI) scans and dual-energy X-ray absorptiometry (DEXA) scans may have merits but are not used in routine clinical practice mainly because of cost and limited availability. A clinical case definition, based on physician and patient agreement, is of limited value for individual patient management because of lack of specificity and we do not recommend its routine use. Anthropometric measurements are safe but need uniformity and more training and specificity. Routine use of waist measurement annually could be useful; however, ethnic-specific cut-off levels are lacking.

9.4 Management of lipoatrophy

Modification of ART by replacing stavudine or zidovudine with tenofovir or abacavir should be considered [207,226]. Antiretroviral therapy modification has been shown to partially restore subcutaneous fat (increasing total limb fat by 400–500 mg/year).

Switching to a regimen not including NRTIs can allow recovery of total limb fat [227]. However, it may increase the risk of dyslipidaemia when used with boosted PIs other than atazanavir [228].

9.4.1 Surgical intervention

This is offered for corrective relief for facial lipoatrophy only. Polylactic acid (PLA) is immunologically inert, causing only a limited inflammatory response, and the majority of patients do well after three or four injections [229–233]. However, funding can be a problem. Hyaluronic acid and collagen produce similar effects but are less durable and repeated injections are often needed after 3–6 months [234]. Transplanting autologous harvested fat cells is more invasive and requires general anaesthesia and hospitalization [235].

Polyalkylamide (Bio-Alcamid) is a permanent filler that has been demonstrated to correct HAART-associated lipoatrophy without significant side effects [236,237]. However, there is a general concern with permanent fillers that, if lipoatrophy continues to worsen, the edges of the filler may become visible and if fat mass increases (after switching NRTIs) the permanent filler may over-correct the original defect and become obvious.

In the majority of cases of mild facial lipoatrophy associated with a thymidine-containing combination, a switch to a nonthymidine HAART should be tried. Where moderate facial lipoatrophy exists or in milder disease when zidovudine or stavudine cannot be switched, PLA is recommended as the facial filler of choice. For patients with severe lipoatrophy, it is unlikely that PLA will correct the defect, and Bio-Alcamid may be preferable although long-term safety data are lacking.

Pharmacological intervention to treat lipoatrophy has not been previously effective and may introduce new complications.

9.5 Lipohypertrophy

The anatomical sites of fat deposits include the abdomen (visceral), breast tissue and head-neck region (dorsocervical, submandibular, trapezio-occipital and mastoid).

9.5.1 Prevention

There is no proven strategy for prevention of lipohypertrophy. Weight gain is expected with effective ART. Hence, weight reduction or avoidance of weight gain may decrease visceral adiposity.

9.5.2 Pharmacological intervention

Metformin decreases visceral adiposity and has its best effects in the presence of insulin resistance [238,239]. It should not be used when there is a low body mass index (BMI). Anabolic steroids have failed to show any good response in the presence of normal blood testosterone levels and should be avoided. Growth hormone analogues have shown some promising results in initial studies; however, the long-term effect is not known. Lipid profile and insulin sensitivity appear to be better with the drug compared with growth hormones [240,241]. Tesamorelin (previously known as GH9507), a growth hormone-releasing hormone analogue, showed a significant reduction in visceral adipose tissue, noted by both patients and physicians. There was improvement in adiponectin, insulin-like growth factor 1 (IGF-1), lipid profile and glucose profile [242].

9.5.3 Surgical therapy

Treatment options include standard surgical removal and liposuction (ultrasound assisted or tumescent). Using liposuction, reduction of posterior lipohypertrophy is markedly more successful than that of submandibular fat. However, up to half of those with dorsocervical disease develop a recurrence after 1–2 years. Where significant fat has accumulated around the breast, surgery is an option. Breast reduction surgery is invasive and needs to be discussed carefully. Again, there is the possibility of fat return, especially if the patient cannot be established on a PI-sparing regimen. Surgery is not an option for patients with abdominal lipohypertrophy.

9.6 Lactic acidosis and hyperlactataemia

Lactic acidosis is a very rare but life-threatening condition requiring immediate withdrawal of ART (and any other possible contributory agents), exclusion of other causes and other supportive measures [243,244]. Hence, every clinician seeing patients with HIV infection needs to be aware of the full spectrum of possible clinical presentations, and should have a high index of suspicion.

Hyperlactataemia is often asymptomatic [243] and intervention is not required but the individual should be carefully monitored with repeat lactate samples taken uncuffed and at rest. The clinical significance of hyperlactataemia is not established and routine screening of asymptomatic individuals is not currently recommended.

10.0 Recommendations for resistance testing

10.1 Treatment-naïve patients

The prevalence of drug resistance among treatment-naïve patients in the UK is around 8% [245,246]. Prevalence rates have declined in recent years, but previous estimates may have been confounded by selection bias. Although the highest rates of resistance are seen in patients born in the UK [247], rates are increasing in countries currently expanding access to ART [46,248–250] and may soon start to rise among immigrant populations as a result. In some cases, the presence of resistance in an apparently drug-naïve patient may in fact reflect previous undisclosed therapy. There is increasing evidence to indicate that transmitted resistance negatively impacts on treatment responses, particularly in the context of NNRTI-based regimens [251–256].

Testing for resistance is recommended in all newly diagnosed patients. This includes patients with acute seroconversion, established infection or infection of unknown duration, regardless of demographic characteristics, ethnicity or risk group.

The most appropriate sample is the one closest to the time of diagnosis and this should preferably be tested at the time of initial presentation. Although transmitted resistance often remains detectable in plasma for several years [257–260], gradual reversion to low-frequency and archived mutants occurs over time [261–263]. Reversion may occur through intermediates (or 'revertants', e.g. T215D/N/S from T215Y/F). Detection of revertants should be interpreted as an indication that fully resistant mutants are present as either low-frequency quasispecies or archived resistance.

For existing patients who have not undergone resistance testing at the time of diagnosis, testing is recommended at the time of starting therapy. Whenever possible a plasma sample collected as close as possible to the time of diagnosis should be retrieved for retrospective testing. When a stored sample is not available a current sample should be tested.

Following resistance testing at the time of diagnosis, repeat testing is not routinely recommended prior to starting therapy, although it should be considered in selected persons who may have experienced re-infection. The true risk of superinfection remains to be determined but may be significant in persons who engage in high-risk behaviour [264], especially in early infection [265]. Triggers to repeat testing may include a sudden increase in viral load, a sudden drop in the CD4 cell count, and a recurrence of symptoms of acute HIV infection [23]. It should be noted, however, that most patients with sudden changes in viral load and CD4 cell counts do not have evidence of superinfection [266].

Resistant variants present at low frequency (< 20–25%) within the viral quasispecies are missed by routine resistance tests. Low-frequency mutants can impact negatively on responses to therapy, especially in the context of NNRTI-based regimens [101,255,256,267]. Although assays to detect minority species have been developed, they are not routinely available and remain research tools only. In patients without evidence of drug resistance by routine methods, a suboptimal virological response to first-line therapy (< 1 $\log_{10}$ copies/mL reduction in viral load by 4–8 weeks) should prompt resistance testing at that time.

Genotypic resistance tests are recommended in drug-naïve persons, as they are more sensitive and cost-effective than phenotypic tests for the detection of transmitted drug resistance.

10.2 Treatment-experienced patients

The prevalence of drug resistance has declined among treatment-experienced patients in the UK as a result of improved management of ART and treatment failure. Currently, approximately half of treated patients undergoing testing show evidence of drug resistance and around 11% have evidence of triple-class resistance mutations affecting the NRTIs, NNRTIs and PIs [245,268,269]. Resistance testing is recommended in all patients experiencing virological failure while on treatment and changes in therapy should be guided by the results of resistance testing in these patients.

Manufacturers and providers of resistance tests generally recommend a viral load of at least 1000 copies/mL to reliably provide a result. It is possible to obtain results at viral loads < 1000 copies/mL, although the methods used and the success rates vary from laboratory to laboratory [270,271]. The arbitrary cut-off is in part a reflection of the reduced sensitivity of the resistance assays at low viral loads. In addition, there exist reservations as to the accuracy of results obtained from low levels of genome sampling when few viral particles are present. Laboratories should be aware that, where testing is performed at low viral load, there is an increased risk of erroneous results as a consequence of polymerase chain reaction (PCR) contamination [271]. Clinicians are encouraged to discuss and agree the required viral load cut-off for testing with their service providers.

It is recommended that confirmation of virological rebound is rapidly obtained in patients with previously

undetectable viral load prior to performing a resistance test. Resistance testing of viral load 'blips' (defined as one viral load measurement of a few hundred copies/mL preceded and followed by undetectable measurements) is not routinely recommended [96].

Resistant mutants selected during therapy are rapidly outgrown by wild-type virus once therapy is discontinued [272]. To be informative, resistance testing should be performed on samples taken while the patient is on therapy. Despite the apparent disappearance, however, resistant mutants persist at low frequency in the quasispecies and as archived resistance in latently infected cells [273], and can re-emerge rapidly if selective pressure is re-introduced. Interpretation of resistance should take into account the results of all tests performed during the patient's treatment history ('cumulative genotype').

Patients who simultaneously interrupt all drugs in an NNRTI-based regimen are likely to experience a prolonged period of NNRTI monotherapy with a resulting high risk of resistance. Similar considerations apply to women who have experienced single-dose nevirapine for the prevention of mother-to-child HIV transmission [274]. It has been suggested that the impact on responses may not persist past the first 6 months after exposure to NNRTI monotherapy [275], probably reflecting the progressive decline of resistant mutants within the quasispecies in the absence of drug pressure [276]. Pending further data to confirm this finding, it is recommended that the potential impact of NNRTI resistance is regarded as long term in these patients [101].

The interpretation of resistance test results is complex. Although informative interpretation systems have been developed for both genotypic and phenotypic results, none is entirely accurate, and all are subject to change as new data become available. Interpretation is especially difficult with new drugs and this problem affects both genotypic and phenotypic resistance assays. Expert advice should be sought with complex or unusual resistance profiles. It is recommended that laboratories performing resistance testing should also provide expert support to their service.

Genotypic tests are widely available and represent the most cost-effective approach for resistance testing in treatment-experienced patients. In the case of complex mutational patterns, however, phenotypic tests can provide additional useful information.

The availability of new drugs and drug classes provides new treatment options for treatment-experienced patients with multidrug resistance. Clinical trials have repeatedly demonstrated the importance of the background regimen to support the activity of the new drugs [99,112,113,138,150,277–279]. Resistance testing and expert advice should be used to assist with the selection of the appropriate regimen in these patients.

Resistance to small-molecule CCR5 inhibitors occurs by one of two mechanisms [144,280]: the change of co-receptor use from CCR5 to CXCR4 and modifications in glycoprotein 120 (gp120). In most patients studied to date, the change of co-receptor use from CCR5 to CXCR4 appears to result from the outgrowth of pre-existing low-frequency CXCR4- and dual-tropic virus variants. A change in tropism can be demonstrated by phenotypic testing (e.g. the Trofile assay; Monogram Biosciences) [281]. Genotypic prediction software programs based on the sequence of the gp120 V3 loop alongside other parameters (e.g. CD4 cell count) have been developed (e.g. GENO2PHENO) and are currently under evaluation [282–284]. Modifications in gp120, especially in the stem of the V3 loop, allow the virus to enter cells through the occupied CCR5 co-receptor. The genotypic indicators of resistance have not been fully elucidated and phenotypic testing is required to demonstrate gp120-mediated resistance.

10.3 Key principles in the interpretation of antiretroviral resistance in treatment-experienced patients

Drugs have different genetic barriers to the emergence of resistance, reflecting the number of mutations required to confer resistance, the phenotypic effects of the mutations on drug susceptibility and viral fitness, the drug–target interactions, and the drug concentration. The genetic barrier is highest for ritonavir-boosted PIs, intermediate for most NRTIs, and low for lamivudine, emtricitabine, nevirapine, efavirenz and raltegravir. The genetic barrier of second-generation NNRTIs can be regarded as higher than that of nevirapine and efavirenz, especially in the context of a ritonavir-boosted PI-based regimen [110,112,138].

Resistance should be seen as a continuum. For the NRTIs, ritonavir-boosted PIs and second-generation NNRTIs, residual antiviral activity can be observed with intermediate levels of resistance. Increasing drug exposure may overcome low-level resistance, but the clinical utility of inhibitory quotients, which relate drug concentration to the level of either genotypic or phenotypic resistance, remains to be established prospectively.

Hypersusceptibility effects can be demonstrated *in vitro*, whereby certain drug resistance mutations confer resistance to some drugs but increase susceptibility to others. The clinical relevance of this is not clear and resistance test results reflecting these effects should be interpreted with caution.

Resistance mutations often reduce viral fitness and this can translate into a virological and immunological benefit. The benefit, however, is likely to be short lived as new mutations emerge that restore viral fitness ('compensatory mutations'). There is evidence that emergence of compen-

satory mutations can be especially rapid for the protease gene. The Replicative Capacity Assay (Monogram Biosciences) is a clinically available test that provides one measure of viral fitness. The clinical utility of the test has not been demonstrated. Viral load and CD4 cell counts are likely to provide a more immediate reading.

There are subtype-specific treatment-associated mutations that have unknown effects on drug susceptibility [285]. Overall, however, recognized mutations that confer resistance in subtype B also cause resistance in non-B subtypes and vice versa.

Current resistance assays target the reverse transcriptase, protease and envelope regions of HIV. There is increasing evidence that other viral regions, including gag for the PIs and RNase H for the NRTIs, play a role in drug resistance. In most cases these changes alone are not sufficient to confer resistance, but further evidence is awaited.

10.3.1 General recommendations

- Patients should be encouraged to have knowledge of their resistance test results.
- HIV clinics and laboratories should adopt strategies for ensuring that:
  - resistance test results are permanently recorded;
  - resistance test results are forwarded to the new centre of care in the case of a transfer;
  - sequences are stored should future re-analysis become indicated as new resistance data emerge.

11.0 Adherence

Low adherence to ART is strongly associated with detectable viraemia [286–289], progression to AIDS [290] and death [291–293]. The relationship between adherence and viral drug resistance is more complex: lower levels of adherence are associated with an increasing risk of resistance to NNRTIs but a reducing risk for unboosted PIs [294]. A relationship between low adherence and resistance to boosted PIs has not been observed but at a given level of adherence boosted regimens may reduce the risk of resistance in the nucleoside backbone [295]. The effect of low adherence on novel classes such as integrase and entry inhibitors is unknown.

11.1 Assessing adherence

Self-report provides a quick, inexpensive, nonintrusive estimate of adherence; patients reporting nonadherence are twice as likely to have detectable viraemia [296]. However, it overestimates adherence and agreement between different measures is poor [297]. Use of a combination of questions has been recommended, including items on 7-day recall, a 30-day visual analogue scale and whether doses were missed over weekends, because of side effects or because the patient simply forgot [298].

11.2 Interventions to support adherence

Several theoretical models of adherence behaviour have been proposed but there is no evidence to support the use of interventions based on any single theory over the alternatives [299]. Practical steps to reduce barriers to adherence (such as low mood, fear of disclosure, substance misuse and drug intolerance) and simplify regimens [300–302] remain important. An encouraging approach is likely to be more successful than an expectation of perfect adherence, which may reduce disclosure and drive patients to stop treatment completely [303]. Medication with a long elimination half-life may be more forgiving of late or sporadically missed doses and patients should be advised always to take rather than skip late doses [304].

Numerous trials of specific adherence interventions have been published, but they are typically underpowered [305]. A Cochrane review reported that the most beneficial interventions focused on practical skills in self-medicating (rather than psychological constructs such as motivation or self efficacy), addressed individuals rather than groups and were delivered over 12 weeks [306]. A meta-analysis of HAART adherence interventions demonstrated their modest efficacy [odds ratio (OR) 1.5; 95% CI 1.16-1.94]; effective interventions were brief educational interventions centred on practical issues of integrating HAART into daily life [307]. An observational study showed that pillboxes were associated with a significant 4% improvement in adherence and 0.3 $\log_{10}$ reduction in viral load and were cost effective [308]. A combination of individualized support and financial incentives for patients with a history of low adherence was associated with a reduction in plasma viral load but not with achieving <400 copies/mL [309] and the benefit may wane when the intervention ceases [310,311]. Directly administered therapy at a methadone clinic was associated with improved virological outcomes in an observational study [312]; however, a randomized controlled trial in a community setting showed no benefit [313].

Other unsuccessful interventions have included medication alarms [314], scripted telephone adherence support [315], frequent home visits [316] and courses of cognitive behavioural therapy [317]. A study combining written information for patients with brief training on adherence support for treating physicians showed no benefit in improving adherence in those patients with low adherence at baseline [318].

11.3 Costs

Economic modelling has shown that, in the context of their current low efficacy, adherence interventions need to cost <US$100 per month per patient and achieve a 10% reduction in treatment failure in order to remain below the conventional threshold of US$50 000 per quality-adjusted life-year; more expensive interventions could only be justified if they dramatically reduce failure by around 50% [319].

12.0 Pharmacology

More than for any other infection, patients receiving ART require their doctor to have a clear understanding of the basic principles of pharmacology in order to ensure effective and appropriate prescribing. This is especially the case in four therapeutic areas.

12.1 Drug interactions

The importance of considering the potential for drug interactions in patients receiving ART cannot be overemphasized. Drug–drug interactions may involve positive or negative interactions between antiretroviral agents, or between these and drugs used to treat other coexistent conditions [320]. A detailed list is beyond the remit of these guidelines but clinically important interactions to consider when co-administering with antiretroviral drugs include interactions with the following drugs: methadone, (oestrogen-containing) oral contraceptives, anti-epileptics, antidepressants, lipid-lowering agents, acid-reducing agents, certain antimicrobials (e.g. clarithromycin, minocycline and fluconazole), some anti-arrhythmics, tuberculosis therapy, anti-cancer drugs, immunosuppressants, phosphodiesterase inhibitors and anti-HCV therapies. Many of these interactions are manageable (i.e. with/without dosage modification, together with enhanced clinical vigilance) but in some cases (e.g. rifampicin and PIs, proton-pump inhibitors and atazanavir, and didanosine and HCV therapy) the nature of the interaction is such that co-administration must be avoided.

Where should the busy clinician turn when seeking to check for potential drug interactions? In addition to local drug information pharmacists, the University of Liverpool's comprehensive drug interaction website (www.hiv-druginteractions.org) is an excellent and highly recommended resource.

12.2 Therapeutic drug monitoring (TDM)

TDM has been shown to be very valuable in optimizing the management of certain patients; however, the general utility of this test (as with many other diagnostic investigations) in patients receiving ART has been poorly assessed. Although not recommended for unselected use, TDM may aid the management of vulnerable populations (e.g. children, pregnant women, and patients with extremes of BMI) or complex clinical situations (e.g. liver impairment, treatment failure, drug interactions both foreseen and unanticipated, malabsorption, suspected nonadherence, and unlicensed once-daily dosing regimens). More detailed recommendations for the use of TDM from an international consensus panel are available [321].

The window of opportunity for conducting clinical trials of TDM has probably closed for many parts of the world, but studies have evaluated cut-offs for inhibitory quotients (IQs), i.e. the ratio of drug exposure (usually the trough concentration) to some measure of HIV resistance (phenotypic, 'virtual' or genotypic), within the same individual. 'Genotypic' IQ targets have been established for lopinavir, fosamprenavir, atazanavir, saquinavir and tipranavir [321] although, as for TDM, none has been prospectively validated, and the tests are not yet widely available.

12.3 Stopping therapy

Whatever the reason for stopping ART (e.g. drug toxicity, intercurrent illness, after pregnancy, or patient choice), pharmacological issues must be considered in order for a clinician to give guidance. The half-life of each drug included in the regimen is critical. There is the potential for monotherapy or dual therapy if antiretroviral drugs with different half-lives are stopped simultaneously. The risk of resistance development is high when replicating virus is exposed to only one or two agents. Proposed stopping strategies [322] are: (1) simultaneous stop (for half-life balanced regimens: i.e. three short or long half-life drugs can be stopped simultaneously); (2) staggered stop (for unbalanced regimens: i.e. the long half-life drug or drugs are discontinued before the short half-life drugs of the regimen); (3) replacement stop (where the drug with the long half-life is replaced by a drug with a short half-life and a high genetic barrier for a short period of time; for example replacement of efavirenz with lopinavir/ritonavir; the correct length of lopinavir/ritonavir intake is unknown, but 4 weeks is probably advisable with this strategy); (4) protected stop (when the antiretroviral agents are stopped simultaneously despite their different half-lives and lopinavir/ritonavir is administered for 4 weeks); clinical data are being collected to investigate whether this strategy could be recommended.

12.4 Pharmacogenetics

Previously of more intellectual than clinical relevance, the influence of host genes on the response to ART has recently

transformed the use of abacavir through HLA testing (discussed in 'What to start with'), and pharmacogenetic considerations already constitute an integral part of the licensing of new and established drugs [323].

In order for any pharmacogenetic test to be clinically recommended, three conditions must be met, namely that the gene(s) of interest exerts a large or dominant effect, that a clinical scenario exists where knowledge of an individual's genotype could influence prescribing, and finally that pharmacogenetic testing is cost-effective. Of the many candidates investigated, including UGT 1A1 genotyping for hyperbilirubinaemia with atazanavir, CYP 2B6 genotyping for CNS toxicity with efavirenz and HLA-DRB1*0101 testing for nevirapine hypersensitivity, only HLA-B*5701 testing for abacavir hypersensitivity has currently fulfilled all three requirements [324].

13.0 HIV testing

At least a quarter of individuals first present for care in the UK with a CD4 count below 200 cells/μL. There are data to suggest that such individuals have a higher mortality in the earlier months of treatment. Many of these patients have previously come into contact with healthcare professionals often with an indicator disease that should have suggested the diagnosis. The recent UK Chief Medical Officer's "Dear Colleague" letter has promoted the need for more widespread testing for individuals at significant risk of having HIV, including those with indicator diseases or those in high-risk groups [325]. In 2002, the Centers for Disease Control and Prevention (CDC) suggested in the USA that any indicator disease with a prevalence of HIV of more than 1% should lead to a test for infection. Recent analysis has indicated that testing may be cost-effective down to a prevalence of 0.1% [326] because of earlier diagnosis leading to earlier treatment, fewer hospital admissions and reduced mortality. It is also possible that knowledge of HIV status might lead to both earlier treatment and behavioural change, which might reduce onward transmission of the virus and thus the scale of the epidemic. A recent update of the CDC guidance has suggested that testing should be performed for all individuals under 65 years of age coming into contact with the healthcare services on a regular basis [327].

The BHIVA, the British Association for Sexual Health and HIV (BASHH) and the British Infection Society (BIS) are currently developing new guidelines for HIV testing, but in the interim it is the Writing Group's view that the new point-of-care testing techniques should be more widely applied both in and outside conventional healthcare settings. Point-of-care testing in nontraditional environments needs to be piloted to ensure that it is cost-effective. While point-of-care testing is highly specific, the commonest reason for a positive test in a low-risk individual is still a false-positive result. Point-of-care testing is also less reliable in the so-called 'window period' after infection than current fourth-generation enzyme-linked immunosorbent assays (ELISAs) that incorporate a PCR for HIV RNA testing. The pre-test counselling required prior to HIV testing is straightforward and should be in the competence of a wide range of healthcare professionals. A list of indicator diseases that should lead to HIV testing is at present being developed on a pan-European basis and the forthcoming UK guidance is likely to suggest opt-out testing in a variety of situations in addition to the antenatal and genitourinary medicine clinics where such testing is already routine.

14.0 Cost-effectiveness

It should be emphasized that HAART is extremely cost-effective and compares favourably with the cost of management of many other chronic diseases. However, the price of newly introduced HIV medicines is high and generic drugs are becoming available. Third-party buyers world-wide are becoming increasingly aware of the need to obtain value for money. Modelling of cost-effectiveness is a complex issue, but in the context of HIV the two most important issues are the ability to avoid hospital admission and the costs of drugs.

With prevalent drug combinations, minor differences in superiority in the intent-to-treat analysis are largely related to ease of adherence and avoidance of side effects. Thus, it is likely that the outcome in terms of avoiding hospital admission would be very similar for different drug regimens and therefore the cost of the individual drugs becomes the most important consideration, particularly as the UK is moving towards a standard tariff for HIV-positive patients requiring treatment. The clinician and the patient will therefore be faced with difficult choices about how far simpler regimens free of toxicities should command a premium in pricing. Certain long-term toxicities such as cardiovascular risk and the development of lipoatrophy are likely in themselves to be extremely expensive and the BHIVA Writing Group continues to suggest that regimens with an increased risk of these side effects should be avoided wherever possible.

15.0 Conflict of interest

Professor Jane Anderson has sat on advisory panels for, and received sponsorship to attend scientific meetings from, various companies including Roche, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Abbott,

Bristol-Myers Squibb, Merck Sharp and Dohme, and Tibotec. She has also received unrestricted educational grant funding and specific support for research activities from various companies, which include Gilead, Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Tibotec and Roche.

Professor Abdel Babiker is Head of HIV Group, MRC Clinical Trials Unit which has received support from the following drug companies: Abbott (financial support for virology work in DART trial), Boehringer Ingelheim (drug and financial support), Cipla (drug only), GlaxoSmithKline (drug and financial support), Gilead Sciences (drug and financial support), Virco (assays), Novartis (drug only), Abbott (drug only), Indevus (drug only), Sanofi Pasteur (vaccine only), Bristol-Myers Squibb (financial support for resistance database), Tibotec (financial support for resistance database) and Roche (financial support for resistance database).

Dr Marta Boffito has participated as an investigator for clinical trials sponsored by, sat on advisory panels for, received sponsorship to attend scientific meetings from, or acted as a paid speaker for Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme, Gilead Sciences, Boehringer Ingelheim, Abbott Laboratories, Tibotec and Roche.

Dr Gary Brook has participated as an investigator for clinical trials sponsored by Gilead Sciences, has been a paid speaker at an event sponsored by Roche and has received a travel bursary from Bristol-Myers Squibb.

Mr Garry Brough has received sponsorship from Tibotec and Gilead to attend the IAC 2008 in Mexico.

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, GlaxoSmithKline, Merck Sharp and Dohme, Gilead Sciences, Boehringer Ingelheim, DuPont, Abbott Laboratories, Tibotec and Roche.

Dr Ben Cromarty has received honoraria and/or travel grants from the following companies for participating in Community Advisory Board meetings: Abbott and Tibotec.

Dr Satyajit Das, within the last 2 years, has received honoraria and educational grants from, and/or acted in an advisory capacity for, GlaxoSmithKline, Bristol-Myers Squibb, Gilead Sciences, Pfizer and Roche.

Dr Martin Fisher has received honoraria, travelling scholarships and/or research funding from, and/or has acted as an advisor to, the following companies: Abbott, Boehringer Ingelhiem, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Pfizer and Roche.

Dr Andrew Freedman has sat on advisory panels for, and received sponsorship to attend scientific meetings from, various companies, including Roche, Gilead Sciences, Abbott, Bristol-Myers Squibb and Tibotec.

Professor Brian Gazzard has acted as an adviser to Bristol-Myers Squibb, Abbot Pharmaceuticals, Gilead Sciences, GlaxoSmithKline, Wellcome, and Johnson and Johnson.

Dr Anna Maria Geretti has received consultancy and speaker honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Pfizer, Tibotec (Johnson and Johnson), Roche and Virco. She has also received unrestricted research grants from Abbott, Gilead Sciences, GlaxoSmithKline and Virco.

Professor Margaret Johnson has received honoraria, travelling scholarships and/or research funding from, and/or has acted as an advisor to, the following companies: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline and Roche, Pfizer and Merck Sharp and Dohme.

Dr Saye H. Khoo has received research grants, travel grants and speaking honoraria from GlaxoSmithKline, Gilead Sciences, Merck, Tibotec and Bristol-Myers Squibb, and has consulting agreements with Merck, Gilead Sciences, Bristol-Myers Squibb and Tibotec. Therapeutic drug monitoring (TDM) for HIV drugs in the UK is supported by GlaxoSmithKline, Roche, Abbott Laboratories and Merck Sharp and Dohme. The University of Liverpool has spun out TDM to Delphic Europe Ltd, and Dr Khoo serves as nonexecutive Director of Delphic.

Dr Clifford Leen has received travel grants from, has been on the speakers' bureau of, has received an honorarium for speaking from, has sat on the medical advisory boards of, and/or has acted as an advisor for, the following pharmaceutical companies: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Johnson and Johnson, Roche and Pfizer. He has received research grants from the following companies: ARK, Abbott, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche, Pfizer and Tibotec.

Dr Devaki Nair has been on advisory boards for Merck Sharp and Dohme and Astra Zeneca. She has received sponsorship for attending meetings and honoraria for lectures from Bristol-Myers Squibb, Abbott, Pfizer, Merck Sharp and Dohme, Gilead and Merck Pharmaceuticals.

Dr Barry Peters has, in the past 12 months, received reimbursement for a symposium, a fee for speaking, a fee for organizing education, and/or funds for research from various pharmaceutical companies including Roche, Bristol-Myers Squibb, GlaxoSmithKline, Abbott, Gilead, Tibotec and Bionor.

Professor Andrew Phillips has received reimbursement for attending a symposium, a fee for speaking, a fee for organizing education, funds for research, funds for a member of staff and/or fees for consulting from various pharmaceutical companies including Roche, Bristol-Myers

Squibb, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Gilead Sciences, Tibotec, Oxxon Therapeutic and Pfizer.

Professor Deenan Pillay has acted as a consultant and been paid honoria by the following companies: Boeringher Ingelheim, Bristol-Myers Squibb, Gilead and Roche.

Dr Anton Pozniak has been an advisor on HIV therapy and has received travel and educational grants from Roche, GlaxoSmithKline, Bristol-Myers Squibb, Abbott, Boehringer Ingelheim, Gilead, Pfizer, Merck and Tibotec.

Dr John Walsh has, in the last year, received honoraria or grants for educational activities from Boehringer Ingelheim, Bristol-Myers Squibb and Gilead Sciences. He has also received consulting fees for advice on study design from Bristol-Myers Squibb.

Dr Ed Wilkins has received honoraria, travelling scholarships and/or research funding from, and/or has acted as an advisor to, the following companies: Boehringer Ingelheim, Pfizer, Roche, Abbott, Gilead, Bristol-Myers Squibb, Merck Sharpe Dohme, and GSK.

Dr Ian Williams, within the last 2 years, has received research grants from Tibotec, Schering Plough and Boehringer Ingelheim; has received unrestricted educational and travel grants for conference attendance from Bristol-Myers Squibb, GlaxoSmithKline and Tibotec; has been a member of medical advisory boards for Bristol-Myers Squibb, Gilead Sciences, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp and Dohme, and Tibotec; and has participated in industry-sponsored symposia and educational events for GlaxoSmithKline, Gilead Sciences and Roche, for which both he and his employers, University College London, have received honoraria.

Dr Matthew Willams is a member of the steering group of the UK Community Advisory Board.

Dr Mike Youle is a member of various advisory boards and has received travel grants and writing commissions at various times from the major pharmaceutical companies.

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17.0 Appendix

Table A1. Grading of recommendations and levels of evidence

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