

BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)

Writing Group

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†Professor Martin Fisher died in April 2015 – he made a significant contribution to these, many other guidelines and our speciality as a whole – he is greatly missed.

Table of contents

Table of contents	2
1.0 Introduction	6
1.1 <i>Scope and purpose</i>	6
1.2 <i>Methodology</i>	6
1.2.1 Guideline development process.....	6
1.2.2 Involvement of PLWH.....	6
1.2.3 GRADE.....	7
1.2.4 Good practice points	8
1.2.5 Dissemination and implementation	8
1.2.6 Guideline updates and date of next review	8
1.3 <i>Treatment aims</i>	8
1.4 <i>Resource use</i>	9
1.5 <i>Implications for research</i>	10
1.6 <i>References</i>	10
2.0 Summary of recommendations	12
3.0 Involvement of people living with HIV in decision-making	25
3.1 <i>Recommendations</i>	25
3.2 <i>Auditable outcomes</i>	25
3.3 <i>Rationale</i>	25
3.4 <i>References</i>	27
4.0 When to start	30
4.1 <i>Chronic infection</i>	30
4.1.1 Recommendations.....	30
4.1.2 Auditable outcomes	30
4.1.3 Rationale.....	30
4.1.4 References.....	31
4.2 <i>Individuals presenting with AIDS or a major infection</i>	32
4.2.1 Recommendation	32
4.2.2 Auditable outcome	32
4.2.3 Rationale.....	32
4.2.4 References.....	32
4.3 <i>Treatment of primary HIV infection</i>	33
4.3.1 Recommendation	33
4.3.2 Auditable outcomes	33
4.3.3 Rationale.....	33
4.3.4 References.....	35
4.4 <i>Impact of treatment on prevention of onward transmission</i>	37
4.4.1 Recommendations.....	37
4.4.2 Auditable outcome	37
4.4.3 Rationale.....	37
4.4.4 References.....	38
5.0 What to start.....	40
5.1 <i>Summary of recommendations</i>	40
5.1.1 Summary of auditable outcomes	40
5.2 <i>Introduction</i>	41

5.3 Which nucleoside reverse transcriptase inhibitor backbone	41
5.3.1 Recommendations.....	41
5.3.2 Rationale.....	41
5.3.3 Not recommended	43
5.3.4 Lamivudine vs. emtricitabine	43
5.3.5 References	44
5.4 Which third agent.....	47
5.4.1 Recommendations.....	47
5.4.2 Rationale.....	47
5.4.3 Individual agents.....	47
References	51
5.5 Novel antiretroviral therapy strategies	54
5.5.1 Recommendation	54
5.5.2 Recommendation	55
5.5.3 References	56
6.0 Supporting individuals on therapy.....	57
6.1 Adherence.....	57
6.1.1 Interventions to increase adherence to treatment.....	57
6.1.2 Should the choice of first-line antiretroviral therapy combination be affected by risk of non-adherence?	60
6.1.3 Dosing frequency.....	63
6.1.4 Fixed-dose combinations.....	64
6.1.5 Single-tablet regimens	65
6.2 Pharmacology.....	67
6.2.1 Drug interactions	67
6.2.2 Therapeutic drug monitoring	68
6.2.3 Stopping therapy: pharmacological considerations.....	70
6.2.4 Switching therapy: pharmacological considerations.....	71
6.3 Switching antiretroviral therapy in virological suppression	74
6.3.1 Introduction.....	74
6.3.2 Switching antiretrovirals in combination antiretroviral therapy.....	74
6.3.3 Protease inhibitor monotherapy	78
6.3.4 Treatment with one boosted protease inhibitor and one NRTI.....	80
6.4 Stopping therapy	81
6.4.1 Recommendation	81
6.4.2 Auditable outcomes	81
6.4.3 Rationale.....	81
6.4.4 References	81
7.0 Managing virological failure.....	82
7.1 Introduction	82
7.1.1 Summary of auditable measures.....	82
7.2 Blips, low-level viraemia and virological failure	83
7.2.1 Recommendations.....	83
7.2.2 Rationale.....	83
7.3 Individuals with no or limited drug resistance.....	86
7.3.1 Recommendations.....	86
7.3.2 Rationale.....	86
7.4 Individuals with multiple class virological failure with or without extensive drug resistance.....	88
7.4.1 Recommendations.....	88
7.4.2 Rationale.....	88

7.5 individuals with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed.....	90
7.5.1 Recommendations.....	90
7.5.2 Rationale.....	91
7.6 References	92
8.0 Special populations	98
8.1 HIV and TB co-infection	98
8.1.1 When to start ART in TB/HIV co infection	98
8.1.2 What to start in TB/HIV co infection	99
8.1.3 References	100
8.2 Hepatitis B and C virus co-infection	102
When to start ART?	102
8.2.2 Hepatitis B	102
8.2.3 Hepatitis C	104
8.2.4 References	104
8.3 HIV-related cancers	105
8.3.1 When to start ART?	105
8.3.2 What to start	105
8.3.3 Opportunistic infection prophylaxis in HIV-associated malignancy	106
8.3.4 Other considerations from the BHIVA guidelines for HIV-associated malignancies [1].....	106
8.3.5 References	107
8.4 HIV-associated neurocognitive impairment	108
8.4.1. Introduction.....	108
8.4.2 When to start ART	108
8.4.3 What to start with	109
8.4.4 Continuing or worsening NC impairment despite ART.....	110
8.4.5 References	111
8.5 Chronic kidney disease.....	114
8.5.1 When to start antiretroviral therapy.....	114
8.5.2 What to start	114
8.5.3 Need to switch.....	115
8.5.4 References	116
8.6 Cardiovascular disease	119
8.6.1 Introduction.....	119
8.6.2 Definition and assessment of cardiovascular disease risk	119
8.6.3 Issues related to antiretroviral therapy.....	119
8.6.4 What to start	120
8.6.5 Modification of CVD risk factors.....	121
8.6.6 References	124
8.7 Women	130
8.7.1 Introduction.....	130
8.7.2 When to start.....	130
8.7.3 What to start	130
8.7.4 HIV-positive women experiencing virological failure.....	133
8.7.5 References	134
8.8 Mental health	137
8.8.1 Recommendations.....	137
8.8.2 Rationale.....	137
8.8.3 References	138
8.9 Adolescents.....	139

8.9.1 Recommendations for management of HIV, ART and sexual and reproductive health specifically for perinatally acquired HIV	139
8.9.2 UK Epidemiology for YAA with PaHIV.....	139
8.9.3 Transition Process for YAA with PaHIV.....	139
8.9.4 UK Epidemiology for YAA with BaHIV.....	139
8.9.5 Neurocognitive impact of HIV in YAA.....	140
8.9.6 Antiretroviral therapy.....	140
References	140
<i>8.10 Bone disease and antiretroviral therapy</i>	<i>143</i>
8.10.1 Introduction.....	143
8.10.2 When to start antiretroviral therapy.....	143
8.10.3 What to start	143
8.10.4 Switching treatment.....	144
<i>8.11 Considerations for later life</i>	<i>148</i>
8.11.1 Introduction.....	148
8.11.2 When to start ART.....	148
8.11.3 What to start.....	149
9.0 Acknowledgements.....	151
10.0 List of appendices	151

1.0 Introduction

1.1 Scope and purpose

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of adults with HIV infection on antiretroviral therapy (ART). The scope includes: (i) guidance on the initiation of ART in those previously naïve to therapy; (ii) support of people living with HIV (PLWH) on treatment; (iii) management of individuals experiencing virological failure; and (iv) recommendations in specific populations where other factors need to be taken into consideration. The guidelines are aimed at clinical professionals directly involved with and responsible for the care of adults with HIV infection, and at community advocates responsible for promoting the best interests and care of HIV-positive adults. They should be read in conjunction with other published BHIVA guidelines.

1.2 Methodology

1.2.1 Guideline development process

BHIVA fully revised and updated the association's guideline development manual in 2011. Further updates have been carried out subsequently [1]. Full details of the guideline development process, including conflict of interest policy, are outlined in the manual. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and development of recommendations (see below and Appendix 1) [2,3].

The scope, purpose and guideline topics were agreed by the writing group. Questions concerning each guideline topic were drafted and a systematic literature search was undertaken by an information scientist. Details of the search questions and strategy (including the definition of populations, interventions and outcomes) are outlined in Appendix 2. BHIVA guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy were last published in 2013 [4]. For the 2015 guidelines Medline, Embase and the Cochrane library were searched between October 2011 and August 2014. Abstracts from selected conferences (see Appendix 2) were searched between 1 January 2011 and July 2015. For each topic and healthcare question, evidence was identified and evaluated by writing group members with expertise in the field. Using the modified GRADE system, Writing group members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. An important aspect of evaluating evidence is an understanding of the design and analysis of clinical trials, including the use of surrogate marker data. Decisions regarding the clinical importance of difference in outcomes are made by the writing panel.

For a number of questions, GRADE evidence profile and summary of findings tables were constructed, using predefined and rated treatment outcomes (Appendix 3), to help achieve consensus for key recommendations and aid transparency of the process. Before final approval by the writing group, the guidelines were published online for public consultation and an external peer review was commissioned.

For the 2016 interim update the panel reviewed newly licensed products and the writing panel developed a consensus opinion based on critical endpoints; appropriate sections were updated. Formal GRADE analysis of these products will be included in the 2017 update. Small changes were made to the virological failure section. All 2016 amendments are highlighted.

1.2.2 Involvement of PLWH

BHIVA views the involvement of PLWH and community representatives in the guideline development process as essential. The writing group included two representatives appointed through the UK HIV

Community Advisory Board (UK-CAB) who were involved in all aspects of the guideline development process. Community groups were invited to participate in the draft guideline consultation process and a community consultation was held on 6th August 2015.

1.2.3 GRADE

The GRADE Working Group [3] has developed an approach to grading evidence that moves away from initial reliance on study design to consider the overall quality of evidence across outcomes. BHIVA has adopted the modified GRADE system for its guideline development.

The advantages of the modified GRADE system are (i) the grading system provides an informative, transparent summary for clinicians, PLWH and policy makers by combining an explicit evaluation of the strength of the recommendation with a judgement of the quality of the evidence for each recommendation, and (ii) the two-level grading system of recommendations has the merit of simplicity and provides clear direction to PLWH, clinicians and policy makers.

The strength of recommendation is graded as 1 or 2 as follows:

- A Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all PLWH. Most clinicians and HIV-positive individuals should and would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'we recommend'.
- A Grade 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Most clinicians and PLWH would want to follow a weak or conditional recommendation but many would not. Alternative approaches or strategies may be reasonable depending on the individual HIV-positive individual's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'we suggest'.

The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and preferences and, where appropriate, resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and for the purpose of these guidelines is defined as the following:

- Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials (RCTs), or overwhelming evidence of some other sort (such as well-executed observational studies with consistent strong effects and a low likelihood of uncorrected bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.
- Grade B evidence means moderate-quality evidence from randomised trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strengths such as observational studies with consistent effects and exclusion of most potential sources of bias.
- Grade C evidence means low-quality evidence from controlled trials with several very serious limitations or observational studies with limited evidence on effects and exclusion of most potential sources of bias.
- Grade D evidence on the other hand is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there is likely to be little confidence in the effect estimate.

1.2.4 Good practice points

In addition to graded recommendations, the BHIVA writing group has also included good practice points (GPP), which are recommendations based on the clinical judgement and experience of the working group. GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence. They address an aspect of treatment and care that is regarded as such sound clinical practice that healthcare professionals are unlikely to question it and where the alternative recommendation is deemed unacceptable. It must be emphasised that GPPs are not an alternative to evidence-based recommendations.

1.2.5 Dissemination and implementation

The following measures have or will be undertaken to disseminate and aid implementation of the guidelines:

- E-publication on the BHIVA website and the journal *HIV Medicine*.
- Publication in *HIV Medicine*.
- Shortened version detailing concise summary of recommendations.
- Shortened version for BHIVA guidelines app.
- E-learning module accredited for CME.
- Educational slide set to support local and regional educational meetings.
- National BHIVA audit programme.

1.2.6 Guideline updates and date of next review

The guidelines will be next fully updated and revised in 2017. However, the writing group will continue to meet regularly to consider new information from high-quality studies and publish amendments and addendums to the current recommendations before the full revision date where this is thought to be clinically important to ensure continued best clinical practice.

1.3 Treatment aims

The primary aim of ART is the prevention of the mortality and morbidity associated with chronic HIV infection at low cost of drug toxicity. Treatment should improve the physical and psychological well-being of PLWH. The effectiveness and tolerability of ART has improved significantly over the last 15 years. The overwhelming majority of PLWH attending HIV services in the UK and receiving ART experience long-term virological suppression and good treatment outcomes [5], which compare very favourably with other developed countries. Notably, in 2013 around 90% of those diagnosed with HIV in the UK had initiated ART, with 93% of those on ART having a suppressed viral load [5].

A UK analysis of individuals commencing ART between 2000 and 2010 demonstrates that the expected age at death for HIV-positive men from ART start was 68, 73 and 77 years at exact ages 20, 35 and 50 years, respectively, compared with 77, 78 and 79 years in the general population [6]. The corresponding expected age at death for HIV-positive women was 69, 74 and 78 years, compared with 81, 82 and 83 years in the general population. The same study shows that life expectancy in men and women with an undetectable viral load and CD4 greater than 350 is the same as, or slightly better than, that for the general population [6]. Modelling has suggested that for HIV-positive men who have sex with men (MSM) living in a developed country with extensive access to HIV care and assuming a high rate of HIV diagnosis, the life expectancy is 75 years [7]. The authors concluded that the greatest risk of excess mortality is due to delays in HIV diagnosis. Decreasing late diagnosis (and consequently starting ART earlier), maintaining individuals in care and reducing long-term drug toxicity and non-acquired immune deficiency syndrome (AIDS) co-morbidities are crucial to further improving life expectancy and the well-being of people living with HIV infection.

A further aim of treatment is the reduction in sexual transmission of HIV. The use of ART to prevent mother-to-child transmission is universally accepted and best practice is addressed in the BHIVA guidelines for the management of HIV infection in pregnant women [8]. Recently, the size of the effect of ART on reducing the risk of sexual transmission of HIV has been estimated at >95% [9,10]. The PARTNER study investigated the risk of HIV transmission within serodifferent couples where the HIV-positive partner was on suppressive ART (viral load less than 200 copies/mL) and demonstrated no transmissions compared with a predicted 86 new infections had the positive partner not been on effective ART [11]. The upper 95% confidence interval for risk of transmission was 0.4 per 100 couple years for any sex and 1.0 per 100 couple years for anal sex. At a population level, ART is likely to be important in reducing the incidence of HIV infection.

1.4 Resource use

ART is extremely cost-effective and compares favourably with the cost of management of many other chronic diseases. Estimates of the cost-effectiveness of ART have been assessed in studies in North America and Europe [12–14]. Their findings have been consistent with an estimated incremental cost-effectiveness ratio of about US\$20 000 per quality adjusted life year (QALY) for combination ART compared with no therapy based on drug costs and treatment patterns in the USA and Europe [15]. The primary aim of these guidelines is to summarise and base recommendations on the clinical benefits of ART and different ART options.

The number of people living with HIV in the UK continues to increase and by the end of 2013 was estimated to be 107,800 (95% credible interval 101,600–115,800), of whom 24% were undiagnosed. In 2013, 90% (73,290/81,510) of people seen for HIV care were prescribed ART [5]. With ongoing HIV transmission, increased HIV testing and a reduction in the undiagnosed fraction, the number of people diagnosed with HIV and accessing HIV services will continue to increase. It has been estimated that the annual population treatment and care costs rose from £104 million in 1997 to £483 million in 2006, rising to a projected annual cost of £721 million in 2013 [16]. It is likely this estimated projected cost is an overestimate due to various factors, including earlier diagnosis and a lower proportion of individuals with symptoms. However, in the current economic climate containing and reducing costs without affecting the current high standards of care and treatment outcomes will be an immense challenge to commissioners, healthcare professionals and PLWH alike. A collaborative approach is required.

In the UK, higher annual treatment and care costs have been associated with late diagnosis and initiation of ART at lower CD4 cell counts than the BHIVA guidelines recommend [17,18]. In addition to earlier diagnosis and initiation of ART, reducing inpatient episodes, decreasing drug toxicity, preventing HIV-associated co-morbidities and innovations in models of care are likely to have a beneficial effect on costs. However, the cost of antiretroviral (ARV) drugs remains the major factor contributing to treatment and care costs. With the increasing availability of generic drugs and the introduction of a standard tariff for HIV services (in England), commissioners and the NHS will be faced with difficult choices about the value and benefit of different ARV drugs.

The BHIVA writing group recognises that cost of drugs is an important issue in the choice of ART regimens. In addition to drug acquisition costs there are costs associated with, for example, multidisciplinary team meetings, switching ART, co-morbidities and management of drug–drug interactions. There are limited cost-effectiveness data in the UK comparing different ARV drugs and for this reason we did not include cost-effectiveness as an outcome in ART comparisons. However, the writing group believes that decreasing the risks of virological failure, drug resistance and drug-associated toxicity are likely to have a beneficial impact on long-term cost-effectiveness and resource use. In the setting of similar virological efficacy, determining the acceptable threshold at which differences in the risk of toxicity, tolerability and convenience outweigh differences in resource use and cost will be important. These thresholds may differ among clinicians and PLWH alike.

In developing the recommendations in these guidelines, we have taken into account differences in critical treatment outcomes between different drug regimens in determining preferred and alternative treatment regimens. We recognise and support that commissioning arrangements and local drug costs will and should influence ART choice where outcomes, across a range of clinical measures, are similar between individual drugs in the treatment of defined populations. However, we believe that reducing treatment costs should not be at the cost of an increased risk of poorer treatment outcomes and quality of care, not least as these are likely to have a detrimental impact on long-term cost.

1.5 Implications for research

In reviewing quality of evidence, guidelines will identify areas of treatment and care where there is an absence of evidence or limited confidence in the size of effect to influence choice of treatments or determine treatment and management strategies. For this reason, it is not the intention of these guidelines to stifle clinical research but rather to help promote continued research with the aim to further improve clinical care and treatment outcomes. The development and provision of HIV clinical trials within the UK are supported, and participation in a clinical trial should be open and offered to PLWH where appropriate.

1.6 References

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2.0 Summary of recommendations

3.0 Involvement of people living with HIV in decision-making
3.1 Recommendations
<ul style="list-style-type: none"> We recommend PLWH are given the opportunity to be involved in making decisions about their treatment (GPP). Provision of treatment-support resources should include in-house, independent and community information providers and peer-support resources (GPP).
4.0 When to start
4.1 Chronic infection
4.1.1 Recommendations
<ul style="list-style-type: none"> We recommend people with HIV start ART (1A).
4.2 Individuals presenting with AIDS or a major infection
4.2.1 Recommendation
<ul style="list-style-type: none"> We recommend that individuals presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 cell count <200 cells/μL, start ART within 2 weeks of initiation of specific antimicrobial chemotherapy (1B).
4.3 Treatment of primary HIV infection
4.3.1 Recommendation
<ul style="list-style-type: none"> We recommend all individuals with suspected or diagnosed PHI are reviewed promptly by an HIV specialist and offered immediate ART (1B).
4.4 Impact of treatment on prevention of onward transmission
4.4.1 Recommendations
<ul style="list-style-type: none"> We recommend that ART is offered to all PLWH for the prevention of onward transmission (1A). We recommend the evidence that treatment with ART substantially lowers the risk of transmission is discussed with all PLWH (GPP). An assessment of the risk of transmission to others should be made at diagnosis and subsequent visits (GPP).
5.0 What to start

5.1 Summary recommendations

- We recommend that therapy-naïve PLWH start ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir-boosted protease inhibitor (PI/r), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) (1A).

Table 5.1. Summary recommendations for choice of ART

	Preferred	Alternative
NRTI backbone	Tenofovir-DF and emtricitabine Tenofovir-AF and emtricitabine	Abacavir and lamivudine ^{a,b}
Third agent (alphabetical order)	Atazanavir/r Darunavir/r Dolutegravir Elvitegravir/c ^c Raltegravir Rilpivirine ^d	Efavirenz

/r: boosted with ritonavir; /c: boosted with cobicistat

^a Abacavir is contraindicated if an individual is HLA-B*57:01 positive

^b Use recommended only if baseline viral load is $\leq 100,000$ copies/mL except when initiated in combination with dolutegravir in which case abacavir/lamivudine can be used at any baseline viral load.

^c Tenofovir-DF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in individuals with creatinine clearance < 70 mL/min; tenofovir-AF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in patients with estimated CrCl < 30 mL/min

^d Use recommended only if baseline viral load is $\leq 100,000$ copies/mL

NB. The viral load advice for abacavir/lamivudine and rilpivirine applies only to initiating these agents in individuals with a detectable viral load – when these agents are used as a switch option in the context of viral load suppression the baseline viral load can be disregarded.

5.3 Which nucleoside reverse transcriptase inhibitor backbone

5.3.1 Recommendations

- We recommend therapy-naïve individuals start combination ART containing tenofovir-DF or tenofovir-AF and emtricitabine as the preferred NRTI backbone (1A).
- We suggest abacavir and lamivudine is an acceptable alternative NRTI backbone in therapy-naïve individuals. In those with a baseline viral load $> 100,000$, it should be used with caution (2A).
- The caution regarding baseline viral load does not apply if abacavir/lamivudine is used with dolutegravir (2A).
- Abacavir must not be used in individuals who are HLA-B*57:01-positive (1A).

5.4 Which third agent

5.4.1 Recommendations

<ul style="list-style-type: none"> We recommend therapy-naïve individuals start combination ART containing atazanavir/r, darunavir/r, dolutegravir, elvitegravir/c, raltegravir or rilpivirine as the third agent (1A).
<ul style="list-style-type: none"> We suggest that for therapy-naïve individuals, efavirenz is an acceptable alternative third agent (1A).
<p>5.5 Novel antiretroviral therapy strategies</p>
<p>5.5.1 Recommendation</p>
<ul style="list-style-type: none"> We recommend against the use of PI monotherapy as initial therapy for treatment-naïve patients (1C).
<p>5.5.2 Recommendation</p>
<ul style="list-style-type: none"> We suggest the use of darunavir/r-based dual ART regimen with raltegravir in treatment-naïve patients with CD4 count >200 cells/μL and viral load <100,000 copies/mL where there is need to avoid abacavir, tenofovir-DF and/or tenofovir-AF (2A).
<ul style="list-style-type: none"> We recommend against the use of PI-based dual ART with a single NNRTI, NRTI or CCR5 receptor antagonist for treatment-naïve patients (1B).
<p>6.0 Supporting individuals on therapy</p>
<p>6.1 Adherence</p>
<p>6.1.1 Interventions to increase adherence to treatment</p>
<p>6.1.1.1 Recommendations</p>
<ul style="list-style-type: none"> We recommend adherence and potential barriers to it are assessed and discussed with PLWH whenever ART is discussed, prescribed or dispensed (GPP).
<ul style="list-style-type: none"> We recommend adherence support should address both perceptual barriers (e.g. beliefs and preferences) and/or practical barriers (e.g. limitations in capacity and resources) to adherence (GPP).
<ul style="list-style-type: none"> Individuals experiencing difficulties with adherence should be offered additional support from staff within the MDT who have experience in adherence support and/or from organisations offering peer support (GPP).
<p>6.1.2 Should the choice of first-line antiretroviral therapy combination be affected by risk of non-adherence?</p>
<p>6.1.2.1 Recommendation</p>
<ul style="list-style-type: none"> In individuals where there is clinical concern that doses may be missed intermittently, there is insufficient evidence to recommend a PI/r over NNRTI- or INI-based regimens. However, where there is a risk of frequent prolonged treatment interruptions, PI/r-based regimens may be associated with less frequent selection for drug resistance (2C).
<p>6.2 Pharmacology</p>
<p>6.2.1 Drug interactions</p>
<p>6.2.1.1 Recommendations</p>
<ul style="list-style-type: none"> Drug histories should be taken at each clinic visit, and a full medication history (including herbals, recreational drugs and other non-prescribed medications) should be undertaken at least annually

(GPP).
<ul style="list-style-type: none"> All potential adverse pharmacokinetic interactions between antiretroviral drugs and other concomitant medications should be checked before administration (with tools such as www.hiv-druginteractions.org) (GPP). Wherever feasible, PLWH should be counselled about the risks of drug interactions, and advised to use resources such as the Liverpool HIV Drug Interactions App (iOS or Android) (GPP).
6.2.2 Therapeutic drug monitoring
6.2.2.1 Recommendation
<ul style="list-style-type: none"> We recommend against the unselected use of therapeutic drug monitoring (TDM) (GPP). TDM may be of clinical value in specific populations (e.g. children, pregnant women) or selected clinical scenarios (e.g. malabsorption, drug interactions, suspected non-adherence to therapy) (2C).
6.2.3 Stopping therapy: pharmacological considerations
6.2.3.1 Recommendations
<ul style="list-style-type: none"> We recommend individuals stopping ART containing an NNRTI in combination with an NRTI backbone replace all drugs with a PI (darunavir/r once daily) for 4 weeks (1C). We recommend individuals stopping a PI-containing regimen stop all drugs simultaneously and no replacement is required (1C).
6.3.2 Switching antiretrovirals in combination antiretroviral therapy
6.3.2.1 Recommendations
<ul style="list-style-type: none"> We recommend, in individuals on suppressive ART regimens, consideration is given to differences in side-effect profile, drug–drug interactions and drug-resistance patterns before switching any ARV component (GPP). In individuals with previous NRTI resistance mutations, we recommend against switching a PI/r to either an NNRTI or an INI as the third agent (1B).
6.3.3 Protease inhibitor monotherapy
6.3.3.1 Recommendation
<ul style="list-style-type: none"> We recommend against the use of PI monotherapy for routine ART (1A). We recommend against the use of PI monotherapy for individuals whose initial regimen has failed or who have established resistance to one more antiretroviral drugs (1A).
6.3.4 Treatment with one boosted protease inhibitor and one NRTI
6.3.4.1 Recommendation
<ul style="list-style-type: none"> We suggest that a boosted PI plus lamivudine as an alternative to three-drug ART in individuals with viral suppression (2A).
6.4 Stopping therapy

6.4.1 Recommendation
<ul style="list-style-type: none"> We recommend against treatment interruption or intermittent therapy in individuals stable on a virally suppressive ART regimen (1A).
7.0 Managing virological failure
7.2 Blips, low-level viraemia and virological failure
7.2.1 Recommendations
In individuals on ART:
<ul style="list-style-type: none"> A single VL 50–200 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern (GPP). –. We recommend that a single VL >200 copies/mL is investigated further, including a genotypic resistance test, as it is indicative of virological failure (1C). We recommend that in the context of repeated viral blips, resistance testing be attempted (1D).
7.3 Individuals with no or limited drug resistance
7.3.1 Recommendations
<ul style="list-style-type: none"> We recommend for individuals experiencing virological failure on first-line ART with WT virus at baseline and without emergent resistance mutations at failure, switch to a PI/r- or PI/c based combination ART regimen is the preferred option (1C). We recommend individuals experiencing virological failure on first-line ART with WT virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure, switch to a new PI/r- or PI/c-based regimen with the addition of at least one, preferably two, active drugs (1C). We recommend individuals experiencing virological failure on first-line PI/r or PI/c plus two-NRTI-based regimens, with limited major protease mutations, switch to a new active PI/r or PI/c with the addition of at least one, preferably two, active agents of which one has a novel mechanism of action (1C). We recommend against switching a PI/r or PI/c to an INI or NNRTI as the third agent in individuals with historical or existing reverse transcriptase mutations associated with NRTI resistance or past virological failure on NRTIs (1B).
7.4 Individuals with multiple class virological failure with or without extensive drug resistance
7.4.1 Recommendations
<ul style="list-style-type: none"> We recommend individuals with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed at an MDT inclusive of a virologist/referred for expert advice (or through virtual clinic referral) (GPP). We recommend individuals with extensive drug resistance are switched to a new ART regimen containing at least two and preferably three fully active agents with at least one active PI/r such as DRV/r or DRV/c and one agent with a novel mechanism (an INI, MVC or enfuvirtide) with ETV an

option based on viral susceptibility (1C).
<ul style="list-style-type: none"> We recommend individuals with extensive drug resistance including reduced darunavir susceptibility receive DTG as the INI (1C).
<ul style="list-style-type: none"> We suggest that consideration on an individual basis should be given to whether inclusion of NRTIs with reduced activity on genotypic testing will provide additional antiviral activity if the regimen includes three fully active drugs including a boosted PI (2C).
<ul style="list-style-type: none"> We recommend all individuals receive intensive adherence support at the start and at regular intervals to support them on their new ART combination (GPP).
7.5 individuals with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed
7.5.1 Recommendations
<ul style="list-style-type: none"> We recommend accessing newer agents through research trials, expanded access and named individual programmes (GPP).
<ul style="list-style-type: none"> We suggest that consideration on an individual basis should be given to whether inclusion of NRTIs with reduced activity on genotypic testing will provide additional antiviral activity – this may well be the case where it is difficult to construct a regimen with three fully active drugs including a boosted PI (see previous Section) (2C).
<ul style="list-style-type: none"> We recommend against discontinuing or interrupting ART (1B).
<ul style="list-style-type: none"> We recommend against adding a single, fully active ARV because of the risk of further resistance (1D).
<ul style="list-style-type: none"> We recommend against the use of MVC to increase the CD4 cell count in the absence of CCR5 tropic virus (1C).
<ul style="list-style-type: none"> We recommend that in the context of triple class failure and RAL/EVG selected integrase resistance, twice daily DTG should be included as part of a new regimen where there is at least one fully active agent in the background regimen (1C).
8.0 Special populations
8.1 HIV and TB co-infection
8.1.1 When to Start ART in TB/HIV co infection
8.1.1.1 Recommendations
<ul style="list-style-type: none"> We recommend all patients with HIV TB co-infection start ART (1B)
<ul style="list-style-type: none"> We recommend individuals with CD4 is <50 cells/μL start ART as soon as TB treatment is tolerated and wherever possible within 2 weeks (1B).
<ul style="list-style-type: none"> We recommend that for individuals with CD4 cell count ≥50 cells/μL, ART can be deferred until between 8 and 12 weeks of TB treatment, especially when there are difficulties with drug–drug interactions, adherence and toxicities (1B). (Although the data suggest a cut-off of 50 cells/μL, because of the daily variability in CD4, a cut-off of 100 cells/μL may be more appropriate.)
8.1.2 What to start in TB/HIV co infection
8.1.2.1 Recommendations

- We recommend EFV in combination with TDF and FTC as first-line ART (1B) in TB/HIV coinfection
- We recommend that when rifampicin is used with efavirenz standard doses of efavirenz are given whatever the body weight (1B)
- We suggest that RAL should be used with caution with rifampicin (2C)
- We suggest DTG is a possible alternative agent (for which there is currently little evidence) but the dose should be increased to 50mg bd (2D)
- We recommend frequent viral load monitoring if INIs are used (1C)
- We recommend that rifampicin is not used with either NVP or a regimen containing ritonavir or cobicistat (1C)
- We recommend that where effective ART necessitates the use of ritonavir or cobicistat, that rifabutin is used instead of rifampicin (1C)

8.2 Hepatitis B and C virus co-infection

8.2.1 When to start ART in HBV co-infection

Table 8.1. Summary recommendations for the treatment of hepatitis B and C co-infection

HBV requiring treatment*	HBV not requiring treatment	HCV with immediate plan to start HCV treatment*	HCV with no immediate plan to start HCV treatment
Start ART promptly (1A) (include tenofovir-DF and emtricitabine or tenofovir-AF and emtricitabine)	Start ART (1A) (include tenofovir-DF and emtricitabine or tenofovir-AF and emtricitabine)	Start ART before HCV treatment commenced (1C); acceptable to defer if CD4 cell count >500 cells/ μ L. Discuss with HIV and viral hepatitis specialist	Start ART (1A)

*See BHIVA guidelines for the management of hepatitis viruses in adults (www.bhiva.org/hepatitis-guidelines.aspx) for indications to treat hepatitis B and C

8.2.2 Hepatitis B

8.2.2.1 When to start antiretroviral therapy in HBV co-infection

8.2.2.1.1 Recommendations

- We recommend individuals with HIV and hepatitis B virus (HBV) co-infection are treated with fully suppressive ART inclusive of anti-HBV active antivirals, regardless of CD4 cell count (1A).
- We recommend individuals with HIV and HBV co-infection who have an HBV-DNA \geq 2000 IU/mL and/or evidence of more than minimal fibrosis (Metavir \geq F2) are treated with fully suppressive ART inclusive of anti-HBV active antivirals promptly (1C)

8.2.2.2 What to start in HBV co-infection

8.2.2.2.1 What to start recommendations
<ul style="list-style-type: none"> We recommend tenofovir-DF/emtricitabine or tenofovir-AF/emtricitabine as part of a fully suppressive ART combination should be given to all individuals starting HIV treatment (1C).
<ul style="list-style-type: none"> In the absence of renal or bone disease or significant predisposing risk factors for their development, tenofovir-DF or tenofovir-AF can be used unless otherwise contraindicated (1C)
<ul style="list-style-type: none"> We recommend patients with established renal disease with a creatinine clearance ≥ 30 mL/min or osteoporosis or significant predisposing factors for their development should be given tenofovir-AF (1D)
<ul style="list-style-type: none"> We recommend lamivudine/emtricitabine may be omitted from the ART regimen and tenofovir-DF or tenofovir-AF be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of lamivudine/emtricitabine-resistant HBV or HIV (1D).
<ul style="list-style-type: none"> We recommend neither lamivudine nor emtricitabine be used as the sole active drug against HBV in ART due to the rapid emergence of HBV resistant to these agents (1B).
<ul style="list-style-type: none"> We recommend lamivudine/emtricitabine may be omitted from the ART regimen and tenofovir-DF or tenofovir-AF be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of lamivudine/emtricitabine-resistant HBV or HIV (1D).
8.2.3 Hepatitis C
8.2.3.1 When to start antiretroviral therapy in HCV co-infection
8.2.3.1.1 Recommendations
<ul style="list-style-type: none"> We recommend all individuals with HIV and hepatitis C virus (HCV) co-infection be assessed for HCV treatment (GPP).
<ul style="list-style-type: none"> We recommend commencing ART regardless of CD4 cell count (1A).
<ul style="list-style-type: none"> We recommend HCV be considered an additional factor supporting ART in individuals with CD4 >500 cells/μL who are uncertain about commencing ART (2C)
<ul style="list-style-type: none"> We suggest treating HCV before commencing ART is an option if there are concerns about drug–drug interactions or adherence (GPP)
8.3.2.2 What to start in HCV co-infection
8.3.2.2.1 Recommendations
<ul style="list-style-type: none"> We recommend if individuals are commencing ART, and direct-acting antivirals are not being considered, standard first-line ART should be commenced (GPP).
<ul style="list-style-type: none"> We recommend that when direct-acting antivirals are to be used, there is careful consideration of possible drug–drug interactions (1C) and current or archived HIV resistance. All drug interactions should be checked with an expert source (e.g. www.hiv-druginteractions.org).
<ul style="list-style-type: none"> We suggest that if abacavir is to be used with ribavirin, the ribavirin should be weight-based dose-adjusted (2C)
8.3 HIV-related cancers
8.3.1 When to start ART
8.3.1.1 AIDS-defining malignancies

<ul style="list-style-type: none"> We recommend that all patients with AIDS-defining malignancies should start ART promptly (1B).
8.3.1.1.1 Kaposi sarcoma (KS)
<ul style="list-style-type: none"> We recommend that ART should be started promptly in all individuals diagnosed with KS (1B).
8.3.1.1.2 Non-Hodgkin lymphoma (NHL)
<ul style="list-style-type: none"> We recommend that chemotherapy regimens should be combined with ART therapy in Burkitt lymphoma and diffuse large B-cell lymphoma (1B).
<ul style="list-style-type: none"> We recommend that all individuals with primary effusion lymphoma (PEL), plasmablastic lymphoma and primary central nervous system lymphoma should be started on ART if not already on it (1C).
8.3.1.1.3 Cervical cancer
<ul style="list-style-type: none"> We suggest that women with CIN2/3 should commence ART promptly (2B).
<ul style="list-style-type: none"> We recommend that all women living with HIV who are to be treated with chemo-radiotherapy (CRT) for cervical cancer CRT should start ART promptly (1C) and opportunistic infection prophylaxis (1D).
8.3.1.2 Non-AIDS-defining malignancies
8.3.1.2.1 Anal cancer
<ul style="list-style-type: none"> We recommend that all PLWH who are to be treated with chemo-radiotherapy should start ART (1C) and opportunistic infection prophylaxis (1D).
8.3.1.2.2 Hodgkin lymphoma
<ul style="list-style-type: none"> We recommend all PLWH and Hodgkin lymphoma should receive ART during chemotherapy (1A).
8.3.1.2.3 Other non-AIDS-defining cancers
<ul style="list-style-type: none"> We suggest all PLWH who require chemotherapy or radical radiotherapy should receive concomitant ART and opportunistic infection prophylaxis unless contraindicated (level of evidence 2C).
8.3.2 What to start
<ul style="list-style-type: none"> We recommend that all potential interactions between ART, opportunistic infection prophylaxis and cancer therapy should be considered (1C).
<ul style="list-style-type: none"> We suggest that all individuals with non-AIDS-defining malignancies who are due to start chemotherapy or radiotherapy should be started on ART unless contraindicated (2C).
8.3.3 Opportunistic infection prophylaxis in HIV-associated malignancy
<ul style="list-style-type: none"> We recommend that all individuals with AIDS-defining malignancies should start ART immediately (1B).
<ul style="list-style-type: none"> We suggest that all individuals with non-AIDS-defining malignancies who are due to start chemotherapy or radiotherapy should be started on ART immediately unless contraindicated (2C).
<ul style="list-style-type: none"> We recommend herpes simplex virus (HSV) prophylaxis in PLWH with a history of HSV infection who are starting chemotherapy to reduce the incidence and severity of reactivations (1D).
<ul style="list-style-type: none"> We recommend that individuals with antibodies against hepatitis B core antigen (HBcAb) should be treated with prophylactic antivirals in line with BHIVA hepatitis guidelines (1B).

8.3.4 Other considerations from the BHIVA guidelines for HIV-associated malignancies
<ul style="list-style-type: none"> We recommend that potential pharmacokinetic interactions between antiretrovirals and systemic anticancer therapy are checked prior to administration (with tools such as: www.hiv-druginteractions.org) (1C).
<ul style="list-style-type: none"> We suggest avoiding ritonavir (or cobicistat)-boosted ART in HIV-positive individuals who are to receive cytotoxic chemotherapy agents that are metabolised by the CYP450 enzyme system (2C).
<ul style="list-style-type: none"> We suggest avoiding atazanavir in HIV-positive individuals who are to receive irinotecan (2C).
<ul style="list-style-type: none"> We suggest switching antiretroviral agents in HIV-positive patients who are to receive cytotoxic chemotherapy agents to avoid severe and/or overlapping toxicities (2C).
<ul style="list-style-type: none"> Medicines reconciliation prior to chemotherapy to minimise potential pharmacokinetic interactions and overlapping toxicity should be undertaken by an experienced pharmacist (GPP).
8.4 HIV-associated neurocognitive impairment
8.4.2 When to start ART
8.4.2.1 Recommendation
<ul style="list-style-type: none"> We recommend individuals with symptomatic HIV-associated neurocognitive disorders start ART immediately, irrespective of CD4 cell count (1C).
8.4.3 What to start with
8.4.3.1 Recommendations
<ul style="list-style-type: none"> We recommend individuals with HIV-associated NC disorders start standard combination ART regimens (1C).
We recommend avoiding efavirenz-containing regimens in individuals with HIV-associated NC disorders (1C).
8.4.4 Continuing or worsening NC impairment despite ART
8.4.4.1 Recommendations
Best practice management should include (GPP):
<ul style="list-style-type: none"> Reassessment for confounding conditions.
<ul style="list-style-type: none"> Assessment of CSF HIV RNA and genotyping of CSF HIV RNA.
<ul style="list-style-type: none"> In subjects with detectable CSF HIV RNA, modifications to antiretroviral therapy should be based on paired plasma and CSF genotypic results.
8.5 Chronic kidney disease
8.5.1 When to start antiretroviral therapy
8.5.1.1 Recommendations
<ul style="list-style-type: none"> We recommend individuals with HIV-associated nephropathy (HIVAN) start ART immediately irrespective of CD4 cell count (1C).
<ul style="list-style-type: none"> We recommend individuals with end-stage kidney disease who are suitable candidates for renal transplantation start ART immediately (1C).

8.5.2 What to start
8.5.2.1 Recommendations
<ul style="list-style-type: none"> We recommend against the use of ARV drugs that are potentially nephrotoxic in individuals with stages 3–5 CKD if acceptable alternative ARV agents are available (GPP). We recommend dose adjustment of renally cleared ARV drugs in individuals with reduced renal function (GPP).
8.5.3 Need to switch
8.5.3.1 Recommendations
<ul style="list-style-type: none"> We recommend against continued use of tenofovir-DF and atazanavir in individuals with worsening renal function who have developed or are approaching CKD stages 3–5 if acceptable alternative ARV agents are available (GPP).
8.6 Cardiovascular disease
8.6.2.1 Recommendation
<ul style="list-style-type: none"> We suggest that the coronary heart disease (CHD) risk of HIV-positive adults of white ethnicity is estimated as per the BHIVA monitoring guidelines (www.bhiva.org/monitoring-guidelines.aspx)(2C).
8.6.4 What to start
8.6.4.1 Recommendations
In individuals with a high CVD risk:
<ul style="list-style-type: none"> We recommend use of alternatives to fosamprenavir/r (1C) and lopinavir/r (1C) We suggest that atazanavir/r is the preferred PI (2C). We suggest avoiding abacavir (2C) and maraviroc if an acceptable alternative is available. First-line ARV therapy with tenofovir-DF plus (emtricitabine or lamivudine) with dolutegravir or raltegravir or rilpivirine (if viral load <100,000 copies/mL) are preferred first line regimens (GPP). Adverse effects on lipid parameters should be considered when selecting ARVs (GPP).
8.6.5 Modification of CVD risk factors
8.6.5.1 Recommendations
In patients with a high CVD risk:
<ul style="list-style-type: none"> We recommend that traditional modifiable risk factors should be minimised; smoking cessation is of critical importance (1A). We suggest that that this should include switching ARVs to those with a more favourable metabolic profile but only where there is minimal risk of treatment failure (2C).
8.7 Women
8.7.2 When to start
8.7.2.1 Recommendations
<ul style="list-style-type: none"> We recommend therapy-naïve HIV-positive women who are not pregnant start ART (see Section 4.0)

(1A).
8.7.3 What to start
8.7.3.1 Recommendations
<ul style="list-style-type: none"> There are insufficient data to support specific recommendations for HIV-positive non-pregnant women. We therefore recommend therapy-naïve HIV-positive women start ART as per general guidelines (1A).
<ul style="list-style-type: none"> We recommend both HIV-positive women of childbearing potential and healthcare professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of the HIV-positive woman and for that of an unborn child (GPP).
<ul style="list-style-type: none"> We recommend that potential pharmacokinetic interactions between ARVs, hormonal contraceptive agents and hormone replacement therapy are checked before administration (GPP).
8.8 Mental health
8.8.1 Recommendations
<ul style="list-style-type: none"> What to start: we recommend that efavirenz-containing regimens be avoided in individuals with a current or past history of depression, psychosis, suicidal ideation or attempted suicide, or at risk of self-harm (1C).
<ul style="list-style-type: none"> Switching therapy: we recommend that efavirenz-containing regimens should be switched promptly to a viable alternative when PLWH present with depression, psychosis, suicidal ideation or attempted suicide, or self-harm (1C).
8.9 Adolescents
8.9.1 Recommendations for management of HIV, ART and sexual and reproductive health specifically for perinatally acquired HIV
<ul style="list-style-type: none"> Avoid standard-dose (600mg) efavirenz-based regimens in any young person <50kg, with any history of mental health or psychological or neurocognitive problems.
8.10 Bone disease and antiretroviral therapy
8.10.2 When to start antiretroviral therapy
8.10.2.1 Recommendation
<ul style="list-style-type: none"> We recommend that general recommendations for the timing of ART are followed in patients with, or at risk of osteoporosis (1D).
8.10.3 What to start
8.10.3.1 Recommendations
<ul style="list-style-type: none"> We recommend against the use of tenofovir-DF in individuals aged >40 years with osteoporosis, a history of fragility fracture, or a FRAX score of >20% (major osteoporotic fracture) if acceptable alternative ARV agents are available (1B).
8.10.4 Switching treatment

8.10.4.1 Recommendations

- We recommend against continued use of **tenofovir-DF** in individuals >40 years who are diagnosed with osteoporosis, have sustained a fragility fracture, **or have a FRAX score consistent with high risk of major osteoporotic fracture** if acceptable alternative ARV agents are available (1C).

8.11 Considerations for later life

8.11.2 When to start ART

8.11.2.1 Recommendation

- We recommend standard criteria are used to determine when to commence antiretroviral therapy in older PLWH (1C).

8.11.3 What to start

8.11.3.1 Recommendation:

- We recommend standard antiretroviral regimens are commenced in older PLWH (1C).

3.0 Involvement of people living with HIV in decision-making

3.1 Recommendations

- We recommend PLWH are given the opportunity to be involved in making decisions about their treatment (GPP).
- Provision of treatment-support resources should include in-house, independent and community information providers and peer-support resources (GPP).

3.2 Auditable outcomes

- Percentage of PLWH who confirm they have been given the opportunity to be involved in making decisions about their treatment.
- Percentage of PLWH who have been offered signposting or referral to peer support or treatment advocacy services.
- Proportion of PLWH utilising peer support or treatment advocacy services.

3.3 Rationale

PLWH should be given the opportunity to be involved in making decisions about their treatment [1]. Studies show that trust, a good-quality relationship and good communication skills between doctor and PLWH are associated with better adherence and treatment outcomes in HIV and in other disease areas [2–6].

Studies have shown that beliefs about the necessity, efficacy and side effects of ART, the practicability of taking it, and ability to adhere to therapy, all affect adherence [7–9].

Before prescribing ART (treatment initiation or switching), clinicians should assess the individual's readiness to take therapy, including:

- Understanding of HIV therapy, and perceptions of personal need for ART;
- Concerns about taking ART or specific ARV drugs, including potential adverse effects;
- Concerns with possible adverse social consequences, such as disclosure or interference with lifestyle;
- Confidence that they will be able to adhere to the medication (self-efficacy);
- Psychological or neurocognitive issues that could impact on adherence;
- Socio-economic factors that could impact on adherence, including, but not limited to, poverty, housing, immigration status or domestic violence;
- Pregnancy or parenting plans.

Community advocacy and peer support, including clinic-based peer support, are helpful in supporting an individual's understanding and confidence around treatments, and may also help increase readiness to start therapy. Community organisations in the UK have been instrumental in providing a range of information resources for PLWH and peer-support services, including published and web-based information materials, telephone advice lines, treatment advocates and peer-support groups, working in collaboration with

healthcare professionals. They are an important and essential adjunct to clinic-based services and are helpful in addressing the issues discussed below. Peer support is particularly important at diagnosis but there may be other crucial times when peer support is particularly important such as starting/switching ART, disclosing to others or planning a family.

A number of factors may affect adherence, adverse effects and treatment outcomes, including social and cultural beliefs. Depression is significantly associated with low adherence [10,11] and some studies report an independent association between depression and mortality in people with HIV [12]. Adherence can be improved by treating depression [13], so all PLWH should be screened for depression before starting therapy, using simple screening tools such as the Arroll two question quick screen [14]. HIV-positive individuals should also be screened for anxiety and for cognitive impairment using validated tools (see the BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals 2011; www.bhiva.org/Guidelines.aspx).

Current problematic alcohol and recreational drug use are also associated with low adherence [15–17], although a history of injecting drug use, even current use, does not necessarily predict poor adherence [18]. PLWH should be asked about alcohol and recreational drug use and offered support to moderate or manage it if desired.

Conversely, adherence has been associated with positive experiences of quality of life such as having a meaningful life, feeling comfortable and well cared for, using time wisely, and taking time for important things [19]. Self-management skills and courses that teach these to PLWH have been associated with both improved adherence and better clinical outcomes in a number of studies [20–22]. It may be helpful to PLWH to inform them of these and other psychological support options locally available, in line with the BPS/BHIVA/MedFASH Standards for Psychological Support for Adults Living with HIV [23].

An individual's socio-economic status has a direct effect on adherence. For instance, a US study found that poverty had a direct effect on adherence, largely due to food insufficiency [24]. A 2010 report on poverty in people with HIV in the UK found that 1-in-6 people with HIV was living in extreme poverty, in many cases due to unsettled immigration status [25]. In addition, the ASTRA study revealed that after adjustment for demographic factors, increasing financial hardship, non-employment, non-homeownership, non-university education and lack of supportive network were associated with higher risk of virological rebound in ART-treated individuals [26]. Clinicians should be aware of the socio-economic status of HIV-positive individuals and refer to social support where necessary.

Clinicians should establish what level of involvement the HIV-positive individual would like and tailor their consultation style appropriately. They should also consider how to make information accessible and understandable to PLWH (e.g. with pictures, symbols, large print and different languages) [1], including addressing linguistic and cultural issues. Youth is consistently associated with lower adherence to ART, loss to follow-up and other negative healthcare behaviours [27] and some studies have found an independent association between poorer adherence and attendance and female gender [28], so information and consultation style should be age and gender appropriate for the individual.

If there is a question about an individual's capacity to make an informed decision, this should be assessed using the principles in the Mental Capacity Act 2005 [29].

PLWH presenting at the clinic may be at different stages of readiness to take therapy [30] and clinicians' first task is to assess their readiness, by means of open (rather than closed) questions. However, if an HIV-positive individual presents in circumstances that necessitate starting ART immediately, for example with an AIDS diagnosis or very low CD4 cell count, then doctors should prescribe ART and provide support for their adherence, especially through the first few weeks. Recognising symptoms that individuals attribute to ART side effects might avoid loss of adherence and deterioration of trust in the patient–provider relationship [31,32].

A 'perceptions and practicalities' approach should be used to tailor support to meet the needs of the individual, to identify both the perceptual factors (such as beliefs about ART) and practical factors (such as capacity and resources) influencing adherence [1,8].

In terms of preparing PLWH for potentially lifelong ART it is important to explain and discuss the rationale for ART, potential adverse effects, why adherence is essential and the implications of missed/stopped ART. Clear and appropriate explanations of the mechanisms of ART and how different drugs inhibit HIV replication may help clarify the rationale for combination therapy and why it is so important to take the drugs in the right way, at the right time. A review of the individual's social circumstances, support, occupation, social life, options to store ART, ability to follow any necessary food requirements, understanding of drug–drug interactions and where to seek advice are important. The impact of storing or taking ART on potential disclosure to others should be considered. Written information or signposting to online resources should be offered, as should access to peer support. The preparation required for ART will vary from one person to the next and the multidisciplinary team and/or repeat visits should be utilised as indicated.

Supporting PLWH requires good communication not just between clinician and the HIV-positive individual but also between all healthcare staff involved with their care, including those in their HIV services, their general practitioner (GP) and any clinicians involved in management of co-morbid conditions. PLWH should be offered copies of letters about them sent to their GP and other physicians. Disclosure of HIV status to the GP should be considered best practice and should always be discussed. However, an individual's decision not to disclose their status to their GP should be respected, subject to the clinician's duty to protect vulnerable individuals.

3.4 References

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4.0 When to start

4.1 Chronic infection

4.1.1 Recommendations

- We recommend people with HIV start ART (1A).

4.1.2 Auditable outcomes

- Proportion of diagnosed PLWH on ART.
- Proportion of PLWH not on ART where the rationale for this, and a discussion of the benefits of ART, has been documented at least annually.

4.1.3 Rationale

Until recently, BHIVA recommended that individuals with chronic HIV infection should start ART before the CD4 count fell to below 350 cells/ μ L [1]. This recommendation was based on evidence from cohort studies that demonstrated an increased risk of disease progression in individuals who delayed ART until their CD4 count was below 350 cells/ μ L and the absence of robust evidence from RCTs in which the intervention, comparator and populations were similar to our own setting [2–13].

Three trials have randomised people with a CD4 cell count >350 cells/ μ L to start or to defer treatment. The HIV Prevention Trials Network (HPTN) 052 trial [14] randomised individuals to early (initiate ART at a CD4 cell count between 350 and 550 cells/ μ L) or deferred (initiate ART at a CD4 cell count below 250 cells/ μ L) ART. While the study reported a benefit to earlier ART initiation, those in the deferred comparator arm started treatment at a significantly lower CD4 cell count than recommended in the UK since 2008 [15]. This study is thus likely to overestimate the benefits of immediate treatment compared with starting at <350 cells/ μ L. A further study, the ANRS 12136 Temprano trial [16] presented results in early 2015. This study, conducted in the Ivory Coast, randomised persons with a CD4 cell count <800 cells/ μ L to immediate ART or to receipt of ART adhering to WHO criteria for initiation of therapy (these criteria changed several times over the course of the trial). Again, while the trial results demonstrated a clinical benefit associated with earlier ART initiation, the median CD4 cell count at ART initiation in the comparator arm is likely to be much lower than would be considered clinically acceptable in the UK. Furthermore, the population considered in the trial (those in the Ivory Coast with a high incidence of tuberculosis) is substantially different to the UK setting.

More recently, preliminary results of the START study have been presented and published [17]. This study enrolled 4685 adults with CD4 cell counts above 500 cells/ μ L (median CD4 cell count 651 cells/ μ L) in 35 countries, and randomised them to start ART immediately or to defer ART until the CD4 count fell below 350 cells/ μ L. The risk of developing AIDS, a serious non-AIDS event or of death (combined as the primary endpoint) was reduced by 57% in those who were randomised to start earlier, after a median follow-up period of 3 years. The results were similar in high-income when compared to low- and middle-income countries and driven mainly by a difference in rates of AIDS events, particularly TB and cancers. Immediate ART was not associated with higher risk of grade 4 events or unscheduled hospital admissions.

Data on virological efficacy, drug resistance and toxicity, and the results of substudies (examining effects on bone, neurological function, lung function and small arterial elasticity) and quality of life outcomes have not yet been reported. Nevertheless, these results demonstrate a benefit of ART at CD4 counts of >500 cells/ μ L, and suggest that if individuals are able to commit to taking ART, it should be started, regardless of the CD4 count.

Considerations when preparing an individual to start ART are addressed in Section 3.3. It is important to recognise that despite the significant reduction in relative risk of disease progression associated with early ART, the absolute risk of deferring ART was small. In this study, 4.1% of individuals in the deferred arm vs. 1.5% in the immediate treatment arm experienced a serious illness over 3 years of follow-up. The absolute risk of deferring therapy should be considered when making individual decisions.

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4.2 Individuals presenting with AIDS or a major infection

4.2.1 Recommendation

- We recommend that individuals presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 cell count <200 cells/μL, start ART within 2 weeks of initiation of specific antimicrobial chemotherapy (1B).

4.2.2 Auditable outcome

- Proportion of HIV-positive individuals presenting with an AIDS-defining infection or with a serious bacterial infection and a CD4 cell count <200 cells/μL who are started on ART within 2 weeks of initiation of specific antimicrobial chemotherapy.

4.2.3 Rationale

This recommendation is largely based on the ACTG 5164 study that demonstrated fewer AIDS progressions/deaths and improved cost-effectiveness when ART was commenced within 14 days (median 12 days; IQR 9–13 days) compared with initiation after completion of treatment for the acute infection (median 45 days; IQR 41–55 days) [1,2]. Those with tuberculosis (TB) as the primary infection were excluded from this study, and the majority of individuals enrolled had *Pneumocystis* pneumonia. The patients were well enough to give informed consent and to take oral medications, and therefore the findings may not be generalisable to those who are severely unwell or who require intensive care. Previous observational data suggest a survival benefit for HIV-positive patients who are started on ART while in the intensive care unit [3,4], but the data are insufficient to make a recommendation in this group [3,4].

There was no increase in the incidence of immune reconstitution disorders or adverse events generally with early ART initiation in ACTG 5164 [1,5]. However, those with intracranial opportunistic infections may be more prone to severe immune reconstitution disorders with early ART initiation. Some data suggest that particular caution should be exercised with cryptococcal meningitis: two studies from sub-Saharan Africa have demonstrated an increased mortality with early ART initiation; however, both were in very different healthcare settings from the UK and one utilised antifungal regimens that would not be preferred [6,7]. The COAT study highlighted that those with an acellular CSF or with decreased levels of consciousness were at higher risk of death with early ART initiation [7]. It is important to note that immune reconstitution disorders can be difficult to diagnose and case definitions vary across studies. Those presenting with TB and malignancies are discussed in Section 8.

4.2.4 References

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4.3 Treatment of primary HIV infection

4.3.1 Recommendation

- We recommend all individuals with suspected or diagnosed PHI are reviewed promptly by an HIV specialist and offered immediate ART (1B).

4.3.2 Auditable outcomes

- Proportion of individuals with PHI assessed by an HIV specialist within 2 weeks.
- Proportion of individuals with PHI offered immediate ART.

4.3.3 Rationale

Primary HIV infection (PHI) is defined as HIV infection within a maximum of 6 months from the estimated time of HIV transmission. It can be diagnosed based on laboratory test results in the setting of a clinical sexual history [1]. In the setting of the recent results from the START, TEMPRANO and HPTN052 trials, there is now no longer equipoise when counselling all individuals diagnosed with HIV; these studies showed clinical benefit to starting immediate ART over deferral [2–5].

In the context of PHI there are additional considerations to take into account when considering best management. PHI is a distinctive situation where often-significant symptoms consistent with seroconversion occur at a time of the stress of coming to terms with a new HIV diagnosis. Individuals diagnosed with PHI with low initial CD4 T cell counts [6,7], high plasma viral loads (>100,000 copies HIV RNA) [8] and short test intervals (diagnosis within 12 weeks of a previous negative test) [9,10] have a more rapid rate of disease progression than others without these features at PHI, and hence early ART initiation should be prioritised.

ART should be started only when the individual feels ready to do so. However, there are certain clinical presentations of PHI where expedited ART initiation should be recommended. We recommend starting ART as soon as possible for patients presenting with PHI meeting any one of the following criteria known to be associated with morbidity or very rapid disease progression:

- Neurological involvement (1D);
- Any AIDS-defining illness (1A);
- CD4 cell count <350 cells/ μ L (1C);
- PHI diagnosed within 12 weeks of a previous negative test (1C).

The pros and cons of early ART initiation with a view to long-term therapy should be clearly and sensitively presented to any individual diagnosed with PHI. ART once started, should be considered as potentially lifelong due to the increased all-cause mortality observed from treatment interruption in the SMART study [11], which was seen regardless of nadir CD4 cell count.

Table 4.1. The pros and cons of starting ART in PHI

Pros of starting ART in PHI	Cons of starting ART in PHI
Enhanced probability of immunological recovery to normal levels [12-18]	Ambivalence to ART at a time of emotional challenges can risk poor adherence and the development of drug resistance
Individuals with recent HIV diagnosis may feel comforted to know that they are taking immediate control of their infection with evidence to support enhanced immunological and virological benefits [19]	Individuals with recently diagnosed PHI may be in a particularly vulnerable psychological state, and thus ill-prepared to commit to starting long-term treatment.
Reduced risk of onward viral transmission at a time of very high viral load and consequent high risk of transmission [19–24]	
Reduction in morbidity and more rapid disease progression associated with high viraemia [8]	
Recent data from the START, TEMPRANO and HPTN052 trials identify clinical benefit from starting ART irrespective of CD4 count [3–5]	
Earlier intervention within the first 12 weeks of diagnosis confers enhanced immune recovery for this group of individuals who progress more rapidly if ART is deferred [12–17]	
Limitation of viral reservoir to significantly below that seen when treatment deferred [5]	

The rationale for immediate ART initiation amongst individuals diagnosed with PHI include:

- Preservation of immune function and CD4 T lymphocytes in terms of both total CD4 counts and the ratio of CD4:CD8 T cells, which reflects immune activation, inflammation, all-cause mortality that are otherwise impaired by uncontrolled viral replication, and are associated with survival in untreated individuals [13–19].
- Reduction in morbidity associated with high viraemia and profound CD4 cell depletion during acute infection [7–11].
- Reduction in the enhanced risk of onward transmission of HIV associated with PHI [21–26].

There is never likely to be a randomised controlled trial in PHI comparing immediate vs. deferred ART that is powered to a survival outcome, as such a study would require decades to accrue endpoints. Hence recommendations of best management of PHI are based on surrogate markers of mortality and CD4 count. Increasing evidence has identified both rapid and enhanced recovery of surrogate markers of immune system [7–9] in terms of CD4 cell count [10] and CD4:CD8 ratio [11,12] for individuals initiating ART close to the time of HIV transmission compared to deferred ART initiation. A recent analysis demonstrated lower likelihood of achieving a normal CD4 cell count if treatment initiation was delayed more than 12 months after PHI; therefore, even outside the circumstances where prompt ART is advised, starting within 1 year of PHI diagnosis is advisable [18].

Immediate or expedited ART initiation for symptomatic seroconversion and those with very high plasma viral loads will additionally resolve clinical symptoms and limit the enhanced risk of onward viral transmission [12–18]. Furthermore, earlier ART initiation has been shown to correspond with reduced measures of the latent pool of infected cells (viral reservoir) [27–29], the current barrier to HIV remission or cure [30,31]. We

therefore recommend an expedited pathway of care for individuals diagnosed with PHI to ensure a clear and informed discussion of the pros and cons of immediate ART is provided to all individuals to support them making the correct treatment decision. An individual's readiness to start ART should be explored prior to commencing (see Section 3.3).

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4.4 Impact of treatment on prevention of onward transmission

4.4.1 Recommendations

- We recommend that ART is offered to all PLWH for the prevention of onward transmission (1A).
- We recommend the evidence that treatment with ART substantially lowers the risk of transmission is discussed with all PLWH (GPP).
- An assessment of the risk of transmission to others should be made at diagnosis and subsequent visits (GPP).

4.4.2 Auditable outcome

- Record in medical notes of all individuals about the discussion that treatment with ART lowers the risk of HIV transmission and perform an assessment of the current risk of transmission.

The discussion should include the following:

- If the decision to start ART is being driven primarily by transmission risk it should be the HIV-positive individual's choice and must not be due to pressure from partners or others.
- The clinical benefits of ART at all CD4 cell counts should be emphasised.
- Individuals should be reassured about the relatively low risk of tolerability and toxicity issues with modern ART, and the option to switch ART if problems occur.
- Condoms, both male and female, continue to be recommended as protection from other sexually transmitted infections and unplanned pregnancy.
- There are risks associated with interrupting ART, and once started, it should generally be continued.
- Much of the evidence that ART lowers the risk of transmission mainly relates to vaginal sex. Recent data also show that ART greatly reduces the risk of transmission for anal sex, although the upper estimates for risk for anal sex are higher, and more data are needed; therefore, other prevention strategies, including condoms, should be discussed.
- High and consistent adherence to ART is required to maintain viral suppression and minimise transmission risk.
- Taking ART does not result in immediate complete viral suppression; it usually takes several months to achieve an undetectable viral load in blood.

4.4.3 Rationale

The potential effect of HIV treatment to reduce the risk of onward sexual transmission should be discussed with all PLWH as a part of safer sex messages in general. For individuals with a high CD4 cell count, the impact of treatment on the risk of transmission may be an additional factor to aid their decision-making. NHS England approved the use of ART for prevention in July 2015 [1].

The initial evidence base for treatment to reduce transmission was based on a number of cohort studies that found that transmission between heterosexual couples where the HIV-positive partner had an undetectable viral load on treatment was very rare or did not occur [2–6].

This was followed by good evidence from one randomised controlled trial (HPTN 052) [7] that showed ART can markedly reduce (by 96%) the risk of transmission to HIV-negative partners. This is supported by the secondary outcomes of another trial [8] that also found a marked reduction in transmission from partners taking ART (by 92%). It is important to note that 97% of the couples in HPTN 052 were heterosexual and the Partners in Prevention study was conducted entirely with heterosexual couples. The evidence base thus relates mainly to the risk of transmission for vaginal sex in heterosexual couples.

More recently, data from the PARTNER study have demonstrated a protective effect of viral suppression in serodifferent couples where the HIV-positive person is on suppressive ART (viral load less than 200 copies/mL). After 16,800 and 28,000 condomless sex acts in MSM and heterosexual couples respectively,

there were no cases of HIV transmission when 86 would have been expected based on previous incidence studies [9].

Condoms should still be recommended to protect from other sexually transmitted infections, and to lower further any residual risk of transmission.

PLWH should be informed that taking ART does not result in immediate viral suppression. Most individuals commencing ART achieve viral suppression by 3–6 months; integrase inhibitors are characterised by more rapid viral suppression with most individuals achieving an undetectable viral load by 1–3 months [10–12]. PLWH should also be informed about the possibility of virological failure leading to transmission of HIV. Decisions on condom use and safer sex should always be based on a recent viral load test result and not on an assumption that taking ART implies non-infectiousness.

Suppressive ART expands the choices available to sero-different heterosexual people wishing to conceive. Sex without condom use around the time of ovulation (timed UPSI) carries very little if any risk provided the HIV-positive partner has a durably suppressed viral load. Pre-exposure prophylaxis, although recommended in some guidelines [13], is likely to add very little as risk reduction in this scenario. Details of the use of ART to prevent mother-to-child transmission are covered in the *BHIVA guidelines for the management of HIV infection in pregnant women* [14]. Sperm washing is not recommended in the context of viral suppression [15].

4.4.4 References

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5.0 What to start

5.1 Summary of recommendations

- We recommend that therapy-naïve PLWH start ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir-boosted protease inhibitor (PI/r), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) (1A).

Table 5.1. Summary recommendations for choice of ART

	Preferred	Alternative
NRTI backbone	Tenofovir-DF and emtricitabine Tenofovir-AF and emtricitabine	Abacavir and lamivudine ^{a,b}
Third agent (alphabetical order)	Atazanavir/r Darunavir/r Dolutegravir Elvitegravir/c ^c Raltegravir Rilpivirine ^d	Efavirenz

/r: boosted with ritonavir; /c: boosted with cobicistat

^a Abacavir is contraindicated if an individual is HLA-B*57:01 positive

^b Use recommended only if baseline viral load is $\leq 100,000$ copies/mL except when initiated in combination with dolutegravir in which case abacavir/lamivudine can be used at any baseline viral load.

^c Tenofovir-DF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in individuals with creatinine clearance <70 mL/min; tenofovir-AF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in patients with CrCl <30 mL/min

^d Use recommended only if baseline viral load is $\leq 100,000$ copies/mL

NB. The viral load advice for abacavir/lamivudine and rilpivirine applies only to initiating these agents in individuals with a detectable viral load – when these agents are used as a switch option in the context of viral load suppression the baseline viral load can be disregarded.

5.1.1 Summary of auditable outcomes

- Proportion of therapy-naïve individuals starting ART containing preferred or alternative agents.
- Proportion of individuals with undetectable viral load at 6 months and at 12 months after starting ART.
- Proportion of individuals who switch therapy in the first 6 and 12 months.

5.2 Introduction

For the ‘which NRTI backbone’ and ‘which third agent’ questions, evidence profiles and summary of findings tables were constructed to assess quality of evidence across predefined treatment outcomes (Appendix 3). Evidence from randomised controlled trials and systematic reviews was identified from a literature search (Appendix 2). Outcomes were scored and ranked (critical, important, not important) by members of the writing group. The following were ranked as critical outcomes: viral suppression at week 48/96, proportion with virological failure, proportion developing resistance, proportion discontinuing for adverse events, proportion with grade 3/4 adverse events.

Treatments were compared and differences in critical outcomes assessed. Where there were differences, consensus opinion was sought to determine whether the difference in size of effect was above the threshold for clinical decision-making. If conflicting differences were detected, the balance of outcomes was based on consensus opinion of the writing group.

A treatment was defined as preferred or alternative to indicate strong or conditional recommendations with each decision based on the assessment of critical outcomes and the balance of desirable and undesirable effects in a general ART-naïve population. ‘Preferred’ indicates a strong recommendation that most clinicians and PLWH would want to follow unless there is a clear rationale not to do so ‘Alternative’ indicates a conditional recommendation and is an acceptable treatment option for some PLWH and might be, in selected individuals, the preferred option.

Factors including potential side effects, co-morbidities, individual preference and drug interactions need to be taken into account when selecting an ART regimen, and may include both preferred and alternative treatment options.

For guidance on assessment of PLWH before initiation of ART and monitoring individuals on ART the reader should consult the *BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals* (www.bhiva.org/monitoring-guidelines.aspx).

5.3 Which nucleoside reverse transcriptase inhibitor backbone

5.3.1 Recommendations

- We recommend therapy-naïve individuals start combination ART containing **tenofovir-DF** and emtricitabine **or tenofovir-AF and emtricitabine** as the preferred NRTI backbone (1A).
- We suggest abacavir and lamivudine is an acceptable alternative NRTI backbone in therapy-naïve individuals. In those with a baseline viral load >100,000, it should be used with caution if there are clinical reasons to prefer it over **alternative NRTI backbones** (2A).

The caution regarding baseline viral load does not apply if abacavir/lamivudine is used with dolutegravir (2A).

- Abacavir must not be used in individuals who are HLA-B*57:01-positive (1A).

5.3.2 Rationale

The evidence and rationale for which NRTI backbone to use for initial therapy has not changed since the last iteration of the guidelines in 2012 [1]. Three randomised controlled trials have compared **tenofovir-DF/emtricitabine** with abacavir/lamivudine as the NRTI backbone in combination with different third agents: atazanavir/r or efavirenz [2-6], efavirenz [7-9] and lopinavir/r [10].

Assessment of virological efficacy as a critical outcome was complicated by different definitions across the three studies. By GRADE analysis (see Appendix 3), there was no difference in rates of virological suppression at 48 weeks or 96 weeks but the analysis excluded the largest of the three trials (ACTG 5202) and the quality of evidence for this outcome was assessed as low or very low. Assessment of the risk of protocol-defined

virological failure at 48 weeks favoured **tenofovir-DF**/emtricitabine (relative risk [RR] 0.76, 95% confidence interval [CI] 0.53–1.07), although the effect was not statistically significant and heterogeneity in the analysis was relatively high. Assessment of protocol-defined virological failure at 96 weeks showed a significant difference favouring **tenofovir-DF**/emtricitabine (RR 0.73, 95% CI 0.59–0.92). Data were only available from one study [2] for this analysis; however, this was by far the largest of the three trials and the quality of evidence assessment for this outcome was rated as high. The difference in virological failure was assessed to be large enough to be above the clinical threshold for decision-making. The difference equates to a number needed to treat for 1 year to prevent one case of virological failure of approximately 20.

The results of ACTG 5202 [2-4] are complicated by early withdrawal of those individuals receiving abacavir/lamivudine with a baseline viral load >100,000 copies/mL at the recommendation of the Data and Safety Monitoring Board owing to significantly inferior performance. No difference in virological efficacy between the **tenofovir-DF**/emtricitabine and abacavir/lamivudine arms was seen in those in the lower viral load stratum (baseline viral load <100,000 copies/mL). The subsequent 96-week analysis, after discontinuation of those subjects in the higher viral load stratum, may therefore underestimate the difference between the two backbones. HLA-B*57:01 screening was not routine in ACTG 5202 and potentially this may have influenced some of the safety endpoints, but appears not to have influenced the primary virological outcome. In the higher viral load stratum the number of study participants with suspected hypersensitivity reactions was equal between both arms and virological failure in these individuals was infrequent.

With regard to the assessment of the other critical and important outcomes, no difference was shown between **tenofovir-DF**/emtricitabine and abacavir/lamivudine. No data were available to assess quality of life outcomes. For grade 3/4 adverse events (all) and grade 3/4 alanine transaminase/aspartate transaminase elevation there were trends that favoured **tenofovir-DF**/emtricitabine (see Appendix 3).

Although the rate of drug resistance was not different between the NRTI backbones, the number developing drug resistance was higher numerically in those receiving abacavir/lamivudine, given the higher rate of virological failure.

Bone mineral density outcomes significantly favoured abacavir/lamivudine.

Given the favourable virological outcomes of **tenofovir-DF**/emtricitabine compared with abacavir/lamivudine and the lack of other significant differences in critical and important adverse event outcomes, **tenofovir-DF**/emtricitabine is recommended as the preferred NRTI backbone of choice. Abacavir/lamivudine is an acceptable alternative option in individuals with a baseline viral load <100,000 copies/mL (other than in combination with dolutegravir when abacavir/lamivudine can be initiated regardless of baseline viral load), but must only be used after ensuring HLA-B*57:01 is negative.

When selecting an NRTI backbone, factors such as potential side effects, co-morbidities, individual preference and cost should also be considered. Observational studies have variably reported associations between abacavir and cardiovascular disease (CVD)[11-14], and **tenofovir-DF** may cause renal disease [15]. These aspects are discussed in more detail in Section 8. However, based on the balance of current evidence we suggest abacavir is not used in individuals at high risk of CVD (see Section 8.6 Cardiovascular disease) and **tenofovir-DF** is not used in people with stage 3–5 chronic kidney disease (CKD) or at high risk of progression of CKD (see Section 8.5 Chronic kidney disease) if acceptable alternative antiretroviral agents are available.

Tenofovir alafenamide (tenofovir-AF) is a new formulation of tenofovir that yields significantly lower plasma concentrations of tenofovir (the active drug). The hypothesis that lower plasma tenofovir concentrations would result in a less negative impact on renal and bone markers has been borne out in clinical trials [16]. As a substrate of p-glycoprotein (pgp), there are potential drug-drug interactions for tenofovir-AF that do not apply to tenofovir-DF [SPC]. Co-administration of pgp inducers (including some anticonvulsants, rifamycins

and St John's wort) with tenofovir-AF may result lower tenofovir concentrations and loss of efficacy. In 2016 three products including tenofovir-AF were licensed: tenofovir-AF/emtricitabine/elvitegravir/c, tenofovir-AF/emtricitabine and tenofovir-AF/emtricitabine/rilpivirine. Based on non-inferior results for all critical endpoints in comparison with tenofovir-DF-based regimens we recommend tenofovir-AF/emtricitabine as a preferred backbone for initial therapy.

Studies using tenofovir-AF have demonstrated the greatest safety benefits in those at high risk of, or with established, renal disease. Those at low risk of renal disease showed minimal improvements in markers of tubular function. With regards to bone, individuals with low bone mineral density or high fracture risk are likely to most benefit from tenofovir-AF over tenofovir-DF. Clinicians seeking to make the most cost-effective use of current agents should bear this in mind as generic alternatives to proprietary medicines become available.

5.3.3 Not recommended

We believe there is no routine role for other NRTI backbones in the treatment of ART-naïve patients. Zidovudine/lamivudine may be considered in certain specific circumstances (e.g. pregnancy [17]) but should not be given routinely due to the proven association with mitochondrial toxicity, particularly lipoatrophy, with zidovudine. There is no place for the use of stavudine- or didanosine-containing regimens as initial therapy, due to the associations with significant mitochondrial and hepatic toxicities.

5.3.4 Lamivudine vs. emtricitabine

The nucleoside backbone tenofovir-DF/lamivudine has not been well studied in randomised trials. There are no trials investigating tenofovir-AF/lamivudine. This combination warrants further review of evidence as the lower costs associated with generic medications may make this an attractive combination in the future. There are a number of theoretical advantages in using emtricitabine rather than lamivudine, including:

- Emtricitabine triphosphate (TP) has a longer intracellular half-life [18];
- Emtricitabine TP is incorporated more efficiently than lamivudine TP into proviral deoxyribonucleic acid (DNA) [19];
- Greater *in vitro* potency [20].

Extensive review of the literature between 2000 and 2015 identified seven studies in ART-naïve individuals that included randomisation to a lamivudine- or emtricitabine-containing backbone. In two of these lamivudine vs. emtricitabine was the only variable [21,22]. However, neither of these studies has been published and therefore have not been subject to formal peer review. One study, performed in Zambia, randomised 332 subjects to fixed-dose combinations of either tenofovir-DF/lamivudine/efavirenz or tenofovir-DF/emtricitabine/efavirenz. Virological suppression rates at 48 weeks were similar (85.3% vs. 90.1%) but due to wide 97.5% confidence limits (-28.1–18.4%), non-inferiority of the lamivudine-containing regimen was not demonstrated. The other unpublished study in ART-naïve individuals was a double-blind comparison of lamivudine or emtricitabine with stavudine and either efavirenz or nevirapine with virological failure defined as a viral load >400 copies/mL on consecutive visits. The probability of virological failure was reported as 10% with either agent, although a significantly lower rate of M184V mutation development on failure was reported in the emtricitabine-containing regimen [22]. A significantly lower rate of M184V mutation development on failure was reported in the emtricitabine-containing regimen. Of the remaining five studies at least one other component, additional to lamivudine or emtricitabine, differed, therefore prohibiting direct comparison. Three studies compared abacavir/lamivudine with tenofovir-DF/emtricitabine [3,7,10], one compared zidovudine/lamivudine with tenofovir-DF/emtricitabine [23], one compared zidovudine/lamivudine/efavirenz vs. tenofovir-DF/emtricitabine efavirenz vs. didanosine/emtricitabine/atazanavir [24]. A randomised comparison of 440 patients stable on therapy with suppressed viral load substituting lamivudine for emtricitabine showed no difference in virological failure at 48 weeks [25]. However, this is of limited applicability to the question of therapy in ART-naïve patients since

'stable switch' studies are inherently biased in selecting patients who are already doing well on treatment. Of note, no trials using abacavir/emtricitabine as a backbone have been performed.

A number of observational studies and retrospective analyses of randomised controlled trials have sought to find clinical correlates of the pharmacological differences between lamivudine and emtricitabine. In general, these studies focus on the development of resistance, as evidenced by the emergence of the M184I/V mutation on treatment failure. Where data on resistance were available, none of the individual randomised controlled trial trials showed significant differences between lamivudine- and emtricitabine-containing arms. However, a pooled analysis [26] of three trials of lamivudine or emtricitabine with another NRTI plus efavirenz showed significantly less emergent M184V on emtricitabine (odds ratio [OR] 0.32, $P=0.02$) when considering the whole treated population. However, the interpretation of this result is complicated by the use, with lamivudine, of nucleoside analogues that are no longer recommended due to toxicity issues, making it difficult to confidently exclude differences in adherence contributing to the development of resistance. A sub-analysis in this same paper compared the **tenofovir-DF/lamivudine/efavirenz** arm from one randomised controlled trial with **tenofovir-DF/emtricitabine/efavirenz** from another and again found a significantly lower frequency of M184V/I [20]; this type of cross-trial comparison must, however, be interpreted with caution. A WHO appraisal on the interchangeability of lamivudine and emtricitabine concluded that the clinical and virological efficacy and safety of lamivudine and emtricitabine are comparable but the development of the M184V/I mutation is associated to a greater extent with the use of a lamivudine- rather than an emtricitabine-containing regimen [27]. They also stated, however, that the clinical and public health implications of this difference are not clear.

Cohort studies investigating this same question are subject to a number of confounders and have given mixed results. In general, they have shown significantly lower M184I/V development with the use of emtricitabine [28-30] but most have not restricted the analysis to individuals starting their first treatment regimen and have included a diverse range of other antiretroviral agents, so the relevance to recommendations for first-line therapy is open to question. A large UK CHIC analysis, including 5455 HIV-positive individuals, directly compared **tenofovir-DF/lamivudine** with **tenofovir-DF/emtricitabine** and found no significant difference in the emergence of M184V/I. This study was not restricted to treatment-naïve individuals [31]. On the other hand, a cohort study in the Netherlands of 4740 individuals was restricted to those starting first-line therapy with **tenofovir-DF/lamivudine** or **tenofovir-DF/emtricitabine** together with an NNRTI [32]. This study showed higher rates of virological failure for the lamivudine-containing regimens (OR=1.78, $P=0.16$ given with efavirenz) but did not adjust for year of HAART initiation in the multivariable analysis. This is important as lamivudine-containing regimens were started in significantly earlier years than emtricitabine-containing regimens and there has been a well-documented improvement in virological outcomes as the use of HIV therapy has evolved; this and other unidentified confounders may limit the validity of the results [33].

It is clear that the evidence concerning this question is mixed and of variable quality, leaving open the question of whether lamivudine and emtricitabine are interchangeable in first-line therapy. The paucity of sufficiently high-quality evidence addressing this question means that **tenofovir-DF/lamivudine** cannot be clearly recommended as an alternative nucleoside backbone when initiating first-line therapy.

If cost pressures become such that co-formulation is no longer a major driving factor in antiretroviral choice, then it will be reasonable to revisit this recommendation.

5.3.5 References

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5.4 Which third agent

5.4.1 Recommendations

- We recommend therapy-naïve individuals start combination ART containing atazanavir/r, darunavir/r, dolutegravir, elvitegravir/c, raltegravir or rilpivirine as the third agent (1A).
- We suggest that for therapy-naïve individuals, efavirenz is an acceptable alternative third agent (1A).

5.4.2 Rationale

The *BHIVA guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008* [1] recommended efavirenz as the preferred third agent in view of significantly better virological outcomes compared with lopinavir/r [2], subsequently confirmed in a smaller study [3]. In the following version of the guidelines, the preferred third agents were expanded to include more agents based on performance against efavirenz (atazanavir/r [4-9]; raltegravir [10-13]; elvitegravir/c [14]), lopinavir/r (atazanavir/r [15]; darunavir/r [16-18]) and atazanavir/r (elvitegravir/c [19]). Rilpivirine was added as an alternative third agent based on comparison with efavirenz [15,20,21].

Since the latest update to guidelines was published [22], the integrase inhibitor dolutegravir and the fixed-dose combination of abacavir/lamivudine/dolutegravir (Triumeq) has received licensing approval. Additionally there have also been a number of new randomised controlled trials comparing third agents for initial antiretroviral therapy. For the current guidelines, evidence for agreed treatment outcomes for each potential third agent was compared with preferred third agents from the previous guidelines [22], either directly or indirectly depending on the available evidence (Appendix 3):

- Efavirenz vs. rilpivirine [14];
- Efavirenz vs. dolutegravir [19];
- Atazanavir/r vs. darunavir/r vs. raltegravir [16];
- Raltegravir vs. dolutegravir [18];
- Darunavir/r vs. dolutegravir [17];

5.4.3 Individual agents

5.4.3.1 Atazanavir/ritonavir

Atazanavir/r has been compared directly in randomised controlled trials with efavirenz [7,23,24], raltegravir [16] and darunavir/r [16,25].

In ACTG 5202, although rates of virological failure were similar, there were significantly fewer cases of resistance development on atazanavir/r compared with efavirenz (OR 0.24, 95% CI 0.14–0.41) at 138 weeks, $P < 0.00001$). Some adverse events favoured atazanavir/r over efavirenz (see Appendix 3)

In ACTG 5257, the odds ratio for developing resistance at virological failure on raltegravir compared with atazanavir/r was 2.04 (95% CI 0.91–4.57, $P = 0.08$) at 96 weeks. Although, for overall response, atazanavir/r was outperformed by raltegravir (OR 2.04, 95% CI 1.30–3.18, $P = 0.002$) at 96 weeks in favour of raltegravir, driven mainly by significant differences in adverse event discontinuations (OR 0.07 favouring raltegravir at 96 weeks, 95% CI 0.03–0.15, $P < 0.0001$), virological failure rates (% total population) were similar in the two arms (OR 0.88, 95% CI 0.64–1.21, $P = 0.43$). Resistance development was more common on raltegravir than atazanavir/r when considering the proportion of virological failures with resistance (OR 2.57, 95% CI 1.08–6.08), but when considering the proportion of the total trial population developing resistance, this was not statistically significant (OR 2.04, 95% CI 0.91–4.57).

Virological response to atazanavir/r was similar to darunavir/r in ACTG 5257 and ATADAR at 96 and 48 weeks, respectively. There were no significant differences in virological failure or resistance development rates in either study (reported only at week 24 for ATADAR). Compared to darunavir/r, individuals randomised to

receive atazanavir/r in ACTG 5257 were significantly more likely to discontinue due to adverse events (OR 0.30 favouring darunavir/r, 95% CI 0.20–0.46, $P < 0.00001$). Although discontinuation for adverse events is a critical outcome, there was no difference in discontinuations for the specific non-critical outcomes considered (Appendix 3) and around half of discontinuations from atazanavir/r were for hyperbilirubinaemia/jaundice. On this basis it was felt that the difference between atazanavir/r and its comparators was not clinically significant and that atazanavir/r should remain a preferred third agent for initial therapy. However, jaundice is a potentially distressing and stigmatising event and PLWH who do not want to start atazanavir or wish to switch from atazanavir for this reason should have this decision respected. The requirement for pharmacokinetic boosting necessitates caution with respect to drug–drug interactions.

5.4.3.2 Darunavir/ritonavir

Comparison between darunavir/r and atazanavir/r is described in Section 5.4.3.1. For the comparison between darunavir/r and raltegravir in the three-arm ACTG 5257 study [16], overall response was significantly higher for raltegravir (OR 1.83, 95% CI 1.16–2.89 at 96 weeks in favour of raltegravir, $P = 0.009$). The corresponding proportion of patients with an undetectable HIV-1 RNA at 96 weeks by intention-to-treat analysis was 88.3% for atazanavir/r, 93.9% for raltegravir, and 89.4% for darunavir/r. Although there were more virological failures on darunavir/r (OR 0.69 favouring raltegravir, 95% CI 0.51–0.94, $P = 0.02$), individuals on raltegravir were more likely to develop resistance (OR 4.59, 95% CI 1.54–13.65, $P = 0.006$) favouring darunavir/r for percentage of the total population with resistance. There were fewer discontinuations for toxicity in the raltegravir arm (8/603 vs. 32/601 in the darunavir/r arm, OR 0.24, 95% CI 0.11–0.52); however, for the critical outcomes of grade 3 or 4 clinical or laboratory adverse events, grade 3 or 4 headache and grade 3 or 4 diarrhoea there were no significant differences. Darunavir/r was also compared with dolutegravir in the Flamingo study, and is discussed in Section 5.4.3.3. The requirement for pharmacokinetic boosting necessitates caution with respect to drug–drug interactions.

5.4.3.3 Dolutegravir

Dolutegravir has gained marketing authorisation and NHS England approval since the last guidelines update. There are three key randomised controlled trials that investigate dolutegravir for first-line therapy:

- SPRING-2 [18]: double-blind randomised controlled trial of tenofovir-DF/emtricitabine or abacavir/lamivudine plus raltegravir vs. tenofovir-DF/emtricitabine or abacavir/lamivudine plus dolutegravir.
- SINGLE [19]: double-blind randomised controlled trial of tenofovir-DF/emtricitabine/efavirenz (fixed-dose combination) vs. abacavir/lamivudine plus dolutegravir.
- FLAMINGO [17]: open label randomised controlled trial of tenofovir-DF/emtricitabine or abacavir/lamivudine plus darunavir/r vs. tenofovir-DF/emtricitabine or abacavir/lamivudine plus dolutegravir.

In SPRING-2, dolutegravir was non-inferior to raltegravir at weeks 48 and 96 [18]. When analysed by baseline viral load (participants were stratified by baseline viral load at randomisation) there was no significant difference in virological response at baseline viral load $> 100,000$ copies/mL at 48 weeks (OR for success on dolutegravir = 1.57, 95% CI 0.83–2.97, $P = 0.17$) but by week 96 there was a significant difference favouring dolutegravir (OR for success on dolutegravir = 2.10, 95% CI 1.17–3.75, $P = 0.01$). Overall virological failure rates at 48 and 96 weeks were not significantly different; and there was no significant difference for baseline viral load $< 100,000$ copies/mL at 48 or 96 weeks, or for baseline viral load $> 100,000$ copies/mL at 48 weeks. SPRING-2 was not powered for a stratified viral load comparison. Rates of virological failure and resistance development were similar and no differences in other critical or important outcomes were demonstrated.

In SINGLE [19], abacavir/lamivudine/dolutegravir demonstrated superior virological efficacy to tenofovir-DF/emtricitabine/efavirenz, driven by significantly more discontinuations due to adverse events in the tenofovir-DF/emtricitabine/efavirenz arm (OR for discontinuation for adverse events = 0.22 favouring

abacavir/lamivudine/dolutegravir, 95% CI 0.11–0.45, $P < 0.001$). There was no impact of baseline viral load on response rates in SINGLE.

Dolutegravir also demonstrated superior overall efficacy compared with darunavir/r in FLAMINGO (OR for success at 48 weeks = 1.08, 95% CI 1.01–1.17, $P = 0.03$) [17]. There was no difference in rates of virological failure and no instance of drug resistance in either arm. No differences were detected for other critical outcomes, although for important outcomes, there were significantly more clinical serious adverse events in the dolutegravir arm (OR 2.00, 95% CI 1.05–3.80, $P = 0.03$).

The consensus of the Writing Group was that, despite the superiority of dolutegravir in this study, the open-label trial design and lack of difference for other critical outcomes, meant darunavir/r should remain a preferred third agent.

5.4.3.4 Elvitegravir/cobicistat

Elvitegravir/c was a preferred option in the last update and remains so, based on demonstration of non-inferiority to efavirenz and atazanavir/r. In GS-102 [26], elvitegravir/c was non-inferior to efavirenz at weeks 48 and 96 in terms of virological success, virological failure and proportion of people who developed resistance; rates of NRTI and third-agent resistance development in individuals with virological failure were similar. For example, by week 96, 9/17 persons with virological failure on elvitegravir/c developed integrase resistance compared with 9/23 with virological failure on efavirenz. There were no differences in adverse event discontinuations or rate of grade 3/4 adverse event outcomes, with data lacking for some of the non-critical safety outcomes considered by the writing group. Elvitegravir/c has the advantage of simple dosing as a fixed-dose combination with **tenofovir-DF**/emtricitabine; the requirement for pharmacokinetic boosting necessitates caution with respect to drug–drug interactions.

When compared with atazanavir/r in GS-103 [27], elvitegravir/c was again non-inferior with respect to virological success and virological failure rates at weeks 48 and 96. There were no cases of NRTI- or PI-resistance development at weeks 48 and 96 in the atazanavir/r arm compared with five and six cases in the elvitegravir/c arm, respectively. By week 144, there were eight cumulative cases of resistance in the elvitegravir/c arm compared with two in the atazanavir/r (both isolated M184I/V) [28]. Discontinuations for adverse events were similar and the only important outcome that differed was a significantly higher rate of grade 3/4 laboratory events in the atazanavir/r arm (OR 0.07 favouring elvitegravir/c, 95% CI 0.05–0.11, $P < 0.0001$ at week 48). Again, as this was driven predominantly by hyperbilirubinaemia in the atazanavir/r arm, and the consensus of the writing group was that this difference was not clinically important.

Elvitegravir/cobicistat/emtricitabine/tenofovir-AF was non-inferior to elvitegravir/cobicistat/emtricitabine/tenofovir-DF in two blinded randomised trials [29].

Cobicistat is an inhibitor of renal tubular creatinine secretion; exposure to cobicistat results in small increases in serum creatinine and modest reductions (10–15 mL/min) in creatinine clearance [30]. Renal toxicity with elvitegravir/cobicistat/**tenofovir-DF**/emtricitabine is infrequent (0.8–2%) in patients with baseline creatinine clearance at least 70 mL/min [26,27]. The use of elvitegravir/cobicistat/**tenofovir-DF**/emtricitabine is not recommended for patients with creatinine clearance less than 70 mL/min [31].

5.4.3.5 Raltegravir

Raltegravir was compared to atazanavir/r, darunavir/r and dolutegravir in studies outlined in Sections 5.4.3.1, 5.4.3.2 and 5.4.3.3, respectively. In ACTG 5257 virological failure with resistance occurred in 3.0% of study participants assigned to raltegravir (two of whom developed intermediate-level resistance to dolutegravir) and in 1.5% or fewer of those in either boosted PI group [16]. Raltegravir was non-inferior to efavirenz in STARTMRK with similar outcomes for virological response, virological failure and resistance rates at weeks 48 [12] and 96 [11]. The study was unblinded after week 144 and at later points of follow-up (up to week 240) raltegravir demonstrated superior efficacy to efavirenz driven by more discontinuations due to adverse events in the efavirenz arm [32]. There was a trend to more discontinuations for adverse events on efavirenz at weeks 48 and 96 (OR 0.52 and 0.51 favouring raltegravir, respectively) and by week 240, this difference

reached statistical significance. Unlike other preferred third agents for first-line use, the licensed dose of raltegravir is taken twice daily.

5.4.3.6 Rilpivirine

Rilpivirine has been compared directly with efavirenz in three large randomised controlled trial trials: ECHO [33], THRIVE (both double-blind, placebo-controlled, multi-pill studies) [15] and StAR (open-label single-pill fixed-dose combination comparison of **tenofovir-DF/emtricitabine/efavirenz** and **tenofovir-DF/emtricitabine/rilpivirine**) [14]. There were no differences in overall virological success at weeks 48 or 96 in the three studies. However, there were significant differences in drug resistance and virological failure, both in favour of efavirenz. For critical safety outcomes there was a difference in the proportion discontinuing for adverse events in favour of rilpivirine. Pooled analyses by the investigators of the two randomised controlled trial trials showed the risk of virological failure with rilpivirine was highest in participants with a baseline viral load >100,000 copies/mL [15] and when analysis is restricted to individuals with a baseline viral load less than 100,000 copies/mL, virological response to rilpivirine was non-inferior to efavirenz. A 96-week analysis of the same studies, restricted to individuals with baseline viral load less than 100,000 copies/mL, demonstrated virological response rates of 84% on rilpivirine and 80% on efavirenz (95% CI -1.7–9.7%) and virological failure rates of 8% and 6%, respectively ($P=0.46$) [33].

Based on the superior virological success on rilpivirine compared to efavirenz when used within its licensed indication (i.e. at baseline viral load less than 100,000 copies/mL) we believe it should be moved from alternative to preferred third agent status. It is important to note that there are very few data regarding the administration of rilpivirine with an abacavir/lamivudine NRTI backbone. In addition rilpivirine must be administered with food (Appendix 4) and has significant interactions with acid-reducing agents; proton pump inhibitors are contra-indicated.

5.4.3.7 Efavirenz

Efavirenz has long been a preferred agent for initial HIV therapy and has been a 'gold standard' comparator for several clinical trials investigating first-line treatment. However, dolutegravir demonstrated superiority to efavirenz in SINGLE [19], as has rilpivirine in subgroup analyses [34], and raltegravir with longer-term follow-up of STARTMRK [32]. The difference between efavirenz and comparators is driven by a higher rate of discontinuation for adverse events on efavirenz-based regimens, mainly due to its potential for significant central nervous system (CNS) toxicity. Since the last update of the guidelines, a meta-analysis of ACTG studies demonstrated a higher risk of suicidality in those randomised to efavirenz-containing regimens [35]. Individuals with significant past or current mental health issues may be excluded from clinical trial populations so the ACTG analysis could potentially underestimate the impact of efavirenz in higher-risk PLWH. Although, subsequently, an observational cohort study did not demonstrate an association between efavirenz use and suicidality [36] this was a non-randomised, retrospective analysis. Individuals with a history of psychiatric disorders appear to be at a greater risk of serious psychiatric adverse events [37] and for PLWH with a current or previous history of psychiatric disorders, including depression, anxiety and suicidal ideation, caution should be exercised in prescribing efavirenz and strong consideration given to using an alternative third agent. Secondly, although not considered an important outcome for the purpose of these guidelines, efavirenz is associated with an adverse impact on lipids compared to newer agents. Since there are several effective and well-tolerated alternative third agent options available, it is the view of the writing group that efavirenz should be downgraded from preferred to alternative option for initial therapy. The writing group recognises that the majority of individuals who start efavirenz-based therapy tolerate it reasonably well, so it remains a reasonable alternative. For patients stable on efavirenz-based ART, we recommend a review of tolerability, including sleep and mood, at all visits.

5.4.3.8 Previous alternative third agents

Unlike previous versions of the guidelines, lopinavir/r, fosamprenavir/r and nevirapine are no longer listed as alternative options. Efavirenz was superior to lopinavir/r for critical virological outcomes in ACTG 5142 [2];

lopinavir/r and fosamprenavir/r perform similarly [38] and are associated with higher rates of gastrointestinal and metabolic toxicities than preferred PI/r options [39]. Lopinavir/r may be an important option for some individuals such as those with PI resistance mutations and a contraindication for darunavir/r. Nevirapine was non-inferior to atazanavir/r for critical virological outcomes in ARTEN [40] but with the availability of alternative NNRTIs and alternative classes, we feel that the small risk of serious hepatic or cutaneous toxicity is no longer acceptable. Individuals who are stable on nevirapine should, however, be reassured as to the long-term efficacy and safety of this option.

5.4.3.9 Cobicistat

Cobicistat is an inhibitor of CYP3A isozymes [41] and, similarly to ritonavir, is used as a pharmacokinetic enhancer of other antiretroviral drugs. It is a component in the fixed-dose combination pill Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir-DF). Cobicistat as a single drug has also been licensed as a pharmacokinetic enhancer of atazanavir and darunavir.

The efficacy and safety of cobicistat-boosted atazanavir has been evaluated in comparison with ritonavir-boosted atazanavir, in a Phase 3, non-inferiority, randomised, double-blind study in treatment-naïve individuals [42,43]. Atazanavir with cobicistat was shown to be non-inferior to atazanavir with ritonavir in terms of viral suppression. Discontinuation rates due to adverse events were similar, and no major tolerability issues were reported.

The evidence supporting the use of cobicistat to boost darunavir is more limited. Cobicistat enhances darunavir plasma levels to a similar degree as ritonavir, with a similar pharmacokinetic profile [44] and in a single-arm study had acceptable efficacy and safety profiles [45].

Cobicistat affects tubular secretion of creatinine, by inhibiting renal cation transporters. This results in small increases in serum creatinine and decreases in estimated creatinine clearance. However, it does not cause impairment of renal function as actual glomerular filtration rate is not affected [46].

5.4.3.9 Summary

When selecting a third agent from either the preferred or alternative options, factors such as potential side-effects, dosing requirements, dosing convenience, individual preference, co-morbidities, drug interactions and cost should be considered.

In summary, efavirenz should no longer remain a preferred third agent and should now be considered an alternative. Because of similar critical treatment outcomes, atazanavir/r, darunavir/r, dolutegravir elvitegravir/c, raltegravir and rilpivirine are all recommended as preferred third agents (with the caveat that rilpivirine is only recommended within its licence in individuals with a baseline viral load less than 100,000 copies/mL).

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5.5 Novel antiretroviral therapy strategies

5.5.1 Recommendation

- We recommend against the use of PI monotherapy as initial therapy for treatment-naïve patients (1C).

5.5.1.1 Rationale

Data on use of PI monotherapy as initial ART are limited. In one randomised controlled trial comparing lopinavir/r vs. lopinavir/r plus zidovudine and lamivudine, the use of PI monotherapy as initial ART was associated with lower rates of virological suppression at 48 weeks and with the emergence of PI mutations [1]. There were no significant differences in tolerability. For this reason, PI monotherapy is not

recommended as initial ART. However, as with other novel strategies there may be specific circumstances where a rationale for its use may be made.

5.5.1.2 Reference

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5.5.2 Recommendation

- We suggest the use of darunavir/r-based dual ART regimen with raltegravir in treatment-naïve patients with CD4 count >200 cells/ μ L and viral load <100,000 copies/mL where there is need to avoid abacavir, **tenofovir-DF or tenofovir-AF** (2A).
- We recommend against the use of PI-based dual ART with a single NNRTI, NRTI or CCR5 receptor antagonist for treatment-naïve patients (1B).

5.5.2.1 Rationale

A number of studies have assessed the use of PI-based dual ART as initial therapy in treatment-naïve patients.

The combination of an NNRTI with a PI/r has been shown to have similar virological efficacy compared with triple-combination regimens in one study [1]. There were no significant differences in time to either virological or regimen failure with a combination of lopinavir/r and efavirenz compared with either two NRTIs and efavirenz or two NRTIs and lopinavir/r although the NRTI-sparing arm underperformed in individuals with high baseline viral load (greater than 100,000 copies/mL). There was, however, an increased rate of drug resistance in the NRTI-sparing arm, with the emergence of more NNRTI-associated resistance mutations than the comparator arms. An increased rate of grade 3/4 toxicities was observed, predominantly low-density lipoprotein cholesterol and triglyceride elevations.

Two randomised controlled trial trials have evaluated a dual-therapy regimen containing one NRTI with a PI/r compared to standard therapy of a PI/r and two NNRTIs. The GARDEL study demonstrated non-inferiority of the dual regimen of lopinavir/r plus lamivudine compared to lopinavir/r, lamivudine or emtricitabine plus a third NRTI in virological efficacy at 48 weeks [2] irrespective of baseline viral load. A *post hoc* analysis also showed no difference in virological efficacy with respect to the choice of dual NRTI backbone and pre-treatment CD4 cell count (<200 cells/ μ L) [3]. A study comparing **tenofovir-DF** and lopinavir/r to two NRTIs and lopinavir/r failed to demonstrate non-inferiority of the dual-therapy arm compared with a standard triple-therapy combination but numbers were small and the response rates were numerically similar at 51% and 53%, respectively [4]. As lopinavir/r is no longer among the first-recommended PIs, the dual combination with lamivudine, as used in GARDEL study, has not been considered as an alternative first-line regimen.

The efficacy of dual therapy with the CCR5-receptor antagonist maraviroc in combination with a PI/r has been assessed in a number of studies [5–8] but only one [8] was powered to demonstrate non-inferiority. This study compared maraviroc/darunavir/ritonavir to **tenofovir-DF**/emtricitabine/darunavir/r, and showed lower virological efficacy of the dual therapy arm at 48 weeks.

The efficacy of the raltegravir plus a PI/r has been compared with standard triple therapy in several studies [9–13] The NEAT-001/ANRS-143 [10] demonstrated non-inferiority of raltegravir compared to **tenofovir-DF**/emtricitabine when combined with darunavir/r at 96 weeks. However, the dual-therapy arm was associated with higher rates of virological failure and with treatment-emergent integrase resistance (5/28 patients) in those with baseline CD4 cell count <200 cells/ μ L or viral load >100,000 copies/mL. Similarly, a single-arm study investigating raltegravir in combination also with darunavir/r, showed increased risk of

virological failure with emergent integrase resistance with baseline viral load >100,000 copies/mL compared with those with a baseline viral load <100,000 copies/mL [13]. There was no difference in safety between both arms.

The PROGRESS study demonstrated similar virological efficacy of raltegravir plus lopinavir/r compared to **tenofovir-DF**/emtricitabine and lopinavir/r, although the study was relatively small [11,12]. Overall there is evidence to support the use of a PI/r, preferably darunavir/r plus raltegravir, in selected patient populations.

The use of raltegravir with unboosted atazanavir is not recommended due to development of integrase resistance in 4/6 of those who met the criteria for resistance testing [9].

5.5.3 References

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6.0 Supporting individuals on therapy

6.1 Adherence

6.1.1 Interventions to increase adherence to treatment

6.1.1.1 Recommendations

- We recommend adherence and potential barriers to it are assessed and discussed with PLWH whenever ART is discussed, prescribed or dispensed (GPP).
- We recommend adherence support should address both perceptual barriers (e.g. beliefs and preferences) and/or practical barriers (e.g. limitations in capacity and resources) to adherence (GPP).
- Individuals experiencing difficulties with adherence should be offered additional support from staff within the MDT who have experience in adherence support and/or from organisations offering peer support (GPP).

6.1.1.2 Auditable outcomes

- Record in medical notes discussion and assessment of adherence and potential barriers, both before starting a new ART regimen and while on ART.
- Record in medical notes the provision or offer of adherence support.

6.1.1.3 Rationale

Low adherence to ART is associated with drug resistance, progression to AIDS [1] and death [2–4]. Given the multiple adverse consequences of treatment failure (risk of disease progression, increase in complexity and costs of treatment, and risk of HIV transmission) engaging PLWH in treatment decisions and the monitoring and support of adherence are of paramount importance [5] (see Section 3.0). Investing time to prepare an individual for starting ART is important and utilising members of the MDT who have experience in adherence support, such as specialist nurses and pharmacists, should be considered for all individuals starting ART, reporting adherence concerns or who have experienced virological failure.

Non-adherence is best understood as a variable behaviour with intentional and unintentional causes. Most people taking medication are non-adherent some of the time. Unintentional non-adherence is linked to limitations in capacity or resources that reduce the ability to adhere to the treatment as intended. Intentional non-adherence is the product of a decision informed by beliefs, emotions and preferences [6].

BHIVA recommendations on the monitoring of adherence to ART are available (www.bhiva.org/monitoring-guidelines.aspx). The National Institute for Health and Care Excellence (NICE) has published detailed guidance on the assessment and support of adherence to medication in chronic diseases; key recommendations for adherence support are shown in Box 6.1 [7].

Box 6.1. Summary of NICE guidance on adherence support [7]

Assessment
<p>Recognise that non-adherence is common and that most patients are non-adherent sometimes. Routinely assess adherence in a non-judgemental way whenever you prescribe, dispense and review medicines. The purpose of assessing adherence is not to monitor patients but rather to find out whether patients need more information and support.</p>
<p>Make it easier for them to report non-adherence by:</p> <ul style="list-style-type: none"> • Asking the question in a way that does not apportion blame • explaining why you are asking the question • mentioning a specific time period such as ‘in the past week’ • asking about medicine-taking behaviours such as reducing the dose, stopping and starting medicines. • If a patient is not taking their medicines, discuss with them whether this is because of beliefs and concerns or problems about the medicines (intentional non-adherence) or because of practical problems (unintentional non-adherence). • Find out what form of support the patient would prefer to increase their adherence to medicines.
Intervention
<p>Patients may need support to help them make the most effective use of their medicines (e.g. further information and discussion, or practical changes to the type of medicine or the regimen). Any interventions should address the concerns and needs of individual patients. Tailor any intervention to increase adherence to the specific difficulties with adherence the patient is experiencing.</p> <p>Address any beliefs and concerns that patients have that result in reduced adherence.</p> <p>Interventions might include:</p> <ul style="list-style-type: none"> • Suggesting that patients record their medicine taking • Encouraging patients to monitor their condition • Simplifying the dosing regimen • Using alternative packaging for the medicine • Using a multi-compartment medicines system. <p>Side effects can be a problem for some patients. If this is the case you should:</p> <ul style="list-style-type: none"> • Discuss how the patient would like to deal with side effects • Discuss the benefits, side effects and long term effects with the patient to allow them to make an informed choice • Consider adjusting the dosage • Consider switching to another medicine with a different risk of side effects • Consider what other strategies might be used (for example, timing of medicines).

For PLWH it may help to normalise ambivalence and conversations about suboptimal adherence by reassuring the person that many others have doubts and concerns about ART. A person’s motivation to start

and continue medication is influenced by their judgement of their personal need for medication (necessity beliefs), relative to their concerns about potential adverse effects. Delayed uptake and non-adherence are associated with doubts about personal need for ART and concerns about taking it [8,9]. PLWH may not raise adherence concerns so should be encouraged to do so, and provided with feedback, at each visit.

Interventions to support adherence should be tailored to address specific relevant perceptual and practical barriers. A three-step 'perceptions and practicalities approach' [9] may be helpful:

- Identify and address any doubts about personal need for ART;
- Identify and address specific concerns about taking ART;
- Identify and address practical barriers to adherence.

Strategies to improve adherence should be tailored to the patient's needs, and can include the following.

- Elicit understanding of, and educate on, HIV and adherence in a way that is appropriate for the patient [10–12]. Similarly, review clinical outcomes with the patient in a way that is understandable
- Provide a rationale for treatment that is tailored to the individual [6,13].
- Assess misinformation about adherence [14,15].
- Clinicians should not contest miraculous healing beliefs [14,16] but rather offer the compatible belief that medication and God can work together to bring health.
- Limit ART complexity and explore patient's lifestyle and work hours to select the most appropriate regimen [17].
- Many patients find it difficult to remember to take medication on time [17]. Suggestions such as using a phone or watch alarm [18], or linking an established daily behaviour with taking medication – for example, taking ART with a morning cup of tea may help.
- Suggest techniques to make swallowing ART easier, such as taking it with yoghurt to mask the taste.
- Suggest techniques to limit the risk of involuntary disclosure. HIV-related stigma can compromise adherence to ART [17,19], and not taking medication in front of others can be protective [14,20]. Clinicians can offer alternative reasons as to why someone might need to take medication at a particular time to decrease concern about disclosure (e.g. taking birth control/migraine/blood pressure medication).

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6.1.2 Should the choice of first-line antiretroviral therapy combination be affected by risk of non-adherence?

6.1.2.1 Recommendation

- In individuals where there is clinical concern that doses may be missed intermittently, there is insufficient evidence to recommend a PI/r over NNRTI- or INI-based regimens. However, where there is a risk of frequent prolonged treatment interruptions, PI/r-based regimens may be associated with less frequent selection for drug resistance (2C).

6.1.2.2 Rationale

Clinicians are poor at both predicting future adherence to ART in naïve subjects [1] and at detecting non-adherence during ART [2,3]. However, in a case where a clinician or HIV-positive individual has concerns about future adherence, should this influence the choice of first-line therapy?

The consequences of low adherence depend on drug pharmacokinetics, potency, fitness of resistant strains and genetic barrier to resistance [4]. Hence, both the level and pattern of non-adherence must be considered.

Large randomised controlled trials of first-line therapy may not be able to inform this choice as subjects likely to be non-adherent may be excluded from such trials. On the other hand, observational studies often select PLWH already established on ART [5,6] where the observed effects of non-adherence on treatment outcome are likely to differ from those in individuals starting ART *de novo*. This selection bias may exclude those who have either experienced early virological failure, disease progression (or even death) or have defaulted from care. In addition, most studies either pre-date the use of boosted-PI regimens in first-line therapy [5,7] or include large numbers of people on unboosted PI regimens.

Three different outcomes may be considered: virological suppression, selection of drug resistance and effect of pattern of non-adherence.

6.1.2.2.1 Effect of adherence on viral suppression

There are no data from randomised controlled trials that directly address this question. Among subjects reporting <95% adherence in a randomised controlled trial comparing lopinavir/r with once-daily darunavir/r, virological failure was more likely in the lopinavir/r than the darunavir/r arm; there were no differences between the two arms when analysing individuals reporting >95% adherence [8].

Among individuals who were virologically suppressed initially, adherence <95% was associated with an increased risk of failure [6], and very low adherence (<50%) results in virological rebound irrespective of regimen [6,9,10]. However, virological suppression has been observed with only moderate adherence (50–75%) among individuals on NNRTIs [6,9,10] and virological failure has been reported to be significantly more likely on unboosted PI-based regimens where adherence was <95% [6]. However, this finding may have been confounded by the once-daily dosing in the efavirenz group. A further study [11] examined only individuals with undetectable viraemia and found no difference in rates of virological rebound for those on PI/r vs. NNRTIs.

6.1.2.2.2 Effect of adherence on selection of drug resistance

The effect of level of non-adherence on selection of drug resistance varies by class. This was first described for unboosted PI regimens where moderate-to-high adherence was associated with increased risk of resistance [12]. The incidence of resistance in studies of boosted-PI regimens is low [8,13–17] but is observed with adherence just below 80–95% [5,18]. In contrast, for first-generation NNRTIs the selection for resistance has been associated with very low average adherence (<50%) [19,20].

6.1.2.2.3 Effect of pattern of non-adherence

The pattern of non-adherence may also be important. A number of small observational studies have examined short intermittent treatment interruptions (2–7 days) in individuals with prolonged virological suppression. For efavirenz, cycles of 2 days off per week appeared no more likely to result in treatment failure than continuous therapy, as long as the treatment interruption was not prolonged [21,22]. However, cycles of 7- or 28-day treatment interruption resulted in failure of efavirenz and selection of resistance [23,24]. For PI/r, one study found that average adherence, rather than duration of treatment interruption, was associated with virological response [25].

6.1.2.3 References

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6.1.3 Dosing frequency

An overview of systematic reviews of consumer-oriented medication interventions found that simplified dosing regimens improved adherence in the majority of studies in several reviews [1]. A review of adherence interventions for antiretroviral therapy included 19 studies (6312 adult individuals). Average adherence was modestly higher with once-daily regimens than twice-daily regimens (weighted mean difference = 2.55%, 95% CI 1.23–3.87, $P=0.0002$) but virological suppression was similar. Both adherence and viral suppression decreased over time, but adherence decreased less with once-daily than twice-daily dosing. Lower pill burden was associated with both better adherence and virological suppression [2]. NICE [3] reviewed several randomised controlled trials of interventions to reduce dose frequency and found that adherence may increase with once-daily dosing but not in all studies. Once-daily dosing is a reasonable intervention to reduce unintentional non-adherence to ART but no corresponding impact on viral suppression has been observed.

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6.1.4 Fixed-dose combinations

In examining whether fixed-dose combination formulations (FDCs) of drugs improve adherence or treatment outcome, only studies comparing the same drugs with the same dose frequency given as combination or separate pills were considered. No meta-analyses have been published on this subject for ART. A meta-analysis of nine randomised controlled trials and cohort studies in a range of diseases found the use of FDCs was associated with a significant reduction in the risk of non-adherence but in the single HIV randomised controlled trial included no significant difference in treatment failure between groups receiving FDC vs. non-FDC was observed [1]. Gupta *et al.* [2] reported a meta-analysis of cohort studies and found that use of FDCs for anti-hypertensives was associated with increased adherence but with no improvement on the control of blood pressure.

A retrospective study of a pharmacy database found no benefit in persistence on first-line ART for any FDC over separate agents [3]. In the ECHO/ THRIVE studies, a lower virological response rate in individuals with baseline viral load 100,000–500,000 copies/mL was observed for rilpivirine- versus efavirenz-based regimens when dosed as separate agents [4]; this was not repeated when formulated as FDCs in the preliminary 48-week results from the STaR study [5]. Although the use of FDCs may have driven this apparent improvement in performance of rilpivirine, it may also have arisen due to the simpler once-daily regimens in STaR, other methodological differences or by chance.

A further advantage of FDCs is that they prevent individuals from preferentially adhering less closely to one component of a regimen than others. A minority of participants in one study did report such 'differential' adherence, but this was not associated with outcome for currently used first-line strategies [6]. This was also reported in an Italian observational study; however, the difference was small and may have been confounded by other factors [7].

An observational study of outcomes following a switch from Atripla to multi-tablet regimens including swapping emtricitabine for lamivudine provides some evidence that this may not result in an increase in virological failures [8]. In view of the higher-quality evidence in support of FDCs and the implications and costs of treatment failure, there is insufficient evidence to support this strategy at present.

A recent meta-analysis of nine randomised-controlled antiretroviral trials analysed the impact of FDCs on adherence and treatment outcomes [9]. All nine trials were switch studies, regimen components differed between the FDC and non-FDC arms and five of the trials, investigating the impact of FDC backbone, were from several years ago. Four of the trials compared switching to a single-tablet regimen with continuing the existing multi-tablet regimen and there was no difference in virological failure rate; by switch=failure analysis there was a significant difference favouring single tablets.

In summary, FDCs support adherence to treatment, and this may well reduce the risk of virological failure. However, the size of this effect is yet to be defined. This needs to be balanced against the potentially far lower cost of generically available antiretroviral agents as separate or combined preparations of the same drugs.

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6.1.5 Single-tablet regimens

There are currently six single-tablet regimens (STRs) available. Atripla (tenofovir-DF/emtricitabine/efavirenz) was the first STR approved for use in adults and in children at least 12 years old who weighed at least 40 kg [1]. The second available STR, which also contained an NNRTI, was Eviplera (tenofovir-DF/emtricitabine/rilpivirine). Tenofovir-DF/emtricitabine/rilpivirine and the more recent tenofovir-AF/emtricitabine/rilpivirine (Odefsy) are licensed for the treatment of adults, who have no known mutations associated with resistance to NNRTIs, tenofovir-DF or emtricitabine, and have a viral load $\leq 100,000$ HIV-1 RNA copies/mL [2]. STRs containing an INSTI are also available. These are Stribild (tenofovir-DF/emtricitabine/elvitegravir/c) [3], Genvoya (tenofovir-AF/emtricitabine/elvitegravir/c) [4] and Triumeq (abacavir/lamivudine/dolutegravir) [5]. Triumeq is the first STR containing an abacavir/lamivudine backbone and testing for HLA-B*57:01 is recommended before use. If the individual is HBV co-infected, then additional drug treatment should be considered.

Potential advantages of using STRs are improved adherence, reduced selective adherence, patient preference and improvement in quality of life [6,7] although a recent analysis of individuals switching to STRs did not demonstrate significant changes in quality of life [8]. Randomised studies demonstrating these advantages are scarce, and among cohort and observation studies results are varied. One meta-analysis of four randomised switch STR trials has been presented but none of these trials compared the same drugs head to head [8]. In this meta-analysis there was no significant difference for virological failure, discontinuations due to adverse events or switch=failure endpoint. Only two of the trials assessed quality of life and found no difference between STR and control [8].

Disadvantages of STRs include cost, limited choice of regimens and the inability to dose-adjust for weight, renal impairment or drug–drug interactions. Also HLA-B*57:01 testing and hepatitis B status must be considered for abacavir-containing STRs. Transmitted resistance will limit the possible use of STRs.

A cohort study from Denmark reported that switching from an STR to a generic triple-tablet regimen resulted in maintained efficacy, was safe and lower in cost [9]. A retrospective look at switching from FDCs to separate components in the Balearic Islands found lower pharmaceutical cost but higher overall healthcare cost in the first year following the change [10].

STRs have not been compared to the same drugs in multiple-pill regimens in randomised clinical trials. In the switch studies there was no proven benefit, despite the large cost difference. Although there are potential advantages of using STR there are currently no cost-effectiveness data looking at STRs versus generic medications.

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6.2 Pharmacology

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

6.2.1 Drug interactions

6.2.1.1 Recommendations

- Drug histories should be taken at each clinic visit, and a full medication history (including herbals, recreational drugs and other non-prescribed medications) should be undertaken at least annually (GPP).
- All potential adverse pharmacokinetic interactions between antiretroviral drugs and other concomitant medications should be checked before administration (with tools such as www.hiv-druginteractions.org) (GPP).
- Wherever feasible, PLWH should be counselled about the risks of drug interactions, and advised to use resources such as the Liverpool HIV Drug Interactions App (iOS or Android) (GPP).

6.2.1.2 Auditable measure.

- Full medication history at least annually.
- Record in medical notes of potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications.

6.2.1.3 Rationale

The importance of eliciting a complete medication history in order to manage potential drug interactions in patients cannot be overemphasised. Drug–drug interactions may involve positive or negative interactions between ARV agents or between these and drugs used to treat other coexistent conditions. A detailed list is beyond the remit of these guidelines but clinically important interactions to consider when co-administering with ARV drugs include interactions with the following drugs: methadone, oral contraceptives, anti-epileptics, antidepressants, lipid-lowering agents, acid-reducing agents, certain antimicrobials (e.g. clarithromycin, minocycline and fluconazole), some anti-arrhythmics, TB therapy, anti-cancer drugs, immunosuppressants, phosphodiesterase inhibitors and anti-hepatitis C virus (HCV) therapies. Most of these interactions can be managed safely (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, inhaled fluticasone and ritonavir/cobicistat) the nature of the interaction is such that co-administration must be avoided and alternatives sought.

Importantly, education on the risks of drug interactions, including over-the-counter or recreational drugs, should be undertaken and PLWH should be encouraged to check with pharmacies or their healthcare professionals before commencing any new drugs, including those prescribed in primary care.

Large surveys report that about one-in-three-to-four PLWH receiving ART is at risk of a clinically significant drug interaction [1–7]. This suggests that safe management of HIV drug interactions is only possible if medication recording is complete, and if physicians are aware of the possibility that an interaction might exist. Incomplete or inaccurate medication recording has resulted from self-medication, between hospital and community health services [8] and within hospital settings particularly when multiple teams are involved, or when medical records are fragmented (e.g. with separate HIV case notes) [9].

More worryingly, one survey in the UK reported that even when medication recording is complete, physicians were only able to identify correctly one-third of clinically significant interactions involving HIV drugs [2]. In addition to HIV specialist and local drug information pharmacists, the University of Liverpool's comprehensive drug interaction website (www.hiv-druginteractions.org) is an excellent and highly recommended resource for information relating to potential drug interactions. Additional information resources also include the electronic medicines compendium (www.medicines.org.uk/emc) and medical information departments of pharmaceutical companies.

Communication with GPs and other medical specialties involved in care is fundamental in minimising the risk of adverse drug–drug interactions. All clinic letters should carry as a standard header or footer advice to check for interactions, and links to resources, such as www.hiv-druginteractions.org, to address the potential for drug interactions.

6.2.1.4 References

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6.2.2 Therapeutic drug monitoring

6.2.2.1 Recommendation

- We recommend against the unselected use of therapeutic drug monitoring (GPP).
- Therapeutic drug monitoring may be of clinical value in specific populations (e.g. children, pregnant women) or selected clinical scenarios (e.g. malabsorption, drug interactions, suspected non-adherence to therapy)(2C).

6.2.2.2 Rationale

Therapeutic drug monitoring (TDM) has been shown to be valuable in optimising the management of certain individuals; however, the general utility of this test in those receiving ART has been poorly assessed. With the marked improvement in efficacy and tolerability of modern ARV regimens, the role of TDM in clinical management has also evolved. A Cochrane review of randomised controlled trials [1] suggested little value when used unselectively. However, TDM may aid the management of vulnerable populations or complex clinical situations.

- **Monitoring adherence.** While detection of drug at therapeutic or even high plasma concentrations does not exclude low adherence, absence of measurable drug, or else very low levels of drug, strongly suggest lack of medication intake, particularly in the absence of evidence of significant malabsorption. Here, TDM should rarely be interpreted in isolation, but rather integrated with virological rebound, particularly in the absence of any resistance mutations and other features in the history that suggest risk for low treatment adherence.
- **Optimising treatment in vulnerable PLWH.** In vulnerable PLWH (e.g. children, pregnant women [2] and individuals with extremes of body mass index) or in specific clinical situations (e.g. liver and renal impairment, treatment failure, drug interactions both foreseen and unanticipated, malabsorption, suspected non-adherence and unlicensed once-daily dosing regimens). In these scenarios, the aim is to optimise dosing based either on known efficacy or toxicity cut-offs, or else to achieve the range of plasma concentrations encountered in individuals without these factors, who have been recruited to pharmacokinetic studies at licensed treatment doses that are known to be both safe and efficacious.
- **Managing drug interactions (see above).** Where the HIV drug has the potential to be adversely affected by another drug, and the combination is unavoidable, TDM may be used either to manage that interaction, or else discount a significant interaction in a particular individual.
- **Other situations.** Knowledge of plasma drug concentrations may be clinically useful when evaluating whether there is scope for treatment simplification, or else confirming or refuting impaired drug absorption as a reason for virological failure.

More detailed recommendations for the use of TDM are available in the *BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals* (www.bhiva.org/monitoring-guidelines.aspx). As for all other investigations, it is essential that TDM is undertaken correctly, especially with regard to timing (undertaken when steady state has been achieved). A consensus has been achieved for defining targets [3] for many ARVs. With many newer agents, evidence for a defined minimum target for efficacy is either weak or lacking, and evidence for an upper toxicity cut-off for most ARVs is lacking.

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6.2.3 Stopping therapy: pharmacological considerations

6.2.3.1 Recommendations

- We recommend individuals stopping ART containing an NNRTI in combination with an NRTI backbone replace all drugs with a PI (darunavir/r once daily) for 4 weeks (1C).
- We recommend individuals stopping a PI-containing regimen stop all drugs simultaneously and no replacement is required (1C).

6.2.3.2 Auditable outcome

- Proportion of individuals with an undetectable viral load on ART who, on stopping a regimen containing an NNRTI in combination with an NRTI backbone, are switched to PI/r for 4 weeks.

6.2.3.3 Rationale

In general, treatment interruptions are not recommended for most individuals. Whatever the reason for stopping ART (e.g. drug toxicity, intercurrent illness, after pregnancy or individual choice), pharmacological issues must be considered 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 ARV drugs with different half-lives are stopped simultaneously.

NNRTI and NRTI resistance mutations have been detected following discontinuation of previously suppressive regimens [1,2] and may have the potential to affect the likelihood of viral resuppression on restarting an NNRTI- based ART regimen.

There are limited data on which to base recommendations for how to protect against development of resistance in the period immediately following treatment cessation. Several discontinuation strategies have been proposed [3], and choice is influenced by clinical considerations, individual wishes and pharmacological principles. Options include: (i) simultaneously stopping all drugs in a regimen containing drugs with similar half-lives; (ii) a staggered stop, discontinuing the drug with the longest half-life first in a regimen containing drugs with short and long half-lives; or (iii) replacing all drugs with a drug with a short half-life and high genetic barrier to resistance (i.e. a PI). There is no randomised comparison of these three strategies. However, in one study a lower number of emergent resistance mutations were seen in those switching to a PI compared with those undertaking a simultaneous or staggered stop [2]. Therapeutic plasma concentrations of efavirenz can also be detected up to 3 weeks after stopping the drug in some people and thus a staggered stop of 1 week may potentially be inadequate to prevent emergence of NNRTI mutations [4]. The optimal duration of replacement with a PI is not known, but 4 weeks is probably advisable.

6.2.3.4 References

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6.2.4 Switching therapy: pharmacological considerations

6.2.4.1 Recommendations

There are no high quality data on how to switch away from efavirenz to an alternative 'third' agent. Based on pharmacological principles, there is little rationale for any strategy other than straightforward substitution when switching to a PI/r or raltegravir. Pharmacokinetic studies show that straightforward substitution with etravirine, rilpivirine, dolutegravir and elvitegravir/c may result in slightly lower concentrations of either drug for a short period following switching, but limited virological data suggest that risk of virological failure with this strategy is low. Different strategies for switching to nevirapine have been proposed, but no comparative data are available to guide the choice of strategy. Limited data suggest that the dose of maraviroc should be doubled in the week following switching (unless given together with a PI/r).

If switching away from efavirenz is undertaken when viral load is likely to still be detectable (e.g. because of CNS intolerance within the first few weeks of starting efavirenz), substitution with a PI/r in preference to a within-class switch is advised.

6.2.4.2 Rationale

Switching a component of an ART regimen is frequently considered in PLWH to manage drug side effects or address adherence issues. ARVs that either induce or inhibit drug-metabolising enzymes have the potential to affect the plasma concentrations of the new agent. This applies in particular to switching away from NNRTIs. Induction of drug metabolising enzymes by efavirenz is likely to persist for a period beyond drug cessation. Consideration should also be given of whether or not viral load is maximally suppressed when planning how to switch away from efavirenz to an alternative agent. Broadly, strategies for switching from efavirenz to an alternative 'third' agent may be summarised as follows.

6.2.4.2.1 Efavirenz to nevirapine

A pharmacokinetic study performed in HIV-positive individuals suggested that individuals changing from efavirenz to nevirapine should commence on 200 mg twice a day to ensure therapeutic plasma concentrations and potentially avoid selection of resistance to nevirapine [1]. However, no one in the nevirapine lead-in group experienced virological failure in the 3-month follow-up period. Switching without dose escalation is in direct contrast to the information in the Viramune summary of product characteristics, which advises administration of a nevirapine lead-in dose (200 mg once daily for 2 weeks) when starting nevirapine [2], as this has been shown to decrease the frequency of rash.

In ART-experienced individuals who are virologically suppressed with an undetectable plasma HIV RNA level (≤ 50 copies/mL), the risk of hypersensitivity and/or hepatotoxicity on switching to nevirapine is not increased in those with higher CD4 cell counts (above the gender-specific CD4 cell count thresholds) [3]. In ART-experienced individuals with detectable plasma HIV RNA levels, a switch to nevirapine is not advised.

Furthermore, the need to minimise any window for developing resistance is greatest in those who discontinue efavirenz early on when virological suppression has not yet been achieved. The latter scenario is made more complex when enzyme induction has not yet been fully achieved, and if doubt exists, alternatives to switch to should be considered.

6.2.4.2.2 Efavirenz to etravirine

In individuals with undetectable viral loads, switching from efavirenz to etravirine, standard doses of etravirine can be commenced [4]. To date, no data are available on what strategy to adopt in those with active viral replication.

6.2.4.2.3 Efavirenz to rilpivirine

Concentrations of rilpivirine are lowered by previous efavirenz administration. However, 28 days after the switch, they returned to levels comparable with those when rilpivirine was administered without previous efavirenz treatment, except for a 25% lower C_{\min} . Therefore, for individuals with undetectable viral loads switching from efavirenz to rilpivirine, standard doses of rilpivirine can be commenced [5]. To date, no data are available on what strategy to adopt in individuals with active viral replication.

6.2.4.2.4 Efavirenz to a ritonavir-boosted protease inhibitor

Because of the strong inhibitory effect of ritonavir on CYP450 3A4, a modification of the PI/r dose is unlikely to be needed when switching from efavirenz to PI/r. Formal pharmacokinetic data are unavailable. TDM data on atazanavir/r showed that after stopping efavirenz, atazanavir concentrations were above the suggested minimum effective concentration in all studied subjects [6].

6.2.4.2.5 Efavirenz to raltegravir

Although formal pharmacokinetic data are not available, switching efavirenz to raltegravir should not lead to clinically significant consequences, as co-administration of efavirenz with raltegravir led to a 21% decrease in raltegravir C_{\min} and the degree of this reduction is unlikely to be clinically meaningful [7].

6.2.4.2.6 Efavirenz to maraviroc

A formal pharmacokinetic study in HIV-positive individuals showed that the induction effect of efavirenz necessitated an increase in maraviroc dose to 600 mg twice daily for 1 week following the switch [8]. Maraviroc 300 mg twice daily (standard dose) seems to be safe after this period. Although there is an absence of data, when switching from efavirenz to maraviroc plus a PI/r, it is likely that a dose of 150 mg twice daily is safe from the first day after the switch. Whether it is advisable to use maraviroc 150 mg once daily in this context or for how long a twice-daily dose should be used after the switch remains unknown.

6.2.4.2.7 Efavirenz to elvitegravir/cobicistat

Concentrations of elvitegravir are lowered by previous efavirenz administration: elvitegravir AUC/ C_{trough} were 37%/67% and 29%/55% lower 1 and 2 weeks post-switch, respectively, but still above the protein binding-adjusted 95% inhibitory concentration (45 ng/mL). Therefore, for individuals with undetectable viral loads switching from efavirenz to elvitegravir/c, standard doses of elvitegravir/c can be commenced [9]. Pharmacodynamic data from a Phase 3b switch study in HIV-positive subjects are also available [10]. To date, no data are available on what strategy to adopt in individuals with active viral replication.

6.2.4.2.8 Efavirenz to dolutegravir

Mathematical modelling suggests that dolutegravir concentrations achieved target minimum effective concentrations by 3 days following efavirenz discontinuation (6 days in efavirenz poor metabolisers). Importantly, there was no time point where both the efavirenz and dolutegravir concentrations were predicted to be sub-therapeutic [11]. On that basis, straightforward (with no dose adjustment) substitution of efavirenz with dolutegravir is recommended.

6.2.4.2.9 Nevirapine to rilpivirine

A study switching 32 individuals with an undetectable viral load from **tenofovir-DF/emtricitabine + nevirapine** to **tenofovir-DF/emtricitabine/rilpivirine** fixed-dose combination showed that all individuals maintained viral suppression. Mean rilpivirine C_{trough} was above C_{trough} measured in Phase 3 studies by week 1 and the majority of individuals (27/32) had undetectable plasma nevirapine concentrations by week 2 [12]. Therefore, for individuals with undetectable viral loads switching from nevirapine to rilpivirine, standard doses of rilpivirine can be commenced. To date, no data are available on what strategy to adopt in individuals with active viral replication.

6.2.4.2.10 Nevirapine to dolutegravir

Concentrations of dolutegravir have been shown to be moderately decreased ($n=10$) by previous nevirapine administration in PLWH with an undetectable viral load: dolutegravir AUC was lowered by 19% and C_{trough} by 34% [13]. These changes are unlikely to be clinically significant as dolutegravir concentrations are maintained well above the protein binding-adjusted 90% inhibitory concentration (64 ng/mL) during and right after stopping nevirapine administration. Therefore, for individuals with undetectable viral loads switching from nevirapine to rilpivirine, standard doses of rilpivirine can be commenced.

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6.3 Switching antiretroviral therapy in virological suppression

6.3.1 Introduction

In individuals on fully virally suppressive regimens, switching individual components of the ART combination regimen is frequently considered for several reasons, including: management of ARV drug toxicity or intolerance, desire for once-daily dosing and reduced pill burden, management of potential drug–drug interactions, individual preference and cost [1]. Guidance on the management of drug toxicity of individual ARVs is not within the scope of these guidelines. Guidance on interventions to support adherence, including once-daily dosing and fixed-dose combinations is addressed in Section 6.1 (Adherence) and pharmacological considerations on switching ARVs is discussed in Section 6.2.4.

Switching individual components of an ART regimen may well improve adherence and tolerability, but should not be at the cost of virological efficacy. The following guidance concerns the impact on virological efficacy of either switching the third agent or the NRTI backbone in a combination ART regimen or simplifying to boosted PI monotherapy. Evidence from a systematic literature review (Appendix 2) was evaluated as well as the impact on critical treatment outcomes of the different switching strategies assessed. Critical outcomes included virological suppression at 48 weeks, virological failure and discontinuation from grade 3/4 events. Of note, when switching in the context of viral suppression, rilpivirine and abacavir/lamivudine can be used regardless of pre-treatment viral load.

6.3.2 Switching antiretrovirals in combination antiretroviral therapy

6.3.2.1 Recommendations

- We recommend, in individuals on suppressive ART regimens, consideration is given to differences in side-effect profile, drug–drug interactions and drug-resistance patterns before switching any ARV component (GPP).
- In individuals with previous NRTI resistance mutations, we recommend against switching a PI/r to either an NNRTI or an INI as the third agent (1B).

6.3.2.2 Auditable outcome

- Number of individuals with an undetectable viral load on current regimen and documented previous NRTI resistance who have switched a PI/r to either an NNRTI or INI as the third agent.

6.3.2.3 Rationale

Within-class switches are usually undertaken to improve ARV tolerability or to address potential adverse effects. The available evidence for current recommended third agents is limited but switching PI/r or NNRTIs in virologically suppressed individuals has, in a small number of studies, not been associated with loss of virological efficacy [2–4]. Consideration should, however, be given to differences in side-effect profiles, drug–drug interactions, pill burden and food effect (see Appendix 4). When switching between different PIs, a previous history of major PI mutations may potentially have an adverse effect on the virological efficacy of the new PI/r.

6.3.2.3.1 Within class

For NRTIs, recent studies have mainly evaluated switching from a thymidine analogue to either **tenofovir-DF** or abacavir to manage lipoatrophy, or have investigated switching to one of two available NRTI fixed-dose combinations (FDC; **tenofovir-DF** and emtricitabine or abacavir and lamivudine). If screening for HLA-B*57:01 positivity is undertaken before the switch to abacavir, then similar virological efficacy is seen in

subjects switched to abacavir/lamivudine FDC compared with a switch to **tenofovir-DF**/emtricitabine FDC [5]. Switching from abacavir/emtricitabine FDC to **tenofovir-DF**/emtricitabine FDC was also found to maintain viral suppression and is safe [6]. However, switching to simplify to a triple nucleoside regimen is not recommended [7]. For PIs, recent studies have evaluated both within-class switching and simplification to an unboosted regimen [8–12]. These changes have been to reduce bilirubin, lipids or bone and renal biomarkers. For NNRTIs, etravirine and rilpivirine have been evaluated in an intraclass switch [4,13,14]. All study participants maintained virological control and there were no adverse events. With the exception of a small, single arm **tenofovir-DF**/emtricitabine plus raltegravir to Stribild switch study (50 subjects, all of whom maintained virological suppression with minimal impact on renal and lipid markers) [15], there are no integrase inhibitor within-class switch studies. In general, in the absence of previous resistance mutations, switching within class should result in maintaining virological suppression.

6.3.2.3.2 Switch from PI

Several randomised controlled trials have assessed switching between classes (PI to NNRTI or INI, NNRTI to INI) in individuals who are virologically suppressed. A meta-analysis of six trials showed non-inferiority in maintenance of virological suppression when switching from a PI (both ritonavir boosted and unboosted) to nevirapine compared with continuing the PI, but was associated with more discontinuations due to liver toxicity [16]. Previous treatment failure on an NRTI-containing regimen has been associated with an increased risk of virological failure when switching from a PI- to an NNRTI-based regimen [17]. A cohort analysis showed similar rates of virological failure at 12 months in PLWH switching from a first-line PI/r to either efavirenz or nevirapine compared with continuing on the PI/r [18]. If switching to nevirapine, consideration should be given to the risk of hypersensitivity reactions and hepatotoxicity. Similar rates have been reported in virologically suppressed compared with ART-naïve individuals stratified for CD4 cell count and gender [19,20]. Only one randomised controlled trial has assessed the switch from PI to once-daily etravirine in people with HIV RNA suppression [21] and no participants presented with virological failure through to 48 weeks. Switching in virological suppression to rilpivirine from PI-maintained suppression was safe and, with or without K103N, had a high response rate [22–24]. For individuals without previous NRTI or NNRTI resistance mutations switching from a PI/r to any of the current licensed NNRTIs is likely to maintain virological efficacy and choice of NNRTI will depend on side-effect profile, tolerability and individual preference.

Switching from a PI/r to the INI, raltegravir, in virologically suppressed individuals has been evaluated in three randomised controlled trials. Two studies have shown that previous history of NRTI resistance mutations increases the risk of subsequent virological failure on switching compared with continuing on a PI/r [25,26]. This association was not seen in a third trial [6]. However, it is not surprising that switching from an ARV with a high genetic barrier to one with a low genetic barrier to resistance may potentially increase the risk of virological failure if the activity of the NRTI backbone has been compromised by previous NRTI resistance. One randomised controlled trial assessed switching from PI to elvitegravir/c in people with viral suppression (excluding individuals with a history of virological failure or resistance to **tenofovir-DF** or emtricitabine), finding suppression is maintained and regimen is well tolerated [27].

6.3.2.3.3 Switch from NNRTI

Switching from an NNRTI to an alternative third agent (elvitegravir/c or raltegravir [28,29]) in virologically suppressed patients has been assessed. Raltegravir was assessed for patient preference and was found to be acceptable. NNRTI switch to elvitegravir/c maintained viral suppression and was well tolerated. If switching from an NNRTI, consideration must be given to previous treatment history and potential pharmacokinetic interactions. The latter is discussed in more detail in Section 6.2.4.

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6.3.3 Protease inhibitor monotherapy

6.3.3.1 Recommendation

- We recommend against the use of PI monotherapy for routine ART (1A).
- We recommend against the use of PI monotherapy for individuals whose initial regimen has failed or who have established resistance to one more antiretroviral drugs (1A).

6.3.3.2 Auditable outcome

- Proportion of individuals on PI/r monotherapy as ART maintenance strategy and record of rationale.

6.3.3.3 Rationale

For the assessment and evaluation of evidence, GRADE tables were constructed (Appendix 3). Virological suppression, drug resistance and serious adverse events were defined as critical outcomes. From the systematic literature review (Appendix 2), twelve randomised trials and two meta-analyses were identified, investigating the use of either lopinavir/r or darunavir/r in stable, virologically suppressed PLWH without active hepatitis B co-infection [1–14]. Assessment of virological suppression showed significantly fewer on PI monotherapy maintained virological suppression compared with those continuing on standard combination ART (RR 0.95, 95% CI 0.9–0.99), although the difference was small. Viral load rebound is usually at low level, and is easily reversed by reintroduction of NRTIs [10]. There were no differences in the frequency of emergence of viral resistance, or of serious adverse events. The long-term consequences of this viral rebound and resuppression were assessed in the PIVOT trial where primary endpoint was loss of future drug options and secondary endpoints included clinical events [15]. PI monotherapy was non-inferior (inferiority margin 10%) on the primary end point of impact on future treatment options [15]. One potential concern is the development of CNS disease in people on PI monotherapy [7,14,15]; however, PIVOT did not identify any difference in neurocognitive scoring over 5 years [15]. Overall, there is no significant clinical benefit of PI monotherapy compared with standard combination ART and the added disadvantage of a lower rate of viral suppression with PI monotherapy. For this reason PI monotherapy should not be used in unselected populations for maintaining virological suppression where standard ART is an acceptable alternative. There may be potential benefits of PI monotherapy, in terms of drug resistance, long-term drug toxicity and cost [16,17]. We recognise that PI monotherapy may well be an acceptable option in some specific populations and has been found to be safe, well tolerated and cost-effective [15]. Clinicians might consider PI monotherapy in individuals who are unable to tolerate NRTIs due to toxicities or as a short-term measure to manage or bridge complex clinical scenarios (e.g. stopping certain NNRTI-containing regimens or managing toxicity overdose or acute illness). Where PI monotherapy is considered, darunavir/r (dosed once or twice daily) or lopinavir/r (dosed twice daily) should be used but with reintroduction of NRTIs if there is loss of virological control. Atazanavir/r monotherapy is not recommended because it has been associated with higher rates of virological failure [18,19]. PI monotherapy is not recommended in individuals with active hepatitis B co-infection.

6.3.3.3.1 PI monotherapy as second line after first-line treatment failure

Three randomised controlled trials looked at PI monotherapy as second-line therapy compared to triple-ART in treatment failure, all in an African setting. In all three trials the PI monotherapy arm had significantly more participants with virological failure than the triple ART or other arms in the trials [20–22].

This strategy therefore is not recommended.

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6.3.4 Treatment with one boosted protease inhibitor and one NRTI

6.3.4.1 Recommendation

- We suggest that a boosted PI plus lamivudine as an alternative to three-drug ART in individuals with viral suppression (2A)

6.3.4.2 Rationale

Two studies have compared the use of boosted atazanavir or lopinavir with lamivudine versus a conventional three-drug regimen in patients with a suppressed viral load [1,2]. In both studies, the efficacy of dual therapy was non-inferior to conventional therapy after 48 weeks of follow up. In patients who have a suppressed viral load on a conventional regimen, but who have drug toxicity associated with abacavir or **tenofovir-DF**, dual therapy is thus a reasonable option. This approach has not been compared formally with protease inhibitor monotherapy, however, **and the availability of tenofovir-AF may provide an NRTI option for individuals for whom tenofovir-DF and abacavir are unsuitable.**

6.3.4.4 References

1. Arribas JR, Girard PM, Landman R *et al.* Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis* 2015; **15**: 785–792.
2. Perez-Molina JA, Rubio R, Rivero A *et al.* Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. *Lancet Infect Dis* 2015; **15**: 775–784.

6.4 Stopping therapy

6.4.1 Recommendation

- We recommend against treatment interruption or intermittent therapy in individuals stable on a virally suppressive ART regimen (1A).

6.4.2 Auditable outcomes

- Proportion of individuals not on ART having previously been on ART.
- Documentation of reasons for stopping in those who stopped.

6.4.3 Rationale

Several randomised controlled trials have investigated the efficacy of CD4 cell count-guided intermittent therapy as a potential strategy to reduce long-term risk of drug toxicity and drug resistance [1-4]. In the largest of these, subjects were randomly allocated to either CD4 cell count-guided intermittent therapy (stopping ART once CD4 cell count ≥ 350 cells/ μ L, restarting when CD4 cell count falls to 250 cells/ μ L) compared with a continuous ART [4]. The trial showed intermittent therapy was associated with a significantly higher rate of opportunistic disease and all-cause mortality and a higher rate of major cardiovascular, renal or hepatic disease. The effect was seen at all CD4 cell count levels. The study showed for the first time that continuous ART with virological suppression is associated with a reduction in the risk of non-AIDS co-morbidities and all-cause mortality as well as HIV disease progression. For this reason, treatment interruption or intermittent therapy is not recommended.

Once ART has been started in a patient with HIV infection, it should be continued. An interruption of 1–2 days can usually be managed and is unlikely to be associated with adverse outcomes. Longer or frequent interruptions of ART should only be considered in exceptional circumstances. These may include:

- Severe drug toxicity (e.g. hepatotoxicity).
- Severe psychological distress.

Guidance on pharmacokinetic considerations when stopping ART is contained in Section 6.2.3.

6.4.4 References

1. Ananworanich J, Gayet-Ageron A, Le Braz M *et al.* CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. *Lancet* 2006; **368**: 459–465.
2. Cardillo PG, Hassink E, Ananworanich J *et al.* A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. *Clin Infect Dis* 2005; **40**: 594–600.
3. Danel C, Moh R, Minga A *et al.* CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet* 2006; **367**: 1981–1989.
4. El-Sadr WM, Lundgren J, Neaton JD *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; **355**: 2283–2296.

7.0 Managing virological failure

7.1 Introduction

For detailed guidance on HIV viral load (VL), resistance and genotypic tropism testing, the reader should consult *BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals* [1] (www.bhiva.org/Monitoring.aspx).

The following recommendations concern the management of PLWH experiencing virological failure on ART. Populations at the time of virological failure will include those with no or limited HIV drug resistance, those with more extensive resistance or historical virological failure on NRTIs, NNRTIs, and/or PIs and those with limited treatment options, including failure of an integrase inhibitor or X4 tropic virus. For the assessment and evaluation of evidence, priority questions were agreed and outcomes were ranked as critical, important and not important by members of the writing group. For individuals with no or limited HIV drug resistance the following were ranked as critical outcomes: viral suppression to <50 copies/mL at 48 weeks, development of resistance, and discontinuation for clinical and laboratory adverse events. For individuals with three-class failure/few therapeutic options: clinical progression, median CD4 cell count change at 48 weeks, and development of new resistance were ranked as critical outcomes. Treatments were compared where data were available and differences in outcomes assessed. For this update of the guidelines, the benefit of including NRTIs in the context of virological failure/resistance was examined. Details of the search strategy and literature review are contained in Appendix 2.

In the UK, the virological failure rate on first-line NNRTI-based regimens is 18% with approximately 4% failing in the first year [2]. The options for switch depend on the most recent and past ARV treatments as well as current and archived resistance results. As baseline genotypic testing of reverse transcriptase and protease (not integrase at the time of writing) is now performed routinely and is recommended practice, detection of resistance at virological failure is rarely a result of transmitted drug resistance and failure to adapt first-line treatment [3,4].

The general principles for the management of individuals experiencing virological failure are outlined in Boxes 7.1 and 7.2 as GPPs. Details of typical patterns of HIV drug resistance found in individuals with a history of or presenting with virological failure are outlined in Box 7.3.

7.1.1 Summary of auditable measures

- Record in medical notes of resistance result at baseline (HIV diagnosis) or at ART initiation (if former not available) and at first VL >200 copies/mL after prior virological suppression (or less if genotyping successful) and/or before switch.
- Record in medical notes of adherence assessment and tolerability/toxicity to ART in individuals experiencing virological failure or repeated viral blips.
- Proportion of individuals experiencing virological failure on current ART regimen.
- Proportion of individuals experiencing virological failure switched to a new suppressive regimen within 6 months.
- Proportion of individuals on ART with previously documented HIV drug resistance with VL <50 copies/mL.
- Record of individuals with three-class virological failure with or without three-class resistance referred/discussed in multidisciplinary team with expert advice.

7.2 Blips, low-level viraemia and virological failure

Definitions (in the context of continued ART without changes):

Virological suppression: achieving and maintaining a VL level <50 copies/mL.

Virological failure: incomplete virological response after commencing treatment or evidence of confirmed virological rebound to >200 copies/mL.

Incomplete virological response: two consecutive VL >200 copies/mL after 24 weeks without ever achieving VL <50 copies/mL. Consideration of the baseline VL and regimen should be made as some regimens will take longer than others to suppress HIV RNA levels. In individuals with a high baseline viral load (e.g. >100,000 copies/mL) it may take longer for viral load to fall below the limit of detection; in contrast, individuals treated with an integrase inhibitor are more likely to experience more rapid reduction in viral load.

Virological rebound: failure to maintain a VL below the limit of detection (ordinarily <40–50 copies/mL) on two or more consecutive occasions.

Low-level viraemia: a persistent VL between 50–200 copies/mL.

Virological blip: after virological suppression, a single VL between 50 and 200 copies/mL followed by an undetectable result.

7.2.1 Recommendations

In individuals on ART:

- A single VL 50–200 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern (GPP). It should necessitate clinical vigilance, adherence reinforcement, check for possible interactions, and repeat testing within 2–6 weeks depending on ARV regimen.
- We recommend that a single VL >200 copies/mL is investigated further, including a rapid re-test +/- genotypic resistance test, as it may be indicative of virological failure (1C).
- We recommend that in the context of low-level viraemia or repeated viral blips, resistance testing be attempted (1D).

7.2.2 Rationale

7.2.2.1 Blips

Optimal HIV control is ordinarily reflected by complete virological suppression with an undetectable VL. A virological blip is variably defined but for the purposes of these guidelines the definition that has been adopted is a detectable VL between 50 and 200 copies/mL, which is preceded by and followed by an undetectable result without any change of therapy. Blips are frequent, tend to cluster between 50 and 200 copies/mL, (median magnitude 79 copies/mL in one study with range between 51–201 copies/mL) and, when real and not due to laboratory variability, are short-lived (median 2.5 days, range 2–11.5 days) [5-7]. Many individuals have at least one blip at some time [8] and most studies have found no relationship between isolated blips and adverse outcomes such as virological failure or emergent resistance [5,9,10]. However some studies have reported an association between blips and future virological failure [6,11].

There is correlation between level of first detectable viral load and subsequent virological rebound [8,12,13]. One retrospective study of over 3000 individuals found virological failure (defined as consecutive HIV-1 VL >50 copies/mL measured at least 30 days apart, or any VL >1000 copies/mL) in 26%; 14% of rebounds were preceded by transient HIV-1 VL of 50–999 copies/mL but critically, only transient HIV VL >500 copies/mL correlated with rebound in multivariable analyses [12]. This concurs with other studies (see Section 7.2.2.2).

VL assay variation and laboratory processing artefacts account for many blips (i.e. no 'true' increase in viral replication), which partly explains why blips do not appear to compromise long-term outcomes [9,14,15]. Most individuals with short-lived increases in HIV VL to <200 copies/mL can be reassured that such events are relatively common and unlikely to presage failure. However, those with sustained low-level increases in VL (see 7.2.2.2) run a higher risk of virological failure. In keeping with the DHSS guidance [16], these guidelines [17] define virological failure as a confirmed viral load >200 copies/mL, a threshold that eliminates most cases of viral load blips.

A detectable viral load should prompt a review of adherence (and reiteration of the importance of full adherence), as well as looking for any tolerability/toxicity issues, drug–drug interactions/food interactions, and evidence of archived resistance. A VL result of 50–200 copies/mL preceded and followed by an undetectable VL should not be a cause of clinical concern. In the context of repeated blips or persistent low-level viraemia, genotypic resistance testing is recommended [11,18].

7.2.2.2 Low-level viraemia

Low-level viraemia (LLV) is observed in up to 8% of individuals [19] and, when compared to viral suppression to <50 copies/mL, is associated with an increased risk of virological failure and resistance [6,20,21]. The likelihood of re-suppression after LLV is greater for lower magnitudes of viraemia [22]. Indeed it is uncertain whether LLV <200 copies/mL always confers independent risks as viraemia at this level may on occasions reflect assay variation. LLV is associated with resistance (37% in one study [21]) that may be associated with LLV magnitude; in one analysis, maximum VL was higher in those who developed resistance (368 vs. 143 copies/mL, $P=0.008$). In cohort studies [20] and clinical trials [21], individuals on PI/r-based ART are more likely to experience detectable viraemia than those on NNRTI. Many individuals with LLV have low or undetectable plasma drug levels on untimed samples underscoring the importance of assessing adherence [23]; we do not however recommend routine therapeutic drug monitoring in this context (see Section 6.2.2). LLV is also associated with immune activation [10]. Low-level antigenic exposure differentially affects T cell activation and HIV-specific T cell response.

Resistance testing should be considered, where feasible, in all cases of LLV (viraemia between 50 and 200 copies/mL) on treatment. Where resistance is detected, regimens should be modified appropriately. In the absence of clear data, the writing group believes persistent LLV on a low-genetic barrier regimen (including NNRTI-based or INI-based therapy), even in the absence of detectable resistance, warrants prompt regimen change [24,25].

Further evaluation should follow as for that set out in Box 7.1.

Box 7.1. Best practice for the management of individuals with suspected or confirmed virological failure

- Factors affecting adherence and drug exposure, including tolerability/toxicity issues, drug–drug interactions/food interactions, ARV potency, significant renal/liver disease and mental health/drug dependency problems are evaluated.
- Resistance testing is performed while on failing therapy or within 2–4 weeks of discontinuation.
- Past ART and resistance tests are reviewed for archived mutations.
- Tropism testing is performed if maraviroc is being considered.
- Intensification **by adding** a single additional active ARV is not recommended.
- Once virological failure is confirmed and preferably after a resistance-test result is available, the regimen is changed as soon as possible to avoid accumulation of resistance mutations.

The choice of the new ART regimen will primarily depend on the results of resistance testing, prior treatment history and the individual's preference. Additional considerations include the results of tropism and HLA-B*5701 testing, drug–drug interactions/food interactions, co-morbidities and future therapy options. The goal of the new combination is to re-establish a VL <50 copies/mL.

Increasingly, viral load assays have quantification cut-offs lower than 50 copies/mL. Thus, individuals may have persistent viraemia >20 or >40 copies/mL but <50 copies/mL, depending on the assay used. Rates of this 'very low-level' viraemia (VLLV) are as yet unclear. Several studies have evaluated the risk of virological rebound >50 copies/mL in individuals with detectable viraemia below 50 copies/mL. Results are conflicting [26-28]. In one study, subjects were stratified based on the Abbott RealTime Assay into VL 40–49 copies/mL, <40 copies/mL with RNA detected, and <40 copies/mL with no RNA detected [27]. They found that compared to individuals with VL <40 copies/mL and no detected RNA, having viraemia of 40–49 copies/mL increased the risk of rebound to >50 copies/mL by 4.67-fold while having detectable RNA at <40 copies/mL increased the risk by 1.97-fold. The risk of rebound to >400 copies/mL was increased by 6.91-fold and 2.88-fold, respectively. Other studies have reported increased risk of rebound to >50, >200, >400 copies/mL but importantly, not >1000 copies/mL or higher [29]. The majority of the rebounds >200 copies/mL were blips and resistance rarely emerged [29], making the significance of these events unclear.

In the absence of clear data, the writing group believes that, having assessed factors outlined in Box 7.1, no treatment modification is required for individuals with detectable viraemia below 50 copies/mL.

7.2.2.3 Virological failure

In the UK, among drug-experienced individuals who experience virological failure approximately 70% have no major resistance mutations on genotypic resistance testing [30]. Confirmation of virological failure at any stage should lead to the practice set out in Box 7.1.

Box 7.2. Best practice for the management of individuals with three-class virological failure

- In individuals with ongoing viraemia and with **restricted** options to construct a fully suppressive regimen, referral for specialist advice and/or discussion in a multidisciplinary team 'virtual' clinic is imperative.
- In those with significant resistance, include at least two and preferably three fully active agents with at least one active PI/r (preferably darunavir/r) and one agent with a novel mechanism of action (preferably integrase inhibitor, CCR5 antagonist or fusion inhibitor).
- Treatment interruption is not recommended.

Box 7.3. Typical resistance patterns on virological failure

- No resistance (wild-type virus)
- Lamivudine/emtricitabine resistance (M184V/I) following any first-line therapy, including tenofovir-DF/emtricitabine or abacavir/lamivudine.
- NNRTI resistance (e.g. K103N, Y181C/I/V or E138K) and/or lamivudine/emtricitabine resistance (following first-line therapy with an NNRTI-based regimen, including tenofovir-DF/emtricitabine or abacavir/lamivudine).
- INI resistance (e.g. Y143C/R, Q148R/H or N155H) and/or lamivudine/emtricitabine resistance (following first-line therapy with raltegravir or elvitegravir-based regimens, including tenofovir-DF/emtricitabine or abacavir/lamivudine).
- Extended reverse transcriptase resistance (e.g. K65R/L74V or thymidine analogue mutations) (following suboptimal regimens/individuals with more extensive NRTI-based drug history associated with virological failure).
- Three-class resistance (usually NRTI, NNRTI and PI) (following multiple failing regimens).
- Limited or no therapeutic options (following multiple failing regimens, including integrase and R5 inhibitors).

7.3 Individuals with no or limited drug resistance

7.3.1 Recommendations

- We recommend for individuals experiencing virological failure on first-line ART with wild-type virus at baseline and without emergent resistance mutations at failure, switch to a PI/r- **or PI/c**-based combination ART regimen is the preferred option (1C).
- We recommend individuals experiencing virological failure on first-line ART with wild-type virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure, switch to a new PI/r- **or PI/c**-based regimen with the addition of at least one, preferably two, active drugs (1C).
- We recommend individuals experiencing virological failure on first-line PI/r **or PI/c** plus two-NRTI-based regimens, with limited major protease mutations, switch to a new active PI/r **or PI/c** with the addition of at least one, preferably two, active agents of which one has a novel mechanism of action (1C).
- We recommend against switching a PI/r **or PI/c** to an INI or NNRTI as the third agent in individuals with historical or existing reverse transcriptase mutations associated with NRTI resistance or past virological failure on NRTIs (1B).

7.3.2 Rationale

7.3.2.1 First-line treatment failure with no resistance

Seventy per cent of individuals have wild-type virus despite failure of therapy [31-37]. Failure is usually attributable to poor treatment adherence with drug levels that are both insufficient to maintain VL suppression and inadequate to select out viral mutations associated with drug resistance detectable on standard tests. Factors affecting adherence such as tolerability/toxicity issues, regimen convenience, drug-food interactions and mental health/drug dependency problems should be fully evaluated and where possible corrected before initiation of the new regimen. Additional adherence support should be considered and careful discussion with the individual take place. Therapeutic drug monitoring may be of benefit in individuals to confirm low/absent therapeutic drug levels and to enable targeted discussion.

A priority question to address was whether individuals whose NNRTI-based ART had failed without detectable resistance should receive a **boosted** PI-based regimen.

The absence of detectable resistance mutations does not exclude the presence of mutations in minor virus populations, especially with the NNRTIs [9,10,38]. This may increase the likelihood of subsequent failure if the same first-line drugs, or drugs in the same class, are prescribed [39,40]. Nevertheless, testing for minority resistance is a specialist test and expert interpretation by a virologist is essential. There is no indication for routine minority-species testing for individuals with wild-type virus and failed therapy.

We recommend that, following the development of virological failure, or persistent low-level viraemia, on either an NNRTI or INI-based ART regimen with two NRTIs and when no resistance mutations are detected, a switch to a PI/r- **or PI/c**-based regimen is optimal. **Ritonavir and cobicistat demonstrate bioequivalence and sustainable and comparable efficacy in clinical trials.** This should lead to virological suppression, and is least likely to select emergent resistance. Restarting the previous failing regimen is an alternative option, especially where poor adherence has been identified as the likely cause and has been addressed. However, the subject should be monitored carefully and repeat VL performed after approximately 4 weeks. If there is inadequate virological response, resistance testing should be performed to detect any archived resistance. Switching to another NNRTI-, an INI- or maraviroc- (where CCR5 tropism has been confirmed) based ART regimen is the final option but has to be individualised, including history of virological failure, and whether further switches in the combination are occurring. In deciding which option, knowledge as to the likely cause of virological failure especially the details of poor adherence are important. In an NNRTI/2NRTI regimen,

when all three agents have been stopped, the chances of NNRTI resistance are 12–16% depending on whether there is a simultaneous or staggered interruption [41,42]

7.3.2.2 First-line treatment failure with non-nucleoside reverse transcriptase inhibitor resistance

Up to two-thirds of PLWH with virological failure on an NNRTI/2NRTI ART combination harbour viruses with NNRTI and half NRTI mutations at 48 weeks [34-37,43]: with increasing time, there will be accumulation of resistance mutations that may compromise second-line regimens [44]. The finding of associated NRTI resistance is more frequent in those on a thymidine analogue (TA) backbone than on a non-TA one. Although potential options for second-line therapy after failure on an NNRTI-containing regimen include an integrase inhibitor (raltegravir, elvitegravir or dolutegravir), etravirine or maraviroc as the third agent, evidence supports the use of a PI/r or PI/c. A switch to any boosted PI-based regimen should lead to virological suppression and is unlikely to lead to further emergent resistance and should be considered whenever possible. Where NRTI resistance has been documented or likely, the addition of new active NRTIs or another ARV(s) should be considered in combination with a boosted PI. The exception to this is when M184V is present alone, when recycling of NRTIs may be feasible. Combining raltegravir with a boosted-PI has been found to be as efficacious as a boosted PI/r regimen with at least two new or recycled NRTIs [45-47].

There are no direct comparisons of the boosted PIs in second-line treatment after first-line failure on an NNRTI-based regimen and choice should be individualised. Sequencing from an efavirenz- or nevirapine-based regimen to etravirine is not recommended [48] unless switching to a new combination including a boosted PI. Switching to an INI (raltegravir, elvitegravir or dolutegravir) or maraviroc with two active NRTIs is an option but is also not recommended if there are historical or existing reverse transcriptase mutations/previous NRTI virological failure [49].

7.3.2.3 First-line treatment failure on a ritonavir-boosted protease inhibitor-based two nucleoside reverse transcriptase inhibitor regimen with or without protease inhibitor resistance

Less than 1% of individuals with virological failure harbour viruses with primary PI mutations and 10–20% NRTI mutations at 48 weeks, with 75% having wild-type virus [31,34-36,50,51]. For those whose regimens fail with limited or no resistance and where adherence is a concern, remaining on the same regimen may be a reasonable approach but with close monitoring and adherence support. However, the individual should be monitored carefully and repeat VL performed after approximately 4 weeks. If there is inadequate virological response, resistance testing should be performed to detect any additional archived resistance. There are currently limited data regarding the efficacy of switching to another boosted PI, NNRTI, INI or maraviroc-based regimen and again the decision should be individualised. However, switching to an INI, maraviroc or an NNRTI for a person with historical or existing reverse transcriptase mutations is not recommended because of an increased risk of virological failure and further emergence of resistance [49]. By contrast, because of the high genetic barrier of boosted PI, sequencing to a regimen that includes a new boosted PI is unlikely to lead to further emergent resistance and is recommended. Where PI mutations exist, darunavir/r or darunavir/c is the preferred agent (unless resistance is likely) and inclusion of an INI, etravirine or maraviroc (if R5 tropic virus) as one of the additional drugs should be considered. Where darunavir is not suitable, depending on susceptibility, alternative PIs such as tipranavir/r and lopinavir/r may be considered.

7.3.2.4 First-line treatment failure with integrase inhibitor-based resistance

In studies of naïve subjects developing virological failure on raltegravir or elvitegravir regimens, up to one-half have been found to harbour viruses with primary integrase mutations and 25% NRTI mutations at 48 weeks: approximately half have wild-type virus [33,43,50,52]. By contrast, no resistance has been seen in trials in treatment-naïve individuals with dolutegravir/2NRTI-based regimens [53-55]. Again, there are no data supporting a switch to PI/r, NNRTI or maraviroc but sequencing to a new regimen that includes a boosted PI is unlikely to lead to further emergent resistance and is recommended. Similarly, although data from the VIKING-3 study in individuals with pre-existing integrase mutations after failure on raltegravir or

elvitegravir in the context of three-class resistance and with optimisation of the background regimen has shown over half achieve a VL <50 copies/mL [56], there are no **trial** data to support sequencing to dolutegravir after first-line failure. Integrase sequencing of virus from patients failing raltegravir predicts that a third would have reduced response to dolutegravir and a small observational study supports this [57]. Switching to an NNRTI or maraviroc with two active NRTIs is an option but is also not recommended in a person with historical or existing reverse transcriptase mutations or previous NRTI virological failure. Individuals experiencing virological failure on raltegravir or elvitegravir should switch to a new regimen as soon as possible to reduce the risk of accumulating resistance mutations that may affect susceptibility to dolutegravir **when used as part of a fully active switch regimen** where success of response has been linked to the profile and number of resistance mutations.

7.4 Individuals with multiple class virological failure with or without extensive drug resistance

7.4.1 Recommendations

- We recommend individuals with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed **at an MDT inclusive of a virologist** /referred for expert advice (or through virtual clinic referral) (GPP).
- We recommend individuals with extensive drug resistance are switched to a new ART regimen containing at least two and preferably three fully active agents with at least one active PI/r such as **twice-daily** darunavir/r and one agent with a novel mechanism (an INI, maraviroc or enfuvirtide) with etravirine an option based on viral susceptibility (1C).
- We recommend in individuals without DRV resistance associated mutations, **boosted**-DRV can be given once daily (1C)
- We recommend individuals with extensive drug resistance including reduced darunavir susceptibility receive dolutegravir as the INI (1C).
- We suggest that consideration on an individual basis should be given to whether inclusion of NRTIs with reduced activity on genotypic testing will provide additional antiviral activity if the regimen includes three fully active drugs including a boosted PI (2C).
- We recommend all individuals receive intensive adherence support at the start and at regular intervals to support them on their new ART combination (GPP).

7.4.2 Rationale

The risk of extended three-class resistance, defined as the absence of any fully active NRTI, NNRTI, or PI, was only 2% among drug-experienced individuals in Western Europe in 2008 [58]. Ongoing treatment non-adherence drives further virological failure and addressing this and supporting strategies to improve adherence are important considerations before the introduction of any new regimen. Until the **decade**, limited treatment options have been available for people with HIV who have had virological failure with the three original classes of HIV ARV drugs for which many have developed triple-class resistance. Most of these individuals have received prior suboptimal ARV treatment, often from the pre-ART era, or have adhered poorly to multiple regimens and have accumulated resistance. However, with the introduction of second-generation inhibitors of reverse transcriptase and protease that have enhanced activity against resistant virus as well as agents active through novel sites of action, the potential for virological control akin to that achieved in a treatment-naïve person has now become a probability [59,60].

Consequent to more active ARVs and improved strategies of management, there has been substantial improvement in the proportion of people who had virological response after triple-class virological failure between 2000 and 2009 [61]. However, despite improvements in treatments, viral load cannot be

suppressed in some individuals. In most, this is a result of poor adherence but some individuals do have extended drug resistance with minimal treatment options and achieving viral suppression becomes increasingly difficult.

The drugs currently being used in triple-class failure are the boosted PIs (predominantly twice-daily darunavir/r but also on occasions tipranavir/r), the INIs raltegravir and dolutegravir, the CCR5 chemokine receptor antagonist maraviroc, the NNRTI etravirine, and the fusion inhibitor enfuvirtide. The available **trial data in experienced patients with extensive resistance demonstrates that** darunavir/r, tipranavir/r, raltegravir, elvitegravir, dolutegravir, etravirine and enfuvirtide show that they are most effective when used with other active drugs to which the virus is susceptible based on resistance testing and antiviral experience [62-70]. When used as the only effective agent, the likelihood of achieving virological suppression is significantly reduced and the development of emergent resistance to the drug greater, and a future opportunity for constructing an effective regimen is often lost.

In a meta-analysis of 10 trials (excluding dolutegravir) of subjects with triple-class virological failure and virological resistance where the study drug was added to optimised background therapy and compared with placebo, associations were demonstrated with increased virological suppression (pooled OR 2.97) and larger CD4 cell count increases for the active agent [71]. Optimised background therapy genotypic sensitivity scores (GSSs) were also associated with larger differences in virological suppression and CD4 cell count increase between the two groups. In a further non-inferiority study, elvitegravir was found to be non-inferior to raltegravir when accompanied by a boosted PI and a third agent [63].

A non-inferiority trial comparing dolutegravir with raltegravir as the comparator examined those with triple-class experience but who were naïve to integrase inhibitors and had at least two-class resistance and at least one fully active drug as optimised background therapy [72]. Overall, once-daily dolutegravir was superior to raltegravir at 48 weeks in achieving a VL <50 copies/mL. However, there was no benefit in individuals who had not received darunavir/r or had no primary darunavir mutations.

This supports the use of at least two and preferably three of these agents in the new regimen and with this strategy, the goal of an undetectable VL is achievable in most adherent individuals with multi-regimen failure.

A priority question addressed in this group was around the net contribution of recycling NRTIs in the context of virological failure and existing or potential reverse transcriptase mutations. In two studies examining individuals previously naïve to ART for whom an NNRTI/2NRTI regimen subsequently failed [45,46], a boosted PI/r regimen with at least two new or recycled NRTIs was no less efficacious than an NRTI-sparing regimen combining raltegravir with a boosted-PI. Even in the presence of limited or no predicted activity on the basis of genotypic assay, NRTIs retained substantial virological activity equivalent to that of raltegravir without evidence of increased toxicity and therefore may allow the introduction of drugs known to be active to be deferred. However, NRTI inclusion was demonstrated to achieve improved virological control over PI/r monotherapy out to 96 weeks [46].

Once virological suppression has been achieved, the advantage of retaining NRTIs where partial or complete resistance is demonstrated is uncertain. A small randomised open study of 90 virologically suppressed individuals evaluated the safety of withdrawing NRTIs compared to a control arm of maintaining them in the context of partial NRTI activity and the presence of at least two fully active remaining drugs in the regimen. No significant difference in virological failure between the arms was observed out to 48 weeks although there were three cases of virological failure in the simplification arm and none in the NRTI control arm [73].

A fourth study examined individuals who had triple-class failure and/or resistance when randomisation to the new regimen was based on treatment history, tropism testing and resistance profiles including a choice of NRTIs [74]. Following randomisation, the subjects then received the chosen regimen with or without the NRTIs. The results demonstrated omitting NRTIs was non-inferior to their inclusion. Of note, subjects in this

study received an average of three active drugs and therefore the lack of NRTI benefit is not altogether surprising.

A further uncertainty has been whether maintaining lamivudine/emtricitabine provides clinical benefit through the replication deficit provided by the M184V mutation combined with the residual antiviral activity of lamivudine/emtricitabine [75,76]. Studies using lamivudine monotherapy for individuals developing therapy failure have shown that those harbouring M184V who continue on lamivudine maintain lower VLs, have smaller declines in CD4 cell counts, and rarely develop new reverse transcriptase mutations [77-79]. In addition, the presence of M184V mutation enhances *in vitro* susceptibility to **tenofovir-DF** and this translates into a significant HIV RNA response in clinical trials of **tenofovir-DF** intensification [80,81]. Insufficient data exists to guide recommendations as to whether there are clinical benefits of trying to maintain M184V by continuing lamivudine/emtricitabine when switching to new combination ART. It is the belief of the writing group that any decision should be individualised.

For those drugs with a novel mode of action (integrase and fusion inhibitors, and CCR5 antagonists), the absence of previous exposure **invariably** indicates susceptibility, although maraviroc is only active against CCR5-tropic virus. **Although transmitted INI-resistant virus has been described, several studies have demonstrated these are isolated cases and baseline integrase resistance testing is currently not recommended.** For darunavir, tipranavir and etravirine, the number and type of mutations inform the degree to which these drugs are active [82-84]. The potential for drug–drug interactions is also important. Etravirine can be paired with darunavir/r (but not tipranavir/r or dolutegravir) and maraviroc dosing is variable depending on the other drugs in the new regimen; however, raltegravir and enfuvirtide require no alteration.

Some individuals can have a successfully suppressive fully active three-drug regimen constructed without a PI/r [85]. Nevertheless, where feasible, a **boosted** PI such as **twice-daily** darunavir/r should be included because of its protective effect on emergent resistance to the other drugs in the regimen. Darunavir/r can be given as 800 mg/100 mg once daily in treatment-experienced individuals without darunavir resistance-associated mutations [86]. Enfuvirtide is an option despite the inconvenience of subcutaneous injection and injection-site reactions. With the availability of the newer agents, dual PI/r are not recommended [87].

The same principles regarding reviewing adherence, tolerability/toxicity issues, drug–drug interactions/food interactions, and mental health/drug dependency problems apply. Additional adherence support is important in these individuals as the reason triple-class failure has occurred often relates to past poor adherence. Additionally, the pill burden is increased and careful discussion should take place.

7.5 individuals with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed

7.5.1 Recommendations

- We recommend accessing newer agents through research trials, expanded access and named individual programmes (GPP).
- We suggest that consideration, on an individual basis, should be given to whether inclusion of NRTIs with reduced activity on genotypic testing will provide additional antiviral activity – this may well be the case where it is difficult to construct a regimen with three fully active drugs including a boosted PI (see Section 7.4) (2C).
- We recommend against discontinuing or interrupting ART (1B).
- We recommend against adding a single, fully active ARV because of the risk of further resistance (1D).

- We recommend against the use of maraviroc to increase the CD4 cell count when there is evidence for X4 or dual tropic virus (1C).
- We recommend in the context of triple class failure, where darunavir is being used as the boosted PI, it should be given with ritonavir twice-daily
- We recommend that in the context of triple-class failure and raltegravir/elvitegravir selected integrase resistance, twice-daily dolutegravir should be included as part of a new regimen where there is at least one fully active agent in the background regimen (1C).

7.5.2 Rationale

This situation usually occurs following attempts to achieve virological suppression for individuals with triple-class failure with the newer agents, and often indicates adherence issues have not been addressed successfully or sequential addition of the newer agents has occurred without incomplete viral suppression and selection of resistance to the new drug.

There is evidence from cohort studies that continuing therapy, even in the presence of viraemia and the absence of CD4 T cell count increases, reduces the risk of disease progression [88,89] whereas interruption may lead to a rapid fall in CD4 cell count and a rise in VL [90,91]. Other studies suggest continued immunological and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL [92]. Hence, if the CD4 cell count is well maintained (>200 cells/ μ L), there is an argument to continue the failing regimen and not 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 virologically suppressive and durable regimen options. However, the potential benefit must be balanced with the ongoing risk of accumulating additional resistance mutations and the regimen should be maintained only for the shortest period possible [93,94].

In general, adding a single, fully active ARV to a failing regimen is not recommended because of the risk of rapid development of resistance. However, in individuals with a high likelihood of clinical progression (e.g. CD4 cell count <100 cells/ μ L) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits [95].

Several studies and an early meta-analysis suggested that CCR5 receptor antagonists were associated with significant gains in CD4 cell counts even in the presence of C-X-C chemokine receptor type 4 tropic virus. However, a meta-analysis refuted this finding ($P=0.22$) when comparing with other new drugs [71].

VIKING-3 [56] was a study of individuals who had received either raltegravir or elvitegravir and had integrase resistance with the majority having additional triple-class resistance, and where there was at least one fully active agent to use in the optimised background regimen. Dolutegravir 50 mg twice daily was added to the failing regimen and by day 8 and at the time of switching to an optimised background regimen, the mean drop in VL was \log_{10} 1.43. By week 24, 69% had achieved a VL <50 copies/mL. Response was associated with dolutegravir susceptibility and was most reduced in those with Q148 with at least two additional resistance mutations.

Where feasible, PLWH should be given the opportunity to enrol in research studies or expanded access programmes evaluating investigational new drugs. Drug availability is difficult to predict, but many second- and third-generation drugs are in Phase IIb/III studies (e.g. maturation inhibitors [96]) and others with novel sites of action (e.g. CD4 receptor antagonists, etc.) are in earlier phases of development. Drugs developed for, and used in, other settings such as pegylated interferon that have been incidentally demonstrated to decrease VL should not be used without discussion with experienced HIV physicians in a multidisciplinary team because data are either too limited or contradictory.

7.6 References

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8.0 Special populations

8.1 HIV and TB co-infection

This guidance provides a brief summary of the key statements and recommendations regarding prescribing ART in HIV-positive individuals co-infected with TB. It is based on the BHIVA guidelines for the treatment of TB/HIV coinfection 2011 [1], which should be consulted for further information. The full version of the guidelines is available on the BHIVA website (www.bhiva.org/TB-HIV-coinfection-guidelines.aspx).

8.1.1 When to start ART in TB/HIV co infection

8.1.1.1 Recommendations

- We recommend all patients with HIV TB co-infection start ART (1B).
- We recommend individuals with CD4 cell count <50 cells/ μ L start ART as soon as TB treatment is tolerated and wherever possible within 2 weeks (1B).
- We recommend that for individuals with CD4 cell counts \geq 50 cells/ μ L, ART can be deferred until between 8 and 12 weeks of TB treatment, especially when there are difficulties with drug–drug interactions, adherence and toxicities (1B). (Although the data suggest a cut-off of 50 cells/ μ L, because of the daily variability in CD4, a cut-off of 100 cells/ μ L may be more appropriate.)

8.1.1.2 Auditable outcome

- Proportion of individuals with CD4 cell count <100 cells/ μ L started on ART within 2 weeks of starting TB therapy.

8.1.1.3 Rationale

In TB/HIV co-infection, cohort and randomised trial data show that the short-term risk of developing further AIDS-defining events and death is higher if ART is delayed until after the first 8 weeks of TB therapy has been completed. In those with a CD4 cell count less than 50 cells/ μ L, compared to those with greater than 200 cells/ μ L, outcomes were best when ART was started as soon as practicable and within 2 weeks of initiation of TB therapy [2–5]. As there is marked intra-individual variability in CD4 cell count [6], particularly amongst individuals with low counts, a threshold of 100 cells/ μ L may be more practicable. In one study of HIV-associated TB meningitis, no difference in mortality was shown when starting ART early or late [7] but we recommend the guidance above be followed in this situation and consider monitoring of cerebrospinal fluid (CSF) pressure.

Commencement of ART in individuals with low CD4 cell counts and TB is associated with a large pill burden and higher rates of toxicity, drug interactions and immune reconstitution disorders. These issues can be reduced in individuals with CD4 cell counts of more than 100 cells/ μ L who can safely delay starting ART until 8 weeks of TB treatment have been completed. Individuals with HIV and a CD4 cell count >350 cells/ μ L have a low risk of HIV disease progression or death during the subsequent 6 months of TB treatment, depending on age and viral load. There are limited data in this subgroup and another option is for ART to be withheld until the short-course of TB treatment is completed but with regular monitoring of CD4 cell count.

8.1.2 What to start in TB/HIV co infection

8.1.2.1 Recommendations

- We recommend efavirenz in combination with tenofovir-DF and emtricitabine as first-line ART (1B) in TB/HIV co-infection. Tenofovir-AF is not recommended with rifamycins (PGP induction).
- We recommend that when rifampicin is used with efavirenz, standard doses of efavirenz are given whatever the body weight [8] (1B).
- We suggest that raltegravir can be used as an alternative to efavirenz but should be used with caution (2C).
- We suggest dolutegravir is a possible alternative agent to raltegravir (for which there is currently little evidence) but the dose should be increased to 50 mg twice daily (2D).
- We recommend frequent viral load monitoring if INIs are used (1C).
- We recommend that rifampicin is not used with either nevirapine or a regimen containing ritonavir or cobicistat (1C).
- We recommend that where effective ART necessitates the use of ritonavir or cobicistat, that rifabutin is used instead of rifampicin (1C).

8.1.2.2 Auditable outcome

- Proportion of patients with active TB on anti-TB therapy started on ART containing efavirenz.

8.1.2.3 Rationale

HIV-related TB should be treated with a regimen including a rifamycin for the full course of TB treatment, unless there is rifamycin resistance or intolerance. Rifamycins frequently interact with ARV medications and can be associated with similar toxicities, notably rash and hepatitis. Efavirenz is the preferred third agent for ART during TB treatment because of its efficacy in randomised controlled trials [9].

No weight adjustment of efavirenz dose is required as a randomised controlled trial has shown that the standard adult efavirenz dose (600 mg daily) together with two NRTIs is well tolerated and was efficacious in achieving complete viral suppression among adults on concomitant rifampicin-based TB treatment independent of weight [8].

Integrase inhibitors such as raltegravir and dolutegravir should be prescribed with caution with concomitant rifampicin as it decreases serum levels of raltegravir by 40–61% and trough levels are still low after doubling the dose of raltegravir [10]. A Phase 2 trial of standard (400 mg twice daily) and double dose (800 mg twice daily) raltegravir has showed acceptable virological outcomes [11]. Pharmacokinetic data suggest that dolutegravir can be used with rifampicin but the dolutegravir needs to be administered at 50 mg twice daily [12].

When co-administered with rifampicin, concentrations of standard-dose PIs, with or without ritonavir or cobicistat, are decreased below therapeutic targets, and so cannot be recommended [13–16]. Changing the dosing of the PI/r has resulted in increased rates of hepatotoxicity [16–18]. Elvitegravir cannot be administered with rifampicin as it requires boosting.

Rifabutin has little effect on the concentrations of PI/r but rifabutin concentrations are altered when the PI is taken together with ritonavir or cobicistat. Current recommendations are to reduce the dose and/or frequency of rifabutin. Atazanavir/r can be prescribed with rifabutin at a dose of 150 mg thrice weekly. As darunavir/r also acts as an inducer, rifabutin 150 mg once daily can be given to reduce the theoretical risk of rifamycin resistance due to a risk of sub-therapeutic rifabutin concentrations; this may, however, be associated with increased side effects [19–21]. Recent data suggest rifabutin at 150 mg/day maintains adequate levels with lopinavir/r [22]. Therapeutic drug monitoring may be useful in guiding doses.

Raltegravir and dolutegravir can be used with full-dose daily rifabutin without any dosage adjustment but there are few clinical data to support this strategy.

There are few clinical data to support the use of newer NNRTIs and CCR5 receptor antagonists with rifampicin or rifabutin. We recommend that physicians who are considering using these drugs review pharmacokinetic and other data summarised in the current BHIVA guidelines for treatment of TB/HIV co-infection [1]. As new anti-tuberculous agents become available, drug–drug interactions and the potential for overlapping toxicities should be considered when selecting ART.

Rifampicin and other rifamycins induce P-glycoprotein and are therefore expected to decrease the absorption of tenofovir-AF [23]; tenofovir-AF is therefore not recommended.

8.1.3 References

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8.2 Hepatitis B and C virus co-infection

When to start ART?

Table 8.1. Summary recommendations for the treatment of hepatitis B and C co-infection

HBV requiring treatment*	HBV not requiring treatment	HCV with immediate plan to start HCV treatment*	HCV with no immediate plan to start HCV treatment
Start ART promptly (1A) (include tenofovir-DF and emtricitabine or tenofovir-AF and emtricitabine)	Start ART (1A) (include tenofovir-DF and emtricitabine or tenofovir-AF and emtricitabine)	Start ART before HCV treatment commenced (1C); acceptable to defer if CD4 cell count >500 cells/ μ L. Discuss with HIV and viral hepatitis specialist	Start ART (1A)

*See BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV 2013 [1] for indications to treat hepatitis B and C

8.2.2 Hepatitis B

8.2.2.1 When to start antiretroviral therapy in HBV co-infection

8.2.2.1.1 Recommendations

- We recommend individuals with HIV and hepatitis B virus (HBV) co-infection are treated with fully suppressive ART inclusive of anti-HBV active antivirals, regardless of CD4 cell count (1A).
- We recommend individuals with HIV and HBV co-infection who have an HBV-DNA \geq 2000 IU/mL and/or evidence of more than minimal fibrosis (Metavir \geq F2) are treated with fully suppressive ART inclusive of anti-HBV active antivirals promptly (1C).

8.2.2.1.2 Rationale.

Because of the negative effect of immune depletion on HBV disease progression, the availability of single drugs with high-level dual HBV and HIV antiviral activity, and the increased risk of liver-related deaths in individuals with CD4 cell counts \geq 500 cells/ μ L, co-infected individuals with active HBV disease (HBV viral load \geq 2000 IU/mL or Metavir F2 or above) and those with CD4 cell counts below 500 cells/ μ L should start ART inclusive of anti-HBV active antivirals without delay. Individuals with CD4 cell counts \geq 500 cells/ μ L and HBV DNA of \geq 2000 IU/mL, minimal or no evidence of liver inflammation or fibrosis, and a repeatedly normal ALT should start ART, regardless of CD4 cell count, when they are ready to do so. Anyone who chooses to defer treatment should be monitored not less than 6-monthly with HBV DNA and ALT and at least annually for evidence of fibrosis.

For more information on starting treatment for HBV please refer to the BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV [1].

8.2.2.2 What to start in HBV co-infection

8.2.2.2.1 What to start recommendations

- We recommend **tenofovir-DF/emtricitabine** or **tenofovir-AF/emtricitabine** as part of a fully suppressive ART combination should be given to all individuals starting HIV treatment (1C).
- In the absence of renal or bone disease or significant predisposing risk factors for their development, **tenofovir-DF** can be used unless otherwise contraindicated (1C)
- We recommend patients with established renal disease with a creatinine clearance ≥ 30 ml/min or osteoporosis or significant predisposing factors for their development should be given **tenofovir-AF** (1D)
- We recommend **lamivudine/emtricitabine** may be omitted from the ART regimen and **tenofovir-DF** or **tenofovir-AF** be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of **lamivudine/emtricitabine-resistant HBV** or HIV (1D).
- We recommend neither **lamivudine** nor **emtricitabine** be used as the sole active drug against HBV in ART due to the rapid emergence of HBV resistant to these agents (1B).
- We recommend **lamivudine/emtricitabine** may be omitted from the ART regimen and **tenofovir-DF** or **tenofovir-AF** be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of **lamivudine/emtricitabine-resistant HBV** or HIV (1D).

8.2.2.2.2 Rationale.

Tenofovir-DF, **tenofovir-AF**, **emtricitabine** and **lamivudine** are agents that have good antiviral activity against both HIV and HBV. They are recommended agents in these guidelines for the treatment of HIV-1 infection. The efficacy of **tenofovir-DF and lamivudine** against HBV have been assessed in randomised trials extending out to 5 years in mono-infected patients [1].

All HBV co-infected individuals should commence a regimen containing **tenofovir-DF** or **tenofovir-AF** and **emtricitabine**. Hepatitis B treatment options for patients declining ART are discussed elsewhere [1].

In the presence of established renal or bone disease or where there are significant factors for their development (e.g., diabetes mellitus, hypertension) and when the creatinine clearance is ≥ 30 ml/min, or where an individual has become intolerant or developed toxicity to **tenofovir-DF**, then **tenofovir-AF** should be used in preference to **entecavir**. **Entecavir** demonstrates modest anti-HIV activity and can select for HIV resistance and should only be used in addition to a fully suppressive combination ART regimen. No individual co-infected with HBV should receive a regimen containing **lamivudine** or **emtricitabine** monotherapy as its use may result in the selection of the YMDD mutation. **Tenofovir** resistance has not been clearly described and resistance is unlikely to provide an explanation for most cases of suboptimal responses. In combination with **emtricitabine**, **tenofovir-DF and tenofovir-AF** have been demonstrated to be effective at suppressing HBV DNA, inducing HBeAg seroconversion, and reducing the risk of HBV breakthrough [1]

Where there is primary non-response or partial response to HBV-active antivirals, or where there is virological breakthrough, assessment of drug adherence and HBV resistance testing should be undertaken. Co-infected individuals who need to start a new ART regimen for reasons such as ART virological failure should ensure that effective anti-HBV therapy is continued in addition to their new ART regimen. Abrupt withdrawal of effective treatment may lead to a flare in HBV replication with liver damage. This may be particularly severe in patients with cirrhosis.

8.2.3 Hepatitis C

8.2.3.1 When to start antiretroviral therapy in HCV co-infection

8.2.3.1.1 Recommendations

- We recommend all individuals with HIV and hepatitis C virus (HCV) co-infection be assessed for HCV treatment (GPP).
- We recommend commencing ART regardless of CD4 cell count (1A).
- We recommend HCV be considered an additional factor supporting ART in individuals with CD4 >500 cells/ μ L who are uncertain about commencing ART (2C).
- We suggest treating HCV before commencing ART is an option if there are concerns about drug–drug interactions or adherence (GPP).

8.2.3.1.2 Rationale

HIV has an impact on HCV infection. Individuals with HCV co-infection have higher HCV viral loads, faster rates of fibrosis progression and an increased risk of cirrhosis compared to those with HCV alone. End-stage liver disease, hepatocellular carcinoma (HCC) and liver-related death occur more frequently, at an earlier age, and within a shorter time period with the risk of liver-related mortality and HCC increasing as the CD4 cell count declines. The efficacy of pegylated interferon (PEG-IFN) lessens as the CD4 cell count declines (PEG-IFN-free regimens seem to not be affected by HIV markers) and although ART slows the progression of liver disease it is still likely to be faster than in HCV mono-infection.

For these reasons, individuals with HIV and HCV infection with CD4 cell counts \geq 500 cells/ μ L should start ART; this should be immediate irrespective of whether HCV treatment is planned or not. For those with CD4 cell counts between 350 and 500 cells/ μ L, initiation of anti-HCV treatment should be delayed until after start of ART unless there is an urgent indication for anti-HCV treatment when ART should be commenced as soon as the patient has been stabilised on HCV therapy.

Individuals with a CD4 cell count greater than 500 cells/ μ L who defer HCV therapy should be given the option to commence ART. If they opt to defer, they should be monitored closely for HIV or hepatitis C disease progression, including at least an annual assessment of liver fibrosis.

8.3.2.2 What to start in HCV co-infection

8.3.2.2.1 Recommendations

- We recommend if individuals are commencing ART, and direct-acting antivirals are not being considered, standard first-line ART should be commenced (GPP).
- We recommend that when direct-acting antivirals are to be used, there is careful consideration of possible drug–drug interactions (1C) and current or archived HIV resistance. All drug interactions should be checked with an expert source (e.g. www.hiv-druginteractions.org).
- We suggest that if abacavir is to be used with ribavirin, the ribavirin should be weight-based dose-adjusted (2C).

8.2.4 References

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8.3 HIV-related cancers

Please see the BHIVA guidelines for HIV-associated malignancies 2014 [1] for further details (www.bhiva.org/malignancy-guidelines.aspx).

8.3.1 When to start ART?

8.3.1.1 AIDS-defining malignancies

Kaposi sarcoma, high-grade B-cell non-Hodgkin lymphoma and invasive cervical cancer are all AIDS-defining illnesses and are thus indications to commence ART regardless of CD4 cell count or HIV viral load.

- We recommend that all patients with AIDS-defining malignancies should start ART promptly (1B).

8.3.1.1.1 Kaposi sarcoma (KS)

- We recommend that ART should be started promptly in all individuals diagnosed with KS (1B).

8.3.1.1.2 Non-Hodgkin lymphoma (NHL)

- We recommend that chemotherapy regimens should be combined with ART therapy in Burkitt lymphoma and diffuse large B-cell lymphoma (1B).
- We recommend that all individuals with primary effusion lymphoma (PEL), plasmablastic lymphoma and primary central nervous system lymphoma should be started on ART if not already on it (1C).

8.3.1.1.3 Cervical cancer

Women with HIV and cervical intra-epithelial neoplasia (CIN) 2/3 treated by excisional procedures have a significantly higher treatment failure rate than HIV-negative women. A number of studies show such relapse is less frequent in the presence of ART, higher CD4 cell counts or undetectable viral load.

- We suggest that women with CIN2/3 should commence ART promptly (2B).
- We recommend that all women living with HIV who are to be treated with chemo-radiotherapy (CRT) for cervical cancer should start ART promptly (1C).

8.3.1.2 Non-AIDS-defining malignancies

8.3.1.2.1 Anal cancer

- We recommend that all PLWH who are to be treated with chemo-radiotherapy should start ART (1C).

8.3.1.2.2 Hodgkin lymphoma

- We recommend all PLWH and Hodgkin lymphoma should receive ART during chemotherapy (1A).

8.3.1.2.3 Other non-AIDS-defining cancers

- We suggest all PLWH who require chemotherapy or radical radiotherapy should receive concomitant ART unless contraindicated (level of evidence 2C).

8.3.2 What to start

- We recommend that all potential interactions between ART, opportunistic infection prophylaxis and cancer therapy should be considered (1C).
- We suggest that all individuals with non-AIDS-defining malignancies who are due to start chemotherapy or radiotherapy should be started on ART unless contraindicated (2C).

8.3.3 Opportunistic infection prophylaxis in HIV-associated malignancy

- We recommend that all individuals with AIDS-defining malignancies should start ART immediately (1B).
- We suggest that all individuals with non-AIDS-defining malignancies who are due to start chemotherapy or radiotherapy should be started on ART immediately unless contraindicated (2C).
- We recommend that individuals with antibodies against hepatitis B core antigen (HBcAb) should be treated with prophylactic antivirals in line with BHIVA hepatitis guidelines (1B).

8.3.4 Other considerations from the BHIVA guidelines for HIV-associated malignancies [1]

- We recommend that potential pharmacokinetic interactions between antiretrovirals and systemic anticancer therapy are checked prior to administration (with tools such as: www.hiv-druginteractions.org) (1C).

Significant pharmacokinetic and pharmacodynamic interactions have been reported between antiretroviral drugs and systemic anticancer therapies. The mechanisms of the pharmacokinetic interactions include the inhibition and induction by antiretroviral agents of enzymes, especially the cytochrome P450 family and UGT (uridine diphospho-glucuronosyl transferase) isoenzymes, involved in the catabolism and activation of cytotoxic chemotherapy agents. In addition, competition for renal clearance, intracellular phosphorylation and abacavir (ATP binding cassette) transporters, has been hypothesised to contribute to these drug interactions [2]. Similarly, pharmacodynamic interactions, in particular overlapping toxicities between antiretrovirals and systemic anticancer therapy suggest that some drug combinations should be avoided in patients with HIV associated cancers. Much of the guidance on the use of individual antiretroviral agents with systemic anticancer therapy comes from reviews of potential drug interactions rather than from clinical studies [2–4]. The pharmacokinetic interactions between antiretrovirals and systemic anticancer therapy are not confined to cytotoxic chemotherapy agents and extensive interactions with newer targeted therapies such as imatinib, erlotinib, sorafanib, bortezomib and temsirolimus have been described [4].

- We suggest avoiding ritonavir (or cobicistat)-boosted ART in HIV-positive individuals who are to receive cytotoxic chemotherapy agents that are metabolised by the CYP450 enzyme system (2C).

In general, clinically important pharmacokinetic drug interactions with systemic anticancer therapies are most common with ritonavir-boosted protease inhibitor-based ART and most clinicians avoid these combinations where possible. For example, in a cohort study, the rates of severe infections and severe neutropenia following chemotherapy for AIDS-related NHL were significantly higher amongst individuals receiving concomitant PI (mainly ritonavir boosted) than in those on NNRTI-based ART regimens, although there was no difference in survival between the groups [5]. Furthermore, case reports of clinically significant life-threatening interactions between ritonavir-boosted-based ART and docetaxel [6], irinotecan [7], vinblastine [8] have been published.

- We suggest avoiding atazanavir in HIV-positive individuals who are to receive irinotecan (2C).

The camptothecin cytotoxic agent, irinotecan, is extensively metabolised by UGT1A1 isoenzymes that are inhibited by atazanavir [9]. In people with Gilbert's syndrome, who have a congenital deficiency of UGT1A1, irinotecan administration has led to life-threatening toxicity [10].

- We suggest switching antiretroviral agents in HIV-positive patients who are to receive cytotoxic chemotherapy agents to avoid severe and/or overlapping toxicities (2C).
- Medicines reconciliation prior to chemotherapy to minimise potential pharmacokinetic interactions and overlapping toxicity should be undertaken by an experienced pharmacist (GPP).

Both antiretroviral agents and systemic anticancer therapies have substantial toxicity and where these overlap it is likely that the risk of toxicity is greater. For example zidovudine commonly causes myelosuppression and anaemia [11], which are also frequent side effects of cytotoxic chemotherapy and so these should not be co-prescribed where possible. Similarly, stavudine, didanosine and zalcitabine cause

peripheral neuropathy [12], a common toxicity of taxanes and vinca alkaloids, so co-prescribing should be avoided.

8.3.5 References

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8.4 HIV-associated neurocognitive impairment

8.4.1. Introduction

With the widespread use of effective combination antiretroviral therapy, the incidence of severe HIV-associated cerebral disease has declined dramatically [1]; however, more subtle forms of brain disease, known as HIV-associated neurocognitive (NC) disorders are reported to remain prevalent [2]. This NC deficit may present with a wide spectrum of clinical symptoms and typically includes patterns involving ineffective learning and difficulties in decision making or executive function, rather than pure difficulties in formulating new memory (the cortical defect typical of Alzheimer's disease [3]).

Given the changing picture of this disease, a research nomenclature system has proposed classifying subjects with abnormal neuropsychological testing results in to three categories based on symptoms, measured via the activities of daily living (ADL) scale [2]. Subjects with abnormal neuropsychiatric testing results, who are otherwise asymptomatic are classified as having HIV-associated asymptomatic neurocognitive impairment (ANI); those who are mildly symptomatic are classified as having HIV-associated mild neurocognitive disorder (MND); and those who are severely symptomatic are classified as having HIV-associated dementia (HAD). The clinical relevance of ANI, namely asymptomatic subjects with abnormal results on neuropsychological testing, remains unclear. Although the presence of ANI has been linked to progression of symptomatic cognitive impairment in one longitudinal study [4], the presence of other co-morbidities was also higher in individuals progressing to symptomatic cognitive impairment. These guidelines will focus only on symptomatic subjects.

Reports describing rates of NC impairment vary with some groups describing up to 50% of HIV-positive subjects meeting the above criteria [5]. However, such reports should be interpreted with caution as asymptomatic subjects are often included and not all reports correct for effective antiretroviral use. More selective cohorts including only aviraemic and symptomatic subjects suggest the prevalence of MND to be between 6 and 19% [6,7].

Risk factors for the development of NC disorders are poorly understood and are likely to be multifactorial including both HIV disease factors [8] and concomitant diseases [9]. Although it is possible that the choice of combination antiretroviral therapy subjects receive may influence NC function, this is a controversial area without definitive evidence. The following recommendations apply to individuals with symptomatic HIV-associated NC disorders.

8.4.2 When to start ART

8.4.2.1 Recommendation

- We recommend individuals with symptomatic HIV-associated neurocognitive disorders start ART immediately, irrespective of CD4 cell count (1C).

8.4.2.2 Rationale

Current evidence suggests NC function improves after commencing antiretroviral therapy for the first time [10] in both cognitively symptomatic [11] and asymptomatic [12] subjects. However, these studies have been undertaken in individuals with other indications to commence antiretroviral therapy, in general with CD4 cell counts <350 cells/ μ L. For subjects with higher CD4 cell counts, the ongoing neurology substudy in the START study will prospectively assess NC function in HIV-positive subjects commencing antiretroviral therapy at an earlier stage of HIV disease.

In the absence of scientific data, in cognitively symptomatic subjects with higher CD4 cell counts, a recommendation to commence antiretroviral therapy [13] is first based on the observed improvements in cognitive function reported in subjects with lower CD4 cell counts commencing therapy [10]; and secondly, in order to avoid a future decline in CD4 cell count in such subjects, given the well-described association between low nadir CD4 cell count and NC impairment [8].

Sub-optimal adherence to therapy may occur more frequently in subjects with NC impairment, hence adequate support services to optimise adherence are essential.

8.4.3 What to start with

8.4.3.1 Recommendations

- We recommend individuals with HIV-associated NC disorders start standard combination ART regimens (1C).
- We recommend avoiding efavirenz-containing regimens in individuals with HIV-associated NC disorders (1C).

8.4.3.2 Rationale

8.4.3.2.1 Including zidovudine in a regimen

Although during the earlier years of antiretroviral therapy, clear benefits on cerebral function of individual antiretroviral drugs such as zidovudine were reported [14] and the benefits of combination therapy overall described [10], data are sparse regarding any differences in these benefits between individual agents or combinations. Within cohort studies, the use of the NRTI class within antiretroviral regimens has been associated with a reduced risk of severe HAD [15] compared to the use of other regimens; however, the confounders of a cohort study limit the interpretation of these data.

The improvements in NC function observed with zidovudine monotherapy [14] and the greater improvements in NC function observed with a zidovudine-containing quadruple nucleoside regimen compared to other ART regimens [16], raise the possibility of selecting a zidovudine-containing antiretroviral regimen in subjects with NC impairment. Conversely, a lack of comparator data for zidovudine monotherapy, and potential toxicities arising from zidovudine use, may limit the relevance of these data. Of note, further to peripheral toxicities, which are well described with zidovudine use, biomarker data suggest there may also be central nervous system toxicities associated with the use of zidovudine-containing regimens [17].

8.4.3.2.2 Considerations regarding the CPE score

Recently, attempts have been made to establish a relationship between cognitive function and CNS antiretroviral drug delivery based on an antiretroviral scoring system known as the clinical penetration effectiveness (CPE) score [18]. The CPE score aims to rationally score the cerebral effects of individual antiretroviral agents. However the system is predominantly designed around pharmacokinetic modelling rather than pharmacodynamic endpoints such as data describing changes in NC function. Studies that have assessed the correlation between the CPE scores of antiretroviral regimens with NC function report conflicting findings with some cohorts reporting a positive association [19,20] while other cohorts describe a negative association [21,22]. In a small prospective study no differences in cognitive outcomes were observed in subjects randomised to higher CPE score-containing antiretroviral regimens compared to standard therapies [7]. Given these factors, the CPE score should not influence therapeutic decisions in subjects with NC impairment commencing antiretroviral therapy.

8.4.3.2.3 Considerations for not including efavirenz

Although early neuropsychiatric side effects are widely recognised and common with efavirenz therapy, recent reports have highlighted concerns regarding poorer NC function being associated with efavirenz-containing regimens. One cohort study has reported poorer cognitive function to be associated with current efavirenz use [23]. Two randomised controlled studies have assessed the cognitive effects of efavirenz. In one small study, improvements in cognitive function were poorer in those allocated efavirenz-containing therapy [16] and in a recent large study, the time to development of cognitive impairment was quicker in subjects allocated efavirenz-containing therapy [24]. Antiretroviral switch studies have reported

improvement in central nervous system symptomatology when modifying therapy to non-efavirenz-containing regimens [25,26]. Conversely, virological efficacy and low pill burden are key components of therapies for individuals with NC impairment. We therefore only recommend avoiding efavirenz-containing regimens in situations where other regimens with comparable virological efficacy and convenience can be initiated.

8.4.3.2.4 Novel antiretroviral strategies

Novel antiretroviral strategies, including protease-inhibitor monotherapy continue to be of interest given the potential for reduced long-term toxicities. Concerns have been raised regarding the cerebral effects of PI monotherapy [27], and dual therapies [28]. Such concerns are based on the hypotheses that novel strategies comprise only one or two effective antiretroviral agents that may not adequately suppress ongoing HIV replication in sanctuary sites such as the CNS and are based on pharmacokinetic modelling that suggests not all PIs have optimal penetration across the blood–brain barrier [18]. Furthermore, isolated cases describing the evolution of CNS disease in previously stable HIV-infected subjects receiving PI monotherapy have been reported [29].

One study was specifically designed to assess the cerebral effects of lopinavir/ritonavir monotherapy [30]. However, this study was terminated early due to a lack of efficacy in the plasma compartment. Although cases of CNS disease were reported within this study, such results must be interpreted with caution as virological endpoints in the plasma compartment were not met and therefore such cases may be driven by poor antiretroviral efficacy *per se*, rather than distinct CNS disease itself [31].

In the PIVOT study, the largest study of PI monotherapy to date, no differences in cognitive-function parameters were noted over 5 years of follow up in subjects randomised to continue standard therapy versus commence PI monotherapy [32]. Although reassuring, this study did not recruit neurologically symptomatic subjects and only enrolled subjects on antiretroviral therapy with undetectable viraemia.

Given the above theoretical concerns regarding the CNS activity of novel antiretroviral strategies, and for the majority of HIV-infected subjects it may be possible to select other antiretroviral regimens, we suggest this approach is currently avoided where possible in neurologically symptomatic subjects.

8.4.4 Continuing or worsening NC impairment despite ART

8.4.4.1 Recommendations

Best practice management should include (GPP):

- Reassessment for confounding conditions.
- Assessment of CSF HIV RNA and genotyping of CSF HIV RNA.
- In subjects with detectable CSF HIV RNA, modifications to antiretroviral therapy should be based on paired plasma and CSF genotypic results.

8.4.4.2 Rationale

Several randomised controlled studies, assessing both intensification of antiretroviral therapy with new antiretroviral agents [7,33] and with adjunctive therapies [34–37] have been published. Unfortunately, none of these studies describes improvements in cognition subsequent to the study interventions. Without evidence-based interventions, a best-practice approach based on the current literature is outlined.

As HIV-associated NC disorders are diagnoses of exclusion, re-evaluation of subjects with ongoing NC impairment despite antiretroviral therapy for confounding conditions, with expert input from other clinical specialties such as psychiatry, neurology and neuropsychology is recommended and, where possible, input from an HIV-neurology service. Given the presence of non-infectious co-morbidities reported to be a risk factor for NC impairment [9], such conditions should be optimally managed.

Assessment of CSF HIV RNA and genotypic analysis of CSF RNA may be useful tools in the management of subjects with ongoing NC for the following reasons: first, data from cohorts of untreated HIV-positive subjects would suggest CSF HIV RNA to be greater in subjects with HIV-associated dementia and cognitive decline [38–40] and therefore suppression of CSF HIV RNA may be beneficial for cognitive function. Secondly, in subjects with ongoing NC impairment, higher degrees of genetic diversity between HIV viral strains in the CSF and plasma compartment may exist [41], even in subjects with undetectable plasma HIV RNA [4,42]. Therefore, assessment for CSF HIV resistance is justified in order to tailor antiretroviral therapy.

Management should also involve consideration of any potential antiretroviral toxicities and side effects. For instance, a trial of switching from an efavirenz-containing regimen to an alternative may be considered along with any potential disadvantages of treatment modifications as outlined above.

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8.5 Chronic kidney disease

8.5.1 When to start antiretroviral therapy

8.5.1.1 Recommendations

- We recommend individuals with HIV-associated nephropathy (HIVAN) start ART immediately irrespective of CD4 cell count (1C).
- We recommend individuals with end-stage kidney disease who are suitable candidates for renal transplantation start ART immediately (1C).

8.5.1.2 Auditable outcome

- Proportion of individuals with HIVAN started on ART within 2 weeks of diagnosis of chronic kidney disease.

8.5.1.3 Rationale

HIV-associated nephropathy (HIVAN) is typically encountered in black individuals with advanced immunodeficiency and detectable HIV RNA levels [1-5]. The use of ART has been associated with a decline in the incidence of HIVAN in cohort studies [5], with renal histological improvement in case reports [6], and with (a trend towards) delayed progression to end-stage kidney disease in case series [2-4,7]. For those with HIVAN, ART is indicated and should be commenced as soon as possible. PLWH at risk of HIVAN: black individuals with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² and/or significant proteinuria (>500 – 1000 mg/24 h) should be referred to a nephrologist for a kidney biopsy. Those found to have HIVAN should be offered ART irrespective of CD4 cell count.

Immunodeficiency is a potent risk factor for chronic kidney disease (CKD) [8,9]. Although HIV replication is a risk factor for immune-complex kidney disease [2], and HIV replication, immune activation and inflammation may contribute to kidney disease progression [10,11], several antiretrovirals have been associated with eGFR decline [8,12]. There are currently insufficient data to suggest that HIV-positive individuals with, or at risk of CKD benefit specifically from earlier ART initiation.

Kidney transplantation is an attractive treatment modality for subjects with end-stage kidney disease. Excellent results have been achieved in those with suppressed HIV RNA levels and CD4 cell counts >200 cells/ μ L [13-15].

8.5.2 What to start

8.5.2.1 Recommendations

- We recommend against the use of ARV drugs that are potentially nephrotoxic in individuals with stages 3–5 CKD if acceptable alternative ARV agents are available (GPP).
- We recommend dose adjustment of renally cleared ARV drugs in individuals with reduced renal function (GPP).

8.5.2.2 Auditable outcomes

- Proportion of individuals with CKD stages 3–5 on ARVs who commence **tenofovir-DF** or atazanavir and a record of the rationale.
- Record in medical notes of calculated dose of renally cleared ARVs where eGFR <50 mL/min/1.73m².

8.5.2.3 Rationale

There are no data from randomised controlled trials to inform ART decisions in individuals with CKD. Observational data suggest that kidney function improves in those with impaired kidney function following initiation of ART [16,17]. Nonetheless, an eGFR <60 mL/min/1.73m² at baseline is a powerful predictor of kidney disease progression [18,19], and ART with nephrotoxic potential (tenofovir-DF [20-22] and atazanavir [22-24]) is probably best avoided in this population. Although lopinavir/r has also been associated with an increased risk of CKD in some cohorts [12,25], there are no reports of lopinavir/r-induced renal injury in HIV-positive patients.

In individuals with impaired renal function, specific ARV drugs (all NRTIs except abacavir) may need to be dose-adjusted [26] (see also Appendix 5 Considerations for antiretrovirals in renal impairment). Impaired survival has been reported with ART prescription errors in individuals undergoing dialysis [27]. While the Cockcroft–Gault formula has been most widely used in clinical practice to assess the need for dose reduction of renally cleared drugs in individuals with impaired renal function, recent data suggest that the eGFR (CKD-EPI equation) provides superior concordance with measured GFR in HIV-positive individuals and better performance in terms of correct dosing of tenofovir-DF and emtricitabine [28]. Hence, we recommend dose adjustment of renally cleared NRTIs in those with eGFR <50 mL/min/1.73m², and of maraviroc eGFR <80 mL/min/1.73m² if co-administered with ritonavir or cobicistat. For further information and advice, the reader should refer to the summary of product characteristics for each ARV.

8.5.3 Need to switch

8.5.3.1 Recommendations

- We recommend against continued use of tenofovir-DF and atazanavir in individuals with worsening renal function who have developed or are approaching CKD stages 3–5 if acceptable alternative ARV agents are available (GPP).

8.5.3.2 Auditable outcome

- Number of individuals with CKD stages 3–5 on ARVs who continue tenofovir-DF or atazanavir with eGFR <60 mL/min/1.73m² and a record of the rationale.

8.5.3.3 Rationale

The risk of CKD is increased with older age, reduced estimated glomerular filtration rate (eGFR), hypertension, diabetes and with exposure to tenofovir-DF [8,9,11,29,30], atazanavir [8,30] and lopinavir [8,12]. Tenofovir-DF has been associated with reductions in eGFR [8,12,29,30], accelerated decline in eGFR [9,31], acute renal failure [32], tubulo-interstitial nephritis [22], renal tubular dysfunction [33,34] and Fanconi syndrome [20,21]. Atazanavir has been associated with reductions in eGFR (when co-administered with tenofovir-DF) [35], nephrolithiasis and tubulo-interstitial nephritis [22-24,33,36,37]. To date, no cases of lopinavir-associated kidney injury have been reported [38]. Of note, several antiretroviral drugs, including rilpivirine, ritonavir, cobicistat, raltegravir and dolutegravir inhibit tubular creatinine excretion and thereby result in modest plasma creatinine elevations and corresponding reductions in eGFR. These changes in eGFR typically manifest within 2–4 weeks, are non-progressive thereafter, not associated with haematuria, proteinuria or glycosuria, and do not reflect clinically significant kidney injury [38].

The nephrotoxic potential of tenofovir-DF appears to be increased, and the reversibility of eGFR decline following tenofovir-DF discontinuation diminished, in those with eGFR <90 mL/min/1.73m² [9,26,27]. Similarly, the nephrotoxic potential of atazanavir may be increased among individuals with eGFR <60 mL/min/1.73m² [23]. As CKD is a risk factor for death, AIDS, and non-AIDS events including end-stage kidney disease and cardiovascular disease events [18,39,40], we recommend that the need for continued tenofovir-DF and atazanavir use is reviewed in individuals with worsening renal function who have developed or who are approaching CKD stages 3–5. Tenofovir-AF is the preferred formulation for those with (or at risk of) stage

3 CKD [41]; the renal safety of tenofovir-AF in patients with eGFR <30 mL/min/1.73m² has not been established. Preliminary data suggest that tenofovir-AF may also be an option for patients who developed tubulopathy whilst receiving tenofovir-DF (or adefovir) [42,43] although further safety data are required before such a strategy can be recommended in clinical practice.

8.5.4 References

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8.6 Cardiovascular disease

8.6.1 Introduction

Cardiovascular disease (CVD) is a significant contributor to the excess risk of non-AIDS disease and death in HIV-positive populations [1–12] but there are encouraging recent data that rates of ischaemic stroke [10] CVD-related deaths may be falling over time [13].

The heightened risk of CVD has been attributed to intersecting epidemics of smoking and inactivity, an ageing HIV-positive cohort, increased prevalence of surrogate markers of CVD (such as dyslipidaemia), HIV viraemia, immune dysfunction and the pro-inflammatory state associated with HIV infection. HIV-related factors may be only partially mitigated by ART and may be exacerbated by effects not fully explained by conventional CVD risk factors. Therefore it would be wrong to presume that interventions proven to reduce CVD risk in the general population will have the same magnitude of effect in HIV-positive individuals [14].

8.6.2 Definition and assessment of cardiovascular disease risk

8.6.2.1 Recommendation

- We suggest that the coronary heart disease (CHD) risk of HIV-positive adults of white ethnicity is estimated as per the BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-infected individuals (www.bhiva.org/monitoring-guidelines.aspx) (2C).

8.6.2.2 Rationale

For the purposes of these guidelines, individuals with an elevated CVD risk are those with established atherosclerotic CVD; diabetes mellitus type 1 over the age of 40 years; an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² and/ or albuminuria; familial hypercholesterolaemia; a high calculated CVD risk [15].

NICE recommends the QRISK2 calculator for the English population [15] but this may not be appropriate for HIV-positive people. Myocardial infarction (MI) rates in HIV-positive people parallel those predicted by the Framingham risk equation [16] but in US males it underestimated risk of MI by 50% [9] while in D:A:D it appeared to overestimate risk in never smokers but underestimate it in women, diabetics and ex-smokers [17]. Although absolute risk of CVD is lower in HIV-positive women than men, the risk relative to HIV-negative women is significantly higher [6,18,19]. The D:A:D calculator more accurately predicted CHD risk among European/Australian HIV-positive populations, defining 5-year risk as low (<1%), moderate (1–5%), high (5–10%) and very high (>10%) risk of CHD over a 5-year period [18]. However, it has not been externally validated, it lacked power to predict risk beyond 5 years and was underpowered for women and those of non-white ethnicity [20]. There is no HIV-specific CVD risk calculator for those of non-white ethnicity; one approach might be to use the QRISK2 equation and apply a correction for HIV status of 1.6 [21] (2D).

Whether HCV co-infection is a CVD risk is unclear; with studies reporting a significant association for acute coronary events [22] and stroke [23], a non-significant trend for MI [23], or no association [24].

8.6.3 Issues related to antiretroviral therapy

Two randomised controlled trials have included CVD endpoints: SMART and START; although neither were powered specifically for a CVD endpoint. In the SMART trial, fewer major CVD events were observed in the viral suppression arm but the difference was not statistically significant [25]. In a *post hoc* analysis, neither viral load or CD4 cell count was significantly associated with CVD events [26]. In START, rates of CVD events were similar in both arms; but this was a young population with a low CVD risk (median 10-year Framingham risk 1.9%) [27]. START does not answer the question of whether HAART affects CVD incidence in those at high CVD risk.

A meta-analysis showed an increased risk of CVD events in those on ARVs compared to treatment-naïve individuals, but the source studies pre-dated currently available PIs [21]. Several observational studies have examined changes in rate of cardiovascular events in HIV-positive populations but there are no clear protective effects for those on ART, those with a nadir or current CD4 cell count >350 cells/μL or suppressed viraemia (Table 8.1).

Carotid intima-media thickness (cIMT) may be increased in HIV-positive adults [28–30] although this has not been a consistent finding [31]. Non-calcified coronary arterial plaques were more prevalent on CT in HIV-positive participants in the MACS cohort than among controls and severe coronary arterial stenosis was associated with lower nadir CD4 cell count and longer duration of ART, but not current viral load or CD4 cell count [32].

8.6.4 What to start

8.6.4.1 Recommendations

In individuals with a high CVD risk:

- We recommend use of alternatives to fosamprenavir/r (1C) and lopinavir/r (1C)
- We suggest that atazanavir/r is the preferred PI (2C).
- We suggest avoiding abacavir (2C) and maraviroc if an acceptable alternative is available.
- First-line ARV therapy with **tenofovir-DF** plus (emtricitabine or lamivudine) with dolutegravir or raltegravir or rilpivirine (if viral load <100,000 copies/mL) are preferred first line regimens (GPP).
- Adverse effects on lipid parameters should be considered when selecting ARVs (GPP).

8.6.4.2 Rationale

No randomised controlled trial has been powered for the CVD risk associated with the use of individual ARVs and a history of CVD may be an exclusion criterion. A systematic review found a harmful association with recent PI exposure and cumulative increased risk per year of exposure to lopinavir/r and indinavir [33]. Early studies of PI exposure and risk of MI gave conflicting results, some reporting an increased risk [3,34] while others did not [2,35,36]. The D:A:D cohort, with longer follow-up, reported an increasing risk of MI with years of PI exposure (independent of measured metabolic effects) [37]. Cumulative exposure to indinavir and lopinavir/r were associated with increasing risk of MI [38]. Case-control studies reported similar associations for PIs [39], lopinavir/r [8,40] and fosamprenavir/r [40] although not all controlled for established risk factors [8]. Others found no association between PI use and cerebrovascular events [10,11]. No association has been reported between use of atazanavir/r and risk of MI [41] but there were insufficient data to include darunavir/r in this analysis. Preliminary data showed slower progression of cIMT in subjects on atazanavir/r versus darunavir/r (raltegravir was intermediate) [42] but whether this equates to a reduction in CVD risk is unclear.

Four papers analysing pooled data from clinical trials of abacavir [43–45] found no excess risk of MI for abacavir, but there was significant overlap in the source trials for these analyses. In contrast a *post hoc* analysis of the SMART study did find an increased risk (although use of abacavir was not randomised) [46]. A systematic review of CVD events associated with ARVs did find a harmful association with recent abacavir exposure [33]. Two cohorts found a strong association between recent abacavir use and MI [38,47,48] while others did not [49–51]; all were limited in their ability to adjust for presence of CVD risk factors. One case-control study, which did not adjust for important CVD risk factors, did find an elevated risk of MI associated with abacavir use [8] but others did not [38,52]. Cerebrovascular events were more common in individuals exposed to abacavir in two cohort studies [11,51] while another found a protective effect [49]. These divergent findings may be explained by unmeasured confounding, detectable viraemia (in studies of people commencing ARVs), younger participants in trials than in cohorts, lack of power in trials due to smaller number of MI events and differences in case ascertainment [14,53]. In view of the uncertainty about the

safety of abacavir in individuals with a high CVD risk, we suggest the use of alternative agents where possible. There are currently no data on the impact of tenofovir-AF on CVD events nor, beyond lipids, surrogate markers of CVD risk. While there is insufficient evidence to recommend avoiding tenofovir-AF we do suggest tenofovir-DF/emtricitabine should be the first choice NRTI backbone for individuals with CVD or at high risk of CVD.

In the MOTIVATE studies for treatment-experienced individuals, coronary artery disease events were only reported in the maraviroc arm (11 in 609 patient years versus 0 in 111 patient years in controls). No such signal was found in the MERIT study for treatment-naïve individuals. Maraviroc has also been associated with postural hypotension when used at higher than recommended doses in healthy volunteers; people with a history of postural hypotension, renal impairment or taking antihypertensive agents may be at increased risk [54]. In view of the limited data available, caution should be exercised in the use of maraviroc in individuals with a high CVD risk and use of alternative agents, where possible, considered.

For those with a high CVD risk, the newer agents dolutegravir, raltegravir and rilpivirine offer advantages including their lack of effect on plasma lipids (Table 8.2) and absence of interactions with statins. However, as yet, there is insufficient experience in their use to exclude an unexpected adverse CVD risk.

The effects on plasma lipids reported in randomised controlled trials of first line antiretrovirals are shown in Table 8.2. The studies were not usually powered for these comparisons and it is not possible to make cross-study comparisons as they differed in their populations, baseline lipids and length of follow up. Low high-density lipoprotein (HDL) cholesterol is a common finding in untreated HIV infection and may persist on ART [55]. Several studies report increases in both total and HDL cholesterol and no effect on total cholesterol (TC)/HDL ratio. However, HDL rises due to ARVs may not have the same cardioprotective effect as untreated HDLs as they may be larger, less stable and bind less readily to hepatocyte receptors relative to HIV-negative normolipaemic subject [56]. Moreover other pharmacological interventions to increase HDL in HIV-negative individuals on statins have failed to reduce CVD risk [57]. Therefore, favourable changes in HDL on treatment should be interpreted cautiously.

8.6.5 Modification of CVD risk factors

8.6.5.1 Recommendations

In patients with a high CVD risk:

- We recommend that traditional modifiable risk factors should be minimised; smoking cessation is of critical importance (1A).
- We suggest that this should include switching ARVs to those with a more favourable metabolic profile but only where there is minimal risk of treatment failure (2C).

8.6.5.2 Rationale

There is no clinical trial evidence that interventions to modify plasma lipids will reduce CVD risk in the context of HIV disease. However, there is good evidence from the general population that reducing total and LDL cholesterol reduces CVD risk. Switching ARVs in order to contribute to this reduction may therefore be beneficial. Switch studies that have reported lipid outcomes are shown in Table 8.3 and the same caveats apply as to Table 8.2 (above). In addition, the data are expressed in terms of the mean; whether the effect size differed in those with the most adverse lipid profiles is not reported. A switch should only be considered if the risk of treatment failure is minimal.

Table 8.1. Summary of observational studies reporting CVD risk independently associated with low CD4 cell count (cells/ μ L), elevated plasma viral load (copies/mL) or ARV exposure.

Type of study	Year	Outcome	First CD4 cell count (cells/ μ L)	Nadir CD4 (cells/ μ L)	Recent CD4 cell count (cells/ μ L)	First viral load (copies/mL)	Current VL (copies/mL)	ARVs	Ref
Co	1993–2001	Composite ⁶	—	—	—	—	—	↔	[35]
Co	1999–2002	MI	No	No	—	No	—	↑	[58]
Co	1997–2003	Death	—	—	—	—	—	↑	[59]
Co	1996–2004	Death	—	—	—	—	—	↓	[60]
Co	2000–2004	Admission / death	—	—	No	—	—	↔	[61]
CC	2000–2006	MI	—	Yes ⁵	No ⁵	—	Yes ⁵	—	[39]
Co	1998–2008	MI	—	No	<200	No	No	↔	[62]
RCT	2000–2008	Composite ¹	—	—	No	—	—	—	[63]
Co	2000–2008	MI or Composite ⁴	—	—	No	—	No	—	[17]
Co	2002–2009	Composite ⁷	<350	No	—	No	—	↔	[64]
CC	2002–2009	Composite ⁷	No	No	<350 & 350-500	No	—	↔	[64]
Co	2003–2009	MI	No	—	<200	No	>500	—	[9]
Co	2003–2010	Composite ²	—	—	No	—	Prolonged rebound >400	—	[65]
Co	1996–2011	Ischaemic stroke	No	No	<200	—	No	No effect	[10]
Co	1996–2011	MI	—	<200 & 200- 500 ³	No	—	No	No effect	[66]

Co: cohort study; CC: case-control study; RCT: randomised controlled trial

¹ MI, stroke, and invasive coronary procedures

² MI, stroke, and invasive coronary procedures, other fatal heart/vascular events and sudden death

³ Relative to HIV-negative population; the risk for 350–500 cells was not reported

⁴ MI, stroke, and invasive coronary procedures, other fatal heart/vascular events, sudden death and carotid endarterectomy

⁵ Lower nadir increased risk on univariate analysis only

⁶ Admissions with MI, angina, stroke, subarachnoid haemorrhage, transient cerebral ischaemia, invasive coronary procedures, other fatal cardiovascular events

⁷ MI, stroke, coronary artery disease, angina and peripheral arterial disease

Table 8.2. Increases in plasma lipids in randomised controlled trials of first-line antiretroviral exposure. Where a significant difference was reported, the mean is shown in mmol/L.

Class	Drug	Versus	TC	LDL	HDL	TC/HDL	TGs	Ref
NRTIs	ABC/3TC	TDF/FTC	0.88 vs. 0.49	0.44 vs. 0.16	0.31 vs. 0.23	NS	NS	[67]
NNRTIs	EFV 600mg	EFV 400mg	NS	NS	NS	—	NS	[68]
	NVP	EFV	NS	NS	0.3 vs. 0.2	3.7 vs. 4.2	0.0 vs. 0.2	[69]
	RPV	Baseline	NS	NS	—	NS	NS	[70]
	RPV	EFV	0.03 vs. 0.63	-0.04 vs. 0.31	0.07 vs. 0.24	NS	-0.01 vs. 0.16	[70]
	ETV	EFV	0.4 vs. 1.0	0.2 vs. 0.6	0.1 vs. 0.3	NS	—	[71]
PIs	ATV/r	EFV	0.25 vs. 0.49	0.18 vs. 0.54	0.10 vs. 0.2	-0.1 vs. 0.3	NS	[72]
	ATV/r	NVP	0.51 vs. 0.63	0.27 vs. 0.39	0.10 vs. 0.25	0.13 vs. -0.24	0.31 vs. 0.00	[73]
	ATV/r	RAL	ATV/r 0.31 higher	ATV/r 0.18 higher	NS	—	ATV/r 0.32 higher	[74]
	DRV/r	ATV/r	NS	NS	NS	—	NS	[74]
	DRV/r	RAL	DRV/r 0.28 higher	DRV/r 0.18 higher	NS	—	DRV/r 0.27 higher	[74]
	LPV/r	ATV/r	0.93 vs. 0.52	NS	NS	—	0.62 vs. 0.16	[75]
INI	RAL	Baseline	NS	NS	NS		NS	[76]
	RAL	Baseline	NS	NS	0.16		NS	[74]
	RAL	EFV	0.26 vs. 0.85	0.15 vs. 0.42	0.11 vs. 0.26	NS	-0.03 vs. 0.42	[77]
	ELV/c	EFV	0.41 vs. 0.52	0.31 vs. 0.47	0.16 vs. 0.23	NS	NS	[78]
	ELV/c	ATV/r	NS	NS	NS	NS	NS	[79]
	DTG	Baseline	NS	NS	NS	NS	NS	[76]
CCR5	MVC	EFV	0.05 vs. 0.93	-0.23 vs. 0.54	0.18 vs. 0.35	—	-0.10 v 0.24	[80]

NS: difference not statistically significant; ABC/3TC: abacavir/lamivudine; ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; ELV/c: elvitegravir/cobicistat; ETV: etravirine; LPV/r: lopinavir/ritonavir; MVC: maraviroc; NVP: nevirapine; RAL: raltegravir; RPV: rilpivirine; TDF/FTC: **tenofovir-DF**/emtricitabine

Table 8.3. Changes in plasma lipids reported in trials of switching antiretrovirals. Where a significant difference was reported, the mean is shown in mmol/L.

Class	Drug	TC	LDL	HDL	TC/HDL	TGs	Ref
NRTIs	Kivexa to Truvada ¹	-0.47	-0.23	NS	NS	NS	[81]
NNRTIs	EFV to RAL	-0.36	NS	NS	—	NS	[82]
	EFV to ELV/c	-0.21	-0.20	NS	NS	NS	[83]
	EFV to NVP	NS	-0.34	NS	—	NS	[84]
	EFV to RPV	-0.44	-0.21	NS	NS	-0.29	[85]
	PI/r+2NRTI to RPV/TDF/FTC	-0.62	-0.41	-0.07	-0.35	-0.63	[86]
	EFV to ETV	-0.64	-0.58	NS	NR	NS	[87]
PIs	ATV/r to ATV ²	-0.34	NS	NS	-0.24	-0.36	[88]
	ATV/r to RAL	NS	—	—	—	NS	[89]
	LPV/r to ATV/r	-0.39	NS	NS	—	-0.55	[90]
	LPV/r to RAL	-0.44	—	—	—	-0.49	[89]
	LPV/r to RAL ³	-0.8	NS	—	—	-0.90	[91]
	ATV/r to ELV/c	NS	NS	NS	NS	-0.42	[92]
	DRV/r to ELV/c	NS	NS	NS	NS	NS	[92]

NS: difference not statistically significant; ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; EFV: efavirenz; ELV/c: elvitegravir/cobicistat; ETV: etravirine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; RAL: raltegravir; RPV: rilpivirine; RPV/TDF/FTC: rilpivirine/tenofovir-DF/emtricitabine

¹ With PI/r; ² Atazanavir plus abacavir/lamivudine backbone; ³ Powered for a change in lipids

8.6.6 References

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8.7 Women

8.7.1 Introduction

The following guidance considers issues concerning the initiation and choice of ART for HIV-positive women who are not currently pregnant. For guidance on the management of pregnancy in HIV-positive woman please refer to the BHIVA guidelines for the management of HIV infection in pregnant women [1].

There are few specific data on ART treatment in women other than in pregnancy. Data available are largely from a meta-analysis, *post hoc* analyses or derived from cohort studies. The majority of the randomised clinical trial data on ART comes from studies that have enrolled mostly male subjects. If randomised controlled trials do enrol women, the numbers are often too small to draw significant gender-based conclusions.

Approximately one-third of people diagnosed with, and accessing care, for HIV in the UK are women [2]. The majority are of childbearing age but the age range is increasing, adding the complexity of menopause and its sequelae to the management of HIV-positive women. Many HIV-positive women in the UK are of African heritage and face overlapping challenges to their health and well being [3].

Women's experience of HIV reflects multiple social and cultural influences, which when combined with sex-specific biological factors influence individual responses to HIV.

8.7.2 When to start

8.7.2.1 Recommendations

- We recommend therapy-naïve HIV-positive women who are not pregnant start ART (see Section 4) (1A).

8.7.2.2 Auditable measure

- Proportion of HIV-positive women not on ART.

8.7.2.3 Rationale

Gender differences in HIV viral load and CD4 cell count at different stages of infection have been observed [4] but have not been consistently associated with long-term clinical outcomes for HIV-positive women. Based on current data, the indications for starting ART do not differ between non-pregnant women and men.

Gender-specific socio-economic and cultural factors may impact on women's ability to access care and manage their medication, compromising their ability to initiate and adhere to therapy, necessitating support from the multidisciplinary team.

8.7.3 What to start

8.7.3.1 Recommendations

- There are insufficient data to support specific recommendations for HIV-positive non-pregnant women. We therefore recommend therapy-naïve HIV-positive women start ART as per general guidelines (1A).
- We recommend both HIV-positive women of childbearing potential and healthcare professionals who prescribe ART are conversant with the benefits and risks of ARV agents for both the health of the HIV-positive woman and for that of an unborn child (GPP).
- We recommend that potential pharmacokinetic interactions between ARVs, hormonal contraceptive agents and hormone replacement therapy are checked before administration (GPP).

8.7.3.2 Rationale

8.7.3.2.1 Efficacy

There are few data to guide prescribing of initial ART specifically for women as no randomised controlled trial in PLWH starting ART has been powered to detect gender-based differences in efficacy. From the limited data available, virological outcomes within clinical trial settings generally appear to be no different between men and women.

WAVES is a women-only randomised controlled trial that demonstrated superiority of Stribild over Truvada + atazanavir/ritonavir; this was driven predominantly by more adverse event discontinuations in the atazanavir arm [5].

A meta-analysis of FDA registrational randomised controlled trials analysed data from 20,328 HIV-positive individuals participating in 40 trials for 16 ARVs. Overall, 20% of study participants were women and there were no clinically or statistically significant differences in week 48 virological outcomes between men and women [6].

A subanalysis of a randomised controlled trial comparing atazanavir/r and lopinavir/r in ART-naïve individuals of whom 31% were women, showed comparable virological efficacy at week 96 between the two treatment arms in women [7], although virological response rates were lower in women when compared with men.

In a study comparing atazanavir/r and efavirenz in 1857 ART-naïve individuals of whom 17% were women, female gender was associated with increased virological failure on atazanavir/r compared with efavirenz [8]. No difference was seen with efavirenz between men and women.

The efficacy and tolerability of raltegravir were similar in men and women at 48 weeks in one cohort of treatment-naïve and -experienced individuals [9]. First-line rilpivirine-based ART showed no difference in rates of virological suppression at 48 and 96 weeks between men and women, but the number of women included was low and the study was not designed to investigate gender differences [10,11].

Cohort studies in the UK have reported similar virological outcomes during the first year of treatment in heterosexual men and women [12]. An Italian cohort study reported no significant effect of gender on clinical progression or the risk of developing a clinical event [13]. Data from Spain, which included both naïve and ARV-experienced women, showed them with similar virological responses to men [14].

HIV-positive women starting ART should use ARVs from the list of preferred and alternative drugs outlined in Section 5.1.

8.7.3.2.2 Toxicity, discontinuation and adherence.

Several studies have suggested that gender may influence the frequency, presentation and severity of selected ART-related adverse events. Although data are limited, evidence exists that pharmacokinetics for some ART drugs may differ between men and women because of factors such as body weight, plasma volume, plasma protein levels, cytochrome P450 activity and drug transporter function [15,16].

Adverse events and treatment discontinuations within ART clinical trials and cohort studies published between 2002 and 2007 have been systematically reviewed. The overall event rate is often the same but the adverse event profile may be different. Women were reported to be more likely than men to experience ART-related lipodystrophy, rash and nausea, and to discontinue therapy [4].

Data from the USA have shown that women are more likely than men to discontinue ART for poor adherence, dermatological symptoms, neurological reasons, constitutional symptoms and concurrent medical conditions [16]. UK cohort data found that 11.4% of men compared with 19.3% of women discontinued treatment in the first year of ART (adjusted relative hazard 0.72, 95% CI 0.63–0.83, $P=0.0001$) [12].

An randomised controlled trial of atazanavir/r versus lopinavir/r found worse virological outcomes in treatment-naïve women compared with men due to higher discontinuation rates in women in both treatment arms [7]. CNS side effects of varying severity can occur with efavirenz, particularly at the initiation

of therapy. This may be partly explained by the greater efavirenz exposure associated with a CYP2B6 variant, more commonly found in Africans and African Americans [17]. In the UK population, this is of particular relevance to women, the majority of whom are of African ethnicity. Nevirapine-associated rash occurs more frequently in women than men [18]. Hepatotoxicity associated with nevirapine is more common in women with a CD4 cell count >250 cells/ μ L, or elevated baseline transaminases, and restricts women's use of the drug [19].

Compared with HIV-positive men, women are more likely to experience an increase in central fat with ART [20]. Women have an increased risk of osteopenia/osteoporosis, especially after menopause, and this risk may be exacerbated by HIV and ART [21].

At present, these observed differences do not require women-specific recommendations.

A systematic review of studies on gender and ART adherence published between 2000 and 2011 in the resource-rich world concluded that overall reported adherence is lower in women than men [22]. However, of over 1000 studies initially identified for review, only 44 had adequate data on gender to allow any comparisons to be made. The authors identified the particular factors for lower adherence in women were depression, lack of supportive interpersonal relationships, young age, drug and alcohol use, black ethnicity, ART of six or more pills per day, higher numbers of children, self-perception of abdominal fat gain, sleep disturbances and increased levels of distress.

8.7.3.2.3 Fetal safety.

All women of child-bearing potential should be offered reproductive health counselling including advice around conception, prevention of mother-to-child transmission and contraception as a component of routine medical care [23].

Concerns about potential fetal toxicity of ARVs have influenced prescribing practice in HIV-positive women. Of note, other than zidovudine in the third trimester, no ARV drug has a licence for use in pregnancy.

Pregnancy in women living with HIV who are already on effective therapy is increasing; 80% of HIV-positive pregnant women in the UK in 2013 were diagnosed before the current pregnancy, of whom 60% were already on ART at conception [24]. Where newer drugs are available, women are conceiving on these agents, with zidovudine now rarely used as first-line therapy for adults. European cohort data comparing pregnancies that were managed with zidovudine-containing regimens vs. those without zidovudine found no difference in risk of detectable viral load at delivery, mother-to-child transmission or congenital abnormality when comparing zidovudine-sparing with zidovudine-containing ART [25].

The most robust data on teratogenicity and first trimester ART exposure are from the Antiretroviral Pregnancy Registry (APR) [26]. This international prospective reporting system records rates of congenital birth defects in babies born to women with exposure to ART at any stage of pregnancy. Approximately 200 or more reports need to be received for a particular compound before data are reported for that compound by the APR. There are now over 200 prospective reports in the APR of first trimester exposure for abacavir, atazanavir, darunavir, efavirenz, emtricitabine, lamivudine, lopinavir, nevirapine, ritonavir, **tenofovir-DF** and zidovudine. No signal of increased risk of congenital abnormality has been demonstrated, and a greater than twofold higher rate than in the general population has been excluded. There are, so far, fewer than 200 prospective reports for raltegravir and rilpivirine within the APR and hence reports on these agents are not yet available.

Despite previous concerns over the safety of efavirenz based on preclinical animal studies and retrospective case reports in human subjects, the current data do not provide evidence of excess teratogenicity above the expected baseline for infants exposed to efavirenz in the first trimester. Sufficient numbers of first-trimester exposures of efavirenz have been monitored to detect at least a twofold increase in risk of overall birth defects within the APR, and no such increases have been detected to date [26].

Data from Côte d'Ivoire found no significant increased risk of unfavourable pregnancy outcome in women with first-trimester exposure to efavirenz compared with nevirapine [27]. A systematic review and meta-analysis of observational cohorts carried out in 2010 [28] and further updated in 2014 [29] reported birth outcomes among women exposed to efavirenz during the first trimester. No increased risk of overall birth

defects among the babies of women exposed to efavirenz during the first trimester compared with exposure to other ARV drugs was found. The prevalence of overall birth defects with first-trimester efavirenz exposure was similar to the ranges reported in the general population.

A review of live births to women with HIV in a large unselected UK population between 1990 and 2007 found no increased risk of abnormalities in infants exposed to efavirenz in the first trimester, providing further reassurance that ART *in utero* does not pose a major risk of fetal anomaly [30]. Mathematical modelling using North American cohort data has demonstrated a theoretical loss of life expectancy in women who delay efavirenz at initiation of ARV [31].

Based on current evidence, efavirenz can be initiated in women of childbearing potential, can be continued in women who conceive on the drug and commenced in pregnancy but the data should be discussed in detail with the individual woman when deciding on her preferred treatment regimen. Given that no ARV drug is licensed for use in pregnancy apart from zidovudine in the third trimester, a discussion regarding the potential unknown long- and short-term effects on an unborn child should be had with any woman of childbearing potential who commences any ARV drug regimen. Further details can be found in the BHIVA pregnancy guidelines [1].

8.7.3.2.4 Hormone interactions.

Significant pharmacokinetic and pharmacodynamic interactions have been reported between ARV drugs and hormonal agents and these should be taken into consideration when selecting an ART regimen for women using hormonal contraception. We suggest prescribers refer to the summary of product characteristics for individual drugs, the University of Liverpool drug interaction website (www.hiv-interactions.org) or specialist pharmacy advice within their unit/network. Importantly, in addition to cases of contraceptive failure in women on efavirenz-based ART using a contraceptive implant [32], there are now pharmacokinetic data to show a significant reduction in levonorgestrel concentrations in women on efavirenz [33].

8.7.3.2.5 Menopause

As the average age of the female population living with HIV increases, more women with HIV reach menopause. The menopause raises a number of issues for women with HIV including menopausal symptoms and increased risk of co-morbidities such as cardiovascular disease and osteoporosis. Although data are limited, there is no evidence that menopause has a direct effect on ART efficacy. A subanalysis of responses to ART among a small number of treatment-naïve pre- and post-menopausal women in a US study found no significant differences in the immunological and virological responses between the two groups [34].

8.7.4 HIV-positive women experiencing virological failure

There is very little evidence to guide prescribing ART in HIV-positive women experiencing virological failure on ART, with most studies recruiting approximately 10% of women. One study investigating darunavir/r in ART-experienced individuals recruited a large proportion of women and was powered to show a difference in virological efficacy between men and women; this showed higher discontinuation rates among women than men, with nausea being cited as a particular problem, but overall there was no difference in virological efficacy [35]. A further study has reported similar efficacy and tolerability of raltegravir in ART-experienced HIV-positive women [9].

In HIV-positive women experiencing virological failure on ART, the same principles of management and recommendations apply as per HIV-positive men experiencing virological failure.

8.7.4.1 Psychosocial issues

Women living with HIV often have additional vulnerability factors (psychological and social) that can impact on access to and engagement with care and also adherence and treatment outcomes. Such factors include HIV-related stigma, low socio-economic status, culturally defined gender roles and high levels of intimate partner violence. There are higher levels of mental health problems, particularly depression and post-traumatic stress disorder, in women living with HIV compared with the general population, which can also

adversely affect outcomes. These issues need to be recognised and identified by healthcare professionals and effective interventions offered, in particular psychosocial and peer support

8.7.5 References

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8.8 Mental health

8.8.1 Recommendations

- **What to start:** we recommend that efavirenz-containing regimens be avoided in individuals with a current or past history of depression, psychosis, suicidal ideation or attempted suicide, or at risk of self-harm (1C).
- **Switching therapy:** we recommend that efavirenz-containing regimens should be switched promptly to a viable alternative when PLWH present with depression, psychosis, suicidal ideation or attempted suicide, or self-harm (1C).

8.8.2 Rationale

The summary of product characteristics for efavirenz cautions that ‘patients with a prior history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions’ with a 2% risk of both severe depression and suicidal ideation [1]. In view of this warning, studies exploring efavirenz and risk of depression or suicide are inevitably subject to confounding by indication because individuals most at risk will not have been prescribed efavirenz or entered into randomised controlled trials where one of the arms included efavirenz.

A meta-analysis of four ACTG randomised controlled trials with efavirenz in one arm included 5000 PLWH [2]. ‘Suicidality’ was defined as suicidal ideation or attempted or completed suicide. The incidence of suicidality was 8/1000 patient years (PY) on efavirenz versus 4/1000 PY without it (hazard ratio [HR] 2.3, $P=0.006$). Rates of attempted or completed suicide were 3 versus 1/1000 PY respectively (HR 2.6, $P=0.065$) (eight suicides on efavirenz versus one on comparator regimens). In a secondary analysis of time to suicidal ideation, attempted or completed suicide, or death attributed to substance abuse, homicide or accident (to capture possible under-reporting of suicide) rates were 9 and 5/1000 PY respectively (HR 2.06, $P=0.007$). Incidence of suicidality did not change over length of follow up indicating that risk could emerge at any time.

A number of studies has examined the CNS effects of switching away from efavirenz but did not detect an effect on mood. However, it should be noted that the event rates reported in the ACTG studies were low (<1/100 patient years) and hence the switch studies may have lacked power to detect an effect on mood.

A small Spanish cohort study found no association between depression or suicide attempts and efavirenz but the overall event rate was unusually low and the proportion of those with depression prescribed efavirenz was half that in the main cohort suggesting significant confounding by indication (i.e. less use of efavirenz where there was a concern about mental health) [3]. No association was found in the D:A:D cohort study between efavirenz use and suicide as a reported cause of death, possibly for similar confounding reasons [4].

A retrospective analysis performed by the manufacturer of the US Food and Drug Administration’s Adverse Event Reporting System (FAERS) (i.e. post-marketing surveillance data of spontaneous adverse-event reports from PLWH and healthcare workers) explored the ratio of observed to expected number of suicidality events (O/E ratio) for a variety of drugs [5]. Such data are inevitably subject to reporting biases that make them difficult to interpret. They concluded that there was no association between efavirenz exposure and suicidality because the O/E ratio did not exceed the arbitrarily predefined threshold of 2, while it did for other drugs with a known suicide risk (e.g. fluoxetine). Nevertheless, the O/E ratio for efavirenz was significantly higher than for other ARVs, which is consistent with an increased risk for this drug.

Completed suicide must rank among the most adverse possible effects of any treatment. Unfortunately, depression is under-recognised by PLWH and poorly elicited by healthcare workers [6]. The above data support a precautionary stance of avoiding efavirenz in those with a current or past history of depression or suicidality.

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8.9 Adolescents

Adolescents include all young people defined by WHO as those aged between 10 and 19 years, and young adults aged between 20 and 24 years [1]. For the purposes of these guidelines we will consider adolescents living with HIV by route of transmission: perinatally acquired HIV infection (PaHIV) and behaviourally infected HIV (BaHIV).

For behaviourally infected young people >18 years of age, the management of their HIV disease and associated considerations should be in accordance with BHIVA adult guidelines. The management of adolescents aged less than 16 years within paediatric care should be in accordance with Children's HIV Association (CHIVA) guidelines (<http://www.chiva.org.uk/professionals/health/guidelines/index.html>) and the Paediatric European Network for Treatment of AIDS (PENTA) treatment guidelines [2]. There are limited data and no randomised controlled trial data on long-term complications of PaHIV and ART exposure throughout physical maturity, and the following recommendations are based on pragmatic and good clinical practice.

8.9.1 Recommendations for management of HIV, ART and sexual and reproductive health specifically for perinatally acquired HIV

- Avoid standard-dose (600mg) efavirenz-based regimens in any young person <50kg, with any history of mental health or psychological or neurocognitive problems.

Young adults and adolescents (YAA) represent a uniquely vulnerable group who have poor health outcomes compared to younger children and older adults living with the same condition. This is a feature of lifestyle, adolescent behaviour, lack of engagement in health care services and primary care and often lack of social support. As such, any service providing care for YAA living with HIV must offer appropriate youth-centred services, with an open-door policy, non-judgemental care provision, and opening hours consistent with educational commitments.

8.9.2 UK Epidemiology for YAA with PaHIV

With antiretroviral therapy, the significant fall in HIV-associated morbidity and mortality for perinatally infected children has resulted in increasing numbers entering adolescence and transitioning towards adult services [3,4]. Over 90% of children diagnosed in the UK and reported to the National study of HIV and Pregnancy (NSHPC) are followed prospectively in the Collaborative HIV Paediatric Study (CHIPS; www.chipscohort.ac.uk). Data to the end of March 2014 shows that of 1873 children ever reported, 595 have already transferred to adult services, at a median age of transfer of 17 years [4].

8.9.3 Transition Process for YAA with PaHIV

Transfer to adult services had been associated with increased disease-related morbidity and mortality for a wide range of chronic conditions of childhood prompting the National Service Framework (NSF) 2004 to set standards for the healthcare of young people [5]. Subsequently the Department of Health (DH) has produced a wealth of resources to guide the development of transitional care services [6–8]. Transition is defined as 'A planned, purposeful, process resulting in the point of transfer to adult services'. While several different transition models are described, the key to a successful transition is communication, forward planning and maintaining a young person-centred approach [9,10]. HIV-specific transitional care guidance is available through CHIVA and set within the CHIVA Standards (www.chiva.org.uk) [10].

8.9.4 UK Epidemiology for YAA with BaHIV

Public Health England (PHE) surveillance data reveals 736/5,967 (12%) of new HIV diagnoses in 2013 were in young adults aged 15–24 years. Routes of transmission were: sex between men ($n=462$); heterosexual contact ($n=152$); and IVDU ($n=4$). Both the proportion and number of new HIV diagnoses among MSM aged

15–24 years have increased over the past decade, from 8.7% (250/2,420) in 2004 to 16% (460/2,950) in 2013 [11].

8.9.5 Neurocognitive impact of HIV in YAA

The neurocognitive impact of living with HIV on the developing adolescent brain is becoming increasingly apparent, with poorer school performance, increased psychiatric diagnoses and particular difficulties in executive functioning for PaHIV YAA [12–14]. Recent data suggest that more than two-thirds of treatment-naïve BaHIV YAA meet criteria for a diagnosis of HIV-associated neurocognitive disorders, with the most common deficits being in memory and fine motor skills [15]. Optimising virological control with further investigation and referral to expert neurology HIV clinics is recommended.

8.9.6 Antiretroviral therapy

8.9.6.1 Adherence

Poorer adherence to ART is reported with increasing age in childhood and in behaviourally infected young people when compared to older adults [16–18]. PHE data suggests that those aged 15–24 with a CD4 cell count <350 cells/μL are less likely than older adults to be on treatment and for those taking ART, YAA are less likely to achieve viral suppression when compared to older adults [11]. YAA initiating ART therefore require additional adherence support with specific guidance for this population available in the HIV Young Peoples Network Adherence Guidelines (www.hypnet.org.uk). We suggest starting with a robust regimen initially (once daily boosted PI plus two NRTIs) then switching to an NNRTI or integrase single fixed-dose combination for those who achieve virological suppression. PI-based regimens are now the recommended first-line therapy for adolescents in the 2014 PENTA guidelines [2].

8.9.6.2 Toxicity

At standard dose, increased efavirenz toxicity associated with higher plasma drug levels has been reported in adults of lower weight, a weight band that will include many YAA [19]. Additionally, reports of a potential increase in suicidal risk associated with efavirenz is of concern in an age group where suicide is the second most common cause of death in the UK, and is more than three times as common in males when compared to females [20]. Rates of suicide more than double in those aged 20–24 compared with those aged 15–19; suicide has been reported in PaHIV YAA in adult care [20,21].

Prolonged ART exposure resulting in lipodystrophy, at an age when body image is so important, may have a negative impact on psychological wellbeing and a potential impact on adherence to ART [22,23]. Growth stunting and delayed puberty in PaHIV YAA and dermatological conditions associated with HIV, such as scarring from shingles, molluscum contagiosum and seborrhoeic dermatitis may further exacerbate issues around body image and self worth. Multidisciplinary team assessment that includes dietetics, psychology and where appropriate, referral for cosmetic surgery is required.

8.9.6.3 Resistance

Within the UK paediatric cohort, half of the PaHIV adolescents are triple-class experienced and almost one-tenth of the young people who have ever started ART are off therapy due to poor adherence/refusal, with the risk of onward transmission of resistant virus to partners and offspring [22,24]. Decisions as to the optimal regimen for YAA require an individualised approach considering baseline resistance, predicted adherence, substance use and mental health.

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8.10 Bone disease and antiretroviral therapy

8.10.1 Introduction

HIV-1-positive individuals have lower bone mineral density (BMD) at the femoral neck, hip and lumbar spine. In a recent study, HIV was found to be an independent risk factor for low BMD [1]. Among HIV-positive individuals, 25–33% of those >40 years had osteopenia and 5–9% had osteoporosis [1]. Low BMD in HIV-positive individuals has been associated with traditional risk factors (i.e. older age, female gender, low BMI, smoking and glucocorticoids – including use as part of the treatment of *Pneumocystis jirovecii* pneumonia) and with HIV-specific factors (i.e. lower nadir CD4 cell count, longer duration of HIV infection and exposure to ART [2]). Similar rates of osteopenia and osteoporosis were observed in a small cohort ($n=33$) of men with primary HIV-1 infection [3] and men who have sex with men (MSM), irrespective of HIV status or use of amphetamines and other recreational drugs associated with an increased risk of low BMD [4,5]. Several studies have reported an increased rate of fracture of the spine, hip and wrist, with the most pronounced increase in older people living with HIV (>50–60 years) [6-8].

It is important that treatment decisions relative to co-morbidities such as low BMD are placed in context. PLWH may have several co-morbidities and each of these should be considered and weighted appropriately during the treatment-decision process. Furthermore, dual X-ray absorptiometry (DXA) is unable to distinguish low BMD due to osteoporosis from osteomalacia. Vitamin D and parathyroid hormone status should be evaluated and optimised in individuals with low BMD in whom ART or non-ART interventions are being considered.

8.10.2 When to start antiretroviral therapy

8.10.2.1 Recommendation

- We recommend that general recommendations for the timing of ART are followed in patients with, or at risk of osteoporosis (1D).

8.10.2.2 Rationale

Initiation of ART is associated with a reduction in BMD of 2–6%; bone loss is generally restricted to the first year with a relatively stable pattern thereafter [9,10]. Intermittent use of ART (as compared with continuous, uninterrupted ART) in the SMART study was associated with reduced bone loss during follow up [11]. There are no data to suggest that initiation of ART reduces the rate of bone loss or the risk of fracture [12]; general recommendations for the timing of ART should be followed in HIV populations with, or at risk of, osteoporosis.

8.10.3 What to start

8.10.3.1 Recommendations

- We recommend against the use of **tenofovir-DF** in individuals aged >40 years with osteoporosis, a history of fragility fracture, or a FRAX score consistent with high risk of a major osteoporotic fracture, if acceptable alternative ARV agents are available (1B).

8.10.3.2 Rationale

In clinical trials, ART-naïve individuals who initiated **tenofovir-DF**-containing regimens experienced greater reductions in BMD than those initiating **tenofovir-DF**-sparing regimens. For example, in the Gilead 903 study, observed reductions in lumbar spine and hip BMD at 144 weeks were 2.2% and 2.8% in the **tenofovir-DF** arm and 1.0% and 2.4% in the stavudine arm (each co-administered with lamivudine and efavirenz) [13]. In the ASSERT study, the reduction in BMD at the lumbar spine and hip at 48 weeks was 2.4% and 3.6% in the **tenofovir-DF**/emtricitabine arm and 1.6% and 1.9% in the abacavir/lamivudine arm (each given with

efavirenz) [14], while in the ACTG5224s study, in which the third agent consisted of efavirenz or ritonavir-boosted atazanavir, the observed reductions at 96 weeks were 3.3% and 4.0% with **tenofovir-DF/emtricitabine** and 1.3% and 2.6% with abacavir/lamivudine [15]. When analysed together with two other ACTG studies, randomisation to **tenofovir-DF** was associated with a 1.4% greater reduction in total BMD [12]. Considerably smaller BMD reductions (0.7–1.3%) were observed following the initiation of **tenofovir-alafenamide (tenofovir-AF)**, as compared with **tenofovir-DF** (2.9–3.0%) when co-administered with **emtricitabine, cobicistat and elvitegravir** [16]. **Tenofovir-AF is thus the preferred formulation for older patients with osteoporosis and/or increased fracture risk.**

Several studies have examined the effects on BMD of PIs as part of initial ART. Greater bone loss at the lumbar spine (3.1 vs. 1.7%) but not at the hip (3.4% vs 3.1%) was observed with atazanavir/ritonavir as compared with efavirenz in ACTG 5224s [15]. When analysed together with two other ACTG studies, randomisation to ritonavir-boosted protease inhibitors resulted in a 0.8% greater reduction in total BMD [12]. A Danish study observed no differences in BMD change between those who were randomised to zidovudine/lamivudine or lopinavir/r, each given with efavirenz. At 144 weeks, lumbar spine BMD had decreased by 1.9% and 2.5%, respectively, and hip BMD by 5.0% and 6.1% [17]. Several recent trials in treatment-naïve subjects showed more favourable BMD changes with **raltegravir plus lopinavir/r or darunavir/r** as compared with **tenofovir-DF/emtricitabine** [18-20]. There are currently insufficient data to make recommendations regarding the third agent in terms of their effect on BMD.

Tenofovir-AF as part of initial therapy is associated with significantly less decline in BMD compared with tenofovir-DF, consistent with other first-line ARV regimens [21]; in addition, switching from tenofovir-DF to tenofovir-AF containing therapy is associated with improvements in BMD [22]. Tenofovir-AF may therefore be used in individuals with bone-related contra-indication to tenofovir-DF.

8.10.4 Switching treatment

8.10.4.1 Recommendations

- We recommend against continued use of **tenofovir-DF** in individuals >40 years who are diagnosed with osteoporosis, have sustained a fragility fracture, or have a FRAX score of >20% (major osteoporotic fracture) if acceptable alternative ARV agents are available (1C).

8.10.4.2 Rationale

Tenofovir-DF and PIs have been associated with low BMD and bone loss in cohort studies [23-27], and use of **tenofovir-DF** and lopinavir/r or any PI with an increased incidence of fractures [28,29]. In individuals who were virologically suppressed on ART, a switch from zidovudine/lamivudine to **tenofovir-DF/emtricitabine** resulted in a 2.1% reduction in BMD at the lumbar spine and hip at 48 weeks, compared with no change (+0.6% and +0.3%) following a switch to abacavir/lamivudine [30]. Similar, albeit statistically not significant reductions in lumbar spine and hip BMD were observed in the PREPARE study in which PLWH were randomised to switch from zidovudine/lamivudine to **tenofovir-DF/emtricitabine** or remain on their zidovudine/lamivudine-containing regimen [31]. Smaller reductions (~1.9%) in lumbar spine and total hip BMD have been observed with **raltegravir vs. 2–3 NRTI (each administered with lopinavir/ritonavir)** as second line ART [32], and improvements of 2.5–3% following a switch from **tenofovir-DF** to **raltegravir** [33] or a switch from **tenofovir-DF/emtricitabine/efavirenz** to **darunavir/r** [34]. **Recent trials showed that patients who switched from tenofovir-DF to tenofovir-AF experienced 1.1-1.5% improvement in BMD [35], and patients with renal impairment who switched their tenofovir-DF containing regimen to tenofovir-AF, emtricitabine, cobicistat and elvitegravir experienced 1.9-3.0% improvement in BMD [36]. A switch from tenofovir-DF to tenofovir-AF should be considered in older patients who are diagnosed with osteoporosis and/or increased fracture risk.** There are no data from ART switch studies to suggest that PI discontinuation improves BMD.

Of the non-nucleoside reverse transcriptase inhibitors, efavirenz has been associated with vitamin D deficiency in cohort studies and clinical trials [9]. There are no data to suggest that the initiation of efavirenz

containing ART results in greater initial bone loss, or that efavirenz-containing ART is associated with the development of osteoporosis or fractures. A single case of osteomalacia has been reported with the use of efavirenz [37]. Use of PI has been associated with avascular necrosis of bone and these agents may thus be best avoided in those who have developed this complication [38].

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8.11 Considerations for later life

8.11.1 Introduction

PLWH are not only living into older age but older people are also acquiring HIV as they maintain sexually active lifestyles. The proportion of PLWH in the UK aged 50 and over has more than doubled in the last decade: in 2013, 27% (21,910/81,512) were aged 50 years or above compared with 13% (5,286/41,153) in 2004 [1]. Thirty percent (10,730/25,380) of MSM seen for HIV care were aged 50 years or above in 2013 compared to one in five (21%, 5,390/36,230) in 2008 [1]. Older PLWH are more likely to experience co-morbidities and be receiving non-ARV medication. In addition, increased age may be associated with mental health issues, social isolation and financial challenges; HIV-treating clinicians should be mindful of these factors and familiar with appropriate sources of support.

8.11.2 When to start ART

8.11.2.1 Recommendation

- We recommend standard criteria are used to determine when to commence antiretroviral therapy in older PLWH (1C).

8.11.2.2 Rationale

The following factors should be specifically considered.

8.11.2.2.1 Rate of CD4 cell count decline

Older age has been found to be strongly associated with faster CD4 cell count declines [2–4]. A more recent analysis from the COHERE dataset demonstrated older age was significantly associated with higher viral load, which is in turn associated with CD4 cell count decline [5]. As such, older individuals with a high CD4 cell count may experience more rapid decline so older age may be considered an additional factor when deciding how quickly to commence ART at high CD4 strata.

8.11.2.2.2 Absolute risk of disease progression at a given CD4 cell count

The absolute risk of disease progression is significantly higher for a given CD4 cell count in older people, a factor to consider when counselling older individuals about starting ART.

8.11.2.2.3 CD4 cell recovery on commencing antiretroviral therapy

CD4 cell recovery on commencing ART may be limited in the older person [5,6], possibly due to age-associated effects on thymic function or lower baseline CD4 cell counts [5,7,8]. Some studies suggest this is a short-term phenomenon attenuated with longer duration of ART [9] and others suggest that CD4 cell recovery and virological suppression are not affected by age [10,11].

8.11.2.2.4 The presence of non-infectious co-morbidities

HIV infection itself may accelerate age-related conditions. PLWH may therefore develop non-infectious co-morbidities at an earlier age; ‘accelerated frailty’ may be associated with a lower CD4 count and high viral load. While increased frailty has been observed in ART-naïve individuals, and ART may limit this accelerated ageing, long-term ART exposure may also contribute to certain phenotypes associated with co-morbidities, including fat changes, atherosclerosis and sarcopenia [12].

8.11.4.1 References

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8.11.3 What to start

8.11.3.1 Recommendation:

- We recommend standard antiretroviral regimens are commenced in older PLWH (1C).

8.11.3.2 Rationale

The factors below should be specifically considered when commencing therapy in older PLWH.

8.11.3.2.1 Non-infectious comorbidities

Non-infectious comorbidities are more prevalent in older individuals and are reported to occur more frequently and at a younger age in PLWH compared to matched control populations [1]. Considerations

regarding the presence of end-organ disease should be taken into account when tailoring antiretroviral therapy for older individuals.

8.11.3.2.2 Concomitant medication

The use of concomitant medication, both over-the-counter preparations and prescription medication is highly prevalent in older PLWH [2]. Consideration regarding drug–drug interactions with concomitant medications is required when commencing antiretroviral therapy in older PLWH.

8.11.3.2.3 Clinical pharmacology and ageing

All aspects of drug pharmacology, namely absorption, metabolism, distribution and elimination are reported to change with age. Specifically, for the currently available antiretroviral drugs, effects on hepatic metabolism and elimination may be relevant [3]. Regarding hepatic metabolism, CYP3A4 activity may wane with age and therefore, for drugs metabolised via this pathway, plasma exposure may increase with age. In pharmacokinetic studies, exposure of the boosted-protease inhibitors has been reported to increase with age [4], with these effects not reported with other classes such as the integrase inhibitors [5]. Although theoretically this could lead to increased toxicity in older PLWH, this has not been reported in clinical practice. Regarding elimination, renal elimination of drugs reduces with increasing age. Pharmacokinetic studies have described increased exposure of **tenofovir-DF** in older PLWH compared to younger PLWH, which was thought to be due to reduced renal clearance [6]. Again, here there is a theoretical risk of increased toxicity from higher drug exposure; however, clinical data are lacking.

8.11.3.3 References

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9.0 Acknowledgements

The Writing Group thanks Professors Jose Arribas, Francois Raffi and Linos Vandekerckhove for their peer review of the guidelines.

The Writing Group thanks Alison Richards for conducting the systematic literature search; Jacoby Patterson for work on critical appraisal, evidence profiles and construction of GRADE tables; Sara Gibbons and Kay Seden for their work on Appendix 4 Food considerations for antiretrovirals; and the BHIVA Secretariat for administrative help.

10.0 List of appendices

The appendices can be found on the BHIVA website (www.bhiva.org/guidelines.aspx)

Appendix 1 Summary of the modified GRADE system

Appendix 2 PICO questions and search strategies

Appendix 3 Grade tables

Appendix 4 Food considerations for antiretrovirals

Appendix 5 Considerations for antiretrovirals in renal impairment